THE EFFICACY OF ADDING SAFFRON TO FLUOXETINE IN THE TREATMENT OF MILD TO MODERATE DEPRESSION IN TYPE 2 DIABETES MELLITUS PATIENTS: A RANDOMIZED DOUBLE-BLINDED STUDY

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Abstract

Background: Depression is one of the most common psychiatric disorders in diabetic patients, the occurrence of which affects the course of treatment and worsens its prognosis. Recently, accumulating evidence reveals a positive effect of saffron on relieving depressive symptoms. The aim of this study was to evaluate the efficacy of adding saffron to fluoxetine in the treatment of mild to moderate depression in type 2 diabetes mellitus (T2DM) patients.

Methods: This randomized double-blinded study was conducted on patients with DMT2 with a diagnosis of mild to moderate depression (diagnosed using DSM-5 criteria) referring to Imam Khomeini hospital, Ahvaz, in 2021. A total of 60 patients were randomly assigned to receiving 30 mg/day saffron or placebo tablets along with fluoxetine (20 mg/day) for four weeks. The severity of depression was assessed based on the Hamilton Rating Scale for Depression (HRSD) score before and after the intervention, and incidence of treatment-related complications was investigated.

Results: After the intervention, HRSD scores were reduced significantly in the both groups ($P<0.0001$); however, the reduction of depression symptoms in the saffron group was significantly higher in the intervention than in the placebo group ($P=0.001$). At the end of the intervention, all patients in the saffron group (100%) compared to 23 patients in the placebo group (76.7%) had an HDRS score ≤ 7 ($P=0.011$). No significant difference was detected in the incidence of adverse effects between the two groups ($P=0.390$).

Conclusion: Our study's results indicated the beneficial effects of the combination of saffron and fluoxetine on mild to moderate depression in DMT2 patients. Therefore, saffron could be considered as an effective and safe alternative to synthetic antidepressants for treating mild to moderate depression.

Keywords: Depression, Fluoxetine, Saffron, Type 2 diabetes

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Introduction

Diabetes mellitus (DM) and depression are important public health problems worldwide, and the prevalence of both is increasing dramatically (1, 2). Metabolic changes in type 2 diabetes mellitus (T2DM) cause and aggravate mental disorders such as depression and anxiety (3). Depression is one of the most common psychiatric disorders in diabetic patients. Evidence shows that diabetes and depression have a two-way relationship in terms of pathophysiology (2, 4). The incidence of depression in people with diabetes has been reported to be two to three times higher than in the general population (5, 6).

The coexistence of depression and diabetes is associated with impaired quality of life, poor self-care behavior such as less adherence to treatment, poor blood sugar control, and poor outcome (6-8). On the other hand, the course of depression in diabetic patients is chronic and severe. Even with successful treatment, up to 80% of diabetic patients experience relapse of depression (9). Although depression in diabetic patients can be managed with various methods, including antidepressants and psychological interventions such as cognitive-behavioral therapy, the existing guidelines for depression management are insufficient (7, 10). The use of antidepressants for treating diabetic patients is associated with the potential risk of obesity, metabolic disorders, hypoglycemia, and insulin resistance (11, 12).

Considering the many side effects of chemical drugs, identifying safe and effective alternative treatment options that have higher acceptability than chemical drugs is necessary to improve the outcomes of both disorders (13, 14). In this regard, some studies have shown that saffron, as an herbal remedy, can reduce diabetes-associated depression-anxiety (3, 15).

Saffron, with the scientific name of *Crocus sativus L.* from the Iridaceae family, in addition to its traditional value as a food additive, has several therapeutic effects such as antidepressant, sedative, pain reliever, antispasmodic, anti-flatulent, and anticancer activities among many other useful functions (16, 17). The antidepressant effects of aqueous and hydroalcoholic extracts of saffron have been shown in animal models (18, 19). In clinical trials, saffron has shown antidepressant effects similar to fluoxetine (20) and imipramine (21) in patients with mild to moderate depression. The anti-depressant function of saffron is mediated through its two active ingredients, including safranal and crocin, which inhibit the reabsorption of neurotransmitters including dopamine, norepinephrine, and serotonin, and as a result, improve depression symptoms (18, 22).

In several studies, saffron has been reported to be more effective than placebo in the treatment of mild to moderate depression and similar to routine antidepressants (22-24). Also, in several studies, the effectiveness of saffron in reducing the symptoms of depression and anxiety compared to placebo has been observed in diabetic patients (3, 25), but so far, no study has compared the combinational effect of saffron and fluoxetine in these patients (26, 27). So, the present study aims to evaluate the effectiveness of fluoxetine and saffron in alleviating mild to moderate depression in type 2 diabetic patients.

Methods

The present study was a double-blind randomized clinical trial conducted in 2021 on patients with type 2 diabetes mellitus referred to the Ahvaz Diabetes Center with a diagnosis of mild to moderate depression. This study was approved by the Ethics Committee of Ahvaz University of Medical Sciences (Ethical code: IR.AJUMS.HGOLESTAN.REC.1400.176) and registered at the Iranian Registry for Clinical Trials with the registration code IRCT20220309054235N1. Written informed consent was obtained from all patients before starting the treatment. Also, in all stages of this research, the provisions of the ethics statement of Helsinki and the principles of patient information confidentiality were observed.

The sample size was determined according to the following two formulas and with the help of the Sealed Envelope calculator software:

$n = f(\alpha, \beta) \times 2 \times \sigma 2 / d2$ و $f(\alpha, \beta) = [\Phi\text{-}1(\alpha) + \Phi\text{-}1(\beta)]2$

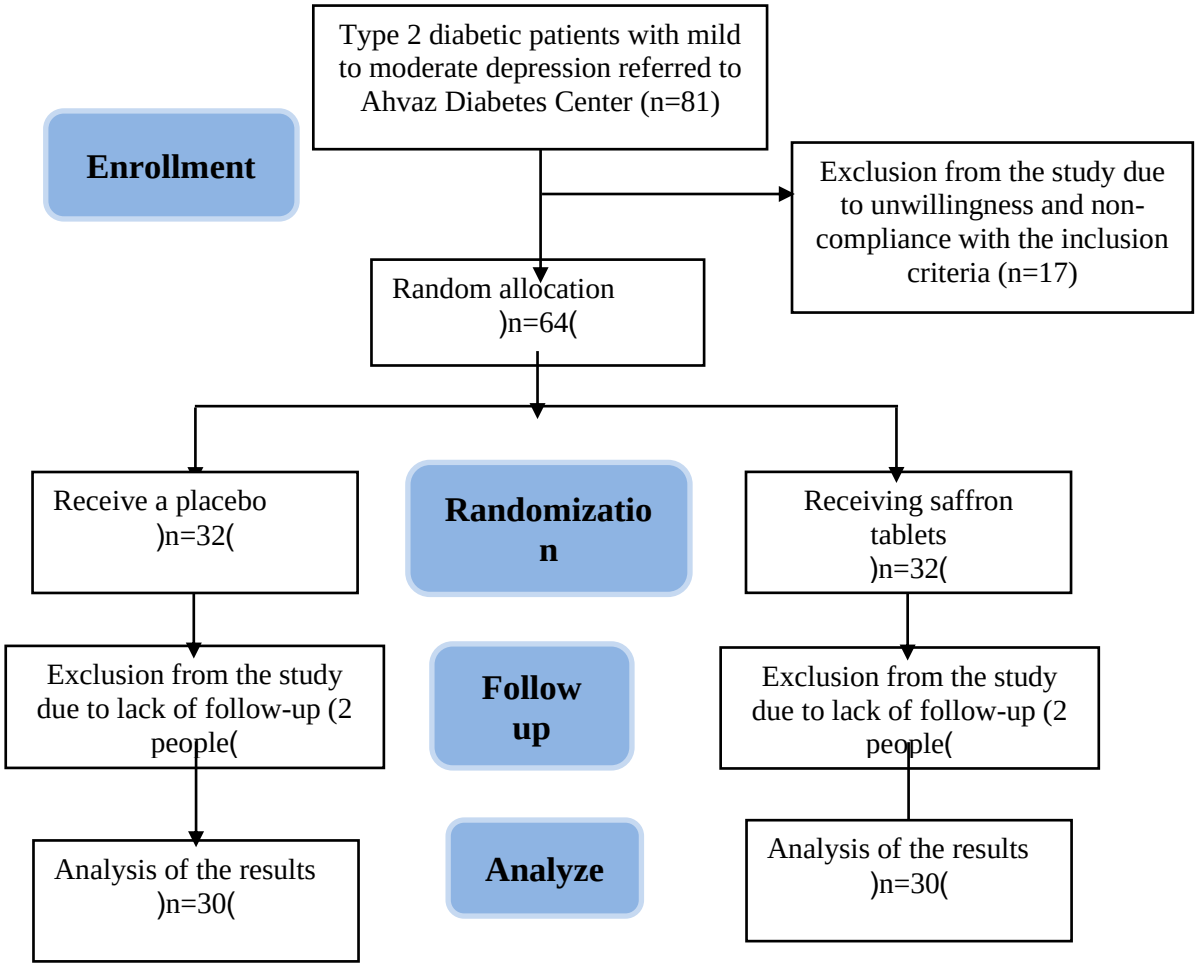
where σ is the standard deviation, and Φ-1 is the cumulative distribution function of the standard normal deviation. Also, based on the results of Kashani et al. (28), reporting a maximum standard deviation of 1.2 (σ=2.1) for the difference between saffron and fluoxetine treatment in postpartum depression, and assuming the non-inferiority limit (d) in the HDRS questionnaire as

2, as well as a confidence of 95%, the sample size for each group was obtained as 24 people (48 people in total). Assuming a dropout rate of 25%, the total sample size was considered to be 60 (30 people in each group).

Patients with type 2 diabetes mellitus with mild to moderate depression, age of 60-18 years, fasting blood sugar less than 126 mg/dL, and body mass index (BMI) between 18.5 and 45 were eligible to enter the study. Also, patients with severe depression, those using psychiatric drugs, drug abusers (excluding those with nicotine dependence), insulin users, patients with uncontrolled blood sugar control (HbA1c above 8% according to the guidelines of the American Medical Association (29)), pregnant and breastfeeding women, females intending to become pregnant in the near future, those suffering from other psychiatric diseases besides depression (including anxiety disorders, psychotic disorders), people with a previous history of depression, mental disability, those experiencing disease aggravation during the study, and patients with intolerable side effects were excluded from the study (30). The diagram of the study process and participant selection has been shown in Figure 1.

At the beginning of the study, a general information questionnaire addressing age, gender, education, occupation, economic status, history of previous depression, and anthropometric characteristics (including height, weight, and BMI) was completed. Also, the patients were evaluated by a trained psychiatrist in order to diagnose depression based on DSM-5 criteria. After this stage, the Hamilton depression scale was completed by a psychiatrist to determine the severity of depression. A score between 10 and 18 in the depression scale was considered as mild to moderate depression. In this way, patients with mild to moderate depression were selected for the study according to the inclusion criteria.

Figure 1- Flowchart of the study



Grouping and intervention

The patients were randomly divided into two groups. Randomization was performed based on the first random permutation of four by a person who had no involvement in the study process. Participants in both groups started fluoxetine treatment (Obeidi Pharmaceutical Company, Iran) at a dose of 20 mg daily for one week. The treatment continued for four weeks in both groups. After the fourth week from the start of the treatment, daily 30 mg tablets containing hydroalcoholic extract of saffron were added to the therapeutic regimen of the intervention group along with fluoxetine for additional four weeks. The control group also received a completely similar tablet containing a placebo without the active ingredient.

Saffron was procured from a reputable company, and after being identified by a botanist, a hydroalcoholic extract was prepared. Tablet containing 30 mg of dry saffron extract and placebos were prepared at the Center for the Development of Pharmaceutical Technologies of Jundishapur University, Ahvaz. The appearance of the placebo was similar to saffron tablets.

The study was conducted in a double-blinded manner, and the patients, the researcher, and the person who checked the results were unaware of the grouping. The patients were asked not to change their physical activity and diet during the study period, and in the case of any possible hemorrhage, nose bleeding, bloody sputum, or bloody stools, they immediately stopped taking the drugs and consulted a doctor. During each visit, blood coagulation tests were also taken from all patients, and if any disorder was observed, the use of auxiliary drugs (either saffron or placebo) was stopped.

Evaluation of consequences

In this study, the 17-item version of the Hamilton Depression Rating Scale (HDRS) was used to evaluate the severity of depression in patients. Before the start of the study and after the end of the intervention (the end of the eighth week), the HDRS questionnaire was completed by the therapist for the patients. Based on changes in the HRDS score, partial response to treatment (25-50% reduction in HDRS score), complete response to treatment (≥50% reduction in HDRS score), and recovery rate (HDRS ≤ 7) were compared between the two groups.

Also, during each visit, the patients were asked to answer questions about the side effects of the treatment, including dry mouth, drowsiness, insomnia, blurred vision, headache, dizziness, digestive problems, increased or decreased appetite, urinary problems, sexual function problems, heart palpitations, sweating, increased body temperature, tremors, weight gain, and serotonin syndrome.

Statistical Analysis

SPSS version 22 was used for statistical analysis. Average, standard deviation, frequency, and percentage were used to describe the data. The normality of the data was evaluated using the Kolmogorov-Smirnov test. Independent t-test was used to compare the means of the variables between the two groups. Paired t-test was used to compare variables before and after treatment, and the Chi-square (or Fisher's exact) test was used to determine the relationship between qualitative variables. The significance level in all tests was considered 0.05.

Results

Sixty type 2 diabetic patients with mild to moderate depression (HDRS≤18), including 30 women (50%) and 30 men (50%), participated in this study. The basic characteristics of the participants in this research in the two groups are presented in Table 1. There were no significant differences between the two groups in terms of age, gender, weight, BMI, education, occupation, economic status, and duration of diabetes (P>0.05).

The changes in the Hamilton depression score during the study in the two groups receiving saffron and placebo are presented in Table 2. After four weeks, a significant improvement in the depression score was observed in both groups (P<0.0001), but the improvement of depression

symptoms in the group receiving saffron was significantly higher than in the group receiving placebo (P=0.001). Also, the recovery percentage in the saffron group was significantly higher than in the placebo group (P=0.001).

In this study, complete response to treatment (≥50 reduction in HDRS score) was observed in all subjects in both groups (100%). Also, in the end of the treatment, all people in the saffron group (100%) showed an HDRS score ≤ 7 compared to 23 people in the placebo group (76.7%) (P=0.011).

Comparison of the frequency of side effects during the study period in two groups showed that seven people in the saffron group (23.3%) had side effects compared to 10 people (33.3%) in the placebo group (Table 3, P=0.390). In this study, no serious side effects leading to drug discontinuation or special interventions, including bleeding, were observed in any of the subjects.

Table 1- Basic characteristics of diabetic patients studied in this clinical trial

Variable	group	Saffron (30 people)	Placebo (30 people)	P-value
Age (years), mean ± SD		46.40 ± 9.51	49.27 ± 11.48	0.297*
Sex, n (%)	Female	16 (53.3)	14 (46.7)	0.606**
	Man	14 (46.7)	16 (53.3)	0.685*
Weight (Kg), mean ± SD		71.46 ± 11.86	73.44 ± 12.53	0.236*
BMI (kg/m2), mean ± SD		26.62 ± 4.33	27.13 ± 5.32	* 0.571
Duration of diabetes (years), mean ± SD		4.86 ± 3.26	5.43 ± 3.12	0.882***
Education, n (%)	High school	5 (16.7)	6 (20.0)	0.758***
	diploma	11 (36.7)	13 (43.3)	0.730***
	Bachelor's degree and higher	14 (46.7)	11 (36.7)	0.297*
Occupation, n (%)	Unemployed/House wife	9 (30.0)	12 (40.0)	0.606**
	free	7 (23.3)	8 (26.7)	0.685*
	Employee	8 (26.7)	6 (20.0)	0.236*
	Retired	6 (20.0)	4 (13.3)	0.571*
Economic status, n (%)	weak	12 (40.0)	14 (46.7)	0.882***
	medium	16 (53.3)	13 (43.3)	0.758***
	Good	2 (6.7)	3 (0.10)	0.730***

* Independent t-test ** Fisher's exact test *** Chi-square

Table 2- Changes in Hamilton depression scale score during the study in two groups

Time	Saffron (30 people(	Placebo (30 people(	*P-value
Before treatment; mean±S.D	16.20 ± 1.91	15.73 ± 2.05	0.364
After treatment; mean±S.D	4.63 ± 1.69	6.03 ± 1.60	0.002
Difference before and after; mean±S.D	11.57 ± 2.82	9.70 ± 1.18	0.001
** P-value	<0.0001	<0.0001	-
Percentage of recovery; mean±S.D	70.68 ± 11.50	62.07 ± 7.03	0.001

*Independent t test

**Paired t test

Table 3- Comparison of the frequency of side effects during the study period between the two groups

Complications	Saffron (30 people(	Placebo (30 people(	*P-value
Headache	2 (6.7)	3 (10.0)	0.640
Nausea	1 (3.3)	3 (10.0)	0.301
Sweating	2 (6.7)	1 (3.3)	0.554
Drowsiness during the day	2 (6.7)	2 (6.7)	1.000
Anorexia	0 (0)	2 (6.7)	0.150
pain	1 (3.3)	3 (10.0)	0.301

* Chi-square test

Discussion

The results of this study showed that adding saffron (30 mg per day) to fluoxetine for four weeks reduced depression symptoms compared to placebo in type 2 diabetic patients with mild to moderate depression. The decrease in the Hamilton depression score and also the recovery rate were significantly higher in the group receiving saffron than in the placebo group. Although a complete response to the treatment was observed in all people of the both groups, at the end of the 8th week of treatment, all people in the saffron group (100%) compared to 76.7% of the placebo group showed an HDRS score of ≤ 7, indicating that the combination of saffron and fluoxetine could improve depression symptoms.

Saffron possesses anti-depressant, insomnia,

sedative, and many other useful functions, and most of the therapeutic functions of saffron are related to the active compounds of crocin (17, 31). The beneficial effects of saffron in the treatment of mild to moderate depression in patients with diabetes mellitus compared to fluoxetine (32) and placebo (3, 25) have also been reported in other studies. In a randomized clinical trial by Mousavi and his colleagues, they showed that the hydroalcoholic extract of saffron at the two doses of 40 and 80 mg per day along with fluoxetine (30 mg per day) for a period of four weeks was effective in the treatment of mild to moderate depression, but Saffron (80 mg) had more antidepressant effects and without serious side effects (32). Therefore, it seems that a higher dose of saffron is probably more effective in treating depression. However, in the current study, only the effect of one dose of saffron (30 mg) was examined, and a clearcut judgment about the effectiveness of higher doses of saffron needs more studies. Also, in our study, fluoxetine was initially used for four weeks, and then saffron was added to this drug for another four weeks at a lower dose than Mousavi et al.'s study. In addition, our study population consisted of diabetic patients suffering from depression, and the combination of depression and other underlying conditions poses a more serious problem than depression alone, requiring more precise management measures. Therefore, differences in the dose of saffron consumed, the duration of treatment, and the presence of depression along with diabetes can influence the results.

Milajerdi et al. (2018) showed in a randomized controlled clinical trial that after eight weeks of treatment with saffron hydroalcoholic extract, the symptoms of depression, anxiety, and sleep disorder significantly improved, while these changes were not significant in the placebo group (3). In another study by Milajerdi et al. (2016), it was also reported that saffron had modulating effects on depression and mild to moderate anxiety in patients with type 2 diabetes (25). These results are consistent with the findings of the present study.

In addition, the positive effects of saffron on reducing the symptoms of mild to moderate depression compared to placebo have been reported in previous studies. In a recent meta-analysis by Dai et al. on the effectiveness and safety of saffron in the treatment of mild to moderate depression, the review of the results of 12 clinical trials showed that saffron compared to placebo had better effectiveness in improving depression symptoms, being as effective as routine drugs. There was no significant difference in the incidence of side effects between the saffron and placebo groups or between the saffron and antidepressant groups (22). In another meta-analysis by Tóth and his colleagues, examining the results of nine randomized controlled clinical trials comparing the effectiveness of saffron and placebo or saffron and routine antidepressants in the treatment of mild to moderate depression, it was shown that saffron reduced the severity of depression symptoms. The effectiveness of saffron was more than placebo and similar to routine antidepressants (23). In another meta-analysis by Khaksarian et al., it was also reported that the consumption of saffron had the same effects as the consumption of fluoxetine in reducing the level of depression (24). In Mazidi et al.'s study, saffron extract (50 mg per day) for 12 weeks compared to placebo was effective in reducing the symptoms of depression and anxiety (15). Also, in the study of Lopresti and his colleagues, saffron extract (30 mg per day) for eight weeks compared to placebo was effective in reducing the symptoms of depression and mild to moderate anxiety in adolescents (33). These results show the effectiveness of saffron compared to placebo in improving depression symptoms and mild to moderate anxiety. However, in the current study, the role of saffron in improving the symptoms of diabetes-associated depression was investigated, making it impossible to accurately compare the results.

Some other studies have also shown that saffron is as effective as chemical antidepressants such as imipramine and fluoxetine in treating mild to moderate depression (20, 34). According to the obtained results, saffron can be considered as an alternative to synthetic antidepressants in the treatment of mild to moderate depression.

The effectiveness of saffron, as a natural source, has been approved in the treatment of depression associated with various conditions other than diabetes, including postpartum depression (28), premenstrual syndrome (PMS) (35), and mild to moderate depression after coronary artery interventions (PCI) (36). Also, saffron has been

reported to reduce depression symptoms in people with metabolic syndrome (37) and major depression (38).

Overall, these results show that there is a great potential for accepting saffron as an herbal medicine for the treatment of mild to moderate depression. However, more studies are needed to investigate its therapeutic effectiveness in major depression and depression associated with other underlying diseases, including diabetes.

The active ingredients of saffron, especially crocins, can potentially be used as antidepressants. However, crocins have poor bioavailability with poor ability to pass through the gastrointestinal tract (39). Therefore, the stability and bioavailability of the drug should be increased so that oral administration, as the optimal route of the drug's uptake, is not disturbed.

The safety of saffron in the treatment of depression in diabetic patients was also confirmed in the present study. In the present study, there was no significant difference in the occurrence of side effects between the two groups, and gastrointestinal side effects and pain were less frequent in the saffron group. One of the side effects reported for saffron is an increase in the possibility of bleeding (20), but in this study, saffron did not cause any abnormal bleeding in patients. In this study, no serious side effects leading to drug discontinuation or special interventions were observed in any of the subjects. In both groups, only some mild side effects such as headache, dizziness, sleepiness, nausea, anorexia, and pain were observed. Also, due to the fact that fluoxetine was prescribed for both groups in our study, most of these side effects could have been related to fluoxetine. In other studies, no significant differences were observed between the groups receiving either saffron or fluoxetine in terms of side effects (20, 28, 36). In Mousavi et al.'s study, mild side effects, including nausea, headache, dizziness, sleepiness, and insomnia, were observed in 26.7% of patients with mild to moderate depression receiving saffron along with fluoxetine (32). In Agha Hosseini's study, the side effects of saffron, including nausea, headache, and drowsiness, were compared with placebo, and no significant difference was observed (35). In Akhundzadeh et al.'s study, nausea, headache, sweating, and insomnia were among common side effects (17).

Although the treatment of depression can improve the clinical outcomes of diabetic patients, currently the guidelines for the management of depression are insufficient (7, 10). The antidepressants used to treat depression in diabetic patients (including SRRI and tricyclic antidepressants) have been associated with obesity, weight gain, hypoglycemia, and insulin resistance (11, 12). Therefore, use of saffron to improve the symptoms of depression in these patients can be beneficial in the management of depression in diabetes. According to our results, the addition of saffron to the treatment regimen of diabetic patients with mild to moderate depression can reduce the dose of fluoxetine consumed and its related side effects, boosting adherence to treatment in these patients.

Finally, it should be noted that this study had some limitations. For example, only the short-term effects of treatment were investigated in this study, so the long-term effects of saffron should be investigated in future. The short duration of the study, the use of a single dose of saffron, and the use of a self-reporting questionnaire to evaluate the effect of treatment limit the generalizability of the results of this study. Better results can be achieved by conducting more studies with a larger sample size in a multicenter manner and investigating the effectiveness of different doses of saffron in longer periods of time.

Conclusion

The results of the present study showed that the combination of saffron and fluoxetine was effective in improving mild to moderate depression symptoms in type 2 diabetic patients without causing serious complications. Therefore, saffron can be used as a cheap and safe drug to alleviate depression and increase the acceptance of treatment in diabetic patients, as well as to achieve better therapeutic outcomes and lower side effects compared to chemical drugs.

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Resources

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice 2019;157:107843.
2. Fakhri, A., Baboli, M., Jahanbani, E., Moradi-Joo, E., Karamianpoor, J., Binandeh, M., ... & Gorjizade, B. The Relationship between Perfectionism, Personality Type A and Meta-cognition with Job Burnout in Staff of Ahvaz Jundishapur University of Medical Sciences. *order*, 2020, 1: 2.
3. Milajerdi A, Jazayeri S, Shirzadi E, Hashemzadeh N, Azizgol A, Djazayery A, et al. The effects of alcoholic extract of saffron (Crocus satious L.) on mild to moderate comorbid depression-anxiety, sleep quality, and life satisfaction in type 2 diabetes mellitus: A double-blind, randomized and placebo-controlled clinical trial. Complementary Therapies in Medicine 2018;41:196-202.
4. Milajerdi A, Jazayeri S, Hashemzadeh N, Shirzadi E, Derakhshan Z, Djazayeri A, et al. The effect of saffron (Crocus sativus L.) hydroalcoholic extract on metabolic control in type 2 diabetes mellitus: A triple-blinded randomized clinical trial. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 2018;23:16.
5. Fakhri, A., Hamedpour, H., Pad, Z., Hamedpour, R., Moradi-Joo, E., Binandeh, M., & Davarpanah, M. Exercise Effect on Anxiety and Depression among Kidney Transplant Patients. Entomol Appl Sci Lett, 2020, 7.2: 77-82.
6. Chireh B, Li M, D'Arcy C. Diabetes increases the risk of depression: A systematic review, meta-analysis and estimates of population attributable fractions based on prospective studies. Preventive medicine reports 2019;14:100822.
7. Sridhar GR. Can the management of depression in type 2 diabetes be democratized? World journal of diabetes 2022;13(3):203-12.
8. Ibrahim KM, Babu RG, Velan MS. Prevalence of psychiatric morbidity (depression) and its effect on drug compliance among patients attending diabetic outpatient clinic. IAIM 2019;6(11):19-28.
9. Bădescu S, Tătaru C, Kobylinska L, Georgescu E, Zahiu D, Zăgrean A, et al. The association between diabetes mellitus and depression. Journal of medicine and life 2016;9(2):120.
10. Pouwer F, Schram MT, Iversen MM, Nouwen A, Holt RIG. How 25 years of psychosocial research has contributed to a better understanding of the links between depression and diabetes. Diabetic medicine : a journal of the British Diabetic Association 2020;37(3):383-92.
11. Roopan S, Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: a systematic review. Acta Neuropsychiatrica 2017;29(3):127-39.
12. Sridhar G. On Psychology and Psychiatry in Diabetes. Indian Journal of endocrinology and metabolism 2020;24(5):387-95.
13. Gholizadeh, B., Moradi-Joo, E., Baghaei, S., Javaherforoosh Zadeh, F., Raeisi, H., Nabavi, S. S. Evaluation of Mental Health in Patients with Heart Failure at Golestan Teaching Hospital in Ahvaz, Southwestern Iran. Health and Medical Research Journal, 2022; 1(2): 70-74.
14. Sulastri T, Sunyoto M, Suwitono MR, Levita J. The effect of red ginger bread consumption on the physiological parameters of healthy subjects. J Adv Pharm Educ Res. 2022;12(3):28-35.
15. Mazidi M, Shemshian M, Mousavi SH, Norouzy A, Kermani T, Moghiman T, et al. A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression.

Journal of Complementary and Integrative Medicine 2016;13(2):195-9.

16. Pandita D. Saffron (Crocus sativus L.): Phytochemistry, therapeutic significance and omics-based biology. Medicinal and aromatic plants: Elsevier; 2021. p. 325-96.
17. Sabbi J, Aijaz AW, Azra NK, Mahpara K. Distribution, chemical composition and medicinal importance of saffron (Crocus sativus L.). African Journal of Plant Science 2014;8(12):537-45.
18. Hosseinzadeh H, Karimi G, Niapoor M, editors. Antidepressant effect of Crocus sativus L. stigma extracts and their constituents, crocin and safranal, in mice. I International Symposium on Saffron Biology and Biotechnology 650; 2003.
19. Karimi GR, Hosseinzadeh H, P KP. Study of antidepressant effect of aqueous and ethanolic extract of Crocus sativus in mice. 2001.
20. Noorbala A, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi A. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. Journal of ethnopharmacology 2005;97(2):281-4.
21. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi A-H, Khalighi-Cigaroudi F. Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. BMC complementary and alternative medicine. 2004;4(1):1-5.
22. 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.
23. Tóth B, Hegyi P, Lantos T, Szakács Z, Kerémi B, Varga G, et al. The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. Planta medica 2019;85(1):24-31.
24. Khaksarian M, Behzadifar M, Behzadifar M, Alipour M, Jahanpanah F, Re TS, et al. The efficacy of Crocus sativus (Saffron) versus placebo and Fluoxetine in treating depression: a systematic review and meta-analysis. Psychology research and behavior management 2019;12:297-305.
25. Milajerdi A, Akhonzadeh S, Jazayeri S, Shirzadi E, Hashemzadeh N, Derakhshan Z, et al. The effect of saffron (Crocus sativus L.) hydro-alcoholic extract on mild to moderate mixed depression-anxiety treatment in type 2 diabetes: a triple-blind randomized placebo-controlled clinical trial. Iranian Journal of Nutrition Sciences & Food Technology 2016;11(3):11-20.
26. Almalki G, Rabah S, Al-Faifi Z, Alharbi A, Sharma M. Phytochemistry Screening, Antioxidant And Antimicrobial Activities Of Euphorbia Inarticulata Schweinf Plant Extract. Pharmacophore. 2022;13(1):91-9
27. Gholizadeh B, Javaherforoosh Zadeh F, Nabavi SS, Moradi-Joo E, Baghaei S. The Relationship between Quality of Life and Mental Health in Patients with Heart Failure. Entomol Appl Sci Lett. 2021;8(3):60-6.
28. Kashani L, Eslatmanesh S, Saedi N, Niroomand N, Ebrahimi M, Hosseinian M, et al. Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial. Pharmacopsychiatry 2017;50(2):64-8.
29. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA, et al. Hemoglobin A1c Targets for Glycemic Control With Pharmacologic Therapy for Nonpregnant Adults With Type 2 Diabetes Mellitus: A Guidance Statement Update From the American College of Physicians. Annals of internal medicine 2018;168(8):569-76.
30. Altukhays IA, Alosaimi SH, Alotaibi MA, Zamzami AA, Slais ZA, Al Zainaldeen AM, Hakami LH, Al Saber BF, Alrashidi AS, Alraddadi KS, Alfardan MA. Congestive Heart Failure: Diagnosis and Management in Primary Health Care. Arch Pharm Pract. 2022;13(1):1-4.
31. Siddiqui SA, Ali Redha A, Snoeck ER, Singh S, Simal-Gandara J, Ibrahim SA, et al. Anti-Depressant Properties of Crocin Molecules in Saffron. Molecules 2022;27(7):2076.
32. Moosavi SM, Ahmadi M, Amini M,

Vazirzadeh B. The effects of 40 and 80 mg hydro-alcoholic extract of Crocus sativus in the treatment of mild to moderate depression. Journal of mazandaran university of medical sciences 2014;24(113):48-53.

33. Lopresti AL, Drummond PD, Inarejos-García AM, Prodanov M. affron®, a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. Journal of Affective Disorders 2018;232:349-57.
34. Shahin A. Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial. BMC Complement Altern Med 2004;4:12-7.
35. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara A, et al. Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology 2008;115(4):515-9.
36. Shahmansouri N, Farokhnia M, Abbasi S-H, Kassaian SE, Noorbala Tafti A-A, Gougol A, et al. A randomized, double-blind, clinical trial comparing the efficacy and safety of Crocus sativus L. with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients. Journal of Affective disorders 2014;155:216-22.
37. Jam IN, Sahebkar AH, Eslami S, Mokhber N, Nosrati M, Khademi M, et al. The effects of crocin on the symptoms of depression in subjects with metabolic syndrome. Advances in Clinical and Experimental Medicine 2017;26(6):925-30.
38. Jelodar G, Javid Z, Sahraian A, Jelodar S. Saffron improved depression and reduced homocysteine level in patients with major depression: A Randomized, double-blind study. Avicenna Journal of Phytomedicine 2018;8(1):43.
39. Asai A, Nakano T, Takahashi M, Nagao A. Orally Administered Crocetin and Crocins Are Absorbed into Blood Plasma as Crocetin and Its Glucuronide Conjugates in Mice. Journal of Agricultural and Food Chemistry 2005;53(18):7302-6.