Original Article

Effects Of Saffron (Crocus Sativus Linn) Supplementation On Happiness And Quality Of Life In Healthy Adults: A Randomized Double Blind Clinical Trial

Mohsen-Keyhan Soltani[1], Jamal Shams[2], Farzaneh Ghaffari[3], Fatemeh Alijaniha[4], Mohsen Naseri[5*]

[1]Department of Traditional Persian Medicine, Faculty of Medicine, Shahed University, Tehran, Iran.
[2]Behavioral Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[3]School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
[4]Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, Iran.
[5*]Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, Iran. E-mail: naseri@shahed.ac.ir
DOI: 10.47750/pnr.2023.14.03.360

Abstract

Background: Saffron is a well-known spice and herbal medicine whose health benefits and therapeutic effects have been widely studied. Also, its properties in exhilarating and boosting brain power have been emphasized in Persian medicine. Since few studies have been performed on the saffron effects in healthy people, this study intends to evaluate its effects on promoting happiness and quality of life in healthy adults.

Material and Methods: Fifty-two healthy adults were randomly allocated to two groups in an equal ratio. 75 mg saffron powder was prescribed for intervention groups twice a day for two weeks, and the other group received a placebo. The Oxford happiness questionnaire (OHQ) and 36-item Short Form Survey (SF-36) scores were evaluated as outcome measures. Also, their body temperature, blood pressure, heart rate and respiratory rate were compared.

Results: Fifty patients completed the study. The two groups were similar in demographic characteristics and mental health assessed by 28-item General Health Questionnaire (GHQ-28). After the intervention, no significant difference was observed between the two groups in terms of the SF-36 questionnaire variables. Although the happiness questionnaire scores in both groups improved significantly, the difference between the saffron and placebo groups was insignificant. Moreover, changes in blood pressure, body temperature, heart rate, and respiratory rate were not significantly different within and between groups.

Conclusion: The study showed that daily consumption of 0.15 g of saffron for two weeks in healthy individuals did not change their quality of life and happiness scores compared to the placebo group. This dose of saffron was well tolerated without any serious adverse effects.

Keywords: Saffron, Happiness, Quality of Life, Healthy People, Subthreshold Depression.

INTRODUCTION

Depression is a common mental disorder affecting approximately 5% of adults worldwide. The depressive disorder has a wide range that varies in severity and pattern of episodes (1). Subthreshold depression is characterized by the incidence of 2 to 4 criteria depression symptoms for 2 weeks or more, as opposed to major depression, which needs 5 to 9 symptoms. Despite the prevalence of subthreshold depression among adolescents, few studies have been performed, with mixed results (2, 3). According to recent research, antidepressants are mainly inefficient as compared with placebo in individuals with subthreshold to mild depression (4). The effectiveness of psychotherapy has been shown in such cases (5). To the best of the authors' knowledge, an effective and suitable natural remedy for improving subthreshold depression or low mood in a healthy population has not been

approved thus far.

Saffron (*Crocus sativus* L.) is a valuable medicinal plant and a popular and expensive spice. Its benefit for general health, cardiovascular system, neuropsychological condition, and aging-related disorders have been confirmed (6, 7). The effectiveness of saffron for both major depression as well as mild to moderate depression have shown by several meta-analyses of clinical studies (8, 9).

Historically, saffron has a great association with Persian culture and has spread from Iran to China and India (7). Persian medicine (PM), one of the oldest traditional medicine systems in the world, may be considered a treasure trove of effective experiences in the prevention and treatment of various diseases (10). Clinical studies have proven the effects of many PM therapeutic strategies in recent years (11-13). The use of saffron has a long history in Iran, and PM scholars have discussed its properties for over a thousand years in ancient resources (13). According to PM literature, saffron temperament is warm and dry. In general, various properties have been attributed to saffron in PM literature, such as diuretic, astringent, maturative, resolvent, modifier, and tonic (14). Being an exhilarant or "mofarreh" agent seems to be among the most important properties mentioned for saffron (it means that saffron can improve mood and induce positive sensations such as happiness, fun, enjoyment, delight, and vitality) (15)

Given that a wide range of seemingly healthy people in society suffers from a lack of vitality and energy or chronic fatigue (16), some safe and natural remedies proposed by PM may be considered a good solution for decreased social vitality, increasing productivity in the active forces of society. Although the effectiveness of *Crocus sativus* L. for mild, moderate, and major depression has been proved by many trials, few studies have been done on the effect of saffron on improving subthreshold depression and low mood in healthy people. Thus, the current study aims to evaluate the saffron supplementation effect on promoting happiness and quality of life in healthy adults.

Materials and Methods

Participants

Eligible volunteers were healthy adults who met the inclusion criteria as follows: age of 20-60 years, no depression (scoring less than 7 in the depression section of the 28-item General Health Questionnaire (GHQ-28), referred to as healthy people; groups are matched in terms of scoring), no pregnancy or breastfeeding, and informed consent.

Volunteers with at least one exclusion criterion were not included in the trial. Exclusion criteria were improper medication use, the occurrence of side effects, unwillingness to continue participating in the study, and the occurrence of pregnancy. Also, if any clinically significant deterioration occurred in the baseline medical condition, the patient would have been excluded.

The participants underwent a primary clinical assessment comprising medical history, and demographic data were recorded. They were also initially screened by GHQ-28 to rule out those with depression or other mental disorders (anxiety, somatic symptom, social dysfunction). The validity of the Persian version of GHQ-28 was defined (17). The personal information of participants will be recorded by main researcher and will be kept confidential before, during, and after the trial.

Clinical Trial Registration Code: IRCT20200813048396N1 (https://fa.irct.ir/trial/53148).

Ethical Approval: Research followed guidelines of the Declarations of Helsinki for humans. The trial was authorized by the Ethical Committee of Shahed University (IR.SHAHED.REC.1399.051, 1399.4.21).

Capsules Preparation and Blinding

Saffron, consisting of the powdered dry stigma of Crucus sativus L., was used as an herbal drug in the intervention group. This is the accepted name, according to the plant list (www.theplantlist.org), belonging to a species in the genus Crocus and family Iridaceae. It was purchased from Tarvand Saffron Co. and was standardized based on safranal, crocin, and some other parameters according to national saffron standard 259-2 (18). The herbal drug was 500 mg hard gelatin capsules containing 75 mg saffron powder plus 425 mg bread powder. Similar capsules were filled with 500 mg bread powder to be used as a placebo. Both saffron and placebo capsules were packaged similarly. Their appearance was identical except for a private code on the label of the container. An independent pharmacist prescribed the saffron and placebo capsules, and the identification codes were kept confidential until the end of the study.

Study Design and Interventions

The current study was a two-week, double blind randomized placebo controlled clinical trial, conducted in several outpatient clinics in Tehran, Iran, during June 2021 to February 2022.

Outcome Measures

Happiness and quality of life scores were the main outcomes evaluated in this study and the Oxford happiness questionnaire

(OHQ) and 36-item Short Form Survey (SF-36) were measuring tools.

RESULTS

Out of 60 volunteers who participated in the study, 52 people met the inclusion criteria and allocated to groups. Finally, fifty people completed the trial. The flow diagram is shown in Fig. 1.

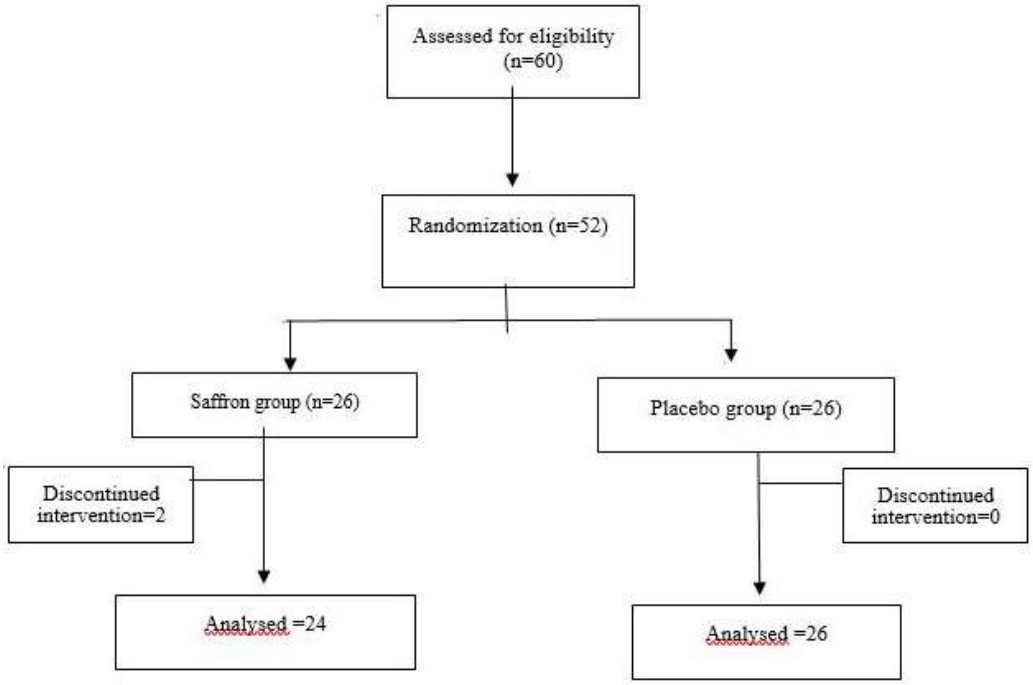

Fig. 1. CONSORT flow diagram of trial

As shown in Table 1, both groups are similar in terms of demographic data including age, gender and mental health (P>0.05).

Table 1: The demographical variables and General Health sub domains at the start of study

Categorical variables		**Group**				**P-value**
		Saffron (n=24)		**Placebo (n=26)**		
		N	**%**	**N**	**%**	
Gender	Female	21	87.5%	20	76.9%	0.467
	Man	3	12.5%	6	23.1%	
Age	≤ 30	5	20.8%	8	30.8%	0.408
	31 - 40	8	33.3%	12	46.2%	
	41 - 50	9	37.5%	5	19.2%	
	51>	2	8.3%	1	3.8%	
Continues Variables		**Mean**	**SD**	**Mean**	**SD**	**P-value**
General Health Questionnaire	Somatic symptoms	6.75	2.21	6.96	2.65	0.899
	Anxiety/insomnia	6.25	2.57	6.12	2.23	0.845
	Social dysfunction	6.92	2.38	6.42	1.81	0.381
	Depression	6.58	1.1	7	1.66	0.304
	Total	26.5	6.13	26.5	5.46	0.907

The SF-36 questionnaire was used to evaluate the quality of life parameters. Table 2 presents the results of the intervention for the studied variables.

At the beginning of the study, the two groups were similar in terms of the SF-35 questionnaire parameters (physical functioning, role limitation owing to emotional problems, role limitations due to physical health, fatigue/energy, emotional well-being, pain, social functioning, and general health) (Table 2). After the intervention, although the changes in some variables were significant in each group compared to the baseline, they were not enough to make a significant difference between groups (P>0.05).

Table 2: The result of SF36 questioner between two groups during study time

Variables	Group	Time				Diff (Post-Pre)	P-value	
		Pre		Post			With in	Between
		Mean	SD	Mean	SD			
Physical functioning	Saffron	85.83	14.27	88.13	17.43	2.3	0.268	0.796
	placebo	89.04	9.90	92.12	7.90	3.08	0.040	
		P-value	0.561					
Role limitations due to physical health	Saffron	71.88	33.23	88.54	20.82	16.66	0.024	0.748
	placebo	78.85	28.89	87.50	21.51	8.65	0.112	
		P-value	0.558					
Role limitations due to emotional problems	Saffron	61.11	45.75	79.17	33.78	18.06	0.047	0.974
	placebo	76.92	30.94	89.74	18.30	12.82	0.029	
		P-value	0.382					
Energy/fatigue	Saffron	66.04	15.81	71.25	15.48	5.21	0.074	0.644
	placebo	62.88	13.65	68.27	13.34	5.39	0.019	
		P-value	0.526					
Emotional well-being	Saffron	74.50	12.75	75.17	14.35	0.67	0.878	0.261
	placebo	70.92	13.97	74.92	10.53	4	0.059	
		P-value	0.446					
Social functioning	Saffron	72.40	19.50	83.33	19.03	10.93	0.009	0.936
	placebo	70.19	19.39	79.33	17.66	9.14	0.008	
		P-value	0.663					
Pain	Saffron	72.71	21.38	80.52	17.05	7.81	0.106	0.750
	placebo	79.13	17.46	83.27	15.19	4.14	0.070	
		P-value	0.312					
General health	Saffron	73.33	15.86	78.54	13.87	5.21	0.138	0.658
	placebo	73.65	11.10	78.85	9.52	5.2	0.013	
		P-value	0.837					
Total	Saffron	74.42	14.48	81.22	13.80	6.8	0.002	0.977
	placebo	77.11	10.59	82.82	8.15	5.71	0.004	
		P-value	0.580					

According to Table 3, before the intervention, the two groups were not significantly different in terms of happiness scores. Although the scores in both groups improved significantly after the intervention, the difference between groups was not significant (P=0.069).

Table 3: The happiness questionnaire scores of saffron and placebo groups

Group	Time				Diff (Post-Pre)	P-value	
	Pre		Post			With in	Between
	Mean	SD	Mean	SD			
Saffron	79.63	14.55	83.13	13.81	3.5	0.008	0.069
placebo	73.23	12.44	80.62	12.51	7.4	<0.001	
	P-value	0.101					

Table 4 presents the measured values of some biological parameters related to the studied cases before and after the intervention. According to this table, before and after the intervention, no significant difference was observed between the groups concerning systolic and diastolic blood pressure, body temperature, heart rate, and breath rate per minute in the participants.

Table 4: The result of systolic blood pressure, diastolic blood pressure, pulse rate, body temperature and respiratory rate of two groups before and after intervention

Variables	Group	Time				Diff (Post-Pre)	P-value	
		Pre		Post			With in	Between
		Mean	SD	Mean	SD			
Systolic blood pressure	Saffron	113.38	11.71	114.75	10.54	1.37	0.317	0.992
	placebo	113.04	10.28	114.81	11.39	1.77	0.301	
		P-value	0.861					
Diastolic blood pressure	Saffron	73.30	8.46	74.13	8.30	0.83	0.558	0.658
	placebo	73.58	9.37	73.81	8.52	0.23	0.646	
		P-value	0.802					
Pulse rate	Saffron	81.79	10.73	80.38	11.30	-1.41	0.307	0.082
	placebo	80.88	10.11	82.12	7.70	1.24	0.165	
		P-value	0.697					
Body temperature	Saffron	36.80	0.19	36.84	0.52	0.04	0.806	0.596
	placebo	36.92	0.34	36.97	0.24	0.05	0.572	
		P-value	0.119					
Respiratory rate	Saffron	15.67	3.31	17.33	2.41	1.66	0.021	0.272
	placebo	15.92	3.47	16.46	2.30	0.54	0.308	
		P-value	0.937					

DISCUSSION

This 2-week, randomized, double-blind, placebo-controlled trial indicated that 150 mg/day supplementation of powdered saffron in healthy adults was related to improved happiness scores and quality of life parameters; however, changes were not significantly different from placebo. Also, no significant changes in body temperature, blood pressure, heart rate, and respiratory rate were observed in the intervention group.

Many clinical trials have confirmed the efficacy of saffron for anxiety and mild to moderate depression (9). Also, in healthy people, reduced depression, improved mood, and happiness after saffron supplementation has been reported in some studies (19, 20).

Kell et al. evaluated the saffron effect in healthy adults using 22 and 28 mg of standardized saffron stigma extract (affron®) daily. According to the HPLC-PAD/MS analysis result, affron® contained 0.03% safranal, 3.99% crocin, and 1.41% total phenolic compound. This four-week study showed that 28 mg/day of the saffron extract significantly reduced negative mood and symptoms associated with stress and anxiety in healthy participants. PANAS questionnaires, DASS-21 scale, Sleep Quality Index (PSQI), and POMS (primary outcome measure)were measuring tools (19).

However, in another study using the same dose of the saffron extract (28 mg/day of affron®) for 6 weeks in healthy, active adults (engaged in nonprofessional but moderate-to-intense aerobic exercise for at least three times per week), no significant difference was observed in the parameters evaluated by Profile of the Mood States, Physical Activity Enjoyment Scale, and Patient-Reported Outcomes Measurement in the saffron group as compared with the placebo group. Further, sleep quality, heart rate variability (HRV), and resting heart rate did not change significantly. The plasma concentration of BDNF, oxytocin, and neuropeptide A did not change either. (20). Similar to the present research, the saffron supplementation had no significant effect on the findings in this study.

Hormonal differences affecting the examined parameters were discussed by Lopersi et al. as a potential reason for the insignificant outcomes. Due to the different effects of saffron on sex hormones, the study results were significant in men but not women in the statistical analysis by sex.

Similarly, since the present study was based on the data obtained from the participants, most of whom were female (82.2%), the insignificant changes in the parameters in the intervention group as compared with the placebo group may be partially due to the lesser effect of saffron in women as supposed by the above study. In this regard, several animal studies have reported the saffron impact on sex hormones (21-23) ; also, the relationship between mood and sex hormones is well-known. (24, 25). Therefore, the lack of equal gender distribution of the participants in the current study may be a factor affecting the response to saffron consumption.

In a recent study by Jackson et al., which examined the effects of 30 mg/day of saffron extract compared to a placebo for 8 weeks in healthy subjects, reduced depression scores, improved social communication, and increased resilience against stressed-related mental disorders were reported. The participants in the study were selected among healthy persons with low mood and subclinical anxiety. They also evaluated the effect of saffron in response to psychological stressors. Chronic effects of saffron were measured by a questionnaire battery [Including Profile of Mood State-2, (POMS)], and acute effects in response to stressor

were measured by HRV (26).

The previously mentioned studies have used saffron extract. Considering the use of saffron powder in the present study, it is not practical to simply match the dose and compare the effects with earlier studies. Also, the outcomes and measurement tools in these studies are different, making comparison difficult.

According to another study that investigated the effects of consuming 150 mg of saffron powder along with resistance training (RT) for 6 weeks, the level of happiness and the serum concentration of 2-Arachidonoylglycerol (2-AG), Anandamide (AEA), β-endorphin (beta-endorphin), serotonin, dopamine, and tryptophan were improved (27). Although this research is similar to the current study in terms of saffron powder consumption, it is different in terms of the dosage, as well as being accompanied by RT and using a visual analog scale instead of OHQ for happiness evaluation. On the other hand, in the mentioned study, the mental health and depression level of the participants was not evaluated before the intervention. However, the measurement of neurotransmitters showed lower baseline levels of serotonin and dopamine in the saffron group, which could be a reason for the lower happiness among its members, unlike the present study, where the baseline happiness scores were slightly higher in the saffron group.

Jackson et al. selected healthy participants among people with low mood or subclinical anxiety, while in the present study, as can be seen in the baseline, the happiness scores of both groups are high, and even the saffron group had higher scores than the placebo group, although there was no significant difference. Also, in another study that reported a significant increase in the scores of the OHQ after daily consumption of 30 mg of saffron for 4 weeks in postmenopausal women, the baseline mean happiness scores in the saffron group were much lower compared to the present work (45.5 vs. 79.6) (28). Thus, possibly the saffron effect in increasing happiness is greater in people with lower baseline happiness scores. No change in happiness scores was observed in the saffron and placebo groups; thus, happiness possibly was at high levels already, leading to "ceiling effects" (29).

In the PM resources, "mofareh" drugs such as saffron are defined as remedies for removing grief and inducing happiness. However, they are recommended along with other therapeutic measures to improve lifestyle (e.g., nutrition modification, exercise, and correction of psychological factors). This view is in line with some recent studies, showing that saffron supplementation enhances the RT effects in healthy people (27).

Therefore, it seems that the efficacy of saffron in improving happiness is more obvious in mild to moderately depressed patients or in healthy people with low mood or subthreshold depression. Overall, as shown in similar studies, the use of the saffron supplement, if combined with other methods such as exercise or psychotherapy, has a significant effect on promoting happiness in healthy people with a low mood. However, it seems that short-term consumption of low doses of saffron alone in healthy people with relatively high happiness scores does not have a significant effect.

Two cases of headache were the only side effects reported due to this intervention. Presenting a novel idea in natural remedies for improving subthreshold depression, studying a dose of saffron not evaluated so far on the happiness of healthy people, and showing the absence of serious adverse effects in its two-week use are some positive points of this study.

The current study had several limitations, which possibly affected the observed findings, one of which was its short duration (two weeks); in other similar studies, the duration of the interventions was from 4 to 8 weeks. Another limitation was that the participants' happiness scores were high, i.e., they were happy within the normal range. Therefore, based on the "ceiling effect," the impact of the intervention with saffron supplementation in increasing happiness may be much lower than in the cases with participants with low happiness or mood. This justifies further research to investigate saffron supplementation in healthy people with low happiness scores.

The subjective nature of the assessed outcomes and lack of quantitative parameters evaluated by the laboratory may be considered another limitation. Further studies with proper duration, follow-up, and larger sample size are suggested.

Conclusion

The current study showed that consumption of 75mg/day of powdered saffron for two weeks in healthy persons with high happiness scores did not significantly change their quality of life and happiness scores as compared with the placebo group. This dose of saffron was well tolerated with few adverse effects.

Acknowledgment

This manuscript is inspired from a PhD student thesis of Traditional Persian Medicine (TPM) in Department of TPM, School of Medicine, Shahed University, Tehran, Iran**.** Also, we thank the financial support of Shahed University, Tehran, Iran.

Conflict of Interest

There is no competing interest to declare.

REFERENCES

1. Organization WH. Depression and other common mental disorders: global health estimates: World Health Organization; 2017 Contract No.: Document Number.
2. Crockett MA, Martínez V, Jiménez-Molina Á. Subthreshold depression in adolescence: Gender differences in prevalence, clinical features, and associated factors. Journal of Affective Disorders. 2020; 272: 269-76.
3. Kroenke K. When and how to treat subthreshold depression. Jama. 2017; 317(7): 702-4.
4. Baumeister H. Inappropriate prescriptions of antidepressant drugs in patients with sub threshold to mild depression: time for the evidence to become practice. Journal of affective disorders. 2012; 139(3): 240-3.
5. Kaviani H, Hatami N, Javaheri F. The impact of mindfulness-based cognitive therapy (MBCT) on mental health and quality of life in a sub-clinically depressed population. Archives of Psychiatry and Psychotherapy. 2012; 1(14): 21-8.
6. Abu-Izneid T, Rauf A, Khalil AA, Olatunde A, Khalid A, Alhumaydhi FA, et al. Nutritional and health beneficial properties of saffron (Crocus sativus L): A comprehensive review. Critical Reviews in Food Science and Nutrition. 2022; 62(10): 2683-706.
7. El Midaoui A, Ghzaiel I, Vervandier-Fasseur D, Ksila M, Zarrouk A, Nury T, et al. Saffron (Crocus sativus L.): A source of nutrients for health and for the treatment of neuropsychiatric and age-related diseases. Nutrients. 2022; 14(3): 597.
8. Ahmadpanah M, Ramezanshams F, Ghaleiha A, Akhondzadeh S, Bahmani DS, Brand S. Crocus Sativus L.(saffron) versus sertraline on symptoms of depression among older people with major depressive disorders–a double-blind, randomized intervention study. Psychiatry research. 2019; 282: 112613.
9. Dai L, Chen L, Wang W. Safety and efficacy of saffron (Crocus sativus L.) for treating mild to moderate depression: a systematic review and meta-analysis. The Journal of nervous and mental disease. 2020; 208(4): 269-76.
10. Alijaniha F, Naseri M, Afsharypuor S, Fallahi F, Noorbala A, Mosaddegh M, et al. Heart palpitation relief with Melissa officinalis leaf extract: double blind, randomized, placebo controlled trial of efficacy and safety. Journal of ethnopharmacology. 2015; 164: 378-84.
11. Araj-Khodaei M, Noorbala AA, Yarani R, Emadi F, Emaratkar E, Faghihzadeh S, et al. A double-blind, randomized pilot study for comparison of Melissa officinalis L. and Lavandula angustifolia Mill. With Fluoxetine for the treatment of depression. BMC complementary medicine and therapies. 2020; 20(1): 1-9.
12. Safari MB, Nozad A, Ghaffari F, Ghavamzadeh S, Alijaniha F, Naseri M. Efficacy of a short-term low-calorie diet in overweight and obese patients with chronic sciatica: a randomized controlled trial. The Journal of Alternative and Complementary Medicine. 2020; 26(6): 508-14.
13. Naseri V, Chavoshzadeh Z, Mizani A, Daneshfard B, Ghaffari F, Abbas-Mohammadi M, et al. Effect of topical marshmallow (Althaea officinalis) on atopic dermatitis in children: A pilot double-blind active-controlled clinical trial of an in-silico-analyzed phytomedicine. Phytotherapy Research. 2021; 35(3): 1389-98.
14. Khorasani M. Aghili. ".Makhzan Al Advieh" Bavardaran Press Research institute for Islamic and Complementary Medicine, Iran University of Medical Sciences, Tehran, Iran. 2001.
15. Yousefi M, Shafaghi K. Saffron in Persian traditional medicine. Saffron: Elsevier; 2020. p. 393-404.
16. Strawbridge R, Sartor M-L, Scott F, Cleare AJ. Inflammatory proteins are altered in chronic fatigue syndrome—a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews. 2019; 107: 69-83.
17. Malakouti SK, Fatollahi P, Mirabzadeh A, Zandi T. Reliability, validity and factor structure of the GHQ-28 used among elderly Iranians. International Psychogeriatrics. 2007; 19(4): 623-34.
18. Standard NI. Saffron methods of analysis. 2005.
19. Kell G, Rao A, Beccaria G, Clayton P, Inarejos-García AM, Prodanov M. Affron® a novel saffron extract (Crocus sativus L.) improves mood in healthy adults over 4 weeks in a double-blind, parallel, randomized, placebo-controlled clinical trial. Complementary Therapies in Medicine. 2017; 33: 58-64.
20. Lopresti AL, Smith SJ. An examination into the mental and physical effects of a saffron extract (affron®) in recreationally-active adults: A randomized, double-blind, placebo-controlled study. Journal of the International Society of Sports Nutrition. 2022; 19(1): 219-38.
21. Ai J, Nekooeian A, Takhshid M, Mostafizi N, Mehrabani D. Effect of aqueous extract of Crocus sativus L. (saffron) stigma on serum levels of gonadotropins and folliculogenesis in adult rats. Journal of Applied Animal Research. 2009; 35(1): 49-52.
22. Modaresi M, Messripour M, Asadi Marghmaleki M, Hamadanian M. Effect of Saffron (Crocus Sativus) extract on level of FSH, LH and testosterone in mice. Journal of Advances in Medical and Biomedical Research. 2008; 16(63): 11-8.
23. Vasegh M, Koohpeyma F, Kargar Jahromi H, Bathaee SH, Saberi R, Azhdari S, et al. Investigating effects of hydroalcoholic extract of saffron on sex hormones in female rats undergoing chemotherapy with cyclophosphamide. Comparative Clinical Pathology. 2015; 24(2): 399-402.
24. Castanho TC, Moreira PS, Portugal-Nunes C, Novais A, Costa PS, Palha JA, et al. The role of sex and sex-related hormones in cognition, mood and well-being in older men and women. Biological psychology. 2014; 103: 158-66.
25. Rainville JR, Hodes GE. Inflaming sex differences in mood disorders. Neuropsychopharmacology. 2019; 44(1): 184-99.
26. Jackson PA, Forster J, Khan J, Pouchieu C, Dubreuil S, Gaudout D, et al. Effects of saffron extract supplementation on mood, well-being, and response to a psychosocial stressor in healthy adults: a randomized, double-blind, parallel group, clinical trial. Frontiers in nutrition. 2021: 365.
27. Moghadam BH, Bagheri R, Roozbeh B, Ashtary-Larky D, Gaeini AA, Dutheil F, et al. Impact of saffron (Crocus Sativus Linn) supplementation and resistance training on markers implicated in depression and happiness levels in untrained young males. Physiology & Behavior. 2021; 233: 113352.
28. Ghorbani M, Tabatabaeichehr M, Bagheri M, Salari E, Nazari S. Effect of saffron on happiness of postmenopausal women: a clinical randomized trial. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2019; 22(4): 11-7.
29. Andrade C. The Ceiling Effect, the Floor Effect, and the Importance of Active and Placebo Control Arms in Randomized Controlled Trials of an Investigational Drug. Indian Journal of Psychological Medicine. 2021; 43(4): 360-1.