IJBPAS, May, 2024, 13(5): 2060-2072

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON HERBAL PLANTS USED IN DEPRESSION

SATI A[1], TOMAR A[*1] AND SAINI N[2]

[1, 2]Department of Pharmacology, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun, India

***Corresponding Author: Ms. Ankita Tomar: E Mail: ankitatomar2222@gmail.com**

Received 19th May 2023; Revised 18th July 2023; Accepted 16th Aug. 2023; Available online 1st May 2024

https://doi.org/10.31032/IJBPAS/2024/13.5.7977

ABSTRACT

Herbal medicines contain a variety of pharmacologically active compounds, and the specific ingredients responsible for their therapeutic effects are not always well understood. Proponents of herbal medicine argue that in many cases, the clinical effects of whole plant extracts are stronger than those of isolated ingredients, but this claim needs to be supported with evidence on a case-by-case basis. While there are numerous pharmaceutical options for treating mental disorders, many patients either cannot tolerate the side effects or do not respond well to treatment. In contrast, many therapeutic herbs have fewer side effects and can serve as an alternative treatment or be used to enhance the effects of prescription medications. This review examines the evidence supporting the clinical effects of various types of herbal medicines commonly used for depression. It aims to determine the quality of evidence for the efficacy of these herbs in treating mental health conditions.

Keywords: Depression, Herbal Plant, Pharmacotherapy

INTRODUCTION

Depression is a common and persistent condition that affects individuals worldwide and is associated with significant levels of morbidity and mortality. The prevalence of major depression worldwide is 4.7%, which means that one out of every 20 people is affected by it **[1]**. However, the prevalence of depression is higher in certain demographic groups, such as elderly people and women. Studies have found that the prevalence of depression in women is about 10-25%, which is roughly twice as high as in men, where the prevalence is about 5-12% **[2]**. This gender difference in depression

rates may be due to various factors, including hormonal differences and social and cultural pressures. It's essential to recognize that depression is a severe and treatable condition that can affect anyone, regardless of gender or other demographic factors **[3]**. The American Psychiatric Association defines depression as a disorder that has a wide range of symptoms, including physiological, behavioural, and psychological symptoms **[4]**. Depression can cause changes in mood, difficulties in thinking, and loss of interest, as well as physical problems such as headaches, sleep disorders, loss of energy, and sexual problems. It is a complex condition with various possible symptoms that can manifest differently in different individuals **[5, 6]**.

There are two main types of depression: unipolar depression and bipolar depression. Unipolar depression is the more common type, accounting for about 75% of cases. It is usually not familial and is clearly linked to stressful life events, and can be accompanied by symptoms of anxiety and agitation. Bipolar depression, on the other hand, accounts for about 25% of cases and is sometimes referred to as endogenous depression. It often has a familial pattern and is not necessarily related to external stresses, and can manifest as oscillating episodes of depression and mania over a few weeks. Patients with depression often show symptoms that reflect a decrease in certain brain monoamine neurotransmitters, such as norepinephrine, serotonin, and dopamine **[7]**.

While there are a number of drugs available for treating depression, clinical evaluations have shown that these drugs can have certain side effects and interactions, as well as a risk of disease recurrence **[8]**. Tricyclic antidepressants, for example, can cause complications such as dry mouth, constipation, dizziness, and sexual dysfunction, among others. Monoamine oxidase inhibitors (MAOIs) can cause relief or behavioural stimulation and an increased risk of postural hypotension **[9]**. Newer antidepressants tend to have fewer side effects and a lower risk of toxicity, but still, less than half of patients respond to these drugs, and some are resistant to pharmacotherapy. As a result, there is a need for new classes of antidepressants. To avoid the adverse effects of synthetic and chemical drugs, medicinal plants have been investigated as an alternative treatment for depression **[10]**.

Biomarkers and Bio-factors Involved in Depression

Depression is a complex disorder that is believed to involve a variety of biomarkers and bio-factors. Biomarkers are measurable indicators of a disease, while bio-factors are biological components that contribute to the development or severity of a disease **[11]**.

Several biomarkers have been associated with depression, including neurotrophic factors such as brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and nerve growth factor (NGF) **[12]**. These factors are involved in the growth, development, and survival of neurons, and may be reduced in patients with depression. Other biomarkers include inflammation markers such as C-reactive protein (CRP) and proinflammatory cytokines, which are elevated in some patients with depression **[13]**. Glutamic acid and gamma-aminobutyric acid (GABA) are important neurotransmitters in the mammalian brain. Glutamic acid is an excitatory neurotransmitter, while GABA is an inhibitory neurotransmitter **[14]**. Both of these neurotransmitters are involved in regulating anxiety and depressive behaviours, and changes in their levels have been linked to depression. Studies have shown that glutamate transmission inhibitors can have antidepressant effects, suggesting that targeting the glutamate system may be a promising approach for treating depression. By modulating glutamate levels in the brain, it may be possible to improve mood and alleviate depressive symptoms **[15-20]**.

Bio-factors that have been implicated in depression include genetics, stress, and environmental factors **[21]**. Genetics may play a role in depression, as certain genetic variations have been associated with an increased risk of developing the disorder. Stressful life events, such as trauma or chronic stress, can also contribute to the development of depression. Additionally, environmental factors such as social support, diet, and exercise can impact an individual's risk for developing depression **[22]**.

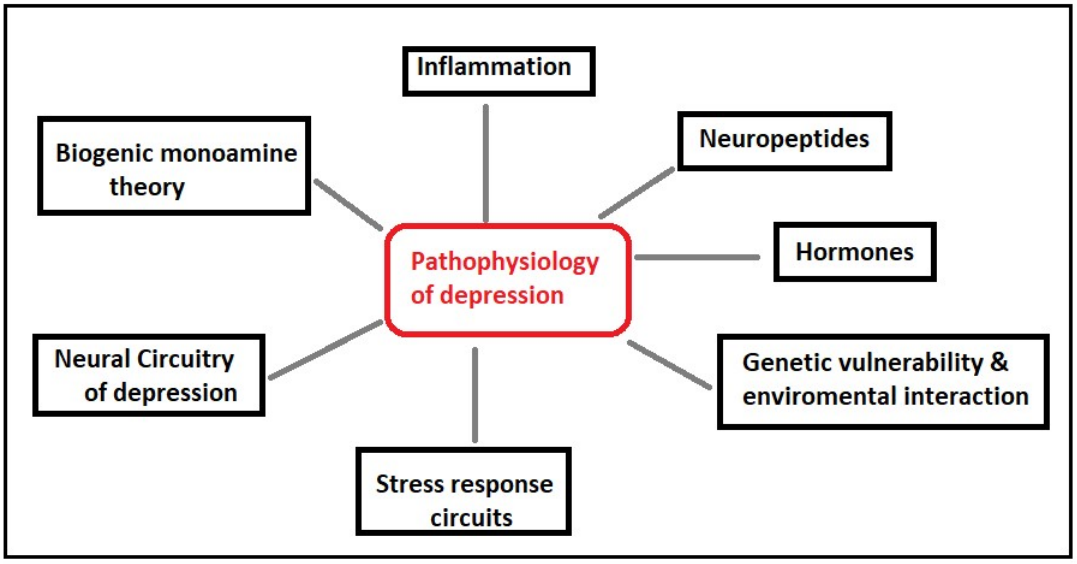

Figure 1: Factors involved in depression

Pharmacotherapy and its mechanism of action of antidepressant drugs:

The discovery of MOA inhibitors and tricyclic antidepressants in the 1950s and 1960s was a significant step in treating depression. Later, drugs such as SSRIs and SNRIs were introduced, which improved therapeutic success and had fewer side effects. However, the rate of recovery and risk of disease recurrence remain high, so more effective and fewer toxic agents are needed **[16]**. Antidepressants have been shown to inhibit the expression of inflammatory cytokines, as well as increase brain-derived neurotrophic factor (BDNF) levels, which improves symptoms of depression. The monoamine hypothesis of depression suggests that depression is caused by a lack of monoamines such as noradrenaline, 5-HT, and dopamine at receptor sites. Conventional antidepressants work by increasing the concentration of these monoamines in the synaptic cleft through various mechanisms, including blocking pre-synaptic monoamine transporters, inhibiting MOA, and binding to pre- or postsynaptic receptors. However, synthetic drugs have side effects such as anxiety, digestive and sexual problems. Medicinal plants are a promising source for developing new antidepressants due to their rich bioactive molecules **[23]**.

Medicinal plants as anti- depressants

Glycyrrhiza uralensis: The study aimed to investigate the impact of liquiritin, a flavones compound found in Glycyrrhiza uralensis, on rats with depression induced by chronic variable stress. The study also aimed to examine the potential link between the antidepressant effects of liquiritin and its antioxidative activity. To assess this link, the study measured the activity of erythrocyte superoxide dismutase (SOD) and the level of plasma malondialdehyde (MDA) in the experimental animals. Previous research has suggested that flavonoids from natural plants have the ability to produce antidepressant-like effects in animal models **[24]**.

***Siphocampylus verticillatus*:** The study investigated the antidepressant effects of the hydroalcoholic extract from the aerial parts of *Siphocampylus verticillatus*, a medicinal plant from Brazil, in mice models of depression and its impact on the uptake of serotonin, noradrenaline, and dopamine in synaptosomes. The results showed a significant reduction in immobility times in both the forced swimming test and tail suspension test with doses ranging from 100-1000 mg/kg when administered intraperitoneally, without affecting ambulation in an open-field test. The extract was found to interact with adrenergic,

dopaminergic, glutamatergic, and serotonergic systems **[25]**.

***Schinus molle L.*:** According to this study, the hexanic extract from the leaves of *Schinus molle L.* (a plant in the Anacardiaceae family) has been investigated for its potential antidepressant-like effects in mice using the tail suspension test (TST). The TST is a commonly used preclinical model to predict antidepressant activity in rodents. The results of the study suggest that the hexanic extract from *S. molle* has some pharmacological effects that are similar to established antidepressants. However, it is important to note that this study was conducted at a preclinical level, and further research is needed to determine the efficacy and safety of S. molle extract as a treatment for depression in humans. It should also be noted that the use of herbal remedies for treating depression should always be discussed with a healthcare professional, as some herbal remedies can interact with prescription medications and may not be safe for everyone **[26]**.

***Piper laetispicum*:** This study investigated the effects of laetispicine, an amide alkaloid found in the stems of Piper laetispicum (a plant in the Piperaceae family), on depression and pain in mice. The study used various tests, including forced swimming, open field, acetic acid writhing, and formalin tests, to assess the effects of laetispicine. The results of the study showed that laetispicine had dose-dependent effects in reducing the number of writhing in mice and attenuating the licking and spitting time of the injected paw in the first phase of formalin test. The antinociceptive effect of laetispicine was not affected by pre-treatment with naloxone (a drug that blocks the effects of opioids). Based on these findings, the researchers concluded that laetispicine had significant antidepressant and antinociceptive properties. These results suggest that laetispicine may be a potentially useful drug for treating depression and pain. However, it is important to note that further research is needed to determine the efficacy and safety of laetispicine in humans **[27]**.

***Emblica officinalis*:** Depression is a psychiatric disorder that affects a significant portion of the population, and predicting which treatment will be effective for an individual patient can be difficult. In traditional systems of medicine, many plants and formulations have been used to treat depression for thousands of years. The aim of this study was to evaluate the potential antidepressant effects of essential oil (EO) using the forced swim test (FST) and tail suspension test (TST) in both acute and chronic administrations. The results showed that the antidepressant activity of EO was comparable to that of the standard drug imipramine in these tests. These findings suggest that EO may have potential as an adjuvant treatment for depression. It is

important to note that further research is needed to confirm the efficacy and safety of EO in treating depression in humans. However, the results of this study provide preliminary evidence for the potential use of EO as a natural and alternative therapy for depression **[28]**.

***Clitoria ternatea*:** The purpose of this investigation was to study the effects of the ethanolic extract of *Clitoria ternatea* on the central nervous system (CNS). The study aimed to determine the extract's impact on cognitive behaviour, anxiety, depression, stress, and convulsions induced by pentylenetetrazole (PTZ) and maximum electroshock (MES). The results of the investigation showed that CT extract had a range of beneficial effects on the CNS, including nootropic, anxiolytic, antidepressant, anticonvulsant, and anti-stress activity. However, further studies are necessary to isolate the active principle responsible for these effects and to understand its mode of action. In summary, this study provides promising evidence for the potential therapeutic use of CT extract in the treatment of various CNS disorders. However, more research is needed to confirm these findings and to determine the safety and efficacy of CT extract in humans **[29, 30]**.

***Ginkgo biloba*:** This study aimed to investigate the potential role of lipophilic extracts of Ginkgo biloba L. leaves in treating depression and stress in rodent models. The study found that lipophilic extracts of Ginkgo leaves (LEG) at doses of 50 and 100 mg/kg, given orally, demonstrated dose-dependent and significant antidepressant activity in behavioural despair tests and learned helplessness rodent models of depression. The results of the study suggest that the bioactive components of the lipophilic extract of Ginkgo leaves with antidepressant and anti-stress activities are intact carboxylic acid groups containing 6-AS. These findings provide valuable insights into the potential therapeutic use of Ginkgo biloba L. leaves in treating depression and stress **[31]**.

***Mimosa pudica*:** Based on the information provided, it appears that a study was conducted to investigate the potential antidepressant effects of aqueous extracts from dried leaves of *Mimosa pudica* in Mexico. The study involved testing the behavioural actions of the extracts at various concentrations and comparing their effects to those of two tricyclic antidepressants. The results of the study apparently showed that *M. pudica* produced an antidepressant-like profile that was similar to the effects of the two tricyclic antidepressants. This suggests that the aqueous extracts from *M. pudica* may have potential as a natural treatment for depression. However, it is important to note that further research is needed to confirm

these findings and to determine the safety and efficacy of using *M. pudica* extracts for the treatment of depression. It is also important to follow appropriate dosages and to seek medical advice before using any natural remedies to treat depression **[32]**.

***Glycyrrhiza glabra L.*:** According to the information provided, a study was conducted to investigate the potential antidepressant effects of an aqueous extract of *Glycyrrhiza glabra L.* (commonly known as liquorice) on depression in mice. The study used two commonly employed tests to assess antidepressant activity, namely the forced swim test (FST) and the tail suspension test (TST). The results of the study apparently showed that the liquorice extract had an antidepressant-like effect, which was mediated by an increase in brain norepinephrine and dopamine, but not by an increase in serotonin. The study suggests that the monoamine oxidase inhibiting effect of liquorice may be contributing favourably to its antidepressant-like activity. Therefore, it can be concluded that liquorice extract may possess an antidepressant-like effect, although further research is needed to confirm these findings and to determine the safety and efficacy of using liquorice extract for the treatment of depression in humans. It is also important to seek medical advice before using any natural remedies to treat depression **[33]**.

***Crocus sativus L.*:** Saffron is the most expensive spice in the world, and recent studies have shown its potential as an anti-cancer agent and memory enhancer **[35-37]**. The value of saffron is due to three main secondary metabolites that are responsible for colour, taste, and odour. Saffron has traditionally been used as a therapeutic plant, aiding in stomach ailments and digestion, and increasing appetite. It is also used to relieve renal colic, reduce stomach ache, and relieve tension. In Persian traditional medicine, saffron is used for depression. Iran, the world's largest producer of saffron, has invested in research into its potential medicinal uses. Clinical findings suggest that saffron is a safe and effective antidepressant **[38]**. In a randomized, double-blind study, 30 mg of saffron extract given for 6 weeks resulted in significant alleviation of depression compared to placebo, and without evident side effects **[39]**. This study followed a preliminary trial in which the same saffron preparation performed as well as imipramine in treating depression in a double-blind trial. In further preliminary work, saffron was compared to the drug fluoxetine and found to perform as well as the drug in the treatment of depression **[40-41]**.

***Apocynum venetum*:** This passage describes the results of an experiment conducted on male rats using an extract of

Apocynum venetum L., a plant belonging to the Apocynaceae family. The experiment found that the extract significantly reduced the immobility time of the rats in a forced swimming test, suggesting that the extract may have an antidepressant effect. The effect was observed at doses ranging from 30 to 125 mg/kg. The passage concludes by stating that the results confirm the assumption that the antidepressant effect of the Apocynum extract in the forced swimming test is specific. This means that the observed effect is not due to a non-specific, general stimulation of the rats, but rather is directly related to the extract's potential antidepressant properties **[42]**.

***Hypericum perforatum L.*:** St. John's wort (SJW) is a well-studied botanical known for its ability to treat mild-to-moderate depression. It is considered safe and effective for children and is available over the counter in the U.S. In Germany, physicians prescribe SJW to patients with similar types of depression **[43-47]**. The active ingredients in SJW, including hypericin and hypericin-like compounds, are thought to reduce the degradation rate of acetylcholine, a neurotransmitter in the brain **[48]**. This can result in sedative effects. Additionally, SJW has been shown to have weak serotonin-reuptake inhibitor (SSRI) activity, which can reduce the side effects of other antidepressant medications. Studies also suggest that SJW affects sigma 1 receptors, which are involved in the mechanism of action of some antidepressants **[49]**. The effectiveness of SJW in treating depression is likely due to the synergistic effects of multiple components within the plant, which act both within and outside of the central nervous system. Overall, SJW is considered a safe and effective alternative to traditional antidepressant medications for people with mild-to-moderate depression **[50]**.

Herbal Plant Name	Common Name	Parts Use	Uses
Glycyrrhiza uralensis	Mulethi	Root	Anti-Inflammatory, Antithrombotic, Antiviral and Antiulcer
Siphocampylus verticillatus	Siphocampylus	Aerial Parts	Arthritis
Schinus molle L	Peruvian Pepper Tree	Leaves	Antioxidant, Anticancer Activity
Piper laetispicum	Piper	Root and Stem	Anti-Inflammatory, Immunomodulatory, Antitumor
Emblica Officinalis	Amla	Fruit	Antimicrobial
Clitoria ternatea	Butterfly Pea	Root and Bark	Anxiolytic, Anticonvulsant Nootropic
Ginkgo biloba	Ginkgo, Maidenhair Tree	Leaves	Memory Enhancer, Dementia
Mimosa pudica	Sensitive plant	Leaves	Leucoderma, Ulcers, Dysentery, Inflammations, Jaundice, Asthma
Glycyrrhiza glabra L	Mulethi	Root	Antimicrobial
Crocus sativus L.:	Saffron	Stigma	Antitussive, Antispasmodic, Carminative, Stomachic
Apocynum venetum	Dogbane	Aerial part	Cardiotonic, diuretic
Hypericum perforatum L	St. John's wort	Flowers and Leaves	Depression, Anxiety

CONCLUSION

The above-mentioned collection of herbal plants exhibiting antidepressant activity was compiled from various journals. This compilation demonstrates that herbal plants are a valuable source of compounds that can enhance antidepressant activity. Overall, the tabulated findings suggest that herbal plants are a rich source of natural substances with potential therapeutic benefits for those with depression.

ACKNOWLEDGEMENT

None

Conflict of Interest

There is no conflict of interest

Financial Support

Nil

REFERENCES

[1] Rahmati B, Kiasalari Z, Roghani M, Khalili M, Ansari F. Antidepressant and anxiolytic activity of Lavandula officinalis aerial parts hydroalcoholic extract in scopolamine-treated rats. Pharm Biol 2017; 55(1): 958-65.

[2] Maria de Souza JM, Lira Ferrari GS, Bucalen Ferrari CK. Correlates of geriatric depression scale with perceived quality of life in an elderly population. Geriatr Persia 2018; 2: e01.

[3] Rajput MS, Sinha S, Mathur V, Agrawal P. Herbal antidepressants. IJPFR 2011; 1(1): 159-69.

[4] Noorbala AA, Akhondzadeh S, Tahmacebi-pour N, et al. Hydroalcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression: A double-blind, randomized pilot trial. J Ethnopharmacol 2005; 28;97(2): 281-4.

[5] Dwyer AV, Whitten DL, Hawrelak JA. Herbal medicines, other than St. John's Wort, in the treatment of depression. Sci Rev Altern Med 2011; 1;16(1): 281-4.

[6] Tegegne MT, Mossie TB, Awoke AA, Assaye AM, Gebrie BT, Eshetu DA. Depression and anxiety disorder among epileptic people at Amanuel Specialized Mental Hospital, Addis Ababa, Ethiopia. BMC Psychiatry 2015; 15(1): 210.

[7] Rang HP, Dale MM, Ritter JM; Pharmacology, 5th edition, Churchill Livingstone, Edinburgh, 2006: 535.

[8] Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ III. Psychotropic drug use and the risk of hip fracture. N Engl J Med 1987; 316(7): 363-9.

[9] Roose SP, Glassman AH, Attia E, Woodring S. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the

treatment of melancholia. Am J Psychiatry 1994; 151(12): 1735-9.

[10] Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron 2002; 34(1): 13-25.

[11] Hindmarch I. Expanding the horizons of depression: beyond the monoamine hypothesis. Hum Psychopharmacol 2001; 16(3): 203-18.

[12] Lee G, Bae H. Therapeutic effects of phytochemicals and medicinal herbs on depression. Bio Med Res Int 2017; 2017(6596241): 1- 11

[13] Barden N, Reul JM, Holsboer F. Do antidepressants stabilize mood through actions on the hypothalamic-pituitary-adrenocortical system? Trends Neurosci 1995; 18(1): 6-11.

[14] Pan Y, Kong LD, Li YC, Xia X, Kung HF, Jiang FX. Icariin from Epimedium brevicornum attenuates chronic mild stress-induced behavioral and neuroendocrinological alterations in male Wistar rats. Pharmacol Biochem Behav 2007; 87(1): 130-40.

[15] Plotsky PM, Owens MJ, Nemeroff CB. Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. Psychiatr Clin North Am 1998; 21(2): 293-307.

[16] Menninger JA, Tabakoff B. Forskolin-stimulated platelet adenylyl cyclase activity is lower in persons with major depression. Biol Psychiatry 1997; 42(1): 30-8.

[17] Pandya CD, Howell KR, Pillai A. Antioxidants as potential therapeutics for neuropsychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 2013; 46: 214-23.

[18] 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 2011; 35(3): 676-92.

[19] Liu B, Xu C, Wu X, et al. Icariin exerts an antidepressant effect in an unpredictable chronic mild stress model of depression in rats and is associated with the regulation of hippocampal neuroinflammation. Neuroscience 2015; 294: 193-205.

[20] Xing H, Zhang K, Zhang R, et al. Determination of depression biomarkers in rat plasma by liquid chromatography-mass spectrometry for the study of the

antidepressant effect of Zhi-Zi-HouPo decoction on rat model of chronic unpredictable mild stress. J Chromatogr B Analyt Technol Biomed Life Sci 2015; 988: 135-42.

[21] Ladep NG, Obindo TJ, Audu MD, Okeke EN, Malu AO. Depression in patients with irritable bowel syndrome in Jos, Nigeria. World J Gastroenterol 2006; 12(48): 7844-7.

[22] Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence. Eur Neuropsychopharmacol 2011; 21(12): 841-60.

[23] Novío S, Núñez MJ, Amigo G, Freire-Garabal M. Effects of fluoxetine on the oxidative status of peripheral blood leucocytes of restraint-stressed mice. Basic Clin Pharmacol Toxicol 2011; 109(5): 365-71.

[24] Zhao Z, Wang W, Guo H, Zhou D (2008). Antidepressant-like effect of liquiritin from Glycyrrhiza uralensis in chronic variable stress induced depression model rats. Behavioural Brain Research 194(1):108-113.

[25] Rodrigues AL, da Silva GL, Mateussi AS, Fernandes ES, Miguel OG, Yunes RA, Calixto JB, Santos AR (2002). Involvement of monoaminergic system in the antidepressant-like effect of the hydroalcoholic extracts of Siphocampylus verticillatus. Life Sciences 70(12):1347-1358.

[26] Machado DG, Bettio LEB, Cunha MP, Santos ARS, Pizzolatti MG, Brighente IMC, Rodrigues ALS (2008). Antidepressant-like effect of rutin isolated from the ethanolic extract from Schinus molle L. in mice: Evidence for the involvement of the serotonergic and noradrenergic system European Journal of Pharmacology 587(1-3):163-168.

[27] Cícero Bezerra Felipe F, Trajano Sousa Filho J, de Oliveira Souza LE, Alexandre Silveira J, Esdras de Andrade Uchoa D, Rocha Silveira E, Deusdênia Loiola Pessoa O, de Barros Viana GS(2007) Piplartine, an amide alkaloid from Piper tuberculatum, presents anxiolytic and antidepressant effects in mice. Phytomedicine 14(9):605-612.

[28] Pemminati Sudhakar, N.H Gopalakrishna, Shenoy K Ashok ,S .S Sudhanshu, Mishra Shishir, Meti Vinayak, Vinod Nair(2010).

Antidepressant activity of aqueous extract of fruits of Emblica officinalis in mice. 2(1), 449-45.

[29] Jain NN, Ohal CC, Shroff SK, Bhutada RH, Somani RS, Kasture VS, Kasture SB (2003). Clitoria ternatea and the CNS. Pharmacology Biochemistry and Behavior 75(3):529-536

[30] Wang Y, Han T, Zhu Y, Zheng CJ, Ming QL, Rahman K, Qin LP (2010). Antidepressant properties of bioactive fractions from the extract of Crocus sativus L. J Nat Med 64(1):24-30.

[31] Sakakibara H, Ishida K, Grundmann O, Nakajima J, Seo S, Butterweck V, Minami Y, Saito S, Kawai Y, Nakaya Y, Terao J(2006). Antidepressant effect of extracts from Ginkgo biloba leaves in behavioral models. Biol Pharm Bull 29(8):1767-1770.

[32] Molina M, Contreras C M, Tellez-Alcantara P (1999). Mimosa pudica may possess antidepressant actions in the rat. Phytomedicine 6(5):319-23.

[33] Dhingra D, Sharma A (2006). Antidepressant-like activity of *Glycyrrhiza glabra* L. in mouse models of immobility tests. Progress in Neuro-Psychopharmacology and Biological Psychiatry 30(3):449-454.

[34] Yao CY, Wang J, Dong D, Qian FG, Xie J, Pan SL (2009). Laetispicine, an amide alkaloid from Piper laetispicum, presents antidepressant and antinociceptive effects in mice. Phytomedicine 16(9):823-829.

[35] Rios JL, Recio MC, Giner RM, Manez S. An update review of saffron and its active constituents. Phytother. Res. 1996; 10, 189- 193.

[36] Abe K and Saito H. Effects of saffron and its constituent crocin on learning behavior and long-term potentiation. Phytother Res. 2000; 14: 149 - 52

[37] Abdullaev FI. Cancer chemopreventive and tumoricidal properties of saffron (*Crocus sativus* L.). Exp. Biol. Med. 2002; 227: 20 - 5.

[38] Hosseinzadeh H, Younesi H. Petal and stigma extracts of Crocus sativus L. have antinociceptive and anti-inflammatory effects in mice. BMC Pharmacol . 2002; 2: 7.

[39] Akhondzadeh S, Fallah Pour H, Afkham K, Jamshidi AH, Khalighi-Cigarodi F. 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

[40] Akhondzadeh S, Tamacebi-pour N, Noorbala AA, Amini H, Fallah Pour H, Jamshidi AH, Khani M. Crocus sativus L . in the treatment of mild to moderate depression: A double-blind, randomized and placebo-controlled trial. Phytotherapy Res. 2005a; 19, 25 - 9.

[41] Noorbala AA, Akhondzadeh S, Tamacebipour 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. Ethnopharmacol. 2005; 97: 281 - 4.

[42] Butterweck V, Nishibe S, Sasaki T, Uchida M (2001). Antidepressant effects of Apocynum venetum leaves in a forced swimming test. Biol Pharm Bull 24(7):848-851.

[43] Kim HL, Streltzer J, Goebert D. St. John's wort for depression: A meta-analysis of well-defined clinical trials. J. Nerv. Ment. Dis. 1999; 187: 532 – 9.

[44] Gaster B and Holroyd J. St. John's wort for depression: A systematic review. Arch Intern Med. 2000; 160: 152 – 6

[45] Hansgen KD, Vesper J, Ploch M. Multicenter double-blind study examining the antidepressant effectiveness of the hypericum extract L160. J. Geriatr Psychiatry Neurol. 1994; 7, S15 – 8

[46] Lieberman S. Nutriceutical review of St. John's wort (hypericum perforatum) for the treatment of depression. J Women's Health 1998; 7: 177 – 82.

[47] Wheatley D. Hypericum in seasonal affective disorder (SAD). Curr. Med. Res. Opin. 1999; 15: 33 – 7.

[48] Gelenberg AJ. St. John's Wort update. Biological Therapies in Psychiatry 2000; 23: 22 – 4.

[49] Rios JL, Recio MC, Giner RM, Manez S. An update review of saffron and its active constituents. Phytother. Res. 1996; 10, 189- 193.

[50] Abe K and Saito H. Effects of saffron and its constituent crocin on learning behavior and long-term potentiation. Phytother Res. 2000; 14: 149 - 52.