

A Randomized, Double-blind, Placebo - controlled Study of Safety of the Adjunctive Saffron on Sexual Dysfunction Induced by a Selective Serotonin Reuptake Inhibitor

Mansoori P (Pharm.D.)¹, Akhondzadeh S (Ph.D.)¹, Raisi F (M.D.)¹, Ghaeli P (Pharm.D.)^{1*},
Jamshidi AH (Ph.D.)², Nasehi AA (M.D.)¹, Sohrabi H (M.D.)¹, Saroukhani S (M.D.)¹

1- School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

2- Department of Pharmacognosy and Pharmaceutics, Institute of Medicinal Plants, ACECR, Karaj, Iran

*Corresponding author: Psychiatric Research Centre, Roozbeh Hospital, Tehran

University of Medical Sciences, South Kargar Street, Tehran 13337, Iran

Tel: +98-21-55412222, Fax: +98-21- 5541-9113

E-mail: mmppg@yahoo.com

Receive: 8 Jan 2011

Acceptance: 9 Mar. 2011

Abstract

Background: Recent studies have indicated potential of saffron for applying in a wide variety of diseases such as psychiatric and neurologic disorders. The concurrent use of saffron with SSRIs can lead to reducing the dose of SSRIs. Saffron at a dose of 200 mg may change some hematological and biochemical parameters.

Objective: The goal of this trial was to assess the safety of concomitant administration of saffron and SSRI in patients with major depressive disorder (MDD).

Methods: Twenty adult outpatients between 18 to 55 years-old with the diagnosis of MDD who were receiving an SSRI for at least 1 month prior to the initiation of the study entered this double-blind trial. They were randomly assigned to receive capsule of saffron (15 mg twice daily) or placebo. Some laboratory parameters were measured at baseline and week 4 of the study. Other side effects checked on a prepared list of side effects, were systematically recorded throughout the study at baseline and on a weekly basis.

Results: Saffron as an add-on medication to SSRIs for 4 weeks did not cause any statistically significant changes in laboratory parameters including AST, ALT, ALP, BUN, Cr., FBS, TG, TC, WBC, RBC, Hgb, Ht, PT, INR, and Pl count.

Conclusion: This preliminary study provides safety evidences of concurrent intake of saffron and SSRI.

Keywords: Saffron, *Crocus sativus*, Adverse effects, SSRI, MDD

Introduction

Saffron, the most expensive spice in the world, is the dried stigma of *Crocus sativus* flowers (which belongs to the Iridaceae family). This plant is mainly produced in Iran [1]. In traditional medicine, saffron is considered as an excellent aid for stomach ailments and an antispasmodic that helps digestion and increases appetite. It is also recommended as an emmenagogue and aphrodisiac herb [2]. Recent experimental studies have demonstrated that saffron or its active constituents have a wide range of activities including anticonvulsant [3, 4], anti-inflammatory [5], antioxidant [6] and antitumor effects [7]. Besides, recent studies indicated its potential as a hypolipidemic and anti-atherosclerotic agent [6]. In addition, bactericidal [8] and antitussive effects of this plant have also been reported [9]. The pharmacological activities of saffron are mainly attributed to three constituents: volatile agents (e.g., safranal), bitter principles (e.g., picrocrocin), and dye materials (e.g., crocetin and its glycoside, crocin) [1]. In Persian traditional medicine, saffron has also been used for depression and dementia [10]. Recent clinical trials have reported that 30 mg of saffron per day is as effective as 20 mg of fluoxetine [11] or 100 mg of imipramine daily in the treatment of depression [12]. In addition, the same dosage of saffron has been reported to be effective in the treatment of premenstrual syndrome (PMS) [13] and Alzheimer's disease [14, 15].

According to the traditional literature doses greater than 10 grams of saffron could be lethal when taken by mouth at once [16]. Meanwhile this dose is said to cause vomiting, vertigo and bleeding [1]. In a placebo-controlled study, safety of 200 mg and 400 mg saffron tablets was evaluated in healthy

volunteers. In this 1 week study, saffron resulted in slight decrease in some hematological parameters including count of erythrocytes, hemoglobin, hematocrit and platelets. Furthermore, saffron increased the level of blood urea nitrogen and creatinine [17]. In a sub-acute study in rat, intraperitoneal injection of saffron extract decreased the count of hematocrit, hemoglobin and red blood cells. However, it did not cause any significant pathological effects on different organs [18].

When considering using doses of 30 mg saffron per day, the majority of clinical trials have demonstrated the efficacy and side effects only in a descriptive way, therefore the objective of the present study was to investigate the safety of 30 mg saffron by laboratory tests. Authors of this study by observing the laboratory data evaluated the safety of 30 mg saffron daily as an add-on medication to selective serotonin reuptake inhibitors (SSRIs) in patients with depression.

Materials and Methods

Study design

This trial was a 4-week randomized double-blind study which was undertaken at the Psychiatric Clinic of Roozbeh Hospital in Tehran, Iran between October 2008 and March 2010.

Participants

Twenty adult outpatients between 18 to 55 years-old with the diagnosis of major depressive disorder (MDD), according to the DSM-IV-TR entered this study. Subjects were receiving an SSRI for at least 1 month prior to the initiation of the study and were using at least one medically accepted mean of birth control during the study. The exclusion criteria included pregnancy or lactation, history of allergy to saffron or multi drug reaction, any

history of blood disorders (anemia, hemophilia, etc.), or other severe medical conditions (e.g. cardiovascular, renal, hepatic, pulmonary, metabolic or endocrine diseases), history of seizure, substance abuse in the previous 6 months, active peptic ulcer, and taking any medication during the study (except for alprazolam up to 0.5 mg per day). Written informed consents were obtained from the patients before entering into the study. This trial was approved by ethics committee at Tehran University of Medical sciences.

Intervention

In this double-blind study, patients were randomized in a 1:1 ratio using a computer-generated code, to receive capsule of *Crocus sativus* 30 mg/day (15 mg twice per day) or capsule of placebo (two capsules per day) for 4 weeks. This daily dose of *C. sativus* was based on previous clinical trials regarding effects of saffron in the treatment of mild to moderate depression [11, 12], PMS [13] and Alzheimer's disease [14, 15].

Preparation of capsules

The saffron capsules that were used in this trial were donated by Green Plants of Life Co. (IMPIRAN; Tehran, Iran) and were identified by the Department of Cultivation and Development of Institute of Medicinal Plants, Tehran, Iran. The extract of stigma was prepared as follows: 120 g of dried and milled stigmas was extracted with 1,800 ml ethanol (80%) by percolation procedure in three steps. Then the ethanol extract was dried by evaporation at a temperature of 35–40°C. Each capsule contained 15 mg of dried extract of *Crocus sativus*, lactose as filler, magnesium stearate as lubricant, and sodium starch glycolate as disintegrant in this formulation. To assess the quality of capsules, the extract was standardized by crocin. Drug samples

were evaluated by crocin value by means of a spectrophotometric method. Crocin value is expressed as direct reading of the absorbance at about 440 nm. Each capsule had 1.65 – 1.75 mg crocin. The capsules of placebo contained starch. Placebo and saffron capsules were visually identical.

Measurements

Before starting treatment with saffron/placebo capsules, baseline fasting blood samples were taken for laboratory investigations. Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Blood Urea Nitrogen (BUN), Serum Creatinine (Cr.), Fasting Blood Sugar (FBS), Triglyceride (TG), Total Cholesterol (TC), White Blood Cell (WBC), Red Blood Cell (RBC), Hemoglobin (Hgb), Hematocrit (Ht), Prothrombin Time (PT), International Normalized Ratio (INR) and Platelet count (Pl) were measured at baseline and week 4 of the study. Other side effects, either reported by patients or checked on a prepared list of side effects, were systematically recorded throughout the study at baseline and on a weekly basis.

Statistical analysis

To compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired student's *t*-test with a two-sided *P*-value was used. Results are demonstrated as mean ± SD. Differences with *P* < 0.05 were considered significant.

Results

No significant gender differences were identified among the patients in the saffron and the placebo receiving groups. Nevertheless there was significant difference regard to age of participants (Table 1).

Through this trial no significant differences were observed in the mean values of evaluated laboratory parameters including AST, ALT, ALP, BUN, Cr., FBS, TG, TC, WBC, RBC, Hgb, Ht, PT, INR, and Pl count (Table 2 and 3).

The difference between the saffron and the placebo group in the frequency of side effects on the basis of a weekly clinical interview as well as reported side effects by patients was not significant (Table 4).

Table 1- Baseline data

Variable	Saffron group	Placebo group	P
Gender (M/F)	7 : 3	5 : 5	NS
Age (mean $\pm$ SD), years	35.30 $\pm$ 5.81	42.40 $\pm$ 8.44	0.04

NS = Nonsignificant

Table 2- Comparing effect of saffron and placebo capsules on blood cells and coagulation factors

Blood cells and coagulation factors	Intervention	Placebo Group	Saffron Group	P
RBC (million/ μ L)	Week 0	5.16 $\pm$ 0.78	5.24 $\pm$ 0.16	0.81
	Week 4	5.17 $\pm$ 0.74	5.18 $\pm$ 0.61	0.95
Hemoglobin (g/dL)	Week 0	13.88 $\pm$ 1.07	14.18 $\pm$ 1.36	0.59
	Week 4	13.88 $\pm$ 1.16	14.17 $\pm$ 1.30	0.60
Hematocrit (%)	Week 0	41.97 $\pm$ 3.01	42.50 $\pm$ 4.28	0.75
	Week 4	42.61 $\pm$ 3.44	42.42 $\pm$ 4.06	0.90
(WBC) $\times 10^3$ /mm ³	Week 0	6.34 $\pm$ 1.67	5.96 $\pm$ 1.34	0.57
	Week 4	6.56 $\pm$ 2.32	5.97 $\pm$ 1.64	0.51
(Platelets) $\times 10^3$ /mm ³	Week 0	226.8 $\pm$ 54.68	251 $\pm$ 65.81	0.38
	Week 4	214.1 $\pm$ 38.45	254.9 $\pm$ 76.15	0.14
Prothrombin Time (PT) (sec)	Week 0	12.62 $\pm$ 0.90	12.53 $\pm$ 0.70	0.80
	Week 4	12.54 $\pm$ 0.45	12.67 $\pm$ 0.91	0.69
International Normalized Ratio (INR)	Week 0	1.07 $\pm$ 0.08	1.01 $\pm$ 0.04	0.08
	Week 4	1.05 $\pm$ 0.06	1.05 $\pm$ 0.12	0.87

Table 3- Comparing effect of saffron and placebo capsules on FBS, lipid profile, liver and renal function tests

Variables	Intervention	Placebo Group	Saffron Group	P
FBS (mg/dL)	Week 0	91.50 ± 7.30	82.60 ± 11.20	0.04
	Week 4	87.20 ± 10.68	84.00 ± 10.57	0.50
Triglyceride (mg/dL)	Week 0	108.70 ± 43.08	138.80 ± 74.29	0.28
	Week 4	128.40 ± 32.25	142.70 ± 85.67	0.62
Cholesterol (mg/dL)	Week 0	183.80 ± 32.34	193.80 ± 34.87	0.51
	Week 4	192.9 ± 30.49	185.9 ± 29.12	0.60
BUN (mg/dL)	Week 0	10.66 ± 5.11	12.1 ± 4.20	0.50
	Week 4	11.33 ± 5.85	12.15 ± 3.24	0.70
Creatinine (mg/dL)	Week 0	0.97 ± 0.18	0.96 ± 0.15	0.91
	Week 4	1.01 ± 0.14	0.95 ± 0.18	0.44
AST (unit/L)	Week 0	23.3 ± 8.64	24.3 ± 6.23	0.77
	Week 4	22.3 ± 7.36	26.3 ± 6.58	0.21
ALT (unit/L)	Week 0	22.8 ± 6.49	25 ± 14.30	0.66
	Week 4	27.4 ± 8.50	29.30 ± 17.12	0.75
ALP (unit/L)	Week 0	133.90 ± 55.72	123.30 ± 46.68	0.65
	Week 4	126.30 ± 53.89	131.40 ± 44.48	0.82

Table 4 - Number of patients with adverse effects based on the prepared check list

Adverse effects	Saffron group, n (%)	Placebo group, n (%)	P
Dry mouth	3 (30)	2 (20)	NS
Restlessness	2 (20)	0	NS
Anxiety	2 (20)	0	NS
Tachycardia	0	1 (10)	NS
Constipation	1 (10)	1 (10)	NS
Nausea	0	1 (10)	NS
Reflux	0	1 (10)	NS
Abdominal pain	0	1 (10)	NS
Headache	0	1 (10)	NS
Dizziness	0	1 (10)	NS
Daily drowsiness	1 (10)	1 (10)	NS
Morning drowsiness	1 (10)	0	NS

NS = Nonsignificant

No major adverse event was reported during the study.

Discussion

MDD currently is the fourth leading cause of disability in women and ranks seventh for men. MDD is predicted to become the second leading factor in the global disease burden in 2020 [19]. Although a multitude of pharmaceutical agents are available for the treatment of mental disorders, physicians believe that many patients do not have adequate adherence to pharmacotherapy [20]. One of the very first reasons is the social stigma associated with mental disorders which may hinder taking synthetic drugs [21]. On the other hand, patients are often reluctant to take antidepressants in their appropriate doses due to their undesirable side effects such as sleep disturbances, gastrointestinal complaints or sexual dysfunction (SD) [20, 22]. Besides, despite numerous advances in manufacturing antidepressants, these drugs may not be more effective than placebo during long term therapy [23]. These findings pose new challenges to find more integrative approaches to treat mental disorders, a part of which may be prescribing herbal medicines (HMs) [10]. Many people find HMs more congruent with their own beliefs as well as their historical and cultural background [20]. Consequently, if evidence-based treatments accord with public attitudes, patients may be more willing to adhere to medications given by physicians [21]. HMs can also be used in combination with conventional treatments which may create a beneficial synergistic effect. Meanwhile this allows for a lower dose of synthetic drugs to be taken, thus reducing their potential side effects [10].

Saffron is a HM which has been widely used in traditional medicine. Animal and human studies in the past decade have indicated its potential for applying in a wide variety of diseases such as psychiatric and

neurologic disorders [1]. Recent clinical trials have demonstrated that 30 mg of ethanolic extract of saffron per day (given by mouth; in two divided doses) is effective in the treatment of mild to moderate depression [11, 12], PMS [13] and Alzheimer's disease [14, 15].

The results obtained in the present trial indicate that patients with MDD who received 30 mg/day of the ethanolic extract of saffron as an add-on medication to SSRIs for 4 weeks did not experience any statistically significant adverse effects either by saffron capsules or by the interaction between SSRI and *C. Sativus*. To the best of our knowledge this study was the first trial which evaluated the safety of 30 mg saffron per day on the basis of laboratory data.

In a placebo-controlled study, safety of 200 and 400 mg saffron tablets was evaluated in healthy volunteers. There were 10 participants in each group. In this 1 week study, saffron slightly decreased count of RBC at both doses and caused a slight decrease in hemoglobin and hematocrit at a dose of 200 mg [17]. In our study these parameters were decreased as well, but their alterations were not significant at all.

In traditional medicine, saffron has been used as an abortifacient herb [2]. One female volunteer in each group of 200 and 400 mg administration of saffron experienced abnormal uterine bleeding during the study performed by Modaghegh et al. However saffron at a dose of 200 mg decreased INR and bleeding time. Meanwhile platelet counts were decreased [17]. In the present study saffron did not change platelet count but increased INR and PT slightly; this alteration for INR was near significant ($p=0.08$). An animal study demonstrated that crocin (the coloring compound of *C. sativus*) prolonged blood coagulation time in mice and inhibited platelet

aggregation in rabbits [24]. Besides, a platelet aggregation inhibitor substance which has been identified as adenosine has been isolated from saffron [25]. The dose of 30 mg per day that was used in our study did not result in a decrease in platelet count. Using higher doses of saffron may cause a different result.

Similar to the results observed in the study by Modaghegh and colleagues [17], WBC in this study did not change. Regarding renal function tests Modaghegh et al. reported that saffron slightly increased the level of blood urea nitrogen and creatinine. According to the Persian traditional medicine, saffron potentially can be harmful for kidneys [16]. However, in our study BUN and Cr. did not change significantly. In our trial, blood samples were taken 4 weeks after the initiation of saffron capsules while in the study by Modaghegh et al, the samples were taken one week after taking saffron tablets. As some side effects are transient, there is the possibility that some effects were diminished after 4 weeks.

An experimental study in mice reported that concomitant administration of saffron and honey syrup has improved the disrupted liver biochemical markers [26]. Additionally, another study in hyperlipidemic rats noted that saffron has been effective in bringing the elevated levels of AST, ALT, ALP as well as TG and TC back to normal substantially due to its antioxidant effects [6]. In the present study, liver function tests including AST, ALT, and ALP and also lipid profile markers including TG and TC levels did not change significantly. Based on the above animal study, saffron may have a potential to reduce these parameters especially in hyperlipidemic patients if used for a longer period of time.

To our knowledge, there was no previous study regarding the effect of saffron on FBS. Because of the importance of drug effects on blood sugar, the authors of the present trial

also studied the effects of saffron on FBS. Although at week 0 of the study there was significant difference between two groups which was diminished at week 4, no significant relationship was noted between saffron intake and alterations in this parameter. Overall, the mean age of participants in the saffron group was lower than that in the placebo group (Table 1). Many studies show a correlation between increasing age and adverse drug reaction rate [27]. Therefore maybe in elderly saffron can cause some adverse effects that were not detected in this study.

The general danger of co-prescription of saffron and SSRI is that, many people falsely believe that HMs have no side effects. Similarly it seems that most patients are not aware of many possible interactions between HMs and concurrently prescribed medications [20]. SSRIs are associated with abnormal bleeding and modifications of hemostasis markers such as decreasing platelet aggregation and activity, and prolongation of bleeding time [28]. Although in our study there was no report regarding abnormal bleeding, we suggest that patients with a history of coagulation disorders or GI ulcers should be monitored in case of co-prescription of saffron and SSRIs. Moreover, a number of investigations have suggested that saffron and its constituents inhibit reuptake of serotonin [29, 30]. Therefore, regarding this co-prescription, the possibility of serotonin syndrome should be considered.

Further investigation is needed to identify more pharmacokinetic aspects of saffron such as half life and its metabolic pathways. This study has several limitations including small sample size and short period of follow up. Also more frequent blood testing is suggested.

Finally, this study shows the possibility of concomitant use of saffron and SSRIs which

can bring new approaches in the management of MDD. Furthermore, there are increasing evidences to suggest the possible efficacy of saffron in the management of SD. Recently, an aphrodisiac activity of saffron aqueous extract and its constituent crocin was demonstrated in rat [31]. Later on, a ten day pilot open clinical trial evaluated this effect in men and indicated that taking 200 mg of saffron extract resulted

in significant improvements in erectile dysfunction [32]. Considering the fact that SD is a very common side effect of SSRIs [33-36], further investigation for evaluating the efficacy of saffron in reducing SSRI-induced SD is recommended.

In summary, this preliminary study provides safety evidences of concurrent intake of saffron and SSRI.

References

- Schmidt M, Betti G, Hensel A. Saffron in phytotherapy: pharmacology and clinical uses. *Wien Med Wochenschr.* 2007; 157 (13 - 14): 315 - 9.
- Ríos JL, Recio MC, Giner RM, Máñez S. An update review of saffron and its active constituents. *Phytother Res.* 1996; 10: 189 - 93.
- Hosseinzadeh H, Khosravan V. Anticonvulsant effects of aqueous and ethanolic extracts of *Crocus sativus* L. stigmas in mice. *Arch Iran Med.* 2002; 5: 44 - 7.
- Hosseinzadeh H, Sadeghnia HR. Protective effect of safranin on pentylenetetrazol-induced seizures in the rat: involvement of GABAergic and opioids systems. *Phytomedicine* 2007; 14 (4): 256 - 62.
- Nam KN, Park YM, Jung HJ, Lee JY, Min BD, Park SU, Jung WS, Cho KH, Park JH, Kang I, Hong JW, Lee EH. Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. *Eur. J. Pharmacol.* 2010; 648: 110 - 6.
- Basheeruddin Asdaq SM, Naseeruddin Inamdar M. Potential of *Crocus sativus* (saffron) and its constituent, crocin, as hypolipidemic and antioxidant in rats. *Appl Biochem. Biotechnol.* 2010; 162: 358 - 72.
- Chryssanthi DG, Dedes PG, Karamanos NK, Cordopatis P, Lamari FN. Crocetin inhibits invasiveness of MDA-MB231 breast cancer cells via downregulation of matrix metalloproteinases. *Planta Med.* 2011; 77 (2): 146 - 51.
- Pintado C, De Miguel A, Acevedo O, Nozal L, Novella JL, Rotger R. Bactericidal effect of saffron (*Crocus sativus*) on *Salmonella enterica* during storage. *J. Foodcont.* 2011; 22 (3 - 4): 638 - 42.
- Hosseinzadeh H, Ghenaati G. Evaluation of the antitussive effect of stigma and petals of saffron (*Crocus sativus*) and its components, safranin and crocin in guinea pigs. *Fitoterapia* 2006; 77: 446 - 8.
- Sarris J. Herbal medicine in the treatment of psychiatric disorders: a systematic review. *Phytother Res.* 2007; 21: 703 - 16.
- Noorbala AA, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi AH. Hydro-alcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. *J. Ethnopharmacol.* 2005; 97: 281 - 4.
- Akhondzadeh S, Fallah-Pour H, Afkham kh, Jamshidi AH., Khalighi-Cigaroudi F. 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.

13. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR, Akhondzadeh S. *Crocus sativus* L. (saffron) in the treatment of premenstrual syndrome: a double-blind randomised and placebo-controlled trial. *Br. J. Obstet. Gynaecol.* 2008; 115 (4): 515 - 9.

14. Akhondzadeh S, Shafiee-Sabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi S.Sh, Yousefi MH, Alimardani R, Jamshidi A, Zare F, Moradi A. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. *J. Clin. Pharm. Ther.* 2010; 35: 581 - 8.

15. Akhondzadeh S, Shafiee-Sabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi S.Sh, Alimardani R, Jamshidi A, Zare F, Moradi A. A 22-week multicenter, randomized, double-blind controlled trial of *Crocus sativus* in the treatment of mild-to-moderate Alzheimer's disease. *Psychopharmacol.* 2010; 207: 637 - 43.

16. Aghili Khorasani. Makhzanoladvieh. Tehran: Publication and education of Islamic revolution. 1371; 2nd ed: 472 - 73.

17. Modaghegh MH, Shahabian M, Esmaili HA, Rajbai O, Hosseinzadeh H. Safety evaluation of saffron (*Crocus sativus*) tablets in healthy volunteers. *Phytomedicine* 2008; 15: 1032 - 7.

18. Karimi G, Taiebi N, Hosseinzadeh A, Shirzad F. Evaluation of subacute toxicity of aqueous extract of *Crocus sativus* L. stigma

and petal in rats. *J. Med Plants* 2004; 3: 29 - 35.

19. Üstün TB. The global burden of mental disorders. *Am. J. Public Health* 1999; 89 (9): 1315 - 18.

20. Akhondzadeh S, Maleki J. Herbal medicines in the treatment of psychiatric and neurologic disorders. *Iran J. Psychiatry* 2006; 1: 1 - 11.

21. Jorme A.F. Public knowledge and beliefs about mental disorders. *Br. J. Psychiatry* 2000; 177: 396 - 401.

22. Dubovsky SL. Beyond the serotonin reuptake inhibitors: rationales for the development of new serotonergic agents. *J. Clin. Psychiatry* 1994; 55: 34 - 44.

23. Patel V, Chisholm D, Rabe-Hesketh S, Dias-Saxena F, Andrew G, Mann A. Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa, India: a randomised, controlled trial. *Lancet.* 2003; 361 (9351): 33 - 9.

24. Ma Sh, Liu B, Zhou S, Xuxiang W, Yang Q, Zhou J. Pharmacological studies of glycosides of saffron (*Crocus sativus*): effects on blood coagulation, platelet aggregation, and thrombosis. *Chin. Trad. Herbal Drugs* 1999; 30: 196 - 8.

25. Okano K, Nishio T, Fukaya C, Yokoyama K, Nishimoto T, Matusmoto K. Isolation and identification of a platelet aggregation inhibitor from saffron (*Crocus sativus* Linne, Iridaceae). *Wakan Iyaku Gakkaishi.* 1992; 9: 175 - 81.

26. Shati AA, Alamri SA. Role of saffron (*Crocus sativus* L.) and honey syrup on aluminum-induced hepatotoxicity. *Saudi Med J.* 2010; 31 (10): 1106 - 13.

27. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *Br. J. Clin. Pharmacol.* 2004; 57 (2): 121 - 6.
28. Halperin D, Rober G. Influence of antidepressants on hemostasis. *Dialogues Clin. Neurosci.* 2007; 9 (1): 47 - 59.
29. Hosseinzadeh H, Karimi G, Niapoor M. Anti-depressant effects of *Crocus sativus* stigma extracts and its constituents, crocin and safranal, in mice. *Acta Hort.* 2004; 650: 435 - 45.
30. Karimi G, Hosseinzadeh H, Khalegh Panah P. Study of antidepressant effect of aqueous and ethanolic extract of *crocus sativus* in mice. *Iranian J. Basic Med. Sci.* 2001; 4 3 (11): 11 - 5.
31. Hosseinzadeh H, Ziaee T, Sadeghi A. The effect of saffron, *Crocus sativus* stigma, extract and its constituents, safranal and crocin on sexual behavior in normal male rats. *Phytomedicine* 2008; 15: 491 - 5.
32. Shamsa A, Hosseinzadeh H, Molaei M, Shekeri MT, Rajabi O. Evaluation of *Crocus sativus* L. (saffron) on male erectile dysfunction: a pilot study. *Phytomedicine* 2009; 16: 690 - 3.
33. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. *J. Clin. Psychiatry* 2001; 62 (supp 3): 10 - 21.
34. Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, Abbasi SH, Akhondzadeh S. Comparison of petal of *Crocus sativus* L. and fluoxetine in the treatment of depressed outpatients: a pilot double-blind randomized trial. *Prog Neuropsychopharmacol. Biol. Psychiatry* 2007; 31: 439 - 42.
35. Moshiri E, Basti AA, Noorbala AA, Jamshidi AH, Hesameddin Abbasi S, Akhondzadeh S. *Crocus sativus* L. (petal) in the treatment of mild-to-moderate depression: a double-blind, randomized and placebo-controlled trial. *Phytomedicine* 2006; 13: 607 - 11.
36. Akhondzadeh S, Jafari S, Raisi F, Nasehi AA, Ghoreishi A, Salehi B, Mohebbi-Rasa S, Raznahan M, Kamalipour A. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. *Depress. Anxiety* 2009; 26: 607 - 11.