

## Research Paper

# The Effects of Crocin Supplementation on Sleep Quality, General Health, and Happiness in Elderly Population: A Randomized, Double-blind, Placebo-controlled Trial



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## ABSTRACT

**Background:** Aging is a period of human life in which general health, especially happiness, and hope, may be impaired. Also, sleep quality, general health, and happiness of the elderly begin to decline at this stage of life. The present study aimed to determine the effect of crocin of saffron on sleep quality, general health, and happiness in the elderly population

**Methods:** In this triple-blind randomized trial, 70 elderly people referred to Kashan health center in 2020 were selected. The study samples were divided into intervention and control groups using computer-generated random numbers to receive 30 mg/d of crocin (2 plus crocin tablet, 15 mg Beck depression inventory [BID]) (n=35) or placebo (2 tablets per day, 15 mg Beck depression inventory [BID]) (n=35), one hour after taking food, for 4 weeks. The sleep quality, general health, and happiness were evaluated at the beginning of the study, 4 and 8 weeks after the intervention. Data were analyzed using Chi-square, independent t-test, and repeated measures analysis of variance (ANOVA).

**Results:** The two groups were matched in terms of demographic characteristics (P>0.05). The independent t-test showed no significant difference between the two groups in the baseline (sleep quality P=0.55, general health P=0.060, and happiness P=0.83) while a statistically significant difference was observed between the two groups on the post-test (P=0.001) and follow-up for three variables.

**Conclusion:** The consumption of crocin by elderly individuals had useful outcomes on sleep quality, well-being, and happiness. Given that the efficacy of the psychological drugs is vital, nurses can use natural medications, such as crocin to improve the psychological disorders of elderly people.

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## 1. Introduction

**A**ging is a period of human life in which general health, especially happiness, and hope, may be impaired. This period usually initiates at the age of 60. Mental and physical variations in this period lead to disturbances in the disorders and performance of his/her adjustments to the environment. General health, sleep quality, and happiness of the elderly in this stage of life start a decreasing pattern. In 2012, the Iranian elderly population was reported approximately 6 million, which includes 5.7% of the entire population in the country. This number is expected to increase to 21% in 2050 [1-4]. The evidence indicates the relationship between the elderly and comorbid conditions, specifically anxiety, depression, general health, and sleep quality disorder [4].

Complementary therapy is one of the suitable choices to deal with mental disorders in the elderly [5]. *Crocus sativus* L., commonly known as saffron, belongs to the iridaceous family. Crocin is one of these agents whose effects on psychological disturbance have already been reported [6, 7]. The effects of crocin on different mental disorders have been assessed in recent years [7, 8]. The result of the randomized trial by Ghaderi et al. on methadone maintenance treatment patients who received 30 mg/d of crocin showed a significant improvement in general health [9]. Current studies indicate that the saffron, at a dosage of 28 mg/d for 1 month, had useful effects on anxiety, stress, and mood control in patients with low mood, but sleep quality score has not improved [10]. Also, recent evidence has demonstrated that oral intake of saffron improves sleep quality in patients with diabetics, and subjects undergoing MMT [11, 12]. One of the most common effects of saffron is its anti-depressant and exhilarant mechanism which leads to a sense of laughter and happiness [13]. Ghorbani et al. said [14] that the consumption of 30 mg/d saffron for 4 weeks by postmenopausal women significantly increased happiness.

Despite the confirmed role of crocin in the treatment of psychological disturbance (e.g. depression, and sleep quality), and happiness, its role in the management of psychological disturbance in the elderly population should be considered given the relatively high prevalence of depression, anxiety, and sleep disorder in the elderly population [12, 15]. Moreover, despite *in vivo* and *in vitro* documentation showing the role of antidepressants, and anti-anxiety agents of crocin, no intervention study has assessed its efficacy in the elderly population. Hence, we aimed to assess whether the administration of crocin in the elderly population improves anxiety and

depression. Therefore, the clinical trial aimed to evaluate the influential activities of crocin on sleep quality, general health, and happiness among the elderly population.

## 2. Materials and Methods

### Study design and participants

This study was a triple-blind randomized clinical trial conducted by the protocol of the Helsinki Declaration [16]. The study was conducted at Kashan health center affiliated with [Kashan University of Medical Sciences](#) between August 2020 and October 2020, where all elderly people are registered.

Based on the randomized controlled trials (RCTs) sample size formula, the type one ( $\alpha$ ) error is considered to be 0.05 and the power is 80% to estimate sample size. In this study, based on a study conducted by Kell et al., on saffron supplements to improve mood and sleep quality in adults, the Mean $\pm$ SD of 2.69 $\pm$ 2.61 for the intervention group and 0.82 $\pm$ 2.77 for the control group were used considering sleep quality as the key variable [10]. Based on a previous study, 30 elderly should have been enrolled in each group. Considering a dropout of 20% of individuals per group, the final sample size was 35 participants in each group.

Eligible participants were people over 65 years of age [17] and the ability to communicate verbally, a score of 22 or higher on the general health questionnaire-28 (GHQ-28) [18], a score of 5 and above on the Pittsburgh sleep quality index (PSQI) [19] and a score of 48 or less on the Oxford happiness questionnaire (OHQ) [20] at the beginning of the study. Initially, 120 registered elderly people in Kashan health center were screened in terms of inclusion criteria. Goldberg General Health [18],

The exclusion criteria included elderly people who consumed crocin, consumed multivitamin-mineral and antioxidant compounds during the last 3 months before the intervention initiation, history of serious physical illnesses, history of kidney, liver disease, and metabolic diseases (such as diabetes, hypertension, thyroid, and cardiovascular disease). [Figure 1](#) shows the flowchart of the participants' selection. Finally, 70 participants were included in the present study. Written informed consent was signed by all participants after receiving the explanations for the study's objectives and design. The study protocol was approved by the Ethics Committee of [Kashan University of Medical Sciences](#). The researcher's registered this trial at the Iranian Registry of Clinical Trials (Code: IRCT20200616047800N1).

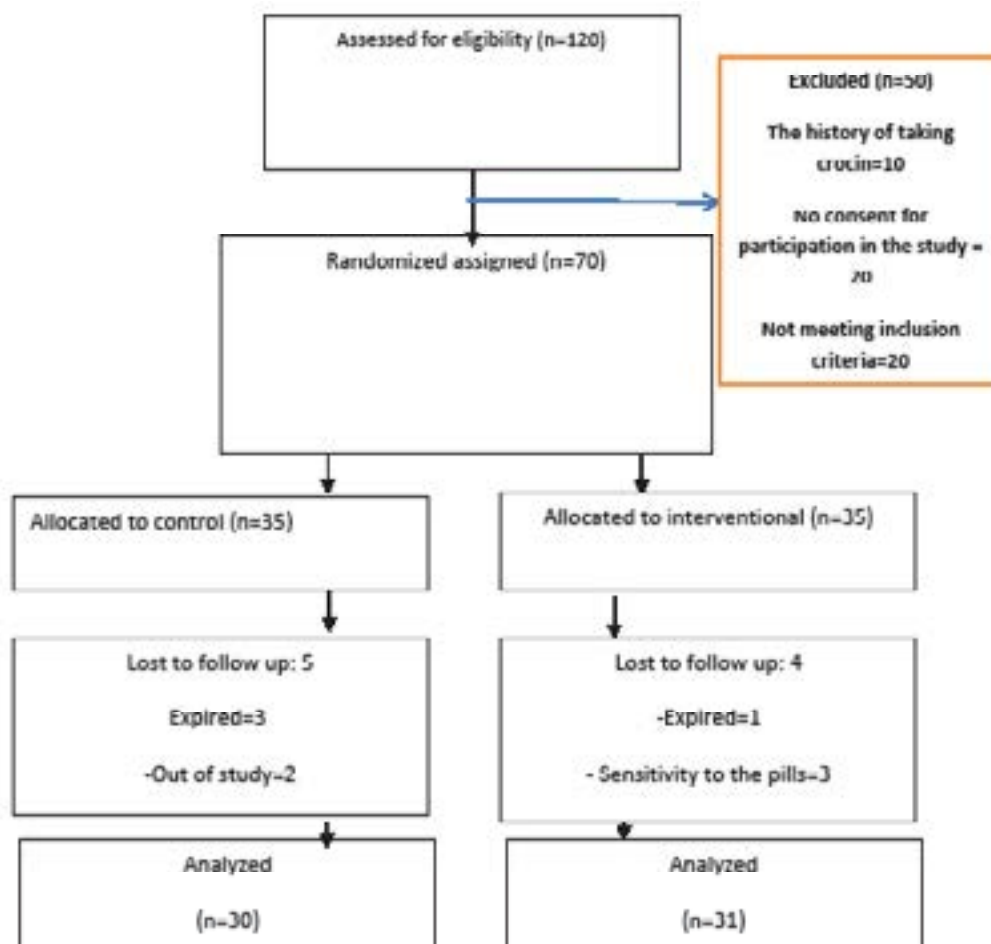


Figure 1. The CONSORT flow diagram

### Study protocol

Finally, after randomly dividing the subjects into two similar groups (total No.=70), the intervention group received 30 mg/d of crocin (2 plus crocin tablet, 15 mg Beck depression inventory [BID]) (n=35) and the control group received placebo (2 tablets per day, 15 mg BID) (n=35), one hour after taking food, for 4 weeks [21].

Due to the lack of evidence about the suitable crocin dose in elderly individuals, the researcher used the above-mentioned crocin dose based on the previous clinical trials in subjects with major depressive disorder (MDD) [21].

Sample randomization of the subjects was done by researchers at the health center using computer-generated random numbers. Randomization and allocation were concealed from the researchers, participants, and statistical analysts until the completion of the final analyses. The crocin and the placebo tablets were arranged in the same shape, color, size, texture, and odor, and each tablet container had a random code number for this triple-blinded trial.

Also, the subjects were asked to attend the health center every 2 weeks (2<sup>nd</sup> and 4<sup>th</sup> weeks) to take their tablets. To assess participants' compliance, they were requested to bring their tablets boxes at each visit to determine the total number of tablets remaining. To increase compliance, all participants were contacted by telephone to remind taking supplements every day.

### Preparation of crocin tablets

Saffron stigmas were purchased from Novin Saffron Co. (Mashhad, Iran). Extraction and crystallization of saffron stigma were carried out according to the protocol of previous studies [22]. The formulation of saffron tablets and placebo was done by the pharmaceutical department of Mashhad Faculty of pharmacy in tablets with a similar film coating. Each tablet contained 15 mg of crocin or a placebo.

### Safety

Participants were assessed for side effects, such as stomach pain, nausea, vomiting, insomnia, sensitivity [23], or complaints during the study. Possible side effects were controlled and recorded at the beginning of the study and during the follow-up period and the pharmacist was responsible for continuing or discontinuing the intervention.

### Measurements

Data were collected at the beginning of the study, 4 and 8 weeks after the intervention using PSQI, GHQ-28, and OHQ by participants through face-to-face interviews with the elderly. If the participant was illiterate, the questionnaires were read and completed by the researcher's colleague.

The PSQI Questionnaire consists of 19 self-assessment questions that are used to measure the quality and pattern of sleep in adults. This questionnaire measures seven dimensions of sleep, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction during the last month [19]. The score of each dimension was 0-3. The seven component scores are then summed to obtain a global PSQI, which has a range of 0-21; higher scores indicated lower sleep quality [19].

The general health questionnaire contains 28 questions that are useful for diagnosing depression, anxiety, social dysfunction, insomnia, and somatic symptoms. The scoring of this questionnaire is on a Likert scale of 0, 1, 2, and 3. The score range of the questionnaire is 0-84. Higher GHQ-28 scores indicate higher levels of distress. Goldberg said that participants with total scores of 23 or below are considered non-psychiatric, while participants with scores >24 may be considered psychiatric [24]. The validity and reliability of the GHQ-28 questionnaire have been examined and confirmed in several studies. Test-retest reliability has been reported to be high (0.78 to 0.9) [25] and inter-rater and intra-rater reliability are excellent (Cronbach's  $\alpha$  0.9–0.95) [26]. High internal consistency has also been reported [26]. The GHQ-28 correlates well with the hospital depression and anxiety scale (HADS) [27] and other measures of depression [25].

The 29-item Oxford happiness questionnaire (OHQ) was designed in the late 1980s with 4 choices each by the psychology department at Oxford University and measures people's happiness [20]. The questionnaire's

reliability is verified in Great Britain [28], Spain, and the USA. OHQ is also used to compare the cultural differences of students in varied cultures of Australia, Canada, Great Britain, and the USA [29].

### Statistical analysis

The normality of the variables was checked by the Shapiro-Wilk test. Descriptive statistics were used to describe and categorize the data (Mean $\pm$ SD). Basic characteristics of study participants were compared between two groups using the student's t-test for continuous variables and the chi-square test for categorical variables. Finally, repeated measures analysis of variance (ANOVA) was used to analyze the effect of time and intervention group on changes in the mean score of sleep quality, general health, and happiness. P values  $P < 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS software, version 16. For continuous comparisons between two groups, an independent t-test and multi-classified chi-square tests were used.

### 3. Results

Out of 70 individuals, 61 elderly completed the study (Figure 1). Five people from the placebo group and four people from the crocin group left the study during the intervention due to sensitivity to the pills and death. Education level, sex, marital status, job, and mean age, were not significantly different between the crocin and placebo groups ( $P > 0.05$ , Table 1).

The mean score of sleep quality in the elderly decreased from 12.25 in the baseline to 4.09 in the post-test and 6.03 in the follow-up in the intervention group ( $P = 0.001$ ). The mean score of general health in the elderly decreased from 44.83 in the baseline to 20.16 in the post-test and 20.25 in the follow-up in the intervention group ( $P = 0.001$ ). The mean score of happiness in the elderly increased from 48.38 in the baseline to 68.29 in the post-test and 65.45 in the follow-up in the intervention group ( $P = 0.001$ ).

No significant difference was observed between the two groups in the baseline (sleep quality  $P = 0.55$ , general health  $P = 0.06$ , and happiness  $P = 0.83$ ) while a statistically significant difference was observed between the two groups in the post-test ( $P = 0.001$ ) and follow-up for three variables ( $P = 0.001$ , Table 2).

**Table 1.** Demographic and clinical characteristics of elderly people

Variables	No. (%) / Mean $\pm$ SD		P	
	Intervention	Control		
Gender	Male	13(42.9)	16(57.1)	0.35
	Female	18(56.2)	14(43.8)	
Education level	Illiterate	13(46.4)	15(53.6)	0.65
	Elementary	14(56)	11(44)	
	Under the diploma	4(57.1)	3(42.9)	
	College education	0(0)	1(100)	
Marital status	Married	25(50)	25(50)	0.78
	Widow	6(54.5)	5(45.5)	
Job	Housewife	18(54.5)	15(45.5)	0.12
	Employee	1(100)	0(0)	
	Retired	5(29.4)	12(70.6)	
Age (y)		68.25 $\pm$ 5.66	66.10 $\pm$ 5.76	0.14
Median		69	65	

Repeated measures analysis of variance (ANOVA) showed the effect of time on the mean score of sleep quality, general health, and happiness, which indicated a change in its mean score over time in both groups. In addition, the interactive effects of time and group on the mean score of sleep quality, general health, and happiness were statistically significant ( $P=0.001$ ), indicating a significant difference between the two groups in terms of changes in the mean score of sleep quality, general health and happiness, where the intervention group experienced a significantly greater reduction in the mean score of sleep quality and general health than the control group and a greater increase in the mean score of happiness than the control group (Table 2).

#### 4. Discussion

This study was conducted to determine the effect of saffron crocin intake on psychological parameters in the elderly population. The results of this study showed the effect of consuming crocin for 4 weeks on the significant improvement of sleep quality, general health, and happiness of the elderly. According to the aforementioned results, saffron crocin is recommended as a nutritional supplement for the elderly population. To the best of our knowledge, this study is the first to evaluate the effects of crocin on the mental health parameters of the elderly population.

#### Effects on sleep quality

One of the common problems in the elderly is sleep disorders caused by retirement, health problems, death of spouse or family members, and changes in circadian rhythm [30]. Our study demonstrated that administration of crocin to elderly people for 4 weeks had significant positive effects on their sleep quality.

Limited studies have investigated the effect of saffron crocin intake on the sleep quality of the elderly. The findings of Kell et al. showed that receiving 22 mg/d and 28 mg/d of saffron for 4 weeks significantly improved the sleep quality of the healthy adult [10]. The findings of another study showed the effect of taking 300 mg/d of saffron for 7 days on reducing anxiety and sleep problems in diabetic patients [31]. Also, the results of Lopresti et al., the study showed that taking 14 mg of saffron twice a day for 28 days improves the quality of sleep in adults with sleep problems [32]. The findings of an animal study showed that crocin increases non-REM sleep in mice [33]. Unlike, Hosseinzadeh and Nouraei found that intraperitoneal administration of crocin does not affect hypnotic activity and anxiety [34]. The effect of crocin on sleep quality can be caused by safranal crocin compounds [32]. Crocin and safranal likely affect the



**Table 2.** Comparison of sleep quality, general health, and happiness in the study groups

Variables	Time	Mean±SD		p <sup>1</sup>	P	
		Control	Intervention		Time <sup>2</sup>	Time×Groups <sup>3</sup>
Sleep quality	Baseline	12.10±0.99	12.25±1.09	0.55		
	Post-test	12.70±1.23	4.09±1.30	0.001	0.001	0.001
	Follow-up	13.00±1.36	6.03±1.42	0.001		
General health	Baseline	45.30±3.31	44.83±3.54	0.60		
	Post-test	43.10±4.67	20.16±3.33	0.001	0.001	0.001
	Follow-up	44.73±3.75	20.25±3.25	0.001		
Happiness	Baseline	48.13±4.88	48.38±4.77	0.83		
	Post-test	50.06±5.03	68.29±5.02	0.001	0.001	0.001
	Follow-up	48.46±4.78	65.45±4.90	0.001		

<sup>1</sup>Independent t-test; <sup>2</sup>Effect of time by repeated measure analysis; <sup>3</sup>Effect of time and group.

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serotonergic and dopaminergic systems and inhibit the reuptake of norepinephrine [35]. Also, crocin may modulate the histaminergic or cholinergic arousal system [33]. The action of saffron is similar to the activity of hypnotic drugs. Similar to diazepam as a benzodiazepine, it has anxiolytic, analgesic, and sleeping effects [35].

### Effects on general health

The findings of the study by Mazidi et al. showed that taking 50 mg of saffron twice a day for 12 weeks reduces the BDI and BAI scores in patients with anxiety and depression [36]. The findings of another study on patients with MDD showed the effect of crocin administration for 4 weeks on the improvement of health parameters, including mood disorders, general health, and anxiety and depression [21]. Saffron intake at a dosage of 15 mg/twice a day for 8 weeks by mothers with mild-to-moderate postpartum depressive disorder significantly reduced their BDI-II scores [37]. In a study, ShahMansouri et al. compared the effectiveness of receiving 30 mg/d of saffron capsules with 40 mg/d of fluoxetine for 6 weeks and reported that receiving saffron capsules has antidepressant effects similar to fluoxetine in depression patients undergoing percutaneous coronary intervention [38].

The effect of crocin on mental health parameters can be caused by the synergistic effects of various compounds in it, including safranal, picrocrocin, and flavonoids [39]. The exact mechanism of crocin's effect on the brain and its effects on mental health scores is

still unclear. Crocin may inhibit the reuptake of monoamine neurotransmitters, including norepinephrine, dopamine, and serotonin in synapses [40]. The effects of crocin on mental health scales may also be due to its antioxidant effects and inhibiting free radicals and pro-inflammatory parameters [41].

### Effects on happiness

Few studies have investigated the effect of taking crocin on happiness. The findings of a clinical trial study in Iran in postmenopausal women showed that the administration of 30 mg/d of oral saffron for 28 days had promising effects on happiness [14]. In a trial by Moghadam et al., 6 weeks of resistance training (RT) with saffron supplementation increased levels of anandamide,  $\beta$ -endorphin, and serotonin concentrations. Moreover, the addition of saffron supplements to chronic RT results in greater improvements in happiness levels than RT alone [42]. Shafiee et al. reported that the antidepressant effect of saffron is similar to antidepressants, such as citalopram, fluoxetine, and imipramine, and possibly fewer side effects were observed [15]. Ahmadpanah et al. found that compared to sertraline, the dosage of 60 mg/d of saffron for six weeks had the same effects on symptoms of depression among a sample of older people with MDD [43]. Based on their role in anxiety, depression, and insomnia [44, 45], the crocin's regulation of the brain levels of those neurotransmitters probably contributes largely to the positive effects of crocin on happiness.

To the best of our knowledge, this is the first study on the effect of crocin on mental health parameters in elderly people. Using the follow-up period for the evaluated outcomes of the study is one of the strengths of this study. Moreover, the participants did not use any psychological medicine during the intervention.

However, the current study had some limitations that should be considered. Using the same dose as other studies may confine the dose-response effect. In addition, the intervention period and sample size were also similar to other studies. To confirm the findings of this study, it is necessary to conduct more studies with different doses of crocin, with the duration of supplement administration, and with a larger sample size.

## 5. Conclusions

Taking crocin improves the quality of sleep, general health, and happiness of the elderly. Given that the efficacy of the psychological drug is vital, nurses can recommend complementary medications, such as crocin to improve the psychological parameters of the elderly population.

## Ethical Considerations

### Compliance with ethical guidelines

All interventions performed in studies including human participants were based on the ethical standards of the institutional and or national research committee and the 1964 Helsinki declaration. The study protocol was approved by the Ethics Committee of [Kashan University of Medical Sciences](#) (Code: IR.KAUMS.NUHEPM.REC.1399.011).

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### Authors' contributions

Study design: Narges Naseri-Borujeni and Hamidreza Sadeghi-Gandomani; Conducting the data collection: Narges Naseri-Borujeni and Fatemeh Shirvanizadeh; Performing the data analysis: Zohreh Sadat; Drafting the manuscript: Amir Ghaderi and Mohammad Afshar; Providing administrative and technical support and revising the paper critically for important intellectual content: Hamid Reza Banafshe and Mohammad Afshar. Obtaining funding: Mohammad Afshar.

### Conflict of interest

The authors declared no conflict of interest.

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