Journal of Pharmaceutical Research International

19(4): 1-12, 2017; Article no.JPRI.36836
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Medicinal Plants Effective on Serotonin Level: A Systematic Review

Kamal Solati[1], Majid Asadi-Samani[2] and Saeid Heidari-Soureshjani[3*]

[1]Social Determinants of Health Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran.
[2]Young Researchers and Elite Club, Islamic Azad University, Shahrekord Branch, Shahrekord, Iran.
[3]Medical Plants Research Center, Basic Health Sciences Institute, Shahrekord University of Medical Sciences, Shahrekord, Iran.

Authors' contributions

This work was carried out in collaboration between all authors. Authors MAS and SHS searched the databases and wrote the draft. Author KS edited the manuscript. All authors read and approved the final version.

Article Information

DOI: 10.9734/JPRI/2017/36836
Editor(s):
(1) Mahadeva Rao, Professor, School of Basic Medical Sciences, Faculty of Medicine, Universiti Sultan Zainal Abidin, Malaysia.
(2) Othman Ghribi, Department of Pharmacology, Physiology & Therapeutics, University of North Dakota, USA.
(3) Ali Nokhodchi, Professor, Pharmaceutics and Drug Delivery, School of Life Sciences, University of Sussex, UK.
Reviewers:
(1) Maria Rosa Avila-Costa, National University of Mexico, Mexico.
(2) Milan Fedurco, Switzerland.
(3) Suprakash Chaudhury, Dr. D. Y. Patil University, India.
Complete Peer review History: http://www.sciencedomain.org/review-history/21810

Review Article

Received 19th September 2017
Accepted 6th November 2017
Published 8th November 2017

ABSTRACT

In recent years, the prevalence of depression and mood disorders has been on the rise. With regards to increased popularity of traditional medicine and medicinal plants, we conducted this review to identify and study the action mechanisms of the medicinal plants that are effective on serotonin, as one of the neurotransmitters of happiness and mood, and depression symptoms. To conduct this systematic review, the key words of interest were used to retrieve articles from the *Information Sciences Institute (ISI)* and the *PubMed*. The articles, published between 2010 and 2017, about the medicinal plants' and their products' potential effects on serotonin and brain serotonergic system were analyzed. Plants and their derivatives may not only exert therapeutic effects on mild depression but also exhibit suitable therapeutic response in treating severe disorders such as major depressive disorder (MDD) to improve mood conditions and eliminate

**Corresponding author: E-mail: heidari_62@yahoo.com;*

depressed mood through affecting the serotonergic system. Plants and their compounds affect serotonergic system function through anti-inflammatory mechanisms, inhibiting noradrenaline and serotonin reuptake, inhibiting monoamine oxidase (MAO), and increasing expression of serotonin transporter (5-HTT) and hepatic tryptophan 2, 3-dioxygenase. They can therefore be used as options for discovering new drugs effective on happiness and depression.

Keywords: Medicinal plant; serotonin; depression; happiness.

1. INTRODUCTION

In recent years, the prevalence of depression and anxiety has been on the rise. Depression and anxiety disrupt different dimensions of human life, including social and occupational, and quality of life [1,2]. Meanwhile, serotonin (hydroxytryptamine, 5-HT-5) is one of the hormones that contribute fundamentally to regulating the mood and cognition in human. The serotonergic system is a complicated system whose dysfunction leads to development of certain diseases such as depression [3]. Currently despite the availability of various psychotherapies [4-10] and chemical treatments for chronic and psychiatric disorders, treatment of depression remains ambiguous [11]. In addition, chemical treatments to induce happiness, to elevate the levels of certain hormones and treat disorders due to decreased levels of serotonin, including depression and other psychiatric disorders, lead to several complications such as certain behavioral disorders in addition to imposing costs on the patients [12-14]. In addition, psychotherapies may be stigmatized, which highlights the significance of alternative treatments [6]. The use of medicinal plants is increasing day by day due to fewer side effects and lower cost. Ethnobotanical and experimental studies have shown that medicinal plants and herbal drugs can be used to prevent and treat many diseases [15-23]. We, therefore, conducted this study to identify and study the action mechanisms of medicinal plants that are effective on serotonin, as one of the neurotransmitters of happiness and mood, and depression symptoms.

To conduct this systematic review, the key words *serotonin* combined with *medicinal plant* or *herb* and *phyto* combined with *depress* or *happiness* and *pleasure* were used to search for relevant articles indexed in the *Information Sciences Institute* and the *PubMed* using *EndNote* software. After detecting available articles and references as well as library information that was drawn from other sources, the articles that directly addressed the effects of medicinal plants and their products on serotonin levels, improvement of mood, and elimination of depression and were published between 2010 and 2017 were retrieved and analyzed. The exclusion criteria were inaccessible full text, no positive effects, review articles, non-English language articles, and the articles that were irrelevant to the purpose of the study. Fig. 1 illustrates the flowchart according to which some articles were included and some others were excluded from final analysis.

Plants and their derivatives may not only exert therapeutic effects on mild depression but also exhibit suitable therapeutic response in treating severe disorders such as major depressive disorder (MDD) to improve mood conditions and eliminate depressed mood through affecting the serotonergic system. Available research findings have indicated that the plants [24-45] (Table 1) and several phytocompounds [46-56] (Table 2) can play a role in inducing feelings of happiness in human through affecting serotonin synthesis and absorption.

In addition, many other plants, combined or formulated, that have antidepressant or anti-anxiety effects have been used in traditional medicine or experimental studies. For example, Yuanzhi-1 is a Chinese herbal drug that, if used at 10 mg/kg concentration, can increase the extracellular concentration of HT-5 and imitate antidepressant properties via triple reuptake inhibitor [57]. Combination of St. John's Wort (*Hypericum perforatum*) and passion flower (*Passiflora incarnata*) can decrease the complications of depression and enhance feeling of happiness through synaptic uptake of serotonin. However, the combination dose of these two plants should be also taken into account to bring about synergistic effect to achieve optimal therapeutic effect [58]. Perment is another plant-based combination that is used for this purpose. This combination consists of *Clitoria ternatea* Linn., *Withania somnifera* Dun., *Asparagus racemosus* Linn., and *Bacopa monniera* Lin. A study on the effects of this combination's compounds on mice showed that the serum levels of serotonin and noradrenaline increased after treatment [59]. A study

investigated antioxidant effects of Suanzaorenhehuan formula. This combination is made up of *Semen ziziphi* Spinosae, *Cortex albiziae*, *Radix paeoniae* Alba, and *Semen platycladi*. After 2-week treatment with this combination, MAO-A and MAO-B were inhibited and therefore depression symptoms improved via elevating the levels of serotonin [60]. Kai Xin San (Ding-Zhi-Xiao-Wan) is a Chinese herbal formula (consisting of Poria, Ginseng, Polygala, and Chang Pu) that was reported to exert antidepressant effects through affecting the central monoaminergic neurotransmitter system and HT-5 in mouse model of depression [61]. Kai-xin-san can be used as a complementary therapy or dietary supplement by increasing happiness neurotransmitters in the brain as well as improving the expression of neurotrophic factors and their receptors' response [62]. In addition, Dong et al. reported that Kai-xin-san promoted the synthesis of HT-5 in the hippocampus and prefrontal cortex in mouse through eliminating defects in the HT-5 system [63]. The combination pill called Sini San that is used in Chinese traditional medicine can interact synergistically when combined with fluoxetine and affect HT-5 levels [64]. Wang et al. [65] studied the antidepressant effects of Zuojin pill (made up of *Coptis chinensis* Franch. and *Evodia rutaecarpa*). They observed that this pill acted through the central monoaminergic neurotransmitter system and 5-HT. Besides that, Zhi-Zi-Hou-Po is a Chinese herbal formulation that helps treat depression through affecting the monoaminergic system [66]. In the other studies with rats, Yiqi Huatan [67], Jie Yu Chu Fan capsule [68], Suanzaorenhehuan Formula [69], and Zhimu-Baihe (Zhimu: Anemarrhena asphodeloides; Baihe: Lilium brownii var. viridulum) [70], which are Chinese herbal combinations, caused increase in the HT-5 levels in the hypothalamus and decrease in the symptoms of depression through modulating the monoaminergic neurotransmitters. Kaixin Jieyu decoction was studied for its potential effects in modulating behavior and improving depressive moods. Results demonstrated that treatment led to increased expression of HT2A receptor mRNA-5 and its modulation in the cerebrum [71]. In addition, Xiachaihutang, after 4-week gavage, caused increase in the HT-5 levels in mouse hippocampus [72]. Another study also reported that this herbal combination helped improve depressive behaviors in mouse through increasing hypothermia and 5-hydroxytryptophan (5-HTP), 5-HT, and hydroxyindoleacetic acid (5-HIAA)-5 as well as increasing HT-5 reversal [73]. Danzhi Xiaoyao San is another combination that is effective on the levels of tryptophan and HT-5 such that it can serve as a nature-based treatment for depression [74]. Chaihu-Shugan-San decreases the symptoms of depression through increasing the expression of HT1A receptor mRNA-5 and hippocampal cell proliferation in the dentate gyrus in epileptic rats [75]. Wang et al. [76] studied the effect of *Ziziphi spinosae* lily powder suspension on depression in rats. They observed that this combination could enhance happiness and improve depressive symptoms in rat through the mechanism of increasing serum levels of peripheral blood and 5-HIAA-5 in the brain.

It has been shown that medicinal plants and their phytochemicals have anti-inflammatory and antioxidant activities [17,77-85]. It is thought that many plants prevent inflammation of the central nervous system (CNS) via anti-inflammatory and antioxidant properties, and decrease the symptoms of depression and improve depressive mood through pro-inflammatory cytokines [86]. Plants can improve depression and induce happiness in the patients through exerting antioxidant properties in the brain, decreasing pro-inflammatory cytokines, increasing pro-opiomelanocortin, and exerting neuroprotective properties [87].

Plants are effective in enhancing happiness and decreasing symptoms of depression due to certain compounds such as flavonoids, lignanes, phenolic acids, coumarins, diterpene alkaloids, terpenes, saponins, amines, naringenin, quercetin derivatives, eugenol, piperine, berberine, hyperforin, riparian derivatives, and ginsenosides [87]. In addition, polyphenol-like compounds such as curcumin, resveratrol, and proanthocyanidins induce happiness in patients with depression through modulating hypothalamic-pituitary-adrenal (HPA) axis activity [88]. In fact, many phytocompounds can fight inflammatory signaling cascades and prevent degradation of serotonin precursors and therefore increase synthesis of serotonin due to antioxidant properties [89]. Certain compounds of plants such as natural stilbenoid imitate the properties of antidepressants and decrease depression and anxiety by inhibiting noradrenaline and serotonin reuptake [90]. Several mechanisms have been proposed. Some plants induce their serotonergic properties directly. Some plants cause increase in serotonin through inhibiting [(3)H]-serotonin reuptake,

inhibiting MAO, or increasing monoamines levels [51,87]. These plants and their derivatives elevate the levels of serotonin, epinephrine, dopamine, and other monoamines in the brain through inhibiting MAO. In addition, plants may eliminate depressive mood through increasing the expression of serotonin transporter (5-HTT) [48]. Some plants increase serotonin levels through preventing the activity of hepatic tryptophan 2, 3 dioxygenase and increasing the expression of synaptic genes [34].

Although the efficacy of plants or their compounds in inducing happiness depends on the levels of the serotonergic 5-HT(1A) in the brain [28], the underlying mechanisms of mood swings and increase in serotonin levels remain to be fully identified. In addition, the doses of active compounds or plant extracts should be considered in treatment process because they may be inefficacious in low doses or lead to poisoning in high doses [24].

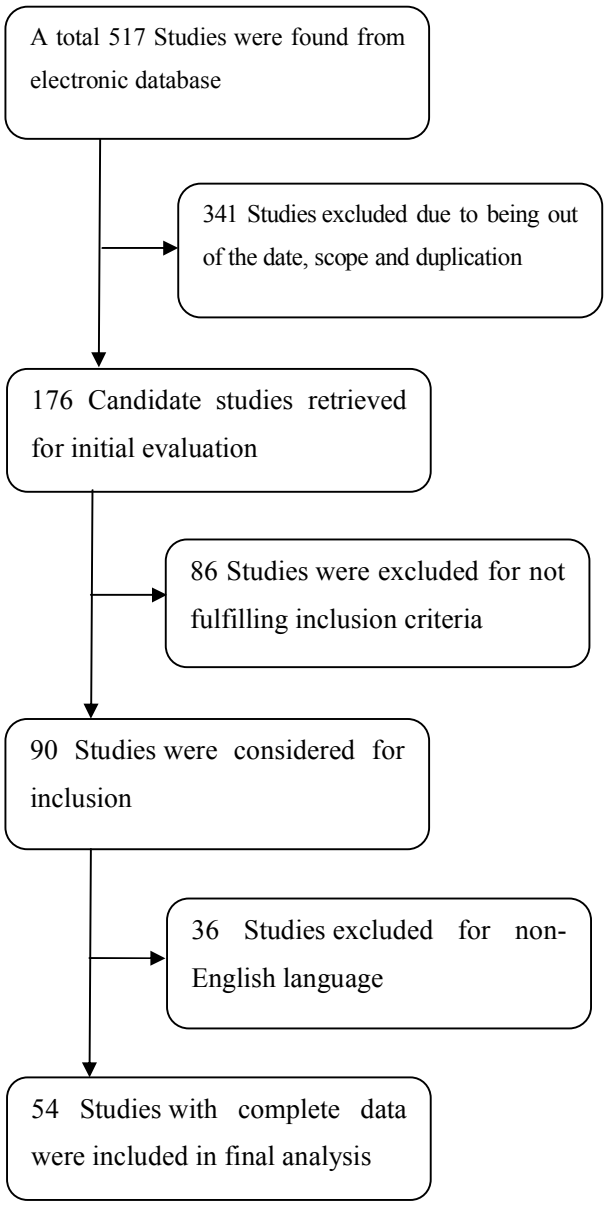

Fig. 1. The flowchart of exclusion and inclusion criteria of the studies

Table 1. Medicinal plants effective on serotonin

Plants	Study design	Main effects and mechanisms	References
Bupleurum falcatum	In the mice	Antidepressant properties through affecting the serotonergic system	[24]
Some plants from Amaryllidaceae family	*In Vitro*	Used to induce happiness and as an antidepressant agent; containing SERT active alkaloids and capable of inducing happiness.	[25]
Tagetes lucida Cav.	In the Rats	Inducing antidepressant properties through affecting serotonergic system and synthesis of serotonin	[26]
Hemerocallis citrina	In the mice	Used to enhance sensations and euphoria; inducing antidepressant property via affecting monoamine neurotransmitters serotonin	[27]
Uncaria lanosa Wallich var. appendiculata Ridsd	In the mice	Ethanolic extract of this plant can help increase HT and 5-HIAA-5 in the cerebral cortex of laboratory mouse.	[28]
Cynanchum auriculatum Royle ex Wight	In the mice	Its monoglycosides can lead to inhibition of [(3)H]-serotonin reuptake in rat.	[29]
Fructus Akebiae	In the Rats	*Fructus akebiae* extracts at 12.6, 25, and 50 mg/kg doses cause increase in extracellular HT-5 according to vivo microanalysis and therefore induction of happiness and antidepressant properties.	[30]
Sideritis species	In the Rats	Extract of S. species, as a triple monoamine reuptake inhibitor, can be used to treat certain diseases such as depression and anxiety.	[31]
Curcuma longa	In the mice	Exerting antidepressant effects through increasing the levels of certain neurotransmitters such as serotonin due to curcumin.	[32]
Annona cherimolia	In the mice	Increasing reversal of HT-5 in mouse brain and therefore decreasing depression	[33]
Hypericum perforatumm	In the Rats	*H. perforatum* extract increases serotonin levels and improves mood in mouse through inhibiting hepatic tryptophan 2, 3 dioxygenase and expression of its genes in mouse.	[34]
Areca catechu nut	In the Rats	Increasing serotonin levels	[35]
Borago officinalis	*In Vitro*	Increasing serotonin levels through affecting serotonin transporter	[36]
Trigonella foenum-graecum	*In Vitro*	Increasing serotonin levels through the MAO-A activity	[36]
Apium graveolens	*In Vitro*	Increasing serotonin levels through the MAO-A activity	[36]
Calluna vulgaris	*In Vitro*	Increasing serotonin levels through the MAO-A activity	[36]
Tagetes erecta L.	In the mice	Capable of imitating antidepressant drugs properties through affecting serotonergic, nitrergic pathway and sigma receptors.	[37]
Paeonia	In the mice	Paeonia glycosidic compounds increase the levels of serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid in the hippocampus of the brain.	[38]
Rosmarinus officinalis	In the mice	The polyphenols of *R. officinalis* cause upregulation of tyrosine hydroxylase and pyruvate carboxylase.	[39]
Hemerocallis citrina	In the mice	The flavonoids of *H. citrina* cause modulation of mood via affecting the serotonergic and dopaminergic systems.	[40]

Plants	Study design	Main effects and mechanisms	References
Lafoensia pacari A. St.-Hil.	In the mice	The chloroform of this plant exerts anti-depressive properties without preventing the MAO enzymes and involving the serotonergic and catecholaminergic systems.	[41]
Moringa oleifera	In the mice	Ethanolic *M. oleifera* extract imitates selective serotonin reuptake inhibitors via affecting the noradrenergic-serotonergic neurotransmission pathway.	[42]
Melissa officinalis L.	In the Rats	It has serotonergic antidepressant-like activity and it plays a role in modulation of serotonergic	[43]
Mangifera indica	In the mice	It can cause modulation of mood via interaction with 5-HT2 receptor, alpha2-adrenoceptor and dopamine D2-receptors	[44]
Gastrodia elata Blume	In the Rats	Aqueous *G. elata* extract can increase cerebral reversal of serotonin and dopamine and decrease depressive behaviors through regulating the monoamine neurotransmitters.	[45]

Table 2. Phytochemicals effective on serotonin

Phytocompounds name	Study design	Main effects and mechanisms	References
Quercetin	In the mice	Inducing serotonergic property via weakening mitochondrial monoamine oxidase-A (MAO-A) in the central nervous system	[46]
Equol	In the Rats	Capable of elevating serotonin levels	[47]
Evodiamine	*In Vitro*	Increasing the expression of serotonin transporter (5-HTT) and therefore enhancing happiness	[48]
Berberine	*In Vitro*	Increasing the expression of serotonin transporter (5-HTT) and therefore enhancing happiness; considered to be an antidepressant drug due to reinforcing monoamine neurotransmission.	[48,49]
Vitexin	In the mice	Improving mood as a mediator via increasing catecholamine in the synaptic cleft and its interaction effect with serotonergic 5-HT1A.	[50]
Turmerone	In the mice	Confirmed antidepressant and happiness-inducing effects via increasing monoamines and decreasing MAO-A activity.	[51]
Auraptenol	In the mice	Serving as a potent antidepressant agent through affecting the serotonergic system.	[52]
Silibinin	In the mice	Inducing happiness via increasing the levels of serotonin (5-HT), brain-derived neurotrophic factor, and norepinephrine.	[53]
Albiflorin	In the Rats	Increasing extracellular 5-HT concentration in mouse hypothalamus in 3.5, 7.0, and 14 mg/kg doses and imitating antidepressant drugs via the activity of reuptake inhibitor 5-HT and therefore improving behavior.	[54]
Echinocystic acid	In the mice	Eliminating serotonin receptors-associated swings and decreasing depressive moods through modulating the proteins of the serotonergic system and removing inflammation	[55]
Chlorogenic acid	In the mice	Exerting antidepressant property through reinforcing expression of synapsin I and increasing serotonin levels.	[56]

Certain compounds in plants, such as silymarin, can act as depressogenic agents through affecting the HT1A-5 receptors of serotonin. Therefore, plant-based depressogenic compounds should be seriously addressed [91]. In certain cases, co-treatment with some medicinal plants, such as St. John's Wort, and fluoxetine can lead to spontaneous adverse drug reaction in the patients [92]. Therefore, It should be taken into account that treating psychiatric disorders and mood disorders is complex and even patient-specific [93]. In addition, the majority of the treatments for depression have been focused on serotonin reuptake inhibitors and/or noradrenaline reuptake inhibitors that indirectly affect dopaminergic neurotransmission; therefore, many comorbidities such as impaired pleasure may remain untreated [94]. Nature-based drugs for improving mood and enhancing happiness should therefore focus on a comparatively wider range of treatments.

2. CONCLUSION

Although introduced medicinal plants and their derivatives can be used in increasing serotonin level and may be effective on happiness and depression, they may exert synergistic effects and lead to spontaneous adverse drug reaction in certain cases such as using St. John's Wort (*H. perforatum*) with depressive antibiotics. It is therefore essential to pay attention to drug dosage and the drug poisoning. Also the medications should be standardized and their structure activity relationship, lethal dose, and effective doses be determined. Finally, randomized double blind placebo controlled studies should be undertaken with patients with definite diagnosis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bandelow B, Michaelis S. Epidemiology of anxiety disorders in the 21st century. Dialogues in Clinical Neuroscience. 2015;17(3):327-35.
2. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. Annual Review of Public Health. 2013;34:119-38.
3. Jenkins TA, Nguyen JCD, Polglaze KE, Bertrand PP. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. Nutrients. 2016;8(1):56.
4. Solati K. The efficacy of mindfulness-based cognitive therapy on resilience among the wives of patients with schizophrenia. Journal of Clinical and Diagnostic Research. 2017;11(4):VC01-VC3.
5. Dehkordi AH, Solati K. The effects of cognitive behavioral therapy and drug therapy on quality of life and symptoms of patients with irritable bowel syndrome. Journal of Advanced Pharmaceutical Technology & Research. 2017;8(2):67-72.
6. Shahbazi K, Solati K, Hasanpour-Dehkordi A. Comparison of hypnotherapy and standard medical treatment alone on quality of life in patients with irritable bowel syndrome: A randomized control trial. Journal of Clinical and Diagnostic Research. 2016;10(5):OC01-4.
7. Solati K, Jafarzadeh L, Hasanpour-Dehkordi A. The effect of stress management based on group cognitive-behavioural therapy on marital satisfaction in infertile women. Journal of Clinical and Diagnostic Research. 2016;10(7):VC01-VC3.
8. Hasanpour-Dehkordi A, Jivad N, Solati K. Effects of yoga on physiological indices, anxiety and social functioning in multiple sclerosis patients: A randomized trial. Journal of Clinical and Diagnostic Research. 2016;10(6):VC01-VC5.
9. Nikfarjam M, Heidari-Soureshjani S, Khoshdel A, Asmand P, Ganji F. Comparison of spiritual well-being and social health among the students attending group and individual religious rites. World Family Medicine. 2017;15(8):160-5.
10. Solati K, Hasanpour-Dehkordi A. Effectiveness of cognitive-behavioural stress management on self-efficacy and relapse of substance use disorders symptoms. Heroin Addiction and Related Clinical Problems. 2017;19(4):25-34.
11. Fajemiroye JO, da Silva DM, de Oliveira DR, Costa EA. Treatment of anxiety and

depression: Medicinal plants in retrospect. Fundamental & Clinical Pharmacology. 2016;30(3):198-215.
12. Young SN. How to increase serotonin in the human brain without drugs. Journal of Psychiatry & Neuroscience. 2007;32(6): 394-9.
13. Evans EA, Sullivan MA. Abuse and misuse of antidepressants. Substance Abuse and Rehabilitation. 2014;5:107-20.
14. Zahreddine N, Richa S. Non-antidepressant treatment of generalized anxiety disorder. Current Clinical Pharmacology. 2015;10(2):86-96.
15. Bahmani M, Sarrafchi A, Shirzad H, Rafieian-Kopaei M. Autism: Pathophysiology and promising herbal remedies. Current Pharmaceutical Design. 2016;22(3):277-85.
16. Asgary S, Kelishadi R, Rafieian-Kopaei M, Najafi S, Najafi M, Sahebkar A. Investigation of the lipid-modifying and antiinflammatory effects of *Cornus mas* L. supplementation on dyslipidemic children and adolescents. Pediatric Cardiology. 2013;34(7):1729-35.
17. Asadi-Samani M, Bagheri N, Rafieian-Kopaei M, Shirzad H. Inhibition of Th1 and Th17 cells by medicinal plants and their derivatives: A systematic review. Phytotherapy Research. 2017;31(8):1128–1139.
18. Raeisi R, Heidari-Soureshjani S, Asadi-Samani M, Luther T. A systematic review of phytotherapies for newborn jaundice in Iran. International Journal of Pharmaceutical Sciences and Research. 2017;8(5):1953-8.
19. Moradi B, Heidari-Soureshjani S, Asadi-Samani M, Yang Q, Saeedi-Boroujeni A. Efficacy and mechanisms of medicinal plants as immunotherapy in treatment of allergic rhinitis: A systematic review. International Journal of Pharmaceutical Sciences and Research. 2017;8(5):1892-9.
20. Mansouri E, Asadi-Samani M, Kooti W, Ghasemiboroon M, Ashtary-Larky D, Alamiri F, et al. Anti-fertility effect of hydro-alcoholic extract of fennel (*Foeniculum vulgare* Mill) seed in male Wistar rats. Journal of Veterinary Research. 2016;60(3):357-63.
21. Mirhoseini M, Moradi MT, Asadi-Samani M. Traditionally used medicinal plants in the treatment of kidney stone: A review on ethnobotanical studies in Iran. Ambient Science. 2016;3(2):16-21.
22. Asadi-Samani M, Bahmani M, Rafieian-Kopaei M. The chemical composition, botanical characteristic and biological activities of *Borago officinalis*: A review. Asian Pacific Journal of Tropical Medicine. 2014;7:S22-S8.
23. Shabanian S, Khalili S, Lorigooini Z, Malekpour A, Heidari-Soureshjani S. The effect of vaginal cream containing ginger in users of clotrimazole vaginal cream on vaginal candidiasis. Journal of Advanced Pharmaceutical Technology & Research. 2017;8(2):80.
24. Kwon S, Lee B, Kim M, Lee H, Park HJ, Hahm DH. Antidepressant-like effect of the methanolic extract from *Bupleurum falcatum* in the tail suspension test. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2010;34(2):265-70.
25. Bay-Smidt MGK, Jager AK, Krydsfeldt K, Meerow AW, Stafford GI, Van Staden J, et al. Phylogenetic selection of target species in Amaryllidaceae tribe Haemantheae for acetylcholinesterase inhibition and affinity to the serotonin reuptake transport protein. South African Journal of Botany. 2011;77(1):175-83.
26. Gabriela GC, Javier AAF, Elisa VA, Gonzalo VP, Herlinda BJ. Antidepressant-like effect of *Tagetes lucida* Cav. extract in rats: Involvement of the serotonergic system. American Journal of Chinese Medicine. 2012;40(4):753-68.
27. Gu L, Liu YJ, Wang YB, Yi LT. Role for monoaminergic systems in the antidepressant-like effect of ethanol extracts from *Hemerocallis citrina*. Journal of Ethnopharmacology. 2012;139(3):780-7.
28. Hsu LC, Ko YJ, Cheng HY, Chang CW, Lin YC, Cheng YH, et al. Antidepressant-like activity of the ethanolic extract from *Uncaria lanosa* Wallich var. appendiculata Ridsd in the forced swimming test and in the tail suspension test in mice. Evidence-Based Complementary and Alternative Medicine. 2012;2012:497302.
29. Ji CX, Li XY, Jia SB, Liu LL, Ge YC, Yang QX, et al. The antidepressant effect of *Cynanchum auriculatum* in mice. Pharmaceutical Biology. 2012;50(9):1067-72.
30. Jin ZL, Gao N, Zhou D, Chi MG, Yang XM, Xu JP. The extracts of Fructus Akebiae, a preparation containing 90% of the active ingredient hederagenin: Serotonin, norepinephrine and dopamine reuptake

inhibitor. Pharmacology, Biochemistry, and Behavior. 2012;100(3):431-9.

31. Knorle R. Extracts of *Sideritis scardica* as triple monoamine reuptake inhibitors. Journal of Neural Transmission. 2012;119(12):1477-82.
32. Kulkarni SK, Akula KK, Deshpande J. Evaluation of antidepressant-like activity of novel water-soluble curcumin formulations and St. John's wort in behavioral paradigms of despair. Pharmacology. 2012;89(1-2):83-90.
33. Martinez-Vazquez M, Estrada-Reyes R, Araujo Escalona AG, Ledesma Velazquez I, Martinez-Mota L, Moreno J, et al. Antidepressant-like effects of an alkaloid extract of the aerial parts of *Annona cherimolia* in mice. Journal of Ethnopharmacology. 2012;139(1):164-70.
34. Bano S, Ara I, Saboohi K, Moattar T, Chaoudhry B. St. John's Wort increases brain serotonin synthesis by inhibiting hepatic tryptophan 2, 3 dioxygenase activity and its gene expression in stressed rats. Pakistan Journal of Pharmaceutical Sciences. 2014;27(5):1427-35.
35. Abbas G, Naqvi S, Erum S, Ahmed S, Atta-ur-Rahman, Dar A. Potential antidepressant activity of *Areca catechu* Nut via elevation of serotonin and noradrenaline in the hippocampus of rats. Phytotherapy Research. 2013;27(1):39-45.
36. Jager AK, Gauguin B, Andersen J, Adsersen A, Gudiksen L. Screening of plants used in Danish folk medicine to treat depression and anxiety for affinity to the serotonin transporter and inhibition of MAO-A. Journal of Ethnopharmacology. 2013;145(3):822-5.
37. Khulbe A, Pandey S, Sah SP. Antidepressant-like action of the hydromethanolic flower extract of *Tagetes erecta* L. in mice and its possible mechanism of action. Indian Journal of Pharmacology. 2013;45(4):386-90.
38. Qiu F, Zhong X, Mao Q, Huang Z. The antidepressant-like effects of paeoniflorin in mouse models. Experimental and Therapeutic Medicine. 2013;5(4):1113-6.
39. Sasaki K, El Omri A, Kondo S, Han J, Isoda H. *Rosmarinus officinalis* polyphenols produce anti-depressant like effect through monoaminergic and cholinergic functions modulation. Behavioural Brain Research. 2013;238:86-94.
40. Du B, Tang X, Liu F, Zhang C, Zhao G, Ren F, et al. Antidepressant-like effects of the hydroalcoholic extracts of *Hemerocallis citrina* and its potential active components. BMC Complementary and Alternative Medicine. 2014;14:326.
41. Galdino PM, Carvalho AA, Florentino IF, Martins JL, Gazola AC, de Paula JR, et al. Involvement of monoaminergic systems in the antidepressant-like properties of *Lafoensia pacari* A. St. Hil. Journal of Ethnopharmacology. 2015;170:218-25.
42. Kaur G, Invally M, Sanzagiri R, Buttar HS. Evaluation of the antidepressant activity of *Moringa oleifera* alone and in combination with fluoxetine. Journal of Ayurveda and Integrative Medicine. 2015;6(4):273-9.
43. Lin SH, Chou ML, Chen WC, Lai YS, Lu KH, Hao CW, et al. A medicinal herb, *Melissa officinalis* L. ameliorates depressive-like behavior of rats in the forced swimming test via regulating the serotonergic neurotransmitter. Journal of Ethnopharmacology. 2015;175:266-72.
44. Ishola IO, Awodele O, Eluogu CO. Potentials of *Mangifera indica* in the treatment of depressive-anxiety disorders: Possible mechanisms of action. Journal of Complementary & Integrative Medicine. 2016;13(3):275-87.
45. Lin YE, Lin SH, Chen WC, Ho CT, Lai YS, Panyod S, et al. Antidepressant-like effects of water extract of *Gastrodia elata* Blume in rats exposed to unpredictable chronic mild stress via modulation of monoamine regulatory pathways. Journal of Ethnopharmacology. 2016;187:57-65.
46. Yoshino S, Hara A, Sakakibara H, Kawabata K, Tokurnura A, Ishisaka A, et al. Effect of quercetin and glucuronide metabolites on the monoamine oxidase-A reaction in mouse brain mitochondria. Nutrition. 2011;27(7-8):847-52.
47. Blake C, Fabick KM, Setchell KDR, Lund TD, Lephart ED. Neuromodulation by soy diets or equol: Anti-depressive & anti-obesity-like influences, age- & hormone-dependent effects. BMC Neuroscience. 2011;12.
48. Hu Y, Ehli EA, Hudziak JJ, Davies GE. Berberine and evodiamine influence serotonin transporter (5-HTT) expression via the 5-HTT-linked polymorphic region. Pharmacogenomics Journal. 2012;12(5): 372-8.
49. Sun SY, Wang K, Lei HM, Li LP, Tu MJ, Zeng S, et al. Inhibition of organic cation

transporter 2 and 3 may be involved in the mechanism of the antidepressant-like action of berberine. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2014;49:1-6.
50. Can OD, Ozkay UD, Ucel UI. Anti-depressant-like effect of vitexin in BALB/c mice and evidence for the involvement of monoaminergic mechanisms. European Journal of Pharmacology. 2013;699(1-3): 250-7.
51. Liao JC, Tsai JC, Liu CY, Huang HC, Wu LY, Peng WH. Antidepressant-like activity of turmerone in behavioral despair tests in mice. BMC Complementary and Alternative Medicine. 2013;13:299.
52. Gu X, Zhou Y, Wu X, Wang F, Zhang CY, Du C, et al. Antidepressant-like effects of auraptenol in mice. Scientific Reports. 2014;4:4433.
53. Yan WJ, Tan YC, Xu JC, Tang XP, Zhang C, Zhang PB, et al. Protective effects of silibinin and its possible mechanism of action in mice exposed to chronic unpredictable mild stress. Biomolecules & Therapeutics. 2015;23(3):245-50.
54. Jin ZL, Gao N, Xu W, Xu P, Li S, Zheng YY, et al. Receptor and transporter binding and activity profiles of albiflorin extracted from Radix paeoniae Alba. Scientific reports. 2016;6:33793.
55. Li S, Han J, Wang DS, Feng B, Deng YT, Wang XS, et al. Echinocystic acid reduces reserpine-induced pain/depression dyad in mice. Metabolic Brain Disease. 2016;31(2): 455-63.
56. Wu J, Chen H, Li H, Tang Y, Yang L, Cao S, et al. Antidepressant potential of chlorogenic acid-enriched extract from *Eucommia ulmoides* Oliver bark with neuron protection and promotion of serotonin release through Enhancing Synapsin I Expression. Molecules. 2016; 21(3):260.
57. Jin ZL, Gao N, Li XR, Tang Y, Xiong J, Chen HX, et al. The antidepressant-like pharmacological profile of Yuanzhi-1, a novel serotonin, norepinephrine and dopamine reuptake inhibitor. European Neuropsychopharmacology. 2015;25(4): 544-56.
58. Fiebich BL, Knorle R, Appel K, Kammler T, Weiss G. Pharmacological studies in an herbal drug combination of St. John's Wort (*Hypericum perforatum*) and passion flower (*Passiflora incarnata*): *In vitro* and in vivo evidence of synergy between Hypericum and Passiflora in antidepressant pharmacological models. Fitoterapia. 2011;82(3):474-80.
59. Ramanathan M, Balaji B, Justin A, Gopinath N, Vasanthi M, Ramesh RV. Behavioural and neurochemical evaluation of Perment (R) an herbal formulation in chronic unpredictable mild stress induced depressive model. Indian Journal of Experimental Biology. 2011;49(4):269-75.
60. Liu J, Qiao W, Yang Y, Ren L, Sun Y, Wang S. Antidepressant-like effect of the ethanolic extract from Suanzaorenhehuan formula in mice models of depression. Journal of Ethnopharmacology. 2012; 141(1):257-64.
61. Zhou XJ, Liu M, Yan JJ, Cao Y, Liu P. Antidepressant-like effect of the extracted of Kai Xin San, a traditional Chinese herbal prescription, is explained by modulation of the central monoaminergic neurotrans-mitter system in mouse. Journal of Ethnopharmacology. 2012;139(2):422-8.
62. Zhu KY, Mao QQ, Ip SP, Choi RC, Dong TT, Lau DT, et al. A standardized chinese herbal decoction, Kai-Xin-San, restores decreased levels of neurotransmitters and neurotrophic factors in the brain of chronic stress-induced depressive rats. Evidence-based complementary and alternative medicine: eCAM. 2012;2012:149256.
63. Dong XZ, Li ZL, Zheng XL, Mu LH, Zhang GQ, Liu P. A representative prescription for emotional disease, Ding-Zhi-Xiao-Wan restores 5-HT system deficit through interfering the synthesis and transshipment in chronic mild stress-induced depressive rats. Journal of Ethnopharmacology. 2013; 150(3):1053-61.
64. Li Y, Sun Y, Ma X, Xue X, Zhang W, Wu Z, et al. Effects of Sini San used alone and in combination with fluoxetine on central and peripheral 5-HT levels in a rat model of depression. Journal of traditional Chinese Medicine = Chung I Tsa Chih Ying Wen Pan. 2013;33(5):674-81.
65. Wang QS, Ding SL, Mao HP, Cui YL, Qi XJ. Antidepressant-like effect of ethanol extract from Zuojin Pill, containing two herbal drugs of Rhizoma Coptidis and Fructus Evodiae, is explained by modulating the monoaminergic neurotrans-mitter system in mice. Journal of Ethnopharmacology. 2013;148(2):603-9.
66. Yao AM, Ma FF, Zhang LL, Feng F. Effect of aqueous extract and fractions of Zhi-Zi-Hou-Pu decoction against depression in

inescapable stressed mice: Restoration of monoamine neurotransmitters in discrete brain regions. Pharmaceutical Biology. 2013;51(2):213-20.
67. Zhou HH, Chen SD, Xu Y, Han YZ, Hu JY. Multiple pharmacological actions of Yiqi Huatan Decoction in a model of depression in rats. Chinese Journal of Integrative Medicine. 2013;19(3):200-5.
68. Ding LL, Zhang XY, Guo HL, Yuan JL, Li SJ, Hu WL, et al. The functional study of a Chinese herbal compounded antidepressant medicine - Jie Yu Chu Fan Capsule on chronic unpredictable mild stress mouse model. PloS One. 2015; 10(7).
69. Liang Y, Yang X, Zhang X, Duan H, Jin M, Sun Y, et al. Antidepressant-like effect of the saponins part of ethanol extract from SHF. Journal of Ethnopharmacology. 2016;191:307-14.
70. Du H, Wang K, Su L, Zhao H, Gao S, Lin Q, et al. Metabonomic identification of the effects of the Zhimu-Baihe saponins on a chronic unpredictable mild stress-induced rat model of depression. Journal of Pharmaceutical and Biomedical Analysis. 2016;128:469-79.
71. Huang SJ, Zhang XH, Wang YY, Pan JH, Cui HM, Fang SP, et al. Effects of Kaixin Jieyu decoction () on behavior, monoamine neurotransmitter levels, and serotonin receptor subtype expression in the brain of a rat depression model. Chinese Journal of Integrative Medicine. 2014;20(4):280-5.
72. Su GY, Yang JY, Wang F, Ma J, Zhang K, Dong YX, et al. Antidepressant-like effects of Xiaochaihutang in a rat model of chronic unpredictable mild stress. Journal of Ethnopharmacology. 2014;152(1):217-26.
73. Su GY, Yang JY, Wang F, Xiong ZL, Hou Y, Zhang K, et al. Xiaochaihutang prevents depressive-like behaviour in rodents by enhancing the serotonergic system. The Journal of Pharmacy and Pharmacology. 2014;66(6):823-34.
74. Zhu X, Jing L, Chen C, Shao M, Fan Q, Diao J, et al. Danzhi Xiaoyao San ameliorates depressive-like behavior by shifting toward serotonin via the downregulation of hippocampal indoleamine 2,3-dioxygenase. Journal of Ethnopharmacology. 2015;160:86-93.
75. Yang P, Li L, Liu XJ, Cai X, Sun MZ, He JF, et al. Effect of Chaihu-Shugan-San on the mRNA expression of the 5-HT1A receptor and cellular proliferation in the hippocampus of epileptic rats with depression. Experimental and Therapeutic Medicine. 2016;11(1):124-30.
76. Wang Y, Huang M, Lu X, Wei R, Xu J. Ziziphi spinosae lily powder suspension in the treatment of depression-like behaviors in rats. BMC Complementary and Alternative Medicine. 2017;17(1):238.
77. Heidarian E, Rafieian-Kopaei M. Protective effect of artichoke (*Cynara scolymus*) leaf extract against lead toxicity in rat. Pharmaceutical Biology. 2013;51(9):1104-9.
78. Rafieian-Kopaei M, Baradaran A, Rafieian M. Oxidative stress and the paradoxical effects of antioxidants. Journal of Research in Medical Sciences. 2013;18(7): 628.
79. Ghatreh-Samani M, Esmaeili N, Soleimani M, Asadi-Samani M, Ghatreh-Samani K, Shirzad H. Oxidative stress and age-related changes in T cells: Is thalassemia a model of accelerated immune system aging? Central-European Journal of Immunology. 2016;41(1):116-24.
80. Shirani M, Heidari-Soureshjani S, Yavangi M. Use of Iranian medicinal plants effective on male fertility indices. Journal of Global Pharma Technology. 2016;10(8):36-43.
81. Shirani M, Shabanian S, Yavangi M. A systematic review of Iranian medicinal plants effective on female infertility. Journal of Global Pharma Technology. 2016;10(8): 44-9.
82. Nikfarjam M, Bahmani M, Heidari-Soureshjani S. Phytotherapy for anxiety in Iran: A review of the most important Anti-anxiety medicinal plants. Journal of Chemical and Pharmaceutical Sciences. 2016;9(3):1235-41.
83. Nikfarjam M, Bahmani M, Heidari-Soureshjani S. Phytotherapy for depression: A review of the most important medicinal plants of flora of Iran effective on depression. Journal of Chemical and Pharmaceutical Sciences. 2016;9(3):1242-7.
84. Heidari-Soreshjani S, Asadi-Samani M, Yang Q, Saeedi-Boroujeni A. Phytotherapy of nephrotoxicity-induced by cancer drugs: An updated review. Journal of Nephropathology. 2017;6(3):254-63.
85. Shirani M, Raeisi R, Heidari-Soureshjani S, Asadi-Samani M, Luther T. A review for discovering hepatoprotective herbal drugs with least side effects on kidney. Journal of Nephropharmacology. 2017;6(2):38-48.

86. van Heesch F, Prins J, Konsman JP, Westphal KG, Olivier B, Kraneveld AD, et al. Lipopolysaccharide-induced anhedonia is abolished in male serotonin transporter knockout rats: An intracranial self-stimulation study. Brain, Behavior, and Immunity. 2013;29:98-103.
87. Bahramsoltani R, Farzaei MH, Farahani MS, Rahimi R. Phytochemical constituents as future antidepressants: A comprehensive review. Reviews in the neurosciences. 2015;26(6):699-719.
88. Ogle WO, Speisman RB, Ormerod BK. Potential of treating age-related depression and cognitive decline with nutraceutical approaches: A mini-review. Gerontology. 2013;59(1):23-31.
89. Strasser B, Gostner JM, Fuchs D. Mood, food, and cognition: Role of tryptophan and serotonin. Current Opinion in Clinical Nutrition and Metabolic Care. 2016;19(1): 55-61.
90. Nabavi SM, Daglia M, Braidy N, Nabavi SF. Natural products, micronutrients, and nutraceuticals for the treatment of depression: A short review. Nutritional Neuroscience. 2017;20(3):180-94.
91. Yaghmaei P, Oryan S, Mohammadi K, Solati J. Role of serotonergic system on modulation of depressogenic-like effects of silymarine. Iran J Pharm Res. 2012;11(1): 331-7.
92. Hoban CL, Byard RW, Musgrave IF. A comparison of patterns of spontaneous adverse drug reaction reporting with St. John's Wort and fluoxetine during the period 2000-2013. Clinical and Experimental Pharmacology & Physiology. 2015;42(7):747-51.
93. Korte SM, Prins J, Krajnc AM, Hendriksen H, Oosting RS, Westphal KG, et al. The many different faces of major depression: It is time for personalized medicine. European Journal of Pharmacology. 2015;753:88-104.
94. Prins J, Olivier B, Korte SM. Triple reuptake inhibitors for treating subtypes of major depressive disorder: The monoamine hypothesis revisited. Expert Opinion on Investigational Drugs. 2011;20(8):1107-30.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/21810