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A REVIEW ON FLAVONOIDS AS POTENTIAL ANTIDEPRESSANT DRUGS

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Abstract:

Depression being a state of sadness characterized by mental and functional activity, sadness, reduction in activity, difficulty in thinking, loss of concentration, perturbations in appetite, hopelessness and generation of suicidal tendencies. Flavonoids are phenolic compounds which found commonly in plants that protect them against the negative effects of environmental insults. Flavonoids are secondary metabolites that explore their potential therapeutic effects in the treatment of disorders of the central nervous system, including anxiety and depression. The present review discusses about some flavonoids as potential antidepressant agents. We describe their behavioural, physiological, and neurochemical effects and mechanism of action of their preclinical antidepressant-like effects. Natural flavonoids produce antidepressant-like effects in validated behavioural models of depression. The mechanism of action of these effects includes the activation of serotonergic, dopaminergic, noradrenergic neurotransmitter systems and an increase in the production of neural factors, including brain- derived neurotrophic factor (BDNF) and nerve growth factor. In conclusion, preclinical research that supports the potential antidepressant effects of some natural flavonoids, which gives new possibilities of evaluating these substances to develop complementary therapeutic alternatives that could ameliorate symptoms of depressive disorders in humans.

Keywords: *Antidepressants, Depression, Flavonoids, Norepinephrine, Serotonin.*

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INTRODUCTION:

Depression is the most common psychotic disorder (mood disorder) [1]. Depressive disorder is characterized by sadness, loss of interest or pleasure, feelings of guilt, low self- worth, disturbed sleep, appetite, feelings of tiredness and poor concentration. The global and regional estimates of prevalence – depression. The proportion of the global population with depression in the year 2015 has been estimated as 4.4%. Depression was more common among females (5.1%) than males (3.6%). Prevalence varies by WHO region from a low of 2.6% among males in the Western Pacific region to 5.9% among females in the African region. Prevalence rates vary by age, peaking in older adulthood above 7.5% among females aged 55.74 years and above 5.5% among males. The total number of people living with depression in the world is over 322 million. In this it shows that total estimated number of people living with depression increased by 18.4% [2]. Prevalence of depression among college students shows that depression status increased since the pandemic caused the closure of campuses this spring compared to fall 2019, while prevalence of substance abuse decreased. A higher proportion of among students is 30.5 percent compared to 21.9 percent the prior fall reported that their mental health negatively affected their academic performance on at least six days during the prior four weeks [3].

Many antidepressant drugs are available to treat the symptoms of depression. Such antidepressants produce their therapeutic effects through actions on diverse neurotransmitter systems, including the serotonergic, noradrenergic, and dopaminergic systems. The principal antidepressant drugs are tricyclic antidepressants (e.g., clomipramine and imipramine), monoamine oxidase inhibitors (e.g., phenelzine and selegiline), selective serotonin reuptake inhibitors (e.g., fluoxetine and fuvoxamine), selective dopamine reuptake inhibitors (e.g., amineptine and methylphenidate), selective norepinephrine reuptake inhibitors (e.g., reboxetine and viloxazine), and antidepressant drugs (e.g., venlafaxine and duloxetine) [4]

Flavonoids are the natural substances with variable phenolic structures are mostly found in fruits, vegetables, grains, barks, roots, stem, flowers, tea and wine [5]. Flavonoids were extracted from many natural plant sources that has been reported to possess antidepressant-like effect in many cell and animal studies. The effects on the CNS by flavonoids is one of their characteristics, but also possess a range of other biological activities [6].

Flavonoids:

Flavonoids are phytonutrients, which act as a part of polyphenols. Flavonoids act as aglycones, glycosides and methylated derivatives. Structure of flavonoids contains 15 carbon atom in their primary nucleus with the skeleton of diphenyl propane [7]. Flavonoids are not synthesized by humans and animals, they are found in human diets [8].

Some natural sources containing different classes of flavonoids [9].

Sl. NO	Subclass of flavonoids	Examples
1.	Flavonol	Kaempferol, Quercetin, Myricetin, Tamarixetin
2.	Flavones	Rutin, Luteolin, Chyrin
3.	Flavonones	Naringenin, Naringin, Herperidin
4.	Flavanol	Epicatechin, Catechin
5.	Anthocyanidins	Malvidin, Apigenidin, Cyaniding
6.	Isoflavones	Genistein, Daidzein

Flavonoids with antidepressant effects:

Flavonoids is most widely used active metabolites. The antidepressant effect on the serotonergic system and MAO-A activity was found with quercetin 4'-O-glucoside or quercetin administered at doses of 10 and 20 mg/kg, p.o., for 7 days in Swiss albino mice of both sexes. These flavonoids produced antidepressant-like effects in mice on FST as well as those subjected to unpredictable, chronic mild stress and evaluated on FST. In this study, a 20-mg/kg dose of quercetin 4'-O-glucoside showed a similar effect as that of fluoxetine at 20 mg/kg, p.o., on FST, with or without prior exposure to CUMS. In these quercetin 4'-O-glucoside reverted this effect, and interpreted as antidepressant. Endogenous anti-oxidants, like reduced glutathione (GSH), enhances MAO-A activity in the brain and consequently, depletes monoamine levels there, especially serotonin 5-HT. The effects observed in that study were blocked by 21 days of treatment with 10 and 20 mg/kg of quercetin 4'-O-glucoside, suggesting a possible mechanism of action with an antioxidant effect that impedes ROS production. Another study found that 10 mg/kg of quercetin administered for 14 days reduced immobility time on TST, but not FST, while doses of 25 and 50 mg/kg produced this effect in female mice on both tests. The mechanisms of action of each drugs were explored on TST, where i.c.v. administration of N-methyl D-aspartate at 0.1 pmol/site and L-arginine at 750 mg/kg, i.p., a nitric oxide inhibitor blocked the antidepressant effect of quercetin. Hence, the antidepressant- like effect of quercetin may involve inhibiting NMDA receptors to decrease intracellular calcium that, in turn, inhibits the protein calmodulin, which then inhibits neuronal nitric oxide synthase to decrease nitric oxide levels (NO). This hypothesis is supported by the finding that administering methylene blue, NO synthase inhibitor at 20 mg/kg, i.p., and soluble guanylate cyclase or 7-nitroindazole at 50 mg/kg, i.p., improved quercetin's antidepressant-like effect on TST. This indicates that the antidepressant effect may be dependent on limiting NO synthesis, either by inhibiting the enzyme or by reducing NO production, perhaps via decreased cyclic guanosine monophosphate (cGMP)[10].

Several types of flavonoids such as quercetin, quercetrin, kaempferol and kaempferol- 3-orhamnopyranoside were isolated from an ethyl acetate extract of *Albizia julibrissin* which could be produce an antidepressant-like effect in a despair mouse model of depression by remarkably reducing the immobility time (FST) extracted icariin, liquiritin and isoliquiritin from *Epimedium brevicornum* which reduced the Forced swim test (FST) and Tail suspension test (TST) immobility time that shows a significant pharmacological treatment for the chronic mild stress-induced behavioural and neuroendocrinological alteration in rats[6].

Flavonoid mechanisms:

Almost every group of flavonoids has a capacity to act as antioxidants. It has been reported that the flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species. Body cells and tissues are continuously threatened by the damage caused by free radicals and reactive oxygen species, which are produced during normal oxygen metabolism or are induced by exogenous damage. The mechanisms and the sequence of events by which free radicals interfere with cellular functions are not fully understood, but one of the most important events seems to be lipid peroxidation, which results in cellular membrane damage. This cellular damage causes a shift in the net charge of the cell, changing the osmotic pressure, leading to swelling and eventually cell death. Free radicals can attract various inflammatory mediators, contributing to a general inflammatory response and tissue damage. To protect themselves from reactive oxygen species, living organisms have developed several effective mechanisms. The antioxidant defence mechanisms of the body include not only the enzymes such as superoxide dismutase, catalase and glutathione peroxidase, but also non-enzymic counterparts such as glutathione, ascorbic acid and α- tocopherol. The increased production of reactive oxygen species during injury results in consumption and depletion of the endogenous scavenging compounds. Flavonoids may have an additive effect to the endogenous scavenging compounds. The theoretical affinity order among flavonoids and amino acid residues seems to have great applications in the theoretical predictions of flavonoid–protein interactions as a high-quality approach to understand the biological activity of flavonoids [11].

Anti-depressant's mechanism of flavonoids: [12,13,14]

1. Kaempferol, Quercetin, Apigenin, Chrysin – Inhibitors of MAO-A and MAO-B.
2. Rutin, Quercetin – 3-O- miquelianin, Isoquercitrin – Increase synthesis of serotonin or noradrenaline.
3. Naringenin – Increased hippocampal serotonin, noradrenaline and GR levels and reduced serum corticosterone level in mice.
4. Nobiletin – Mediated by an interaction with the serotonergic, noradrenergic and dopaminergic systems.
5. Herperidin – Dependent on an interaction with the serotonergic receptors.

6. Orientin - Increase in BDNF, serotonin, and norepinephrine concentrations in the hippocampus and prefrontal cortex in male mice.
7. 7,8-Dihydroxyfavone – Increase in BDNF concentrations in the hippocampus and prefront cortex in male mice.
8. Silymarin - Increase in 5-HT, DA, NE, and BDNF concentration in the hippocampus and cerebral cortex, similar to fluoxetine.
9. Icarin - Increases in BDNF concentrations in the hippocampus.
10. Astilbin - Increase in BDNF concentrations in the cerebral cortex in male mice, similar to imipramine.
11. Baicalein - Restoring of the reduction of extracellular signal-regulated kinase phosphorylation and BDNF expression in the hippocampus.
12. Fisetin - Increases in phosphorylated TrkB (pTrkB) in the hippocampus.

Preclinical studies:

a. Forced swim test

Forced swim test was proposed by Porsolt *et.al.*, 1978. Mice or Rat are individually forced to swim in an open cylindrical container (diameter 15 cm, height 20 cm), filled with water (25±1ºC) to the depth of 15 cm. Each animal will be subjected to a pre-test session (15 minutes) in the vessel 24 hours before the swimming test which last about 6 minutes. The immobility time were observed for each animal individually. Animal were considered as immobile if they made no further attempt to escape, except the movement necessary to keep their head above water. [15]

b. Tail suspension test

Tail suspension method was proposed by Steru et al., 1985. Mice or Rats are used. Each animal was individually suspended on the edge of the table, 35cm above the floor, with the help of adhesive tape place approximately 2cm from the tip of the tail. The total duration of immobility induce by tail suspension were recorded for 6 minutes. Animal were considered as immobile when they do not show any body movement and remain completely motionless. [16]

c. Open-Field Test (OFT)

Open field test (OFT) was proposed by Dews, 1952. Animals were placed individually in open field apparatus after dosing. The open–field apparatus consists of a wooden arena (64cm x 64cm and 40cm high). The floor of the wooden arena is divide into 16 equal squares and mark by black lines. The mice were placed individually in the centre of the arena and allow to explore freely. The number of squares cross by the animal and the number of rearings behavior were recorded during a test period of 5min. The test will be carried out at room temperature of 27 ± 2°C in a noise and light controlled room. [17]

Plants with antidepressant like effects associated with their total flavonoids content:

Sl.no	Author	Doses (Animal)	Plants	Behavioral test	Effect
1.	Kameshwaran *et al* [18]	30 & 100mg/kg	*Tecoma stans* Flower	Tail suspension test Despair swim test	Decrease immobility duration
2.	Purna chander *et al*[19]	100 & 200mg/kg	*Barleria buxifolia*	Forced swimming test	Decrease immobility duration
3.	Tiwari Prashant *et al*[20]	150 & 300mg/kg	*Zingiber officinale*	Forced swim test Tail suspension test	Decrease immobility duration
4.	Rahman *et al*[21]	100 & 200mg/kg	*Sesamum indicum*	Tail suspension test Forced swimming test Open field test	Decrease immobility duration
5.	Aslam Pathan *et al*[22]	100 & 200mg/kg	*Coriandrum sativum*	Forced Swim test Locomotor activity	Decrease immobility duration
6.	Bikomo *et al*[23]	50, 150 & 300mg/kg	*Annona muricata*	Forced Swim test Open field Test	Decrease immobility duration

7.	C. Lalremruati *et al*[24]	200 & 400mg/kg	*Colocasia affinis*	Forced swim test Tail suspension test	Decrease immobility duration
8.	Chaitra SR *et al*[25]	100 & 200mg/kg	*Psidium guajava*	Forced swim test Tail suspension test	Decrease immobility duration
9.	Fekadu *et al*[26]	100, 200 & 400mg/kg	*Rosa abyssinica*	Tail suspension test Forced swim test Open field test	Decrease immobility duration
10.	Mythili *et al*[27]	250 & 500mg/kg	*Justicia gendarussa*	Forced swim test	Decrease immobility Duration
11.	Jamwal Neetu Singh *et al*[28]	250 & 500mg/kg	*Foeniculum vulgare*	Forced swim test	Decrease immobility duration
12.	Parle Milind *et al*[29]	4, 8 & 16% w/v	*Carica papaya*	Tail suspension test Forced swim test	Decrease immobility duration
13.	Kumar Yadav *et al*[30]	100 & 200mg/kg	*Zanthoxylum armatum*	Forced swim test Tail suspension test	Decrease immobility duration
14.	Prathvi Shetty *et al*[31]	100, 250 & 500mg/kg	*Bauhinia purpurea*	Forced swim test Tail suspension test	Decrease immobility duration
15.	Prabhakar Adake *et al*[32]	50, 100 & 200mg/kg	*Boswellia serrate*	Forced swim test	Decrease immobility duration
16.	Kudagi *et al*[33]	100 & 200mg/kg	*Prosopis cineraria*	Tail suspension test	Decrease immobility duration

Antidepressant like effects of Flavonoids in Plant extract.

Flavonoids produce pharmacological actions on the central nervous system which regulate emotional and mood states associated with plastic and neurochemical changes. Preclinical studies have also reported the potential antidepressant-like effects of specific flavonoids.

Hesperidin is a flavonoid that has different pharmacological actions such as antioxidant, antineoplastic, and neuroprotective effects in vitro and in vivo. Hesperidin has been studied as a potential antidepressant agent due to its actions on the serotonergic, dopaminergic, and noradrenergic systems. Administration of 0.1, 0.3, and 1 mg/kg hesperidin (i.p.) for 21 days in Swiss mice shows significantly reduced total immobility time in the tail suspension test. This antidepressant-like effect was associated with a significant increase in BDNF concentrations in the hippocampus and actions at the 5-HT1A receptors [34]. These effects were similar to those produced by 10 mg/kg of the tricyclic antidepressant imipramine.

Naringenin (10, 20, and 50 mg/kg) is an isoflavone, which is isolated from **citrus peel**. In this it shows reduction in total immobility time in the tail suspension test in male mice, similar to the effects of 20 mg/kg fluoxetine, a clinically effective antidepressant drug. These effects were interpreted as potential antidepressant-like effects. This result suggests that the mechanism of action of naringenin involves the activation of serotonergic and noradrenergic neurotransmitter systems in the brain. [35]. Nargenin is present in plants such as ***Annona muricata, Barleria buxifolia, Psidium guajava***.

Glycyrrhiza uralensis belongs to the family Fabaceae. This plant shows the potential antidepressant-like effects that are associated with its content of at least five flavonoids (i.e., **liquiritin, liquiritigenin, isoliquiritigenin, isoononin, and 7,4 - dihydroxyfavone**). An extract of this plant inhibited the production of tumor necrosis factor- α (TNF-α) in microglial cells in mice. These findings are important because TNF-α were detected in high concentrations in patients with anxiety and depression symptoms. Therefore, a reduction of TNF-α could be beneficial for ameliorating symptoms of anxiety and depression, as is the case

with other antidepressant agents. The flavonoid isoliquiritigenin also inhibits TNF-α and increases the concentration of BDNF in the hippocampus and cerebral cortex. Administration of the flavonoid 5,7-dihydroxyfavone (chrysin) at doses of 1 and 10 mg/kg for 60 days increased BDNF concentrations in the hippocampus and prefrontal cortex [36].

Dried root of ***Scutellaria baicalensis*** belongs to the family Labiatae, produces an antidepressant-like effect. In this plant, **Baicalin** were isolated and evaluated the antidepressant effects. Baicalin of dose 25 and 50mg/kg p.o were administered in mice and evaluated antidepressant effects by using forced swim test and tail suspension tests. This effect was similar to that produced by 20 mg/kg of the antidepressant fluoxetine. Apparently, the baicalin effect was associated with inhibition of monoamine oxidase enzymes types A and B, a mechanism of action involved in the therapeutic effect of some antidepressant drugs [37].

Quercetin were administered to the stress induced experimental animals. 5HT levels were increase in immobilization stress in whole brain and produce antidepressant effects. Immobilization stress principal actions of repeated administration of Quercetin on 5-HT may be presynaptical, which inhibits MAO and increase the availability of 5-HT in the synapse. This may stimulate the regulation of 5-HT release through presynaptic 5-HT auto-receptors in mice hippocampus causing the decreased release of 5-HT. These actions of Quercetin may serve to 5-HT function abnormalities under stress [38]. This flavonoids are present in ***Zingiber officinale, Sesamum indicum, Foeniculum vulgare, Coriandrum sativum***.

Apocynum venetum leaf produce antidepressant activity by isolating four flavonoids such as **Quercetin, Kaempferol, Kaempferol-3-O-βD-glucose, Quercetin-3-O-β-D-glucose**. In this study these flavonoids produce significant antidepressant activity by reducing the immobility time of mice and the inhibitory effects on the immobility time were positively related to their polarity. Fluoxetine was selected as the positive control in this study. The mechanism may be related to the increase of NE, DA and 5HT as well as reduction of 5HT metabolism [39].

CONCLUSION:

The preclinical data on the antidepressant like effects of some flavonoids shows behavioural effects and neurochemical actions in the brain. The mechanism of action is relevant because it has been associated with the actions of clinically effective antidepressant drugs. BDNF modulates neurotransmitters and receptor activity and is involved in the activation of serotonergic, noradrenergic, and dopaminergic pathways and neurogenesis in the hippocampus and cerebral cortex, were implicated in the neurobiology of psychiatric disorders, including depression. Some flavonoids (e.g., 7,8-dihydroxyfavone) also act as TrkB receptor agonists and stimulate neurogenesis in the hippocampus. Such studies may eventually demonstrate that some flavonoids are safe alternatives for the treatment of depressive disorders in clinical practice. preclinical research supports the potential antidepressant effects of some natural flavonoids, which opens new possibilities of evaluating these substances to develop complementary therapeutic alternatives that could ameliorate symptoms of depressive disorders in humans.

REFERENCES:

1. Rang and Dale's. Pharmacology: 8th edition; Page no. 569.
2. Global Burden of Disease study 2015 (http://ghdx.healthdata.org/gbd-results-tool).
3. Survey finds higher prevalence of depression among students and difficulties accessing mental health care during pandemic: 2020.
4. Khushboo, Sharma B. Antidepressants: mechanism of action, toxicity and possible amelioration. Journal of Applied Biotechnology & Bioengineering. 2017;3(5):437–448.
5. Diwan, Chandra, Panche. Journal of nutritional science: 2015, 5; 1-15.
6. Khan, H., Food and Chemical Toxicology (2018), https://doi.org/10.1016/j.fct.2018.04.052
7. Harborne JB: The flavonoids- Advances in Research Since 1980. ed 1. London: Chapman and Hall 1988.
8. Middleton E: The flavonoids. Trends Pharmacol Sci 1984; 5: 335-338
9. Karak P: Biological activities of flavonoids: an overview. Int J Pharm Sci & Res 2019; 10(4): 1567-74.
10. Neuropharmacology of Secondary Metabolites from Plants with Anxiolytic and Antidepressant Properties.
11. A. N. Panche, A. D. Diwan and S. R. Chandra. Flavonoids: An overview. Journal of nutritional science; 2016, 5; 1-15.
12. Vikas Gupta, Parveen Bansal, Pawan Kumar, Richa Shri. Anxiolytic and antidepressant activities of different extracts from *Citrus paradisi* var. Duncan: 2010; 3(2) 97-100.
13. Lucian Hritcu, Radu Ionita, Paula Alexandra Postu, Girish Kumar Gupta, Hasan Turkez, Tamires Cardoso Lima, Caroline Uchôa Souza

Carvalho, and Damião Pergentino de Sousa: Antidepressant Flavonoids and Their Relationship with Oxidative Stress. 2017; https://doi.org/10.1155/2017/5762172.
14. Leon Jesus German-Ponciano, Gilberto Uriel Rosas-Sanchez, Eduardo Rivadeneyra-Dominguez, and Juan Francisco Rodriguez-Landa. Advances in the Preclinical Study of Some Flavonoids as Potential Antidepressant Agents: 2018, Article ID 2963565, https://doi.org/10.1155/2018/2963565.
15. Porsolt, R.D., Bertin, A. & Jalfre, M. 'Behavioural despair' in rats and mice: strain differences and the effects of imipramine. Eur. J. Pharmacol; 1928; 51; p 291–294.
16. Steru L., Chermat R., Thierry B., Simon P. The tail suspension test: a new method for screening antidepressants in mic: Psychopharmacology. 1985; 85(3); p. 367–370.
17. Dews PB (1952) The measurement of the influence of drugs on voluntary activity in mice: Br J Pharmacol; 1952; 8; p. 46–48.
18. S.Kameshwaran, R.Sundaraganapathy, S.Thenmozhi, M.Dhanalakshmi, K.Vasuki, C.Dhanapal. Assessment of antidepressant activity of methanol and aqueous extract of Tecoma stans flowers using tail suspension test and forced swim test. International Journal of Pharmacology Research. 2014; 4(2): 78:82.
19. A.Purna chander, M.Nishitha, B.Shravanthi, Y.Haritha Sri, M.Kishore kumar, MD.Baheerudddin. Anxiolytic and antidepressant activity of Barleria buxifolia Linn. BioMedRx 2013,1(2),122-124.
20. Singh Rudra Pratap, Jain Ritesh, Mishra Rahul, Tiwari Prashant. Antidepressant activity of hydroalcholic extract of Zingiber officinale. International Research Journal of Pharmacy. 2012, 3(2): 149-151.
21. Md Rashidur Rahman, Mostakim Sharif, Mohammad Ali and Sheikh Shahriar Rajib, Evaluation of the antidepressant-like activity of the methanolic extract of the seeds of Sesamum indicum. Clinical Phytoscience (2019) 5:2.
22. Aslam Pathan, Abdulrahman Alshahrani, Feras Al-Marshad. Neurological Assessment of Seeds of Coriandrum sativum by Using Antidepressant and Anxiolytic like Activity on Albino Mice. Inventi Impact: Ethnopharmacology, 2015(3):102-105, 2015.
23. Bikomo E. O, Ebuehi O.A, Magbagbeola O.A. Antidepressant Activity of Ethanol Leaf Extract of Annona muricata L., in Sprague-Dawley Rats. American Journal of Biochemistry 2017, 7(1): 1-5.
24. C. Lalremruati, C. Malsawmtluangi, H. Lalhlenmawia. Phytochemical screening and evaluation of antidepressant activity of methanolic extract of the spadix of Colocasia affinis Schott. Volume 18 (4), 104-110.
25. Chaitra SR, Roopa P Nayak, Uttara Krishna. Evaluation of antidepressant effect of aqueous extract of Psidium guajava leaves on Wistar albino rat. International Journal of Basic Clinical Pharmacology. 2019 Feb;8(2):280-283.
26. Fekadu N, Shibeshi W, Engidawork E (2016) Evaluation of the Antidepressant-like Activity of the Crude Extract and Solvent Fractions of Rosa Abyssinica Lindley (Rosaceae) Using Rodent Models of Depression. Clinical Experimental Pharmacology 6: 207.
27. Mythili A, Jothimanivannan C (2017) Evaluation of Anti-Depressant Activity of Ethanolic Extract of Justicia gendarussa Burm with Wister Rat. Int J Drug Dev & Res 9: 07-08
28. Jamwal Neetu Singh, Kumar Sunil, Rana. A.C. Antidepressant Activity of Methanolic Extract of Foeniculum Vulgare (Fennel) Fruits in Experimental Animal Models. Journal of Applied Pharmaceutical Science 3 (09); 2013: 065-070.
29. Parle Milind and Gurditta. Papita fruit: A Delicious remedy for depression. International Journal of research in Ayurveda and Pharmacy, 2(4) 1358-1364.
30. Chandrajeet Kumar Yadav, Kamal Poudel, Piinki Yadav, Roshan Mehta. "Anti-depressant Activity of the Seeds of Zanthoxylum armatum on Swiss Albino Mice". Acta Scientific Pharmacology 1.9 (2020): 03-10.
31. Prathvi Shetty, Manohar V.R, Sara Kurien, Mohandas Rai. Attenuation of depression by Bauhinia purpurea linn. Leaves ethanolic extract in swiss albino mice. International Journal of Comprehensive and Advanced Pharmacology, July-September,2017;2(3):85-87.
32. Adake Prabhakar, Rajan Chandrashekar, Rao S.N. Evaluation of antidepressant activity of Boswelli serrata in swiss albino mice by forced swim test. International Journal of Universal Pharmacy and Bio Sciences 2(3): 2013: 417-424.
33. Parigala Madhavi, B.L. Kudagi, Madhavulu Buchineni, Rama Mohan Pathapati. Evaluation of antidepressant activity of aqueous extract of leaves Prosopis cineraria by using tail suspension test in Swiss albino mice. Advance Pharmaceutical Journal 2018; 3(4):121-123.
34. L. C. Souza, M. G. de Gomes, A. T. R. Goes et al., "Evidence for the involvement of the serotonergic 5-HT1 receptors in the antidepressant-like effect caused by hesperidin in

mice," Progress in Neuro-Psychopharmacology & Biological Psychiatry, vol. 40, no. 1, pp. 103–109, 2013.
35. L.-T. Yi, C.-F. Li, X. Zhan et al., "Involvement of monoaminergic system in the antidepressant-like effect of the flavonoid naringenin in mice," Progress in Neuro- Psychopharmacology & Biological Psychiatry, 2010;34(7):1223–1228.
36. S. P. Patil, C. Liu, J. Alban, N. Yang, and X. Li, "Glycyrrhiza uralensis flavonoids inhibit brain microglial cell TNF-α secretion, p-I αB expression, and increase brain-derived neurotropic factor (BDNF) secretion," Journal of Traditional Chinese Medical Sciences,. 2014; 1(1): 28–37.
37. W. Zhu, S. Ma, R. Qu, D. Kang, and Y. Liu, "Antidepressant effect of baicalin extracted from the root of Scutellaria baicalensis in mice and rats," Pharmaceutical Biology. 2008; 44(7): 503–510.
38. N. Samad, A. Saleem, F. Yasmin, M. A. Shehzad. Quercetin Protects Against Stress-Induced Anxiety- and Depression Like Behavior and Improves Memory in Male. Physiological Research. 2018; 67: 795-808.
39. Shao-Xiao Yan, Jun-Lian Lang, Yan-Ying Song, Yu-Ze Wu, Meng-Han Lv, Xia Zhao, Yan-Hong Liu, Chu-Yan Xu. Studies on antidepressant activity of four flavonoids isolated from Apocynum venetum Linn (Apocynaceae) leaf in mice. Tropical Journal of Pharmaceutical Research. 2015; 14(12): 2269-2277.