

Review on Synthetic Vs Herbal Drugs, Its Various Extraction Methods and Animal Models Related to Depression.

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Abstract

Depression is a neuropsychiatric disorder. The focus of the current review article is on the most recent antidepressant drugs, their mechanisms of action, their pathophysiology, their side effects, and the methods for preventing drug-induced toxicity. There is also a description of phytochemicals that have been found to have antidepressant effects. Widely used synthetic drugs are,

1. tricyclic antidepressants
2. Selective serotonin reuptake inhibitors
3. monoamine oxidase inhibitors,
4. Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

It has been reported that most antidepressants have negative health effects. An account of phytochemicals found to be acting as antidepressant is also included. Their beneficial effects to the human body have been attributed to the presence of active phytochemical ingredients with some efficiency for disease treatment as well as for beauty and health enhancement.

Public awareness on the adverse effects of synthetic chemical products also increased the demand for herbal products. Highly efficient herbal processing and extraction technologies have been developed to obtain the optimal amounts of active ingredients from herbs. Soxhlet extraction, supercritical fluid extraction, cold Maceration Extraction, steam distillation, Hot Water Extraction, microwave assisted extraction. This review focuses on recent findings regarding some of the most widely employed animal models used currently to predict antidepressant potential. Here we, study the assessment behavioral test by using various animal models: force swimming test, tail suspension Test, rotarod test. In that for study of synthetic and herbal drugs in treatment of depression.

Their advantageous effects on the human body have been related to the existence of active phytochemical components that are effective in treating certain diseases as well as enhancing attractiveness and health.

The demand for herbal items increased as a result of growing public knowledge of the negative consequences of synthetic chemical products.

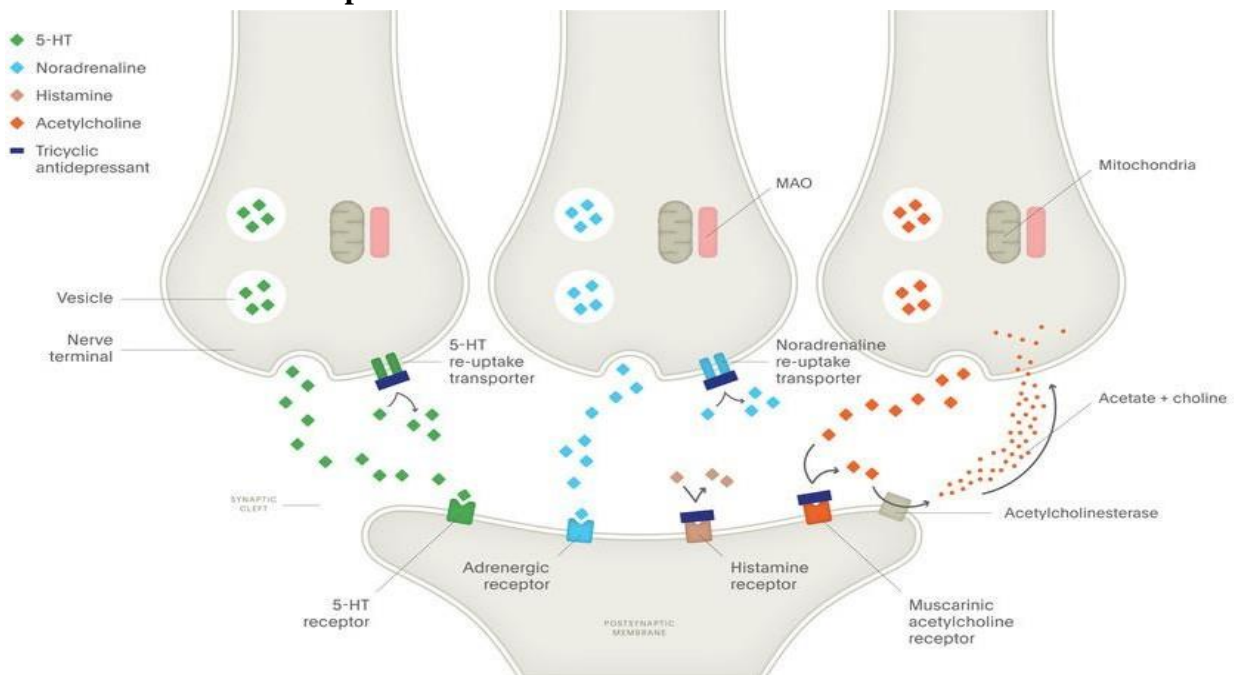
Keywords: Depression, antidepressant, Herbal, synthetic drugs, Extraction technologies, animal models.

Introduction

A diverse collection of neuropsychiatric disorders known as major depression (MD) are linked to considerable morbidity, death, and Disability. (1) Diagnostic and Statistical Methods for Mental illnesses like depression can have a negative impact on a person's feelings, thoughts, behaviors, and even their physical health. Anhedonia, melancholy, a depressed mood, and sluggish movements are some of the primary signs of depression. (2) The prevalence of major depressive episodes is significant and ranges from

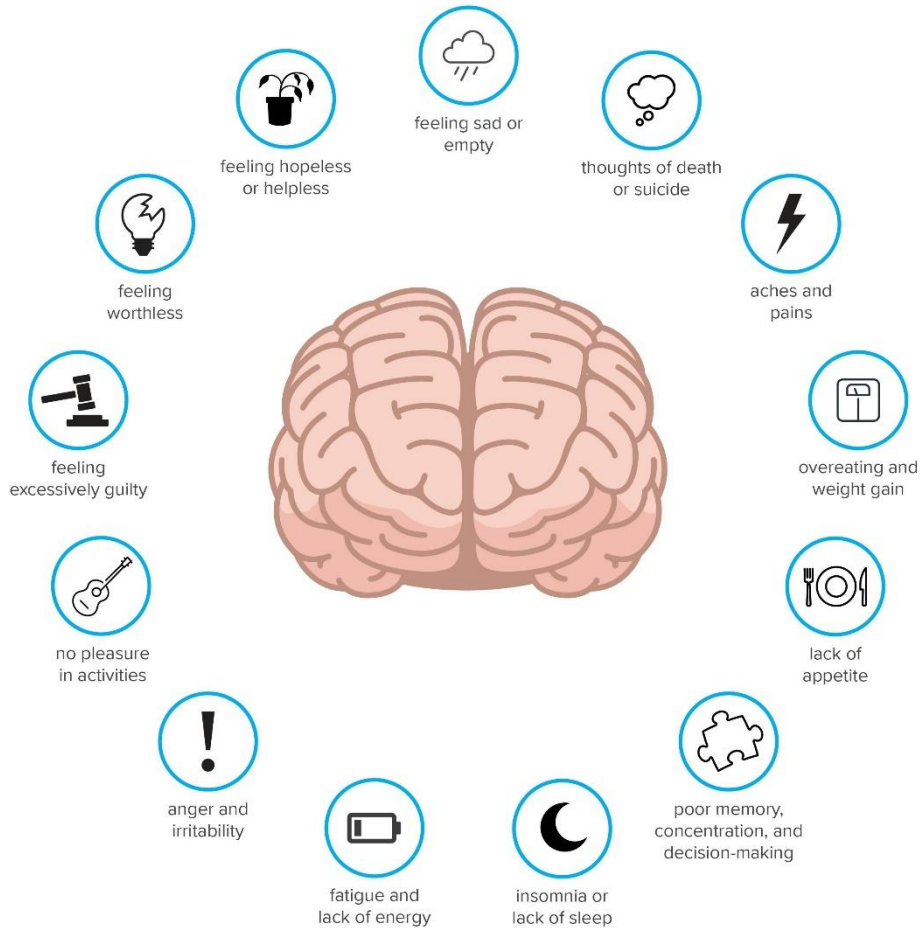
3% in Japan to 17% in the US, with the majority of countries falling between 8 and 12%. The prevalence rate was determined to be -65.4/1000 people in India as opposed to a range of 5 to 8% in North America. Numerous studies have found that women are more at risk than men.(3) For the purpose of diagnosing the pathophysiology of depression throughout a lifetime, there are no useful imaging anomalies or biomarkers. The post-mortem examination revealed no obvious morphological or neurochemical abnormalities in the brain. Most of the available choices Empirical study led to the discovery of medication. Today's most popular theories are Rely on the "amine theory"(4)

Mechanisms of action Antidepressant:




Various antidepressants' modes of action, monoamine oxidase inhibitors(MAOIs), involve the blocking of The enzymatic transformation of NE and 5HT into their related metabolites. When depression is atypical or treatment resistant, MAOIs are typically administered. These substances have a certain level of toxicity. Contrarily, the moclobemide (Manerix) has been shown to Being the first monoamine oxidase A reversible inhibitor (RIMA). This chemical is thought to be safer and comparatively More effective. Nefazodone (serzone), another antidepressant, possesses both of these qualities. It functions similarly to SSRIs in that it inhibits the reuptake of 5HT and also works as an antagonist of the 5HT2 receptor, lessening the stimulating effects that are characteristic of SSRIs. (5)






Common Symptoms of depression:








Material and Method -

Herbal plant act as antidepressant agents

S R	Herb name	Biological source	Part used from Herb	Type of extract, compounds and doses	Effects	Reference
1	Ashwagandha 	Withania somnifera	Aerial part	Bioactive Glycosides, Withanolide	Effects on Anxiety and Antidepressant Action	(7)

2	Garlic 	Allium sativum	Rhizome	Ethanollic Extract,dose-25,50 and 100mg/kg	Behavioural Despair	(8)
3	Betel Nut 	Areca catechu	Fruit	Ethanollic Extract, dose 4-80mg/kg	Effect on Motor Activity	(9)
4	Amla 	Emblica officinalis	Fruit	-	Effect on psychiatric Disorder	(10)
5	Black pepper 	Piper tuberculatum	Fruit	Piplartine(An Amide),dose- 50 and 100mg/kg	Effect of Antidepressant activities, depression	(11)
6	Brahmi 	Bacopa monnieri	Aerial part	Methanollic extract, dose-20and40mg/kg	Significant antioxidant effect,and improve Memory Retention	(12)

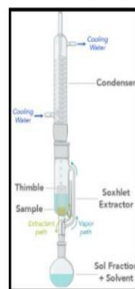
7	<p>Canary Island St. Johnwort</p> 	Hypericum canariense	Aerial part	Methanolic Extract	Neuro pharmacology effect, Help in muscle relaxation, Anticholinergic And sedative properties	(13)
8	<p>Ginkgo, Maidenhair tree</p> 	Ginkgo biloba	Leaves	Lipophilic Extract, dose-50 and 100 mg/kg	Act as Anti-stress and Anti-depressant	(14)
9	<p>Lemon verbena</p> 	Aloysia polystachya	Aerial part	Hydroethanolic Extract	Effect on depressant	(15)
10	<p>Marigolds</p> 	Tagetes lucida	Aerial part		Effect on CNS	(16)

11	Saffron 	Crocus sativus	Stigma	Ethanollic Extract	Effect on Depressant	(17)
12	Sensitive plant 	Mimosa pudina	Leaves	AqueousExtract	Act As Tricyclic Antidepressant	(18)
14	Valerian 	Valeriana officinalis	Root	Ethanollic Extract	Effect on Mild Sleep Disorders and Nervous tension	(20)
15	White Henna 	Rhazyastricta	Leaves	AqueousExtract	Effect on Monoamine Oxidase Inhibition	(21)

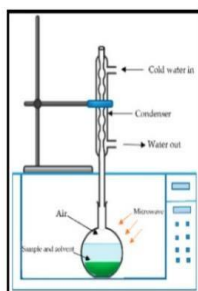
Extraction Methods

The kind of extraction method used while processing herbs can have a significant impact on the resulting natural compounds. To extract the relevant active components from plants, suitable extraction techniques are required. The operating circumstances during the extraction operations can have a significant impact on how effectively a specific technique performs. Important criteria for solid-liquid extractions include a suitable solvent system, the solvent to herb ratio, the particle sizes of powdered and dried plant materials, and Sim et al.'s discussion of the temperature, duration, and agitation rate.(22)

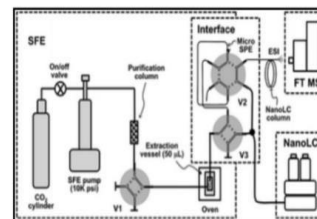
1. Soxhlet Extraction



6. Microwave assisted Extraction.

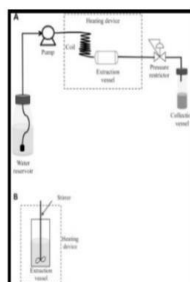


2. Supercritical fluid Extraction (SFE)

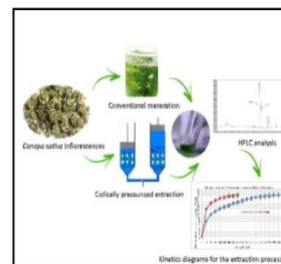


Herbal processing and Extraction methods.

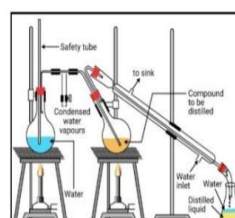
5. Hot water Extraction



3. cold Maceration Extraction



4. steam Distillation Extraction



1).Soxhlet Extraction Method

Extraction using Soxhlet In addition to being a method for phytochemical extraction, Soxhlet extraction is also used as a benchmark for comparing older extraction methods [23]. For the purpose of extracting herbs, a Soxhlet apparatus is used. The sample is put into a thimble holder and fresh solvent is progressively added from a distillation flask . A siphon aspirates the solute from the thimble holder as the liquid reaches the overflow level. This moves the aliquot back into the distillation flask and introduces the extracted analyses into the bulk liquid. This procedure keeps going till the extraction is finished. As the solvent is circulated through the sample, the system runs continuously.using a rotary evaporator at controlled temperatures and low pressure, the extracts are extracted by filtering off the solvent [24]. This extraction method uses a heat source that is delivered directly to the distillation flask to maintain a high system temperature (at the solvent boiling point). This approach is also very easy and reasonably priced [25]. Soxhlet extractions are constrained by the lengthy extraction procedure and the substantial amounts of extractants (solvent) needed. The solvents can damage the environment and be expensive to clean.(26)

2) supercritical Fluid Extraction:

Supercritical fluid extraction (SFE) is one of the extraction techniques used in the processing of herbs because it can provide high yields of high-quality, valuable compounds from herbs.(27)

3) Cold Maceration Extraction:

30mL of ethyl acetate and 6g of *L. macranthoides* were added to a conical flask, which was then tightly wrapped and sealed with a stopper. Twice for a total of 24 hours, the material was immersed in 30mL of ethyl acetate. The final extract for each substance was created by combining the extracts. Each final extract was concentrated and kept in the same manner as for US extraction to enable a thorough comparison.(28)

4) Steam Distillation Extraction:

A steam generation device is included in the steam-distillation process to provide steam to the mixture of solvent and plant raw material. To enable evaporation to occur at lower temperatures, steam can be delivered at a pressure and saturation temperature that are both sufficiently higher than the mixture's boiling point.(29)

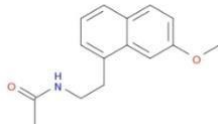
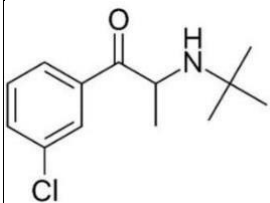
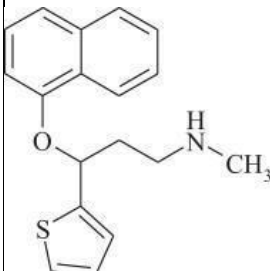
5) Hot Water Extraction:

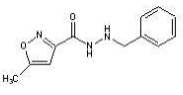
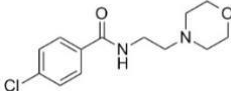
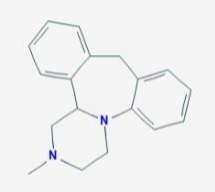
The term "hot water extraction" (HWE) The ASE procedure and hot water extraction are in the same class. However, the HWE extracts with hot water rather than an organic solvent. Water is a less expensive solvent, so using it as a solvent reduces the HWE method's operating costs. Water is a substantially less harmful solvent that is also comparably easier to recover and cure.(30)

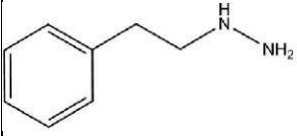
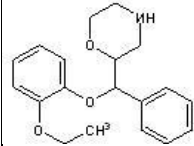

6) Microwave Assisted Extraction:

Microwave-assisted extraction (MAE) is a process that uses a liquid solvent, such as water or alcohol, to extract the active ingredients from herbs. In MAE, the enhanced extraction occurs as the result of changes in the vegetable cell structure caused by electromagnetic waves in MAE(31)

Synthetic Drugs Used as Antidepression:

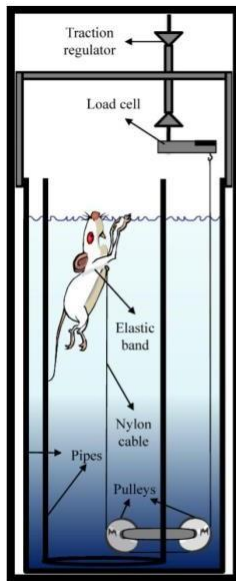
SR. No	Antidepressant substrate (common name)	Dose	Therapeutic index	Side effects	Toxicity in overdose	Uses	Reference
1	Agomelatine 	25-50 mg/day	Narrow	Dizziness abnormal alterations in tests for liver function Internal Pain	Unclear	Antidepressant used to treat depression.	(32)
2	Bupropion 	150 mg/day	Narrow	Sleep problems, nausea, pharyngitis, loss of appetite, constipation, lightheadedness, headaches, and xerophthalmia	Moderate	Adult depression, seasonal affective disorder,	(33)
3	Duloxetine 	60 mg/day	Wide	Asthenia, constipation, diarrhea, drowsiness, fatigue, dizziness, headache, xerostomia, hypersomnia, and insomnia.	Moderate	To Manage major depressive disorder (MDD),	(34)

4	<p>Isocarboxazid</p> 	40-60 mg/day	Wide	Constipation, nausea, tremors, shaking, dry mouth, or any of the following.	High	To treat depression	(35)
5	<p>Moclobemide</p> 	300 mg/day	Wide	Constipation, diarrhea, vomiting, anxiety, restlessness, insomnia, nausea, dry mouth, and dizziness	High	To Treat certain types of mental depression	(36)
6	<p>Mianserin</p> 	30-200 mg/day	Narrow	Coma, arthralgia, edema, tachycardia, bradycardia, vomiting, dizziness and ataxia, anti-cholinergic effects, liver dysfunction, jaundice, gynecomastia, convulsions, hypomania, hypotension, and hypertension	Low	To treat depression	(37)

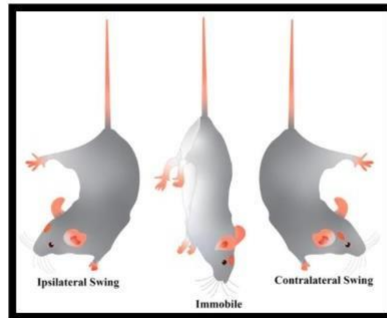
7	<p>Phenelzine</p> 	60 mg/day	Wide	insomnia and hypersomnia), and other symptoms	High	Monoamine oxidase inhibitor. This medication treats depression	(38)
8	<p>Reboxetine</p> 	8mg/Day	Narrow	A urinary tract issue, Sweating, tingling or numbness in the hands or feet, a dry mouth, Impotence, insomnia, headaches, dizziness, nausea, increased blood pressure, heart rate, constipation, Reduced Appetite	Low	For the acute treatment of depressive illness/major depression	(39)
9	<p>Tranylcypromine</p> 	60 mg/day	Wide	Memory loss, ataxia, confusion, and disorientation urinary incontinence, frequency of urination, Bruising In The Corner Of The Mouth.	Low	Treat certain types of depression	(40)

Animal Models And Methods In Depression :

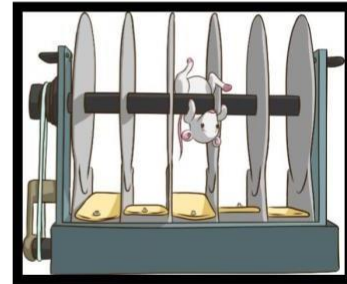
Diffrent animal Models



1. Forced swimming Test



2. Tail suspension Test



3. Rotarod test

1. Forced swim Test:-

Predictive model of Antidepressant activity:-

The FST, first reported by Porosity et al., is one of the tests that researchers employ the most frequently to examine novel antidepressant medications.(41) To assess the effects of antidepressant substances on mice, this test was created as an animal model of depression. The animal is confined inside a water-filled cylinder for this test, making it impossible for it to escape. The animal will initially try to flee, but soon it will adopt an immobile posture, a passive behavior distinguished by the absence of movements other than those required for the animal's snout to stay above the water's surface . Two exposures to swimming make up the mice test. The initial exposure lasts for 15 minutes, and the subsequent exposure takes place 24 hours later. Whereas the TST can only be performed on mice, in humans. The mice's tails are suspended and fastened to the TST by an adhesive tape . The amount of time the animal spends immobile over the course of six minutes is used as a proxy for depressive-like behavior. Different antidepressant drugs work to break this immobility and encourage escape-related behavior. Importantly, rather than being used as animal models of depression, the TST and FST are both regarded as predictive models of antidepressant activity.(42)

2. Tail suspension Test:

The TST has grown to be one of the most popular models for determining the antidepressant-like action of mice since its inception approximately 20 years ago. The experiment is based on the observation that animals who experience the short-term, unavoidable stress of being suspended by their tails adopt a rigid posture.(43)

3. Rotarod Test:-

The Rotarod test is one of the oldest tests used for assessing motor coordination and balance in rodents. It

provides a quick and simple estimation of neuromuscular coordination.

Conclusion

Conclusion:-Although depression is a serious psychological condition, it is treatable with current therapies. Different synthetic medications used to treat depression all have undesirable side effects. Despite this, it may be important to look into plant-based principles as a potential safer and more effective alternative to synthetic medications. A request Herbal of Product Has As the active ingredient in herbs, phytochemicals have increased the effectiveness of natural products already on the market. To get the active components utilized in the creation of herbal products, extraction processes are necessary. Herbal extraction methods are frequently created to reduce the amount of time needed to extract a herb, increase the amount of herb that can be extracted, and improve the quality of the extracted herb. The extraction techq described in this review suitable for solid, liquid extraction OF Plant constituent .Although there are many animal models of depression. It is remarkable that All Animal model Of Depression have Contributed to a better OF neurobiology of depression disorder and offer Fornew pharmacological target for treatment the developed Of model that repressant most symptoms of depression. Understanding Phomanologicalsymptoms of depression This review's extraction method is appropriate for both solid and liquid extraction of plant constituents. Nevertheless, there are several animals that exhibit depression. It is amazing that All Animal simulation .Having depression Improvedour understanding of the neuroscience of depression and the development of a new pharmaceutical treatment strategy that suppresses the majority of depressive symptoms. Understanding Depression pharmacological symptoms. This review aims to provide a comprehensive picture of herbal medications, their numerous extraction techniques, and the models they are employed with.

Reference:

1. Katon W, Sullivan MD. Depression and Chronic medical illness. Vol. 51 Suppl.1990.3Belmaker RH, Agama G. Major depressive Disorder. N Engle J Med 2008;358:55–68. Doi:10.1056/NEJMra073096.
2. Association AP. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association; 2013
3. Andrade L, Caraveo-Anduaga JJ, Berglund P, Bijl R V, de GR, Vollebergh W, et al. The Epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys.[erratum appears in Int J Methods Psychiatr Res. 2003;12(3):165]. Int J Methods Psychiatr Res 2003;12:3– 21. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. LifetimePrevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:593– 602.Doi:10.1001/archpsyc.62.6.593.Kessler RC, Berglund P, Demler O, Jin R, CortezD, Merikangas KR, et al. The Epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095–105. Doi:10.1001/jama.289.23.3095.
4. Standaert. Harvard-MIT Division of Health Sciences and Technology. Neuropharmacology II Antidepressants and Sedatives. USA; 2005. P. 1–8 Moller HJ, Volz HP. Drug Treatment of Depression in the 1990s. Drugs.1996;52(5):625–638.
5. American Psychiatric Association (1994) Diagnostic and Statistical Manual of Mental Disorders (4th edn), American Psychiatric press.
6. Bhattacharya SK, Bhattacharya A, Sairam K, et al. Anxiolytic-antidepressant activity of Withania

- somnifera glyco-withanolides: an experimental study.
7. Phytomedicine. 2000;7(6):463–469.
 8. Dhingra D, Kumar V. Evidences for the involvement of monoaminergic And GABAergic systems in antidepressant-like activity of garlic extract In mice. Indian JPharmacol. 2008;40(4):175–179.
 9. Dar A, Khatoun S. Antidepressant effects of ethanol extract of areca Catechu in rodents. Phytother Res. 1997;11(2):174–176.
 10. Pemminati S, Gopalakrishna HN, Ashok K Shenoy, et al. Antidepressant activity of aqueous extract of fruits of *Embllica officinalis* in mice. International Journal of Applied Biology and Pharmaceutical Technology 2010;1(2):449–454.
 11. Cícero Bezerra Felipe F, Sousa Filho JT, De Oliveira Souza LE, et al. Piplartine, an amide alkaloid from *Piper tuberculatum*, presents anxiolytic and antidepressant effects in mice. Phytomedicine. 2007;14(9):605–612
 12. Sairam K, Dorababu M, Goel RK, et al. Antidepressant activity of standardized extract of *Bacopamonniera* in experimental models of depression in rats. Phytomedicine. 2002;9(3):207–211
 13. Sánchez-Mateo CC, Bonkanka CX, Prado B, et al. Antidepressant properties of some *Hypericumcanariense* L. and *Hypericumglandulosum* Ait. extracts in the forced swimming test in mice. J Ethnopharmacol. 2005;97(3):541–547
 14. Sakakibara H, Ishida K, Grundmann O, et al. Antidepressant effect of Extracts from *Ginkgo biloba* leaves in behavioral models. Biol Pharm Bull. 2006;29(8):1767–1770.
 15. Mora S, Díaz-Véliz G, Millan R, et al. Anxiolytic and antidepressant -like effects of the hydroalcoholic extract from *Aloysiapolystachya* in Rats. Pharmacol Biochem Behav. 2005;82(2):373–378.
 16. Guadarrama-Cruz G, Alarcon-Aguilar FJ, Lezama-Velasco R, et al. Antidepressant-like effects of *Tagetes lucida* Cav. In the forced swimming Test. J Ethnopharmacol. 2008;120(2):277–281.
 17. Wang Y, Han T, Zhu Y, et al. Antidepressant properties of bioactive fractions from the extract of *Crocus sativus* L. J Nat Med. 2010;64(1):24–30
 18. Molina M, Contreras CM, Tellez-Alcantara P. *Mimosa pudica* may possess antidepressant actions in the rat. Phytomedicine. 1999;6(5):319–323.
 19. Yu ZF, Kong LD, Chen Y. Antidepressant activity of aqueous extracts of *Curcuma longa* in mice. J Ethnopharmacol. 2002;83(1-2):161–165.
 20. Dhingra D, Kumar V. Evidences for the involvement of monoaminergic And GABAergic systems in antidepressant-like activity of garlic extract In mice. Indian JPharmacol. 2008;40(4):175–179.
 21. Ali BH, Bashir AK, Tanira MO. The effect of *Rhazya stricta* Decne, a traditional medicinal plant, on the forced swimming test in rats. Pharmacol Biochem Behav. 1998;59(2):547–550
 22. Sim C., Kumaresan S., Sarmidi M.R. (2004) Mass transfer coefficients of *Eurycoma longifolia* batch extraction process. <http://eprints.utm.my/6026/> consulted on Jan. 16, 2016.
 23. Tatke P., Jaiswal Y. (2011) An overview of microwave assisted extraction and its Applications in herbal drug research. Res. J Med. Plant. 5:21-31.
 24. Pihie L., Hawariah A., Zakaria Z.A., Othman F. (2012) Antiproliferative and Proapoptotic Effects of *Labisia pumila* Ethanol Extract and Its Active Fraction in Human Melanoma HM3KO Cells. Evidence-Based Complementary and Alternative Medicine; article ID 123470, Doi:10.1155/2012/123470
 25. Luque de Castro M., Garcia-Ayuso L. (1998) Soxhlet extraction of solid materials: an Outdated technique with a promising innovative future. Anal. Chim. Acta 369(1):1-10.
 26. Luque de Castro M., Priego-Capote F. (2010) Soxhlet extraction: Past and present panacea. J.

- Chromatogr. A. 1217(16):2383-2389.
27. Bernardo-Gil M.G., Roque R., Roseiro L.B., Duarte L.C., Gírio F., Esteves P. (2011) Supercritical extraction of carob kibbles (*Ceratonia siliqua* L.). *The J. Supercritical Fluids*;59(0):36-42
 28. Liang CY, Fu H, Li WL, Xia B, Wu JL. Comparison of different Extraction methods of volatile oil from *Mentha haplocalyx* Briq.,. *Lichen Med Mater Med Res* 2007;18:2085–6.17. Du ZX, Wu HE, Li FY, Guo M, Wu PC, Gong SJ. Chemical
 30. Constituents of volatile oil from *Porella setigera* (steph.) Hatt.,. *Lishizhen Med Mater Med Res* 2010;21:336–8
 31. Ridgway K., Lalljie S.P., Smith R.M. (2007) Sample preparation techniques for the Determination of trace residues and contaminants in foods. *J. Chromatogr. A*;1153:36-53.
 32. Ayala R.S., De Castro M.L. (2001) Continuous subcritical water extraction as a useful tool For isolation of edible essential oils. *Food chem.* 75(1):109-113.
 33. Veggi P.C., Martinez J., Meireles M.A.A. (2013) *Fundamentals of Microwave Extraction Microwave-assisted Extraction for Bioactive Compounds: Springer; Berlin, p. 15-52.*
 34. Tsirulnik-Barts L, Greenblatt DJ. Clinical pharmacology and therapeutics of antidepressants. In: Ciraulo DA, et al. editors. *Pharmacotherapy of Depression. USA: Springer Science & Business Media; 2011. P. 33–124.*
 35. Tsirulnik-Barts L, Greenblatt DJ. Clinical pharmacology and therapeutics of antidepressants. In: Ciraulo DA, et al. editors. *Pharmacotherapy of Depression. USA: Springer Science & Business Media; 2011. P. 33–124.*
 36. Tsirulnik-Barts L, Greenblatt DJ. Clinical pharmacology and therapeutics of antidepressants. In: Ciraulo DA, et al. editors. *Pharmacotherapy of Depression. USA: Springer Science & Business Media; 2011. P. 33–124.*
 37. Bleakley S. Review of the choice and use of antidepressant drugs. *Prog Neurol Psychiatry*. 2013;17(6):18–26.
 38. White K, Razani J, Cadow B, et al. Tranylcypramine vs nortriptyline vs Placebo in depressed outpatients: a controlled trial. *Psychopharmacology (Berl)*. 1984;82(3):258–262.
 40. Tsirulnik-Barts L, Greenblatt DJ. Clinical pharmacology and therapeutics of antidepressants. In: Ciraulo DA, et al. editors. *Pharmacotherapy of Depression. USA: Springer Science & Business Media; 2011. P. 33–124.*
 41. Nierenberg AA, Alpert JE, Pava J, et al. Course and treatment of atypical depression. *J Clin Psychiatry*. 1998;59(Suppl 18):5–9.
 42. Tsirulnik-Barts L, Greenblatt DJ. Clinical pharmacology and therapeutics of antidepressants. In: Ciraulo DA, et al. editors. *Pharmacotherapy of Depression. USA: Springer Science & Business Media; 2011. P. 33–124.*
 43. Pande AC, Birkett M, Fechner-Bates S, et al. Fluoxetine versus phenelzine in atypical depression. *Biol Psychiatry*. 1996;40(10):1017–1020.
 44. Porsolt RD, Le Pichon M, Jafri M. Depression: a new animal model sensitive to antidepressant treatments. *Nature*. 1977;266:730-2.
 45. Castagne V, Moser P, Roux S, Porsolt RD. Rodent models of Depression: forced swim and tail suspension behavioral despair tests In rats and mice. *Curr Protocol Neurosci*. 2011;Chapter 8:Unit 8.10A

46. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a Model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. *Neurosci Biobehav Rev.* 2005;29:571-625.