

# Comparison of Saffron versus Fluoxetine in Treatment of Mild to Moderate Postpartum Depression: A Double-Blind, Randomized Clinical Trial

## Authors

Ladan Kashani<sup>1\*</sup>, Sophia Eslatmanesh<sup>2\*</sup>, Nafise Saedi<sup>3\*</sup>,  
Nasrin Niroomand<sup>3</sup>, Mahbod Ebrahimi<sup>3</sup>, Masoumeh Hosseini<sup>4</sup>,  
Tahereh Foroughifar<sup>5</sup>, Samrand Salimi<sup>5</sup>, Shahin Akhondzadeh<sup>2</sup>

## Affiliations

- 1 Arash Hospital, Infertility Ward, Tehran University of Medical Sciences, Tehran, Iran
- 2 Psychiatric Research Center, Roozbeh Hospital, Tehran University of Medical Sciences, Tehran, Iran
- 3 Yas Women General Hospital, Tehran University of Medical Sciences, Tehran, Iran
- 4 Trauma Nursing Research Center, Kashan University of Medical Sciences, Kashan, Iran
- 5 Baharloo Hospital, Tehran University of Medical Sciences, Tehran, Iran

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## Correspondence

Prof. S. Akhondzadeh  
Psychiatric Research Center Roozbeh Psychiatric Hospital  
Tehran University of Medical Sciences  
South Kargar Street, 13337 Tehran  
Iran  
[s.akhond@neda.net](mailto:s.akhond@neda.net)

## ABSTRACT

**Introduction** Postpartum depression is a common mental health problem that is associated with maternal suffering. The aim of this double-blind clinical trial was to compare safety and efficacy of saffron and fluoxetine in treatment of mild to moderate postpartum depression.

**Methods** This was a 6-week, double-blind, randomized clinical trial. Subjects were women aged 18–45 years with mild to moderate postpartum depression who had Hamilton Depression Rating Scale (HDRS 17-item) score  $\leq 18$ . Eligible participants were randomized to receive either a capsule of saffron (15 mg capsule) or fluoxetine (20 mg capsule) twice daily for 6 weeks. The primary outcome measure was to evaluate efficacy of saffron compared to fluoxetine in improving depressive symptoms (HDRS score).

**Results** There was no significant effect for time  $\times$  treatment interaction on HDRS score [ $F(4.90, 292.50) = 1.04, p = 0.37$ ] between the 2 groups. 13 (40.60 %) patients in the saffron group experienced complete response ( $\geq 50$  % reduction in HDRS score) compared with 16 (50 %) in the fluoxetine group and the difference between the 2 groups was not significant in this regard ( $p = 0.61$ ). Frequency of adverse events was not significantly different between the treatment groups.

**Discussion** The results of this study may suggest that saffron is a safe alternative medication for improving depressive symptoms of postpartum depression. Nevertheless, it should be mentioned that the trial is not well powered and should be considered a preliminary study. Therefore, large clinical trials with longer treatment periods and comparison with placebo group would be appropriate for future studies.

## Introduction

Postpartum depression is a common and serious mental health problem that is associated with maternal suffering and numerous negative consequences for offspring [1]. It has been reported that 10–15 % of women suffer postpartum depression following childbirth [2]. Postpartum depression can harm the mother and child relationship, which in turn negatively impacts children in terms of nutrition and care, as well as physical and mental development [3]. Self-esteem, childcare stress, life stress, social support, marital re-

lationship, infant temperament, marital status, socioeconomic status, unwanted pregnancy, previous psychiatric disorder, method of childbirth, previous abortion and biological changes are related to postpartum depression [2]. Etiologies of mood balance, depressive disorders in particular, are not completely understood. However, substantial evidence has accrued that serotonergic systems play a central role [4–7]. Selective serotonin reuptake inhibitors (SSRIs) are the first line of pharmacotherapy in postpartum depression. Despite beneficial effects of SSRIs on depressive symptoms in postpartum depression, rate of remission remains low and risk of relapse and recurrence remains high [8–13]. Furthermore, most of

\* The first three authors contributed equally in this study.

these antidepressant agents produce several adverse reactions, such as anticholinergic effects, orthostatic hypotension, arrhythmias and sexual dysfunction [14, 15]. Thus there is need for more effective and less toxic agents. Plant extracts are some of the most attractive sources of new drugs and have shown promising results for treatment of depression [16, 17]. Saffron is produced from the tiny, dried stigma of lily-like *Crocus sativus* blossom [18]. In Asian medicine, and particularly in Persian traditional medicine, it is used to treat menstrual disorder, difficult labor, inflammation, vomiting and diseases affecting the throat [18–20]. Several controlled studies have shown beneficial effects of *Crocus sativus* on depression, premenstrual symptoms and Alzheimer's disease [19, 21–26]. Our objective was to compare the efficacy of *Crocus sativus* (stigma) with fluoxetine in treatment of mild to moderate postpartum depression in a 6-week, double-blind, randomized clinical trial.

## Method

### Trial design

A 6-week, multicenter, randomized, double-blind, parallel-group clinical trial was conducted in the outpatient clinics of Yas Women General Hospital, Arash and Baharloo Hospitals (all affiliated with Tehran University of Medical Sciences, Tehran, Iran) between September 2015 and December 2015.

The trial protocol was approved by the institutional review board (IRB) of Tehran University of Medical Science (Grant No: 23220) and conducted consistent with the Declaration of Helsinki and subsequent revisions. The trial was registered at the Iranian registry of clinical trials ([www.irct.ir](http://www.irct.ir); registration number: IRCT201509201556N82) prior to the study. Written informed consent was obtained from all eligible participants and/or their legally authorized representatives. Patients were informed that they were free to withdraw from the trial at any time without any adverse effect on their relationship with their health care provider and their therapy.

### Participants

Women between 18–45 years of age, with a diagnosis of postpartum depression based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria were eligible to participate in the trial (4–12 weeks after childbirth). Patients were required to have mild to moderate postpartum depression at time of randomization, having a score  $\geq 10$  and  $\leq 18$  in the 17-item Hamilton Depression Rating Scale (HDRS) [27, 28].

Exclusion criteria included: women with psychotic depression, history of suicidal or infanticidal thoughts, a history of bipolar disorder, substance or alcohol dependence (with the exception of nicotine dependence), lactation, hypothyroidism and acute medical illness. Patients suffering from any diagnosis other than postpartum depression on the DSM-IV-TR axis I were also excluded.

### Interventions

Patients underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview and medical history. Eligible participants were randomized to receive either

a capsule of saffron (SaffroMood®, IMPIRAN, containing 15 mg of saffron extract) twice daily or a fluoxetine capsule (Abidi, Iran, 20 mg capsule; each capsule had 1.65–1.75 mg crocin) twice daily for 6 weeks. Participants were not allowed to use any psychotropic drug or receive any behavioral intervention therapy during the course of the trial.

### Outcome

All participants were assessed using HDRS score at baseline and at weeks 1, 3 and 6. The HDRS contains 17 questions (on a 3-point or 5-point scale) that assess severity of depressive symptoms. This scale has been applied in many clinical trials in Iran exploring depression therapeutic efficacy [27–32]. The primary outcome measure of this trial was to evaluate efficacy of saffron compared to fluoxetine in improving depressive symptoms in postpartum individuals using general linear model repeated measures. The 2 groups were also compared regarding improvement in HDRS scores from baseline HDRS score at each time point, partial responders (25–50 % reduction in the HDRS score), responders ( $\geq 50$  % reduction in HDRS score), remitters (HDRS score  $\leq 7$ ) and the time needed to respond to treatment. Response rate ( $\geq 50$  % decrease in the HDRS score) and remission rate (HDRS score  $\leq 7$ ) were compared between 2 groups.

In terms of adverse events, a 25-item checklist was provided to systematically record the adverse events during the course of the trial. All participants were asked about any adverse event that was not mentioned in the checklist. Participants were also asked to immediately inform the research team about any unexpected symptom during the study period.

### Sample size estimation

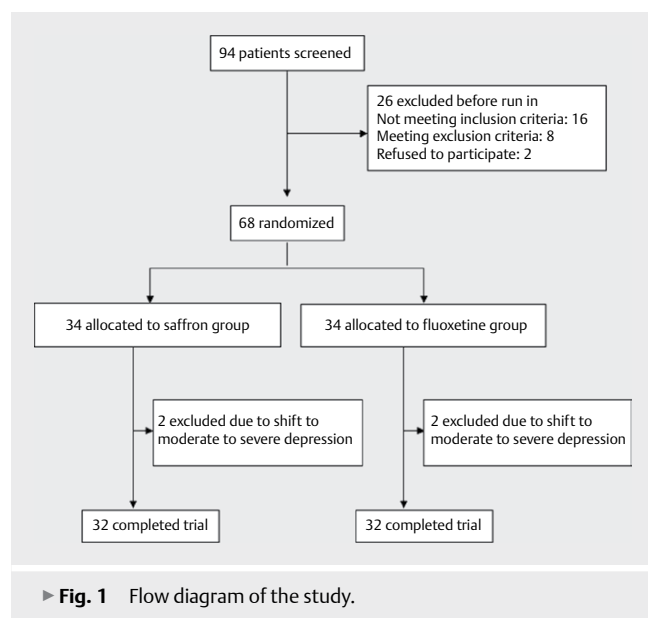
Assuming a mean difference of 3 on the HDRS score between the saffron and the fluoxetine groups, with a standard deviation (SD) of 3 on HDRS score, a power of 95 % and a 2-tailed significance level of 0.05, 27 patients were needed in each group. Moreover, after assuming 25 % attrition rate, 34 patients were needed in each group.

### Randomization, allocation concealment and blinding

An independent party, who was not involved elsewhere in the trial, randomized codes by permuted randomization block (blocks of 4, allocation ratio 1:1). Concealment of allocation was performed using sequentially numbered, sealed opaque envelopes. An aluminum foil inside the envelopes kept them impermeable to intense light. Study participant, research investigator and the rater were all blind to the treatment allocation. Saffron and fluoxetine capsules were indistinguishable in their shape, size, texture, color and odor.

### Statistical analyses

Frequency of categorical variables and mean  $\pm$  SD of continuous variables are reported. General linear model repeated measure was used to compare HDRS scores between the saffron and the fluoxetine groups. Whenever Mauchly's test of sphericity was significant, Greenhouse-Geisser adjustment was used for degrees of freedom. Independent t-test was used to compare mean of continuous variables between treatment groups. Categorical variables were

► **Table 1** Baseline characteristics of the participants.

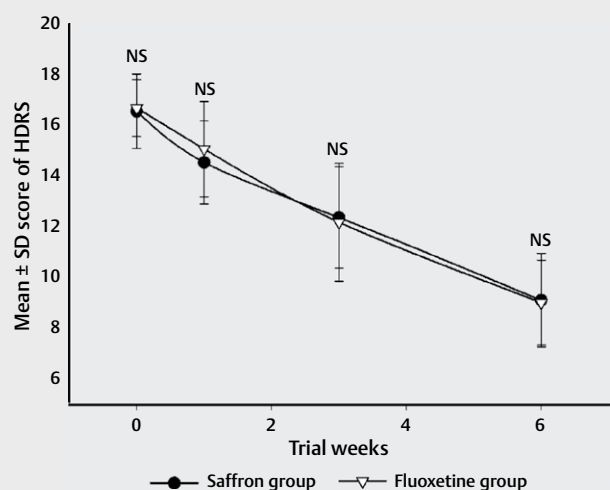
Variable	Saffron group (n = 32)	Fluoxetine group (n = 32)	P-value
Age, years, mean ± SD	29.21 ± 7.69	32.09 ± 4.99	0.08
Smoking, n (%)	4 (12.5 %)	3 (9.4 %)	1.00
History of depression, n (%)	7 (21.9 %)	9 (28.1 %)	0.56
Working, n	26	24	1.00
Education			
• Primary school	4	5	1.00
• High school diploma	26	24	
• University degree	2	4	
Baseline HDRS score, mean ± SD	16.53 ± 1.48	16.65 ± 1.12	0.70

n = number; SD = standard deviation; HDRS = Hamilton Depression Rating Scale

compared using chi-square test and Fisher's exact test where appropriate. Statistical analysis was performed using Statistical Package of Social Science Software (SPSS version 20, IBM Company, USA).

## Results

Among 94 women who were screened for the eligibility criteria, 68 women were entered into the trial and randomized to receive either saffron (n = 34) or fluoxetine (n = 34). 4 women were excluded from the trial due to their shift to moderate to severe depression, and a total number of 64 patients (32 patients in each group) completed the trial (► **Fig. 1**). Baseline characteristics of the study participants were not significantly different between the treatment groups (► **Table 1**).



► **Fig. 2** Repeated measure for comparison of the effects of 2 treatments on Hamilton Depression Rating Scale (HDRS). Values represent mean ± standard deviations. P-values show the result of the independent t-test for comparison of scores between the 2 groups at each time interval. NS indicates non-significant.

## Outcomes

### HDRS score

Baseline HDRS scores were not significantly different between the saffron and the fluoxetine groups ( $16.53 \pm 1.48$  vs.  $16.65 \pm 1.12$ , respectively, [MD (95 % CI) =  $-0.12$  ( $-0.78$  to  $0.53$ ),  $t(57.84) = -0.38$ ,  $p = 0.70$ ]). General linear model repeated measures demonstrated insignificant effect for time × treatment interaction on HDRS score [ $F(4.90, 292.50) = 1.04$ ,  $p = 0.37$ ] (► **Fig. 2**). There was no significant difference between the 2 groups in terms of reduction in HDRS score from baseline to each time, for partial responders, responders and remitters (► **Table 2**). Remission rates were almost equal between 2 groups as ► **Table 2** shows 6 (18.8 %) patients in the saffron group and 7 (21.9 %) in the fluoxetine group reached a HDRS ≤ 7 by the end of this trial ( $p = 1.00$ ). 13 (40.60 %) patients in the saffron group experienced complete response ( $\geq 50$  % reduction in HDRS score) compared with 16 (50 %) in the fluoxetine group, and the difference between the 2 groups was not significant in this regard ( $p = 0.61$ ). Partial response rates were not significantly different between the 2 groups as well; all 32 patients in the both group who completed the trial show  $\geq 25$  % reduction in HDRS score by week 6 ( $p = 1.00$ ).

### Side effects

The frequencies of adverse events observed during the trial are summarized in ► **Table 3**. Patients in the fluoxetine group experienced more headache, dry mouth, daytime drowsiness, constipation and sweating than the saffron group. However, frequencies of adverse events were not significantly different between the 2 groups. No major adverse event and no death occurred.

## Discussion

A postpartum depression takes a great toll on women and negatively affects social interaction and infant development [3]. Mood

► **Table 2** Comparison of score changes between the 2 groups and response to treatment.

HDRS score	Saffron group (Mean ± SD)	Fluoxetine group (Mean ± SD)	Mean difference Saffron – fluoxetine (95% CI)	P-value
Reduction from baseline to week 1	2.03 ± 1.35	1.62 ± 1.53	0.40 (– 0.31 to – 1.31)	0.27
Change from baseline to week 3	4.22 ± 2.09	4.53 ± 1.90	– 0.31 (– 1.31 to 0.68)	0.53
Change from baseline to week 6	7.50 ± 1.97	7.71 ± 1.69	– 0.22 (– 1.13 to 0.69)	0.63
Outcome	Saffron group (n = 32)	Fluoxetine group (n = 32)	Odds ratio	P-value
Number (%) of partial responders at week 3	15 (49.6%)	18 (56.2%)	0.68	0.61
Number (%) of partial responders at week 6	32 (100%)	32 (100%)	–	1.00
Number (%) of responders at week 3	2 (6.2%)	2 (6.2%)	1	1.00
Number (%) of responders at week 6	13 (40.60%)	16 (50%)	0.68	0.61
Number (%) of remitters at week 6	6 (18.8%)	7 (21.9%)	0.82	1.00

► **Table 3** Frequency of adverse events in the 2 study groups.

Saffron (n = 32)	Saffron (n = 32)	Saffron (n = 32)	Saffron (n = 32)
Headache	1 (3.1%)	5 (15.6%)	0.19
Dry mouth	2 (6.2%)	4 (12.5%)	0.67
Nausea	4 (12.5%)	4 (12.5%)	1.00
Daytime drowsiness	1 (3.1%)	4 (12.5%)	0.35
Constipation	2 (6.2%)	4 (12.5%)	0.67
Sweating	1 (3.1%)	3 (9.4%)	0.61

control, especially the etiology of depressive disorders, is not completely understood. However, substantial evidence has accumulated that serotonergic systems play a central role [4–7]. Saffron is used as an antispasmodic, eupeptic, gingival, sedative, antitarrhal, nerve sedative, carminative, diaphoretic, expectorant, stimulant, stomachic, aphrodisiac and antidepressant [18]. The search for new and more effective therapeutic agents includes the study of plants used in traditional medicine to treat mental disorders [13]. Saffron is used for the treatment of depression in Persian traditional medicine [22]. Corcin and safranin, 2 major components of saffron, inhibit reuptake of dopamine, norepinephrine and serotonin [19]. This study was carried out to compare the antidepressant effect of saffron with fluoxetine in mild to moderate postpartum depression. The results of this study emphasize saffron is a safe alternative and as effective as fluoxetine in improving symptoms of depression.

In this double-blind, randomized clinical trial, *Crocus sativus* was found to be effective almost like fluoxetine. Our findings are in line with recently published studies that show *Crocus sativus* antidepressant effect [19, 21–24, 33]. A trial that compared the petal of *Crocus sativus* and fluoxetine in the treatment of depressed patients showed that the petal of *Crocus sativus* is as effective as fluoxetine [21]. Another clinical trial demonstrated that saffron is as effective as imipramine in treatment of mild to moderate depression. Also, in the imipramine group, anticholinergic effects such as dry mouth and sedation were observed more often as predicted [22]. A placebo-controlled trial showed that patients with mild to moderate depression receiving saffron experienced statistically significant benefits in their mood after 6 weeks of treatment compared

to placebo [23]. In another clinical trial, saffron was found to be effective in relieving symptoms of PMS [24]. Shahmansouri et al. showed that short-term therapy with saffron capsules was associated with the same antidepressant efficacy in comparison with fluoxetine in patients with a prior history of post percutaneous coronary intervention who were suffering from depression [33]. In our study, patients in the fluoxetine group experienced more headache, dry mouth, daytime drowsiness, constipation and sweating than the saffron group. However, frequencies of adverse events were not significantly different between the 2 groups. Limitations of the present trial include lack of a placebo group, a small number of participants and short period of follow-up. Since the trial is not well powered, large clinical trials with longer treatment periods and comparison with placebo group would be appropriate for future studies. It should be mentioned that the trial was the first study of saffron in the treatment of postpartum depression. Therefore, we recruited only mild to moderate depression and, as a result of this, the SD of severity score in the participants was quite small. In addition, the findings of this study cannot be generalized to severe depression. Nevertheless, the results of this study emphasize efficacy of saffron in treatment of postpartum depression. On the other hand, the fewer side effects of saffron compared with the classical antidepressant confirm application of saffron as an alternative treatment of depression in traditional medicine.

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## Conflicts of Interest

None of the authors contributing to this article have any conflicts of interest to report.

## References

- [1] O'Hara MW, McCabe JE. Postpartum depression: Current status and future directions. *Annu Rev Clin Psychol* 2013; 9: 379–407
- [2] Couto TC, Brancaglion MY, Alvim-Soares A et al. Postpartum depression: A systematic review of the genetics involved. *World J Psychiatry* 2015; 5: 103–111
- [3] McLearn KT, Minkovitz CS, Strobino DM et al. Maternal depressive symptoms at 2 to 4 months post partum and early parenting practices. *Arch Pediatr Adolesc Med* 2006; 160: 279–284
- [4] Doornbos B, Fekkes D, Tanke MA et al. Sequential serotonin and noradrenalin associated processes involved in postpartum blues. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32: 1320–1325
- [5] Delgado PL, Price LH, Miller HL et al. Rapid serotonin depletion as a provocative challenge test for patients with major depression: Relevance to antidepressant action and the neurobiology of depression. *Psychopharmacol Bull* 1991; 27: 321–330
- [6] Owens MJ, Nemeroff CB. Role of serotonin in the pathophysiology of depression: Focus on the serotonin transporter. *Clin Chem* 1994; 40: 288–295
- [7] Newport DJ, Owens MJ, Knight DL et al. Alterations in platelet serotonin transporter binding in women with postpartum onset major depression. *J Psychiatr Res* 2004; 38: 467–473
- [8] Pearlstein T, Howard M, Salisbury A et al. Postpartum depression. *Am J Obstet Gynecol* 2009; 200: 357–364
- [9] Yonkers KA. Special issues related to the treatment of depression in women. *J Clin Psychiatry* 2003; 64 (Suppl 18): 8–13
- [10] Epperson N, Czarkowski KA, Ward-O'Brien D et al. Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. *Am J Psychiatry* 2001; 158: 1631–1637
- [11] Molyneaux E, Howard LM, McGeown HR et al. Antidepressant treatment for postnatal depression. *Cochrane Database Syst Rev* 2014; 9 CD002018
- [12] Donoghue JM, Tylee A. The treatment of depression: Prescribing patterns of antidepressants in primary care in the UK. *Br J Psychiatry* 1996; 168: 164–168
- [13] Richelson E. Pharmacology of antidepressants – Characteristics of the ideal drug. *Mayo Clin Proc* 1994; 69: 1069–1081
- [14] Demyttenaere K. Compliance during treatment with antidepressants. *J Affect Disord* 1997; 43: 27–39
- [15] Moshiri E, Basti AA, Noorbala AA et al. *Crocus sativus* L. (petal) in the treatment of mild-to-moderate depression: A double-blind, randomized and placebo-controlled trial. *Phytomed* 2006; 13: 607–611
- [16] De Smet PAGM, Nolen WA. St John's wort as an antidepressant. *BMJ* 1996; 313: 241–242
- [17] Ernst E. St. John's wort, an anti-depressant? A systematic, criteria-based review. *Phytomed* 1995; 2: 67–71
- [18] Ríos JL, Recio MC, Giner RM et al. An update review of saffron and its active constituents. *Phytotherapy Res* 1996; 10: 189–193
- [19] Karimi G, Hosseinzadeh H, Khaleghpanah P. Study of antidepressant effect of aqueous and ethanolic of *Crocus sativus* in mice. *Iranian J Basic Med Sci* 2001; 4: 11–15
- [20] Hosseinzadeh H, Younesi HM. Antinociceptive and anti-inflammatory effects of *Crocus sativus* L. stigma and petal extracts in mice. *BMC Pharmacol* 2002; 2: 7
- [21] Akhondzadeh Basti A, Moshiri E, Noorbala AA et al. 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: 439–442
- [22] Akhondzadeh S, Fallah-Pour H, Afkham K et al. Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: A pilot double-blind randomized trial [ISRCTN45683816]. *BMC Complement Altern Med* 2004; 4: 12
- [23] Akhondzadeh S, Tahmacebi-Pour N, Noorbala AA et al. *Crocus sativus* L. in the treatment of mild to moderate depression: A double-blind, randomized and placebo-controlled trial. *Phytother Res* 2005; 19: 148–151
- [24] Agha-Hosseini M, Kashani L, Aleyaseen A et al. *Crocus sativus* L. (saffron) in the treatment of premenstrual syndrome: A double-blind, randomized and placebo-controlled trial. *BJOG* 2008; 115: 515–519
- [25] Akhondzadeh S, Sabet MS, Harirchian MH et al. 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: 581–588
- [26] Akhondzadeh S, Shafiee Sabet M, Harirchian MH et al. 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: 637–643
- [27] Arabzadeh S, Ameli N, Zeinoddini A et al. Celecoxib adjunctive therapy for acute bipolar mania: A randomized, double-blind, placebo-controlled trial. *Bipolar Disord* 2015; 17: 606–614
- [28] Mohammadinejad P, Arya P, Esfandbod M et al. Celecoxib versus diclofenac in mild to moderate depression management among breast cancer patients: A double-blind, placebo-controlled, randomized trial. *Ann Pharmacother* 2015; 49: 953–961
- [29] Jafari S, Ashrafizadeh SG, Zeinoddini A et al. Celecoxib for the treatment of mild-to-moderate depression due to acute brucellosis: A double-blind, placebo-controlled, randomized trial. *J Clin Pharm Ther* 2015; 40: 441–446
- [30] Abbasi SH, Mohammadinejad P, Shahmansouri N et al. Simvastatin versus atorvastatin for improving mild to moderate depression in post-coronary artery bypass graft patients: A double-blind, placebo-controlled, randomized trial. *J Affect Disord* 2015; 183: 149–155
- [31] Zeinoddini A, Sorayani M, Hassanzadeh E et al. Pioglitazone adjunctive therapy for depressive episode of bipolar disorder: A randomized, double-blind, placebo-controlled trial. *Depress Anxiety* 2015; 32: 167–173
- [32] Zeinoddini A, Ahadi M, Farokhnia M et al. L-lysine as an adjunct to risperidone in patients with chronic schizophrenia: A double-blind, placebo-controlled, randomized trial. *J Psychiatr Res* 2014; 59: 125–131
- [33] Shahmansouri N, Farokhnia M, Abbasi SH 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. *J Affect Disord* 2014; 155: 216–222