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EFFECTS OF CUSCUTA CHINENSIS LAM. VERSUS FLUOXETINE FOR TREATMENT OF MAJOR DEPRESSION: A DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL

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Abstract:

Background: Depression is a common psychiatric disorder and a major worldwide health problem. Although several pharmaceutical agents are available for the treatment of depression, they are sometimes ineffective because patients cannot tolerate the side effects and stop taking their medication. Many herbs can play an important role in the treatment of psychiatric disorders with fewer side effects.Objective: To compare the efficacy of Cuscuta chinensis with fluoxetine in the treatment of major depression.Design and setting: Sixty-eight adult outpatients who met the criteria for major depression based on the structured clinical interview as defined by the Diagnostic and Statistical Manual of Mental Disorders (5th edition) participated in a six-week two-armed double-blind randomized controlled trial.Intervention: Patients were randomly assigned to receive C. chinensis or fluoxetine for six weeks.Outcome measures: Both groups filled out the Beck Depression Inventory (BDI-II) and a questionnaire to evaluate side effects at baseline and at 2, 4 and 6 weeks after onset of treatment.Results: The C. chinensis group recorded a significant decrease in BDI-II scores compared to the fluoxetine group ($p < 0.001$). There were no significant differences between groups in terms of observed side effects; however, some complications were significantly lower in the C. chinensis group compared to the fluoxetine group.Conclusion: C. chinensis appears to have antidepressant properties with fewer side effects. This herb is effective and safe in the treatment of major depression and could be administered to depressed patients.

Keywords: *Cuscuta chinensis; Major depressive disorder; Herbal medicine; Fluoxetine; Traditional Persian Medicine.*

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INTRODUCTION:

Background

Major depressive disorder (MDD) is a common mental disorder characterized by alterations in mood, cognition, thinking ability, appetite, sleep and psychomotor activity for at least two weeks [1-3]. Depression is a chronic, recurring and debilitating illness that has a significant effect on quality of life, including on the health, work, overall functioning, social and family life of the depressed person[4-6]. It is the fourth highest cause of disability globally, with over 150 million people estimated to be suffering from depression [7,8]. The World Health Organization (WHO) predicts that, by 2020, major depression will be the second most common risk for morbidity after cardiovascular disease [9].

MDD has the highest life time prevalence (almost 17%) of any psychiatric disorder and its prevalence in the general population is 3% to 10% [9,10]. MDD is twice as common among women as men [11]. Depression is a multi-factorial and complex disease, the etiology of which is not well understood. The pathophysiology of MDD includes at least three main categories: peripheral hormone-type factors, pro-inflammatory cytokines and dysregulation of the hypothalamic-pituitary-adrenal axis [10,12-14]. Recently, it has been suggested that an imbalance between the oxidative-anti-oxidative system and a decrease antioxidant status, plays important roles in the pathophysiology of MDD [15-18]. First line treatment choices include selective serotonin reuptake inhibitors (SSRIs) because they are effective, safe and can be tolerated. Among SSRIs, fluoxetine is most frequently prescribed for treatment of depressive disorder [8,19].

Although antidepressants can produce adverse reactions such as anticholinergic effects, orthostatic hypotension, nausea, constipation, sedation, arrhythmia, cardiac toxicity, weight gain or loss, sexual dysfunction and drug interactions [20-22]. Psychiatrists have found that some patients cannot tolerate the complications, do not respond adequately or stop taking their medication [23,24]. This highlights the need for effective, well-tolerated and less harmful agents for the treatment of depression.

Complementary and alternative medicine plays an important role in treatment of psychiatric disorders, including depression [25-27]. Most herbal products are fairly safe with fewer side effects and drug interactions than chemical drugs such as antidepressants [28, 29]. Cuscuta chinensis Lam. (Convolvulaceae) is an important herb in traditional medicine. It has been used to improve liver and kidney function, treat sexual dysfunction, prevent miscarriages, improve vision and treat autoimmune and cardiovascular diseases [30,31]. Modern pharmacological experiments have demonstrated the different biological activities of this plant. These include hepato-protective, anti-cancer, anti-oxidation, anti-inflammatory and anti-aging effects. It has also show immunomodulatory activity and can enhance memory by inducing PC12 cell differentiation [32,33]. In traditional Persian medicine (TPM), Cuscuta (koshouth) has been used for neurologic and psychotic disorders, including depression.

To the best of our knowledge, only one clinical study on the antidepressant effect of Cuscuta in combined therapy with conventional antidepressants was conducted in 2014. This clinical study showed that Cuscuta could be a potentially effective herb in the treatment of depression [34]. Multiple TPM textbooks refer to the antidepressant effect of C. chinensis, but no evidence-based information has been found. The current study was undertaken to evaluate the antidepressant effect of C. chinensis Lam. as compared to fluoxetine in a six-week double-blind randomized trial.

MATERIAL AND METHODS:

Study design and patients

This study was a two-armed randomized double-blind clinical trial performed over a six-week period. It was conducted from July 2015 to April 2016 at Hafez Psychiatric Clinic at Shiraz University of Medical Sciences in the city of Shiraz in Iran.

Out patients who met the criteria for major depression as assessed by at least two psychiatrists based on Diagnostic and Statistical Manual of mental Disorders (5^{th} edition; DSM-V) criteria and the Beck Depression Inventory (BDI-II) were asked to participate in the trial. The Persian translation of the BDI-II has been validated in previous studies.

The inclusion criteria were a diagnosis of MDD according to DSM-V criteria, age range 18-65 years, providing informed consent, no history of heart disease, renal disease, diabetes, hepatic disease, gastrointestinal ulcers, seizures and respiratory disease, no history of clinical disorders

that can simulate depression (i.e. hypothyroidism) and not being pregnant. The exclusion criteria were a current or past history of other psychiatric disorders, the diagnosis of a mental disorder or mental retardation, the use of a psychotropic medications for at least four weeks prior to the onset of intervention, addiction to drugs or alcohol, history of suicide attempts or significant suicidal ideation, history of allergies to any plant in the Convolvulaceae family, an allergy to SSRIs and the individual requiring electroconvulsive therapy.

All participants provided written informed consent forms and the protocol satisfied the Shiraz University of Medical Sciences Ethics Committee requirements (reference number: IR.SUMS.REC.1394.4) and was registered in the Iranian Registry of Clinical Trials (ID: IRCT2015060722584N1).

Preparation of drugs

The fruits of C. chinensis Lam. have been purchased from local medicine herbal market in Tehran. The specimens are identified at the herbarium, department of Pharmacology, Tehran University of Medical Sciences (TUMS), Tehran - Iran, and kept under a voucher number PMP -374. Quality control of Cuscuta chinensis Lam., was done via total flavonoid analysis using HPLC in parallel investigation (Routinm, Hyperoside, Isorhamnetin, Kaempferol). As the C. chinensis is not heat resistance and its constituents will be destroyed so the formulation was prepared in a crude form. Total parts of the herbs were washed, dried, and then powdered.

Cuscuta chinensis capsules were filled up with 500 mg of C. chinensis powder and all the pharmaceutical controls were done. In parallel, fluoxetine capsules were filled up with 20 mg fluoxetine as same as the Cuscuta capsule in shape, color, size, texture and smell. The capsules were packed in the same container with a specific code number.

Intervention

The patients were randomly divided in to the intervention group (C. chinensis group) and the control group (fluoxetine group) at a 1:1 ratio using computer-generated codes (block randomization). Both groups consumed one capsule per day for five days, which was then increased to two capsules per day. The patients in intervention group were given C. chinensis (500 mg BID) and those in the control group were given fluoxetine (20 mg BID) for six weeks. The capsules were provided by a pharmacist; thus, the physician, patients and other investigators were all blind during the trial. Patients were not allowed to receive any other antidepressant drugs or behaviour therapy during the study. The patients were administered the Beck Depression Rating Scale at baseline and at 2, 4 and 6 weeks after onset of intervention. At the beginning of the study, the phone number of the responsible researcher was given to all patients and they were asked to contact the researcher if they experienced any side effects during the study or after stopping. Any possible side effects were evaluated with a self-report questionnaire completed by the patients. A mean decrease in BDI-II score from baseline was considered to be the main outcome.

Complication and side effects

The patients were requested to advise investigators about any side effects or complaint during the study. Possible side effects were checked and registered at baseline and each visit.

Randomization, blinding and allocation concealment

Block randomization was done by a statistician with Microsoft Excel. Patients were randomly allocated to 2 groups in parallel design. The allocation was done by the secretary of the clinic who was wanted to use a block randomization list consecutively. The researchers, physicians and the statistician were blind to assignments.

Statistical analysis

The sample size was estimated by considering a one-side significance level of 0.05 (α=0.05), 0.2 (β=0.2), 0.80 power (power=80%), 30 patientss in each group. Results were presented as mean ± standard deviation (SD) and the P value less than 0.05 was considered significant. The Chi-square test for statistical comparison of nominal variables in the baseline of the two groups was used. The repeated measure analysis of variance (ANOVA) for time-treatment interaction during the trial was used. The two groups as a between-subject factor (group) and the six weekly measurements during treatment as the within-subject factor (time) were considered. To compare the two groups at baseline and the outcome of two groups at the end of the trial, independent t-test was applied. To compare the demographic data and frequency of side effects between the protocols, Fisher's exact test was used.

The SPSS software (version 22, IBM Corporation) was performed for data analysis.

RESULTS:

Demographic characteristics of participants

Among the 101 participants initially assessed for the study, 33 were excluded because they did not meet the inclusion criteria. The remaining 68 patients were randomized in two groups. Six patients were unable to complete the trial; 62 patients successfully finished the study (Fig. 1).

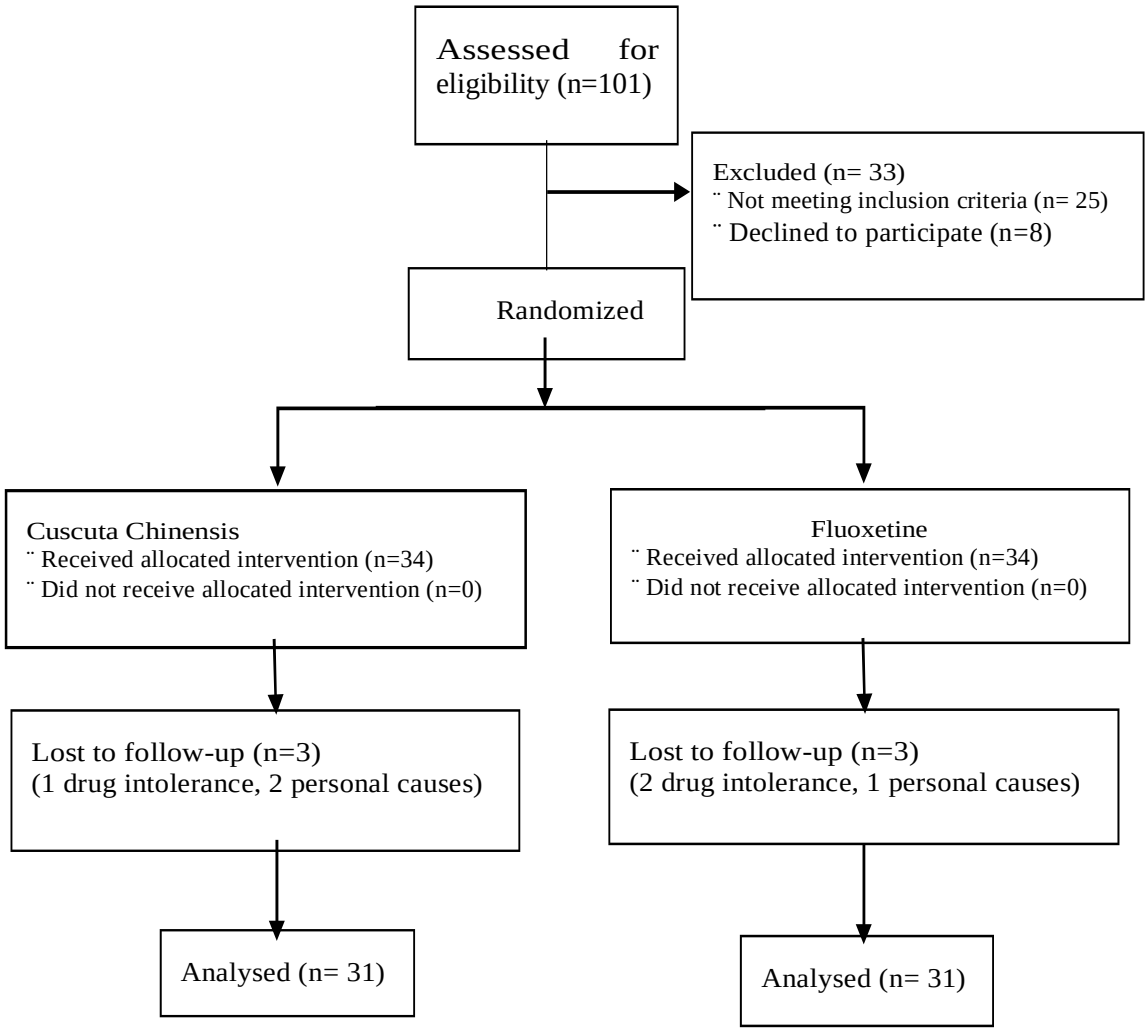

Fig.1: Consort flowchart of the trial.

Baseline demographic and clinical characteristics are shown in Table 1. Among the 62 patients who completed the study, 43 (69.35%) were female and 19 (30.65%) were male. The mean age of the patients was 39.78 ± 11.64 years. Of these, 16 patients (26%) were single and 46 (74%) were married, 37 (60%) were unemployed and 13 (21%) had not completed high school. There were no significant differences in the demographic characteristics of the patients between groups (Table 1).

Table1: Baseline demographic data of the patients in both study groups.

Variable	C.Chinensis % (n)	Fluoxetine % (n)	P
Age in years, mean ± SD	39.35 ±11.38	40.22 ±11.89	0.61
Weight ± SD	71.17 ±11.34	72.06±14.48	0.8
Height ± SD	1.66 ±0. 09	1.66 ± 0. 09	1
BMI ± SD	25.42 ± 4.06	24.16 ± 3.46	0.9
Gender			
Female	67.70 (21)	70.09 (22)	0.9
Male	32.20 (10)	29.03 (9)	
Material status			
Single	19.35 (6)	32.25 (10)	0.66
Married	80.64 (25)	67.74 (21)	
Job			
Unemployed	67.74 (21)	51.61 (16)	0.39
Employed	32.25 (10)	48.38 (15)	
Education			
Under diploma	22.50 (7)	19.30 (6)	0.86
Diploma	38.74 (12)	41.94 (13)	

Efficacy: chinensis versus fluoxetine

The mean ± standard deviation scores of the Beck Depression Inventory questionnaire of two groups of patients are shown in Fig. 2.

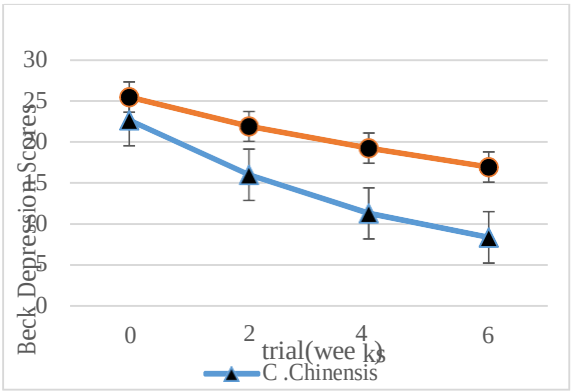

Fig.2. Mean depression scores in 0, 2, 4 and 6weeks of intervention in C. chinensis and fluoxetine group

There were no significant differences between the two groups at the baseline on the BDI-II scores. Both groups showed a significant difference in the BDI-II scores during the study (groups-by-time interaction, Greenhouse–Geisser correction; F=6.90, d.f.=3, p<0.001) (Table 2).The difference between the two groups was significant as indicated by the effect of group as the between-subject factor (Greenhouse–Geisser correction; F=15.72, d.f.= 1, p<0.001) (Table 2, Fig.2).

In addition, a one-way repeated measures analysis of variance (ANOVA) showed a significant difference in the BDI- II scores during the study period in each group (p<0.001) (Table 2)

Table2: Mean depression scores in 0, 2, 4 and 6weeks of intervention in C. chinensis and fluoxetine groups.

Time	C .Chinensis	Fluoxetin	P value from ANOVA*
Base line (Mean ±SD)	22.67±7.11	25.48±9.56	<0.001
2nd Week (Mean ±SD)	16.03±9.10	21.90±11.07	
4nd Week (Mean ±SD)	11.32±9.54	19.25±10.61	
6nd Week (Mean ±SD)	8.46±8.87	16.96±11.18	
P value from ANOVA**	<0.001	<0.001	

*P value of treatment-group interaction between two groups.

**P value of treatment-time interaction in each group

Clinical complications and side effects No serious side effects was reported in the trial. There were no significant differences between groups in terms of observed side effects; however, some complications were significantly lower in the C. chinensis group compared to the fluoxetine group.These complications included sexual dysfunction, palpitation, dry mouth, abdominal discomfort and decrease appetite (Table 3)

Table3: Clinical complications and side effects were reported as number per group.

Side effects	C. Chinensis	Fluoxetine	P
drowsiness	4	9	0.076
insomnia	1	1	1
Headache	1	4	0.155
sedation	1	0	0.312
decrease appetite	0	4	0.032*
Increase weight	2	3	0.857
constipation	1	3	0.298
Abdominal discomfort	1	6	0.038*
diarrhea	2	1	0.554
Sexual dysfunction	0	9	<0.001*
Palpitation	0	7	0.002*
respiratory complaint	0	1	0.312
Dry mouth	0	6	0.006*
thirst	4	2	0.147

*P ≤0.05 considered significant

DISCUSSION:

The aim of the study was to compare the effect of C. chinensis and fluoxetine for the treatment of depression. The experimental results showed that both drugs decreased BDI-II scores after six weeks of treatment, but the C. chinensis group recorded significantly lower BDI-II scores that the control group.

The findings indicate that oral administration of C. chinensis significantly improved depressive symptoms over that of fluoxetine treatment. The data showed that C. chinensis caused no serious adverse effects at therapeutic doses. No significant difference was observed between groups for the frequency of adverse effects; however, some side effects were significantly lower for the C. chinensis group. These included sexual dysfunction, palpitations, dry mouth,abdominal discomfort and decreased appetite.

To our knowledge, this is the first study examining the efficacy of C. chinensis versus a conventional antidepressant drug (fluoxetine) for the treatment of patients with major depressive disorder. In previous study we evaluated the effect of C. planiflora as an adjuvant therapy along with conventional antidepressant drugs for major depression. The results showed that C. planiflora was a potentially effective agent with which to treat 43 patients with depression [34]. In the current study, larger sample sizes of outpatients (62 subjects) were tested for six weeks. In previous study used C. planiflora (another species of Cuscuta) as adjuvant therapy versus conventional treatment with an unknown Pharmacological category. While C. chinensis is the main species which has commonly use in Persian medicine and there was no clinical investigation for this species. In the current study, participants were required to be free of all psychotropic medications for at least four weeks before the onset of the study.

The need for more effective and well-tolerated therapeutic agents for the treatment of depression has prompted researchers to study herbal medicines that have traditionally been used to treat mental disorders [35, 36]. In ancient Persian medical manuscripts, C. chinensis has been recommended by scholars such as Avicenna (980-1037 CE) and Rhazes (865-925 CE) for the treatment of psychiatric disorders, including depression [37,38]. Although a number of Persian medicinal plant textbooks refer to its antidepressant effects, no evidence-based document has been uncovered thus far.

The mechanisms of action for herbal medicines used for treatment of psychiatric disorders involve modulation of neuronal communication by specific plant metabolites that bind to the neurotransmitter/neuromodulator receptors and stimulate or sedate CNS activity, regulating or supporting the healthy function of the expression of antioxidant system [28,39,40]. The active constituents in C. chinensis include flavonoids, lignans, cinnamic acid and polysaccharides [39,40]. These compounds have been suggested to be responsible for the pharmacological activity of the plant. Flavonoids are the main biologically-active constituents in C. chinensis [41]. Polyphenols and flavonoids have shown multiple pharmacological activities, including antioxidant, antineoplastic and antidepressant effects [42]. The polyphenolic and flavonoid contents of C. chinensis may be responsible for the antidepressant effect recorded in the current study. Although the role of C. chinensis in the treatment of depression has not been determined, some studies have suggested that oxidative stress may play an important role in the pathogenesis of neurological and psychiatric diseases such as depression [43,44]. Several studies have demonstrated that oxidative stress increases in depressed patients and have indicated a relation between a decrease oxidative stress and antidepressant treatment [15,17,45,46]. Onset of the therapeutic effect of the fluoxetine is known to be 4 to 6 weeks after onset of treatment. In the current study, the effect of C. chinensis manifested quickly, at two weeks. This is promising for treatment of depressed patients and further study is suggested to determine the efficacy of C. chinensis.

No serious adverse effects were observed in the current study. Sexual dysfunction (delayed ejaculation, reduced libido and lack of orgasm) is an important adverse effect of fluoxetine and has been reported to cause many patients to discontinue used of this medication [47]. There are no records of similar adverse effects for C. chinensis. In fact, it has been used to treat impotence and delayed ejaculation and to prevent miscarriages in China for thousands of years [48,49]. Improvement of sexual impairment also has been demonstrated in animal models [50,51]. The current study showed reduction of sexual dysfunction, palpitation, dry mouth, decreased appetite and abdominal discomfort in the C. chinensis group as compared to the fluoxetine group. These findings indicate a significant decrease in unwanted adverse reactions in the C. chinensis group. As stated, adverse reactions are known for current antidepressant drugs, such that patients may discontinue their use [52,53]. The use

of this natural, effective, less toxic and well-tolerated agent is suggested to avoid such unwanted adverse effects.

The current study was for a short period of time, but the experimental findings showed a decrease in depressive symptoms in patients and in the multiple side effects which have drawn researchers to investigate natural effective antidepressant agents.

Although the results of current study showed the efficacy of C. chinensis Lam. as an effective natural antidepressant, the study also had limitations that should be considered. The small sample size was one limitation. Sampling was restricted to a particular outpatient psychiatric clinic and did not have the large sample size that would be possible in some multi-centre studies. The short duration of follow-up was another limitation. Because MDD is a chronic and recurring disorder, it is also important to collect data about its long-term tolerability. The use of a fixed dose of the test drug could be considered another limitation of this study. The lack of a placebo control group was another limitation which means the possibility of spontaneous remission of depression cannot be excluded from the results.

CONCLUSION:

The findings of this study indicate that C. chinensis may have antidepressant properties with fewer side effects over the short term. We recommend further studies conducted with larger sample sizes, longer trial periods and higher doses. Future trials also are required to determine the active components responsible for the antidepressant effect of chinensis and clarify the mechanisms of action of this effect.

Conflict of interest
Authors of this manuscript have no conflicts of interest.

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REFERENCES:

1.Rashidkhani B, Gargari BP, Ranjbar F, Zareiy S, Kargarnovin Z. Dietary patterns and anthropometric indices among Iranian women with major depressive disorder. Psychiatry Res. 2013;210:115–120.

2.Association AP. DSM-5: Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington DC: American Psychiatry Publishing; 2013.

3.Belmaker, R.H. and Agam, G., 2008. Major depressive disorder. N Engl j Med, 2008(358), pp.55-68.

4.Sahraian A, Jelodar S, Javid Z, Mowla A, Ahmadzadeh L. Study the effects of saffron on depression and lipid profiles: A double blind comparative study. Asian journal of psychiatry. 2016 Aug 31;22:174-6.

5.Cameron C, Habert J, Anand L, Furtado M. Optimizing the management of depression: primary care experience. Psychiatry research. 2014 Dec 31;220:S45-57.

6.Philip NS, Carpenter LL, Tyrka AR, Price LH. Pharmacologic approaches to treatment resistant depression: a re-examination for the modern era. Expert opinion on pharmacotherapy. 2010 Apr 1;11(5):709-22.

7.Epstein I, Szpindel I, Katzman MA. Pharmacological approaches to manage persistent symptoms of major depressive disorder: rationale and therapeutic strategies. Psychiatry research. 2014 Dec 31;220:S15-33.

8.World Health Organization (WHO). Investing in mental health. 1–52. 2003. Available at: http://www.who.int/mental_health/en/investing_in_mnh_final. pdf. Accessed February 12, 2013.

9.Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry. 2014.

10.Velehorschi C, Bleau P, Vermani M, Furtado M, Klassen LJ. Understanding the role of adjunctive nonpharmacological therapies in management of the multiple pathways to depression. Psychiatry research. 2014 Dec 31;220:S34-44.

11.Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Archives of general psychiatry. 2005 Jun 1;62(6):617-27.

12.Bufalino C, Hepgul N, Aguglia E, Pariante CM. The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. Brain, behavior, and immunity. 2013 Jul 31;31:31-47.

13.Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biological psychiatry. 2009 May 1;65(9):732-41.

14.Bogdan R, Nikolova YS, Pizzagalli DA. Neurogenetics of depression: a focus on reward processing and stress sensitivity. Neurobiology of disease. 2013 Apr 30;52:12-23.

15.Kotan VO, Sarandol E, Kirhan E, Ozkaya G, Kirli S. Effects of long-term antidepressant treatment on oxidative status in major depressive disorder: a 24-

week follow-up study. Progress in neuro-psychopharmacology and biological psychiatry. 2011 Jul 1;35(5):1284-90.
16.Maes M, Galecki P, Chang YS, Berk M. A review on the oxidative and nitrosative stress (O&NS) pathways in major depression and their possible contribution to the (neuro) degenerative processes in that illness. Prog Neuropsychopharmacol Biol Psychiatry 2010. doi:10.1016/j.pnpbp.2010.05.004.
17.Baek SE, Lee GJ, Rhee CK, Rho DY, Kim DH, Huh S, Lee SK. Decreased total antioxidant activity in major depressive disorder patients non-responsive to antidepressant treatment. Psychiatry investigation. 2016 Mar 1;13(2):222-6.
18.Kim YK, Na KS, Myint AM, Leonard BE. The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the neuroendocrine system in major depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2016 Jan 4;64:277-84.
19.Ren Y, Zhu C, Wu J, Zheng R, Cao H. Comparison between herbal medicine and fluoxetine for depression: a systematic review of randomized controlled trials. Complementary therapies in medicine. 2015 Oct 31;23(5):674-84.
20.Sarkar P, Chakraborty K, Misra A, Shukla R, Swain SP. Pattern of psychotropic prescription in a tertiary care center: A critical analysis. Indian journal of pharmacology. 2013 May;45(3):270.
21.Akhondzadeh S, Kashani L, Fotouhi A, Jarvandi S, Mobaseri M, Moin M, Khani M, Jamshidi AH, Baghalian K, Taghizadeh M. Comparison of Lavandula angustifolia Mill. tincture and imipramine in the treatment of mild to moderate depression: a double-blind, randomized trial. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2003 Feb 28;27(1):123-7.
22.Akhondzadeh S, Tamacebi-pour N, Noorbala AA, Amini H, Fallah Pour H, Jamshidi AH, et al. Crocus sativus
L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo controlled trial. Phytother Res 2005;19:25–9.
23.Basti AA, Moshiri E, Noorbala A-A, Jamshidi A-H, 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;31:439–442.
24.Minmin XI, Jiang W, Haibo YA. Efficacy and safety of the Chinese herbal medicine shuganjieyu with and without adjunctive repetitive transcranial magnetic stimulation (rTMS) for geriatric depression: a randomized controlled trial. Shanghai archives of psychiatry. 2015 Apr 25;27(2):103.
25.Ravindran AV, da Silva TL. Complementary and alternative therapies as add-on to pharmacotherapy for mood and anxiety disorders: a systematic review. Journal of affective disorders. 2013 Sep 25;150(3):707-19.
26.Solomon D, Adams J. The use of complementary and alternative medicine in adults with depressive disorders. A critical integrative review. Journal of affective disorders. 2015 Jul 1;179:101-13.
27.Deligiannidis KM, Freeman MP. Complementary and alternative medicine therapies for perinatal depression. Best Practice & Research Clinical Obstetrics & Gynaecology. 2014 Jan 31;28(1):85-95.
28.Saki K, Bahmani M, Rafieian-Kopaei M. The effect of most important medicinal plants on two importnt psychiatric disorders (anxiety and depression)-a review. Asian Pacific journal of tropical medicine. 2014 Sep 1;7:S34-42.
29.Cheung F, Feng Y, Wang N, Yuen MF, Tong Y, Wong VT. Effectiveness of Chinese herbal medicine in treating liver fibrosis: a systematic review and meta-analysis of randomized controlled trials. Chinese medicine. 2012 Feb 29;7(1):5.
30.Yen FL, Wu TH, Lin LT, Cham TM, Lin CC. Concordance between antioxidant activities and flavonol contents in different extracts and fractions of Cuscuta chinensis. Food chemistry. 2008 May 15;108(2):455- 62.
31.Wang J, Tan D, Wei G, Guo Y, Chen C, Zhu H, Xue Y, Yin C, Zhang Y. Studies on the Chemical Constituents of Cuscuta chinensis. Chemistry of Natural Compounds. 2016 Nov 1;52(6):1133-6.
32.Yang, S., Xu, H., Zhao, B., Li, S., Li, T., Xu, X., ... & Li, X. (2016). The difference of chemical components and biological activities of the crude products and the salt-processed product from semen cuscutae. Evidence- Based Complementary and Alternative Medicine, 2016.
33.Yen FL, Wu TH, Lin LT, Lin CC. Hepatoprotective and antioxidant effects of Cuscuta chinensis against acetaminophen-induced hepatotoxicity in rats. Journal of Ethnopharmacology. 2007 Apr 20;111(1):123-8.
34.Firoozabadi A, Zarshenas MM, Salehi A, Jahanbin S, Mohagheghzadeh A. Effectiveness of Cuscuta planiflora Ten. and Nepeta menthoides Boiss. & Buhse in major depression: a triple-blind randomized controlled trial study. Journal of evidence-based complementary & alternative medicine. 2015 Apr;20(2):94-7.
35.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. Journal of ethnopharmacology. 2005 Feb 28;97(2):281-4.
36.Dwyer AV, Whitten DL, Hawrelak JA. Herbal medicines, other than st. John's wort, in the treatment of depression: A systematic review. Alternative Medicine Review. 2011 Mar 1;16(1):40-50.

37.Ibn-Sina A. Al-Qanon fi al-Tibb. V. 2. Lebanon: Al-Aelami le-Al-Matbooat Institue; 2005. p. 187 [Arabic].
38.Rhazes M. Al-Havi. International Academy of Medical Sciences, Tehran, Iran (Original work published 10th century) [Arabic], 2005, p. 40.
39.Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. European neuropsychopharmacology. 2011 Dec 31;21(12):841-60.
40.Eyre H, Baune BT. Neuroplastic changes in depression: a role for the immune system. Psychoneuroendocrinology. 2012 Sep 30;37(9):1397-416.
41.Hajimehdipoor H, Amin GR, Adib N, Rastegar H, Shekarchi M. Development of a validated HPLC method for the simultaneous determination of flavonoids in Cuscuta chinensis Lam. by ultra-violet detection. DARU Journal of Pharmaceutical Sciences. 2012 Oct 16;20(1):57.
42.Kolouri S, Firoozabadi A, Salehi A, Zarshenas MM, Dastgheib SA, Heydari M, Rezaeizadeh H. Nepeta menthoides Boiss. & Buhse freeze-dried aqueous extract versus sertraline in the treatment of major depression: A double blind randomized controlled trial. Complementary therapies in medicine. 2016 Jun 30;26:164-70.
43.Talaei A, Moghadam MH, Tabassi SA, Mohajeri SA. Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. Journal of affective disorders. 2015 Mar 15;174:51-6.
44.Panahi Y, Badeli R, Karami G-R, Badeli Z, Sahebkar A. A randomized controlled trial of 6-week Chlorella vulgaris supplementation in patients with major depressive disorder. Complement Ther Med. 2015;23:598– 602.
45.Chung CP, Schmidt D, Stein CM, Morrow JD, Salomon RM. Increased oxidative stress in patients with depression and its relationship to treatment. Psychiatry research. 2013 Apr 30;206(2):213-6.
46.Maria Michel T, Pulschen D, Thome J. The role of oxidative stress in depressive disorders. Current pharmaceutical design. 2012 Dec 1;18(36):5890-9.
47.Shahmansouri N, Farokhnia M, Abbasi SH, Kassaian SE, Tafti AA, Gougol A, Yekehtaz H, Forghani S, Mahmoodian M, Saroukhani S, Arjmandi-Beglar A. 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 Feb 28;155:216-22.
48.Liu J, Tian J, Li J, Azietaku JT, Zhang BL, Gao XM, Chang YX. The in-capillary DPPH-capillary electrophoresis-the diode array detector combined with reversed-electrode polarity stacking mode for screening and quantifying major antioxidants in Cuscuta chinensis Lam. Electrophoresis. 2016 Jul 1;37(12):1632-9.
49.Lai N, Zhang Z, Wang B, Guo Y, Yao C, Wang Z, Wang L, Ma R, Li X, Jiang G. Regulatory effect of traditional Chinese medicinal formula Zuo-Gui-Wan on the Th17/Treg paradigm in mice with bone loss induced by estrogen deficiency. Journal of ethnopharmacology. 2015 May 26;166:228-39.
50.Yang J, Wang Y, Bao Y, Guo J. The total flavones from Semen cuscutae reverse the reduction of testosterone level and the expression of androgen receptor gene in kidney-yang deficient mice. Journal of ethnopharmacology. 2008 Sep 2;119(1):166-71.
51.Ma HX, You ZL, Wang RG. Effect of total flavones from Cuscuta chinensis on expression of Th type-1/Th type-2 cytokines, serum P and PR in abortion rats model. Zhong yao cai= Zhongyaocai= Journal of Chinese medicinal materials. 2008 Aug;31(8):1201-4.
52.Sarris J, Kavanagh DJ, Byrne G. Adjuvant use of nutritional and herbal medicines with antidepressants, mood stabilizers and benzodiazepines. Journal of psychiatric research. 2010 Jan 31;44(1):32-41.
53.Bahceci B, Bagcioglu E, Ozturk A, Bulbul F, Sahiner IV, Tuncer BE, Guzel Hİ, Hocaoglu C. Complementary and alternative medicine use in patients with mental disorders in Turkey. Complementary therapies in clinical practice. 2013 Nov 30;19(4):221.