

A TRADITIONAL APPROACH TO MANAGE DEPRESSION - EMPHASIZING ON MEDICINAL HERBS AND PHYTOCHEMICALS AS ANTI DEPRESSANTS

Seema Mehdi, K.L. Krishna

JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India.

Kishor M

JSS Medical College and Hospital, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India.

Keywords: Depression, neurotransmitters, natural, diagnosis, biomarkers, stress, neurogenesis, psychotherapy, illness, relapse, metabolites, fatigue, sadness, somatic, cytokines, antioxidants, phytochemicals, herbs, anti-depressants, Ayurveda, dopamine, serotonin, intervention

Contents

1. Introduction
 - 1.1. Types of Depression
 - 1.2. Signs and Symptoms of Depression
2. Pathophysiology and Etiology of depression
 - 2.1. Hypothesis of Depression
 - 2.2. Role of Biomarkers in the Etiology of Depression
3. Treatment – Conventional Treatment and their Targets
4. Intervention and complimentary management of depression
 - 4.1. Introduction
 - 4.2. Whole Medical Systems (or) Alternative Medical System
 - 4.3. Dietary and Nutritional Supplements
 - 4.4. Energy Healing
 - 4.5. Mind-body Therapies
 - 4.6. Manipulative and Body-Based Methods
5. Ancient System of Herbal Therapy
 - 5.1. Benefits of Herbal Therapy
 - 5.2. Concept of Ayurveda
 - 5.3. Traditional Knowledge
 - 5.4. World of the West
 - 5.5. Vata
 - 5.6. Pitta
 - 5.7. Kapha
6. Herbs and Phytochemicals
 - 6.1. Introduction
 - 6.2. Herbs and Phytochemicals as Antidepressant
 - 6.3. Flavanoids
 - 6.4. Non-flavonoid Phytochemicals
7. Limitations of Herbal Medicines
8. Challenges Associated with Herbal Medicine

9. Myths and Facts about Mental Health

9.1. Myth: Depression is not a Genuine Problem.

9.2. Myth: The Easiest Way to Treat Depression is Always to Use Medicine.

9.3. Myth: Only Traumatic Experience Often Causes Depression.

9.4. Myth: Depression is a Natural Component of Development

9.5. Myth: After Giving Birth, all Women Experience Depression and it gets Resolved Naturally

9.6. If a Family Member Has Depression The Other Members of The Family Would Also Start Feeling The Same

9.7. Myth: Keeping Busy Cures Anxiety and Depression

9.8. Myth: Being Silent in Depression Solves the Problem or Talking Makes Depression Worse

9.9. Myth: If One Drug at the Beginning Doesn't Work, then the Other Drugs also will not work either

9.10. Whenever I feel like I'm doing well I can end my course

9.11. I don't need Speech Therapy if I'm taking Psychiatric Medication

10. Safety Concerns of Herbal Therapy in Depression

10.1 Need for Pharmacovigilance

11. Conclusion

Glossary

Bibliography

Biographical Sketches

Summary

Depression is one of the major and complex mental disorders, reported to be a leading cause of disability and death worldwide. Even though numerous antidepressants are available, many are dissatisfied because of their negative effects and hence, it has become a challenge to conquer this condition. Therefore, a lot of efforts have been made by researchers to deliver an effective and safe alternative drug treatment, where, nature provides a package with wonderful remedies for the management of many diseases including depression. Now, the research is expanding to understand the depth of active ingredients present in the medicinal plants and their enormous benefits. The efforts have been made to enhance the information on herbal data, emphasizing on its evaluation and characterization of the active constituents for their antidepressant property. This chapter describes about a potential alternative therapy available for depression. It summarizes the pathophysiology, conventional drug treatment, complementary management of depression and mechanism of action of medicinal herbs and phytochemicals having antidepressants activity. Additionally, it also provides a list of herbs and phytochemicals emphasizing the challenges associated with them. It also addresses the safety concerns to improvise the scope of medicinal herbs and phytochemicals as antidepressants. An interesting part of the chapter is its focus on limitations of herbal medicines along with the myths and facts prevailing among the population in the management of depression. The world needs a paradigm shift in finding an alternative and safe drug treatment, though conventional antidepressants use has declined for various reasons. It is recommended not to ignore the condition, but to choose for a better treatment option. Hence by understanding the acceptability of herbal medicines worldwide, the authors

have summarized various aspects of the antidepressant activity of medicinal plants and phytochemicals as a novel and safe approach to manage the depression.

1. Introduction

Depression is the most common mental illness leading to lifetime risk and global burden of disability worldwide. It involves the stimulus of grief, causing a characterized depressed mood, feeling of worthlessness, sadness, gradual decline in the amount of sleep, lifestyle changes, irritability, fatigue, hopelessness which can affect overall thinking ability, emotions and suicidal ideation.

Depression in humans is basically in response to any kind of stress. Most of us undergo an experience of low mood or certain emotional circumstances and the situations which makes an individual mentally unstable. When such difficulties are faced an individual feels helpless and emotionally detached and it takes a long way to find peace in the inner soul. Difficulty in the inner soul means it is a fight between the soul and mind. It is about the manipulation with oneself and his or her emotion. Then the individual starts feeling helpless and this feeling of helplessness bridges the negative thoughts stronger. Depressed persons may not be able to explain what it feels when they are undergoing such negative part of life but still, they continue to struggle with life and day to day activity. This affects to an extent that the depressed person suffers from inadequate sleep, where sleep is considered as an important part of life in which the body requires to rest, but the first thing an individual with depression loses is peace of mind that doesn't allow adequate sleep, and this continues to affect daily routine with restlessness, loss of appetite, noticeable change in the behavior, little or no interest in the activities or hobbies which were once enjoyed, stressful appearance, blaming oneself for every little matter. It would appear as though whatever negative or bad events are happening around is because of them and their presence might worsen the situation, worrying on simple matters, feeling incapable and incompetent with the world, impaired ability to concentrate, irritability, fearful, feels like the illness is a punishment and life is not worth living, ultimately all these will lead to suicidal ideations and attempts. All these symptoms and the mental illness are so common throughout the world in the present scenario that, health sectors are working hard to reduce vulnerability to depression. Depressed condition has become a disease of burden affecting major parts of populations worldwide. World Health Organization (WHO) estimates that around 350 million people are depressed and depression is soon going to be the second leading cause of death based on the reports. The prediction is that depression is leading to disability worldwide hence global disability will worsen and suicide rates will increase. Reports have shown that around 0.8 million people die due to depression, Nine out of every ten cases of postpartum reports after suicide are of depression. Globally the number is increasing irrespective of age and gender. Still women are more susceptible and teenagers' rate of suicide has increased. There are many factors - genetic, psychological, biochemical, domestic violence, economic condition, fame, stressful events in life, loss of a loved one, association of comorbid condition, age, socio cultural, substance induced, toxin exposure and many more which are involved in the pathophysiology of depression. According to the reports of World Health Organization International Consortium of Psychiatric Epidemiology (WHO-ICPE), 6-15% of the total population suffers from depression and the situation may worsen.

Though depression is treatable and manageable with proper care and diagnosis, it goes mostly undiagnosed due to the stigma associated with its treatment among the population and not seeking proper support due to various cultural disputes and beliefs. Hence, depression alone becomes the largest contributor to global disability and second largest cause for death especially among the young population. It is reported to be the leading cause of disability throughout the world which contributes significantly to the global burden of disease. These effects of depression if long-lasting or recurrent, can dramatically affect an individual's ability to function and live normally.

In the past, depression was often expressed as a 'chemical imbalance' in the brain, this is reported by the many theories which suggest that, neurotransmitters play a key role in the etiology of depression. The main neurotransmitters involved are serotonin (5-HT) and Dopamine, norepinephrine (NE) and many other neuronal and hormonal theories have also been put forth by the present research which adds to the knowledge and understanding of the pathophysiology of depression. These neurotransmitters are stated to be 'feel good' type of substances in the brain and the current drug treatment aims at elevating the levels of those neurotransmitters in the brain.

The functional parts in the brain also play an important role in the pathophysiology; the research says that, the brain of a depressed individual has shown neuronal atrophy and the hippocampus in particular tends to be smaller and deterioration of neuronal cells is found compared to that of the normal and other areas have also been observed for their damage emphasizing on the areas which control emotions and cognition.

Reports suggest that, stress is the main reason which imbalances the availability of neurotransmitters in the brain and the current drug therapy aims at stimulating the levels of neurotransmitters like serotonin and promote neurogenesis because serotonin levels have an indirect effect on the brain cells. Though the current therapy includes numerous antidepressants which are synthetic compounds, they also come with many side effects. This is the major stigma and drawback associated with the antidepressants. This motivated the researches to make in-depth studies and find effective and safe treatment for the patients in the present world, where 6-15% of total world's population suffers from depression once in lifetime.

Though there are many causes reported till now which are involved in the pathophysiology of depression, the prime cause is yet to be identified. Research suggests that a combination of environmental, genetic factors and altered brain chemistry are the direct influencers. Studies have reported that, there were variations found in serotonin gene transporter and such individuals are more vulnerable for depression. The challenge in finding the exact cause has focused research on finding a promising drug treatment which can act by targeting the multiple causes and directly enhance the neurogenesis or promote the release of neurotransmitters which stimulate the neurogenesis. Current available treatment for depression includes, antidepressants, psychotherapy, herbal medicines, electro-convulsive shock therapy, whereas herbal medicines and phytochemicals are considered as one of the safest and effective treatment.

The available medicines for the treatment of mental illnesses like mood disorders, mania, depression, insomnia, anxiety are very well prescribed and accepted by patients but 10-40% of patients are reported to have no improvement with the existing therapies or to have trouble in tolerating the adverse effects showing inadequate response and they eventually drop the medication which leads to relapse. Cost of the medications and long-term side effects are also factors for discontinuing the medication and this can cause relapse. It is reported that by 2030, unipolar depressive disorders will be the first cause for disability-adjusted life years (DALYs). Hence, it is very essential to find a better approach than the current approach acting precisely on depression. Many medicinal plants with very fewer side effects have been discovered for their potential role, which can be an alternative treatment or can be used in combination to enhance the efficacy and safety of the presently prescribed medications.

The present treatment focus is on the symptomatic relief by antidepressants, whereas, antidepressants are well known to have multiple adverse effects. Switching from antidepressant medications is recommended if the treatment is not effective or shows drug interactions or to be free from the side effects. Safe and better options are more important. This has led to search for alternative and effective therapies like psychotherapy, behavioral therapy, electroconvulsive shock therapy and herbal remedies. The herbal remedies are natural and eco-friendly, safe, acceptable, inexpensive and available with fewer side effects. Plants are important to humans not only environmentally and industrially, but also medicinally. The diversity in the phytochemical components has revealed their benefits for their therapeutic action in many indications which includes mental illness such as depression. If there are limitations associated with inadequate response to drugs used in the treatment of depression and/or intolerance to higher doses or perhaps some combination of antidepressant drugs which give rise to serious side effects, then herbs by virtue of their phytochemicals play a major role as an add-on or alternative to existing therapy or as an adjuvant or as catalyst with the current treatment since it increases the efficacy with minimal or no side effects.

Many medicinal herbs or various plant derivatives are used for their therapeutic properties as a safer alternative to the current drug therapy. Herbal medicines are one type of dietary supplement. They are sold as tablets, capsules, powders, teas, extracts, and fresh or dried plants. People use herbal medicines with a thought of wellbeing and safety to maintain or improve their health.

Herbal medicines have been in use from many decades. They are reported to have beneficial effects on various mental illnesses. Currently, their use has been found to be considerable as the world is becoming aware of the importance of herbal medicines allude to their wide acceptance due to their safety, cost effectiveness with therapeutic effects that are more prominent with minimal side effects and above all they being from natural sources.

Various Plant based metabolites from a wide class including polyphenolic compounds (flavonoids, phenolic acids, lignans, coumarins), and other compounds like alkaloids, terpenes and terpenoids, saponins and saponinins, carbohydrates and amines which have been predominantly reported to have beneficial effects in the treatment of

depression, apart from these few other category of plant derivatives like Naringenin, derivatives of quercetin, eugenol, piperine, berberine, hyperforin, diterpene alkaloids, riparin derivatives, ginsenosides, as well as β -carboline alkaloids are among the most accurate and relevant with concern to antidepressant activity.

Depression needs early diagnosis and a safe treatment mechanism. Medicinal herbs and phytochemicals have a potential therapeutic role in treating and managing depression. So, the important note is to know which are those phytochemicals and medicinal herbs that are useful in the effective management of depression and which can also help in early recovering from the symptoms, reducing its relapse and incidence so, paying a special interest to emphasis on the phytochemistry, pharmacological properties, safety and the future directions for the usage of these herbal medicines can be an ideal regimen to implement in the management of depression.

1.1. Types of Depression

Depression is classified into many types based on the symptoms and severity levels.

- **Unipolar Depression:** It is the most common type of depression in which people have reported to experience several typical symptoms such as feeling of weakness, low mood, gloomy and hopelessness, lack of interest, lack of motivation, fear, obsessed, body pains, inadequate sleep and appetite which are seen for more than two weeks. This depressive disorder is diagnosed based on the syndromic criteria, clinical history and physical examination. Clinical interview with the patients may provide the necessary information for a better understanding of differential depression, presence of risk factors such as family history of major depression, and stressful life events.
- **Persistent Depressive disorder (dysthymia)** is a depressed mood disorder that is reported to lasts for at least two years. An individual diagnosed with this depressive disorder has reported episodes of major depression probably with less severe symptoms, but symptoms shown should be persistent and must last for two years to be considered as persistent depressive disorder.
- **Psychotic Depression** is sub type of major depression which occurs when an individual is reported with severe depression along with few signs of psychosis, like delusions, false belief, hearing ringing sound, negative thoughts and visual hallucinations. The psychotic symptoms typically have a depressive “theme,” which says about having delusions of guilt, failure, poverty, pain or illness.
- **Seasonal Affective Disorder** is related to the change in the season characterized by the onset of depression during the winter months when there is less natural sunlight, sapping up of energy and draining off which makes an individual to sleep continuously, social withdrawn, moody, less active and gain weight. This type of depression is generally increased during spring and summer.
- **Bipolar disorder** is different from of depression; it is a mental condition which causes severe mood swings. It is included in this list is because the reported symptoms of bipolar depression are extreme high – euphoric or irritable – moods called “mania” or a less severe form called “hypomania. Extremely low mood which is an alarming sign of depression and known as “bipolar depression”. This can affect an individual’s sleep, energy level and daily activities, ability to think and behavior.

- **Postnatal Depression** is a type of depression that many parents experience after having a baby. It's a common problem, affecting more than 1 in every 10 women during pregnancy or within a year of giving birth. It can also affect fathers. It majorly involves the feeling of extreme sadness, exhaustion, anxiety, anger and make it more difficult for new mothers to take care of themselves and their new born.

The most common issue is many women do not realize at all that they are suffering from such a phase of depression, because it develops gradually and most of the time it is ignored and considered as part of maternity, but the one who is suffering will not be in a position to overcome and deal with the situation with confidence; hence having a safe and effective treatment especially during postnatal phase is a bigger challenge and while researchers have reported a big list of conventional antidepressants which cannot be used or which have limitations during pregnancy or postnatal phase. Perhaps that becomes an ideal opportunity to think about alternative or complementary treatment. Depression makes one feel lonely, distressed and frightened, but support and effective and safe treatment are necessary to provide and implement.

1.2. Signs and Symptoms of Depression

- Trouble concentrating, remembering personal information or decision making
- Helplessness, Fatigue, Feelings of guilt and worthlessness
- Gloomy, Pessimism and hopelessness
- Insomnia, early-morning wakefulness, or sleeping too much
- Irritability and Restlessness
- Loss of interest in pleasurable activities, including sex
- Excess of eating, or loss of appetite
- GIT disturbances, nausea, vomiting
- Persistent sadness and anxiousness.
- Loneliness, Suicidal thoughts or attempts
- Low mood and feeling of sadness seen persistent
- Activities once enjoyed has no enjoyment anymore
- Lack of interest in the day-to-day activities
- Feeling of tiredness almost the entire day.
- Starts feeling difficulty to bond with family and friends
- Fearful and hurtful thoughts

Management and Treatment

- **Psychological Therapy:** Any general practitioner or a psychiatrist may advise on self-help counseling or may refer the patient to cognitive behavioral therapy (CBT)
- **Self-help:** This is an important aspect to address. WHO has come up with the slogan –"Let's talk" which clearly means that there is a need to express and things would change with extended support. The things which one can try include talking to family and close friends about the suffering, worry and feelings and seeking help without hesitation and finally how well the support is extended from the family and friends, rewarding own self by spending time on things which were enjoyed,

providing sufficient rest to body and soul, following healthy lifestyle which includes exercising regularly, healthy diet and good sleep. Certainly, these modifications would bring a big change and induce confidence in dealing with the negative thoughts or low mood.

- **Cognitive Behavioral Therapy:** It is a type of talk therapy where a therapist will address and talk about the ways to manage depression. It will be useful in understanding the thinking capabilities and thought process of the individual suffering from mental illness. That can also help in boosting up with the positive thoughts and ideas.
- **Psychoeducation:** It involves counseling sessions for the depressed individual which help the depressed individual to understand about the disorder. Knowing about own mental health may help the individual in self management.
- **Interpersonal and Social Rhythm Therapy:** (IPSRT) focuses on monitoring the regular habits, such as sleeping, eating, and exercising. Balancing these everyday basics can help manage the disorder.
- **Antidepressants:** Most commonly prescribed medications which help to relieve symptoms of depression, the main aim is to correct the imbalance of neurochemicals in the brain which plays a role in mood alteration and behavior. These drugs are often used when the symptoms of depression are more severe, at the same time they are reported with a lot of side effects and it is reported that only few patients respond to the antidepressants and rest will not achieve the full remission, this becomes a barrier for its successful treatment and the most tragic consequence of depression if its not treated leads to suicide. Hence, it gives a scope to understand the nature of the symptoms and behavioral impairment associated with the depressive patients to have alternative drug treatment or an adjuvant therapy along with antidepressants to achieve effective and standard care for depression.

2. Pathophysiology and Etiology of Depression:

There are many theories which have explained about the pathophysiology of depression, but currently it is very important to understand the neurophysiology involved in the depression because. More often failure to understand the neuropsychiatry and its physiology has resulted in ambiguity and discrepancies with the antidepressant treatment and this has resulted in a huge failure providing best treatment outcome. Hence, the lacuna and urge of having a safe and effective drug treatment remains unanswered. So, this may help the researchers in achieving a holistic approach to aid an effective treatment of depression and also assist in providing a desirable result for the interventions and co-medications given along with antidepressants.

2.1. Hypothesis of Depression

2.1.1. The Biogenic Amine Hypothesis

This theory has explained in detail about the deficiency of neurotransmitters such as serotonin, dopamine and norepinephrine in the brain cells, as serotonin has a direct effect on mood, behavior and other somatic functions. Dopamine has its effects on rewarding, attention and motivation and NE levels along with serotonin and dopamine

mediate a wide spectrum of functions in brain such as appetite, sex, motivation, mood, interest and concentration. Furthermore, these neurotransmitters act as a fundamental component in the pre- and post-synaptic neurons in the brain hence it is also known as “monoamine hypothesis”. Hence the biogenic amine hypothesis proposes to have the cognitive impairment and depression which result from the abnormalities of neurotransmitters receptor function.

2.1.2. The Serotonin Only Hypothesis

One of the oldest theories which showered light on serotonin (5HT) in the pathophysiology of depression back in the 1960s. It emphasized on the role of serotonin in the brain and its deficiency leads to depression. The serotonergic hypothesis (Figure 1) is a result of the pathology of the stress and more concerned with the anxiety disorders, eating disorders and aggregation of the prenatal stress and coping for the social support and personality. The major risk factors enhance the serotonergic vulnerability and result in depression which can be reversed by antidepressants which would help in restoring the normal functioning of serotonin in depressed patients.

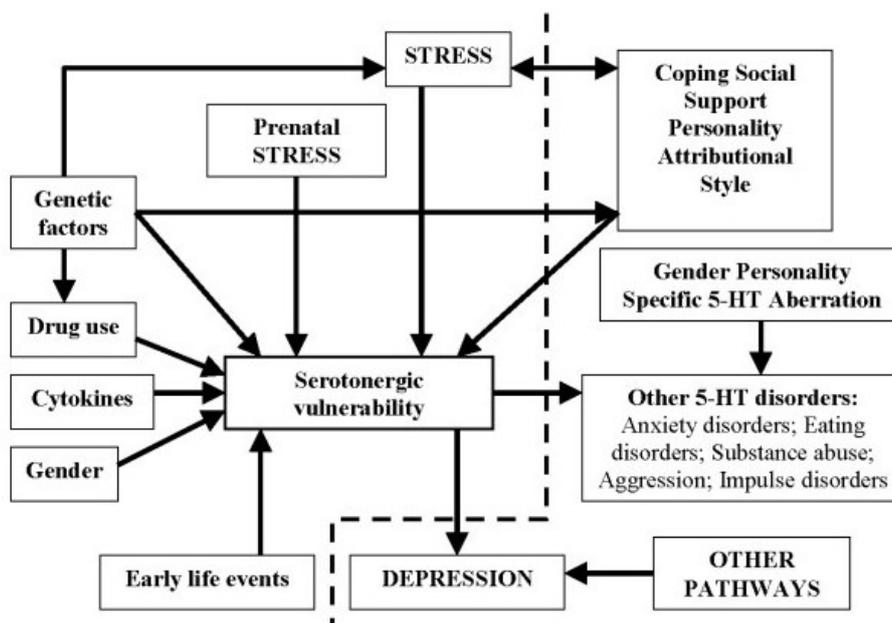


Figure 1. Serotonin hypothesis

Low levels of Serotonin neurotransmitters due to various etiological factors like genetic, drug abuse, cytokines, gender, life events, prenatal stress, and many other biological and environmental factors are evolving to cause depression as shown in Figure 1. It also describes those other disorders which lead to insufficiency of serotonin in the brain would be the major cause for altering emotions and causes depression.

From molecules to mind, genes to behavior, and laboratory to the bedside, scientists are working hard to understand the pathophysiology of depression and the mechanisms that underpin the success of antidepressant therapy.

The 5-HT system remains at the heart of recent developments in most of these domains. The development of the human and animal brains is thought to be dependent on 5-HT.

The richness, originality, and quality of the data that a hypothesis helps to create are frequently used to determine its heuristic value. In this way, the 5-HT theory of depression defies the passage of time due to the vast amount of data it continues to produce through research.

2.1.3. The Electrolyte Membrane Hypothesis

The electrolyte membrane hypothesis talks about the role of calcium in depressive disorders like hypocalcemia and hypercalcemia. If there is increase in the levels of calcium in the electrolytic membrane the patient becomes depressed and if the levels of calcium fall below the level in the electrolytic membrane the person becomes maniac. Figure 2 explains that, the sodium- and potassium-activated adenosine 5'-triphosphatase (Na^+ , K^+ -ATPase) pump, or sodium- and potassium-activated adenosine 5'-triphosphatase (Na^+ , K^+ -ATPase), is an important protein that controls the electrochemical gradient across cell membranes.

It's an ion transporter that also serves as a ligand for cardenolides in addition to exchanging cations. This enzyme controls the entry of K^+ and the exit of Na^+ from cells, ensuring that the Na^+/K^+ balance is maintained throughout neuronal membranes.

Evidence suggests that depressive illnesses are caused by a mix of genetic susceptibility genes and stress in the environment. In humans, a decrease in Na^+ , K^+ -ATPase expression and function is linked to depressive illnesses.

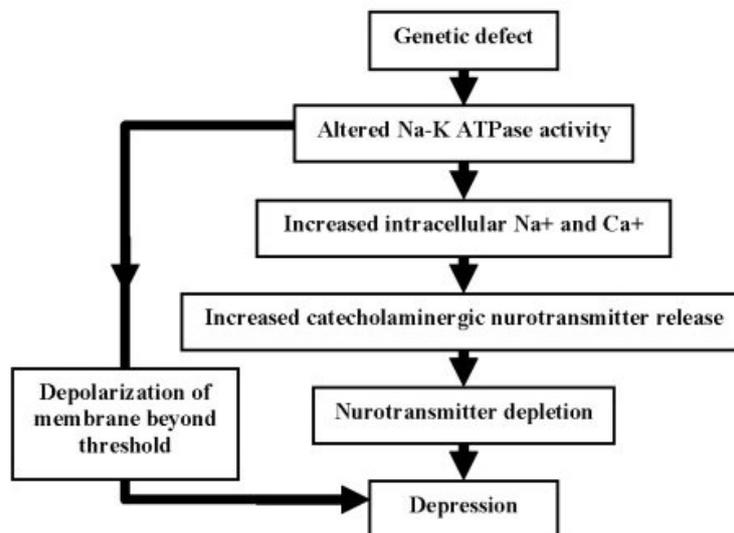


Figure 2. Electrolyte membrane Hypothesis (Source Rodrigues et al, 2014)

Changes in the activity of the membrane sodium- and potassium-activated adenosine triphosphatase pump (Na,K -ATPase) are thought to be the cause of changes in neuronal excitability and activity. By increasing membrane excitability and lowering

neurotransmitter release, a decrease in Na,K-ATPase activity can causes depression as shown in figure 2.

Protein phosphorylation is the main chemical mechanism by which the function of brain proteins is modulated in response to external signals, such as neurotransmitter impulses, at the nervous system level. Hence this would be a possible target for the antidepressant activity of many herbs and phytochemicals.

2.1.4. The Neuroendocrine Hypothesis

Stress is a mentally or emotionally disruptive or distressing condition arising in response to unpleasant external influences as well as a stimulus or scenario creating such a condition, it is the major etiology that plays a role in the development of depression, it causes a reduction in glucocorticoid receptors, which leads to an increase in stress hormone known as cortisol.

Figure 3 explains the interlink between stress, inflammation, reduced levels of serotonin, and altered HPA axis that are known to play major role in the pathophysiology of depression.

The inflammatory response can be triggered by psychological stress and these different forms of stressors can cause an increased inflammatory activity, which can exacerbate depression symptoms as shown in figure 3.

Furthermore, the link between stress-induced C- reactive Protein (CRP) and pro-inflammatory cytokines and depression appears to be bidirectional, as both chronic stress and current depressive symptoms, both linked to neurophysiological changes (e.g., glucocorticoid resistance).

Changes in tryptophan (TRP) metabolism evoked by stress and proinflammatory cytokines has gotten a lot of interest as a new way to explain the aetiology and pathophysiology of major depression.

The main TRP metabolic pathway is the kynurenine (KYN) pathway. It has TRP in common with the 5-HT serotonin pathway. Proinflammatory cytokines increase the KYN pathway, deprive the 5-HT pathway of TRP, and limit 5-HT production in response to stress.

The reduction in 5-HT production, as a result, could be linked to the monoamine theory of major depression which manifests the brain for long-term changes in the neuroendocrine (HPA), neurochemical, and behavioural responses to stressful stimuli.

The pathological states of depression including the mood disorders are explained based on the function of the endocrine system. That is, if there is altered function of the endocrine system the patient automatically experiences mood swings or the negative thought process is triggered with the abnormal functioning of thyroid hormone, altered growth hormone and HPA axis dysfunction.

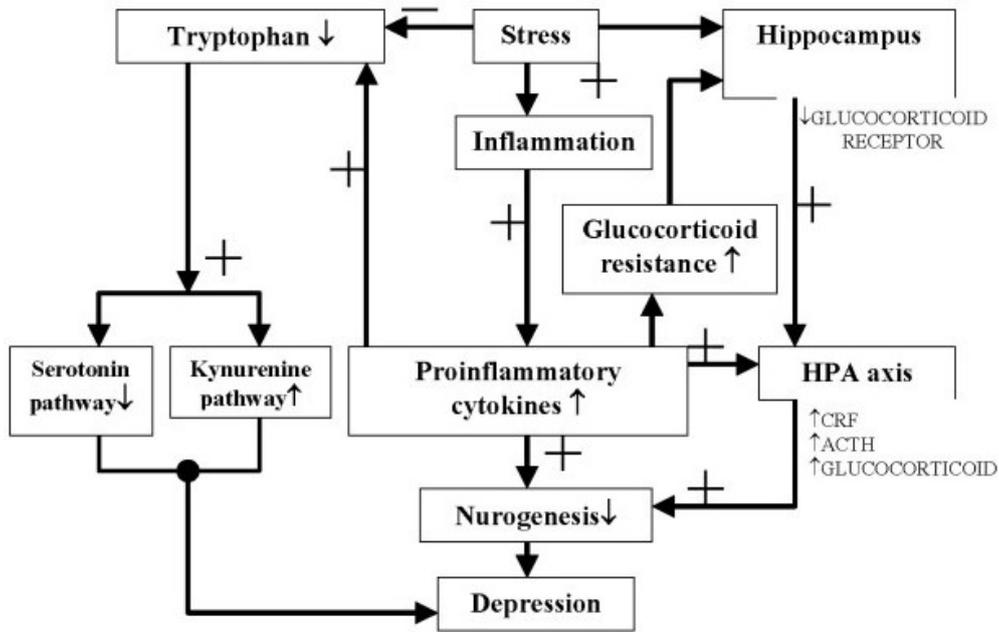


Figure 3. Neuroendocrine Hypothesis (de Mello et al, 2003)

2.1.5. Glucocorticoids and Depression

This theory explains how corticosteroids can influence neurotransmitter mainly in hippocampus and prefrontal cortex. Depression leads to secretion of corticosteroid which is increased by the neurotransmitters. Perhaps, much attention in this field has been focused on having a targeted drug therapy on the areas of the brain showing high levels of corticosteroid. Receptor expression for the corticosteroids is found abundantly in hippocampus and more often reported in the prefrontal cortex. These two are the major brain areas, that are mutually interlinked and employ an inhibitory neural control over the hypothalamus-pituitary-adrenal axis (HPA axis), and thus tend to restrain excess of corticosteroid secretion. Association of hypercortisolism in depression results in impairments of neural and endocrine mechanisms governing negative feedback in the limbic-hypothalamic-pituitary-adrenal (LHPA) axis. This is entirely dependent on the certain factors like intensity and duration of the stress, genetics, psychological state, comorbid conditions and individual lifestyle to which the endocrine responds and causes stress.

-
-
-

TO ACCESS ALL THE 48 PAGES OF THIS CHAPTER,
Visit: <http://www.eolss.net/Eolss-sampleAllChapter.aspx>

Bibliography

- Hammen, C. (2005). Stress and depression. *Annu. Rev. Clin. Psychol.*, 1, 293-319. [This article provides information about how stress, low mood, change in behavior are responsible in causing depression]
- Park, C., Rosenblat, J. D., Brietzke, E., Pan, Z., Lee, Y., Cao, B.,... and McIntyre, R. S. (2019). Stress, epigenetics and depression: a systematic review. *Neuroscience and Biobehavioral Reviews*, 102, 139-152. [this article reviews how environmental stressors, such as childhood maltreatment, have been recognized to contribute to the development of depression.]
- Liu, Y., Zhao, J., and Guo, W. (2018). Emotional roles of mono-aminergic neurotransmitters in major depressive disorder and anxiety disorders. *Frontiers in Psychology*, 9, 2201. [this article provides information about the role of neurotransmitters in major depressive disorder]
- Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., and Cui, R. (2017). The role of neural plasticity in depression: from hippocampus to prefrontal cortex. *Neural Plasticity*. [This article provides information about the involvement of hippocampus and monoaminergic neurotransmitter in major depressive disorder]
- Clevenger, S. S., Malhotra, D., Dang, J., Vanle, B., and IsHak, W. W. (2018). The role of selective serotonin reuptake inhibitors in preventing relapses of major depressive disorder. *Therapeutic Advances in Psychopharmacology*, 8(1), 49-58. [This article provides information about the mechanism of antidepressant drugs in regulating neurotransmitters]
- Stanton, K., Khoo, S., Watson, D., Gruber, J., Zimmerman, M., and Weinstock, L. M. (2019). Unique and transdiagnostic symptoms of hypomania/mania and unipolar depression. *Clinical Psychological Science*, 7(3), 471-487. [This article provides information about the signs and symptoms of unipolar depression and mania.]
- Meesters, Y., and Gordijn, M. (2016). Seasonal affective disorder, winter type: current insights and treatment options. *Psychology Research and Behavior Management*. [This article provides information about current insights and treatment options for seasonal affective disorder]
- Netsi, E., Pearson, R. M., Murray, L., Cooper, P., Craske, M. G., and Stein, A. (2018). Association of persistent and severe postnatal depression with child outcomes. *JAMA Psychiatry*, 75(3), 247-253. [This article provides information about clinical symptoms and treatment options for postnatal depression]
- Bhardwaj, S., Verma, R., and Gupta, J. (2018). Challenges and future prospects of herbal medicine. *International Research in Medical and Health Science*, 1(1), 12-15. [This article provides information about the future challenges of herbal medicines.]
- Devarbhavi, H. (2018). Ayurvedic and herbal medicine-induced liver injury: It is time to wakeup and take notice, *Indian Journal of Gastroenterol* (January–February 2018) 37(1):5–7 <https://doi.org/10.1007/s12664-018-0820-6>. [This article provides information about the side effects of herbal medicines]
- Enioutina, E. Y., Salis, E. R., Job, K. M., Gubarev, M. I., Krepkova, L. V., and Sherwin, C. M. (2017). Herbal Medicines: challenges in the modern world. Part 5. status and current directions of complementary and alternative herbal medicine worldwide. *Expert Review of Clinical Pharmacology*, 10(3), 327-338. [This article provides information about Herbal Medicine challenges in the modern world. status and current directions of complementary and alternative herbal medicine worldwide.]
- Rehman, S. Z., and Al Rashid, S. (2020). Safety of Medicinal Tropical Natural Products—Concerns and Issues. *Journal of Pharmacovigilance and Drug Safety*, 17(1), 10-14. [This article mainly focused on safety and pharmacovigilance of herbal medicines.]
- Fokunang, E. T., Fonmboh, D. J., Mballa, R. N., Nyuyki, A. B., Fokunang, L. B., Kaba, N.,... and Fokunang, C. N. (2020). Pharmacovigilance of Natural Herbal Medicines Research for Efficacy, Safety and Quality Assurance of Phytomedicine Products. *Journal of Complementary and Alternative Medical Research*, 21-37. [This article mainly focused on Pharmacovigilance of Natural Herbal Medicines, Research for Efficacy, Safety and Quality Assurance of Phytomedicine Products.]
- Ekor, M. (2014). The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4. doi: 10.3389/fphar.2013.00177. [This article

provides information about the growing use of herbal medicines, issues relating to adverse reactions and challenges in monitoring safety]

George, P. (2011). Concerns regarding the safety and toxicity of medicinal plants-An overview. *Journal of Applied Pharmaceutical Science*, 1(6), 40-44. [This article provides information about Concerns regarding the safety and toxicity of medicinal plants]

Barnes, J. (2003). Pharmacovigilance of herbal medicines. *Drug Safety*, 26(12), 829-851. [This article mainly focused on importance of pharmacovigilance to build up reliable information on the safety of herbal medicines]

Vetter, J. (2004). Poison hemlock (*Conium maculatum* L.). *Food and Ch* [This article provides information about poisonous nature, and Active constituents of the herb]

Çaksen, H., Odabaş, D., Akbayram, S., Cesur, Y., Arslan, Ş., Üner, A., and Öner, A. F. (2003). Deadly nightshade (*Atropa belladonna*) intoxication: an analysis of 49 children. *Human and Experimental Toxicology*, 22(12), 665-668. [This article provides information about poisonous nature of plant atropa belladonna]

Usman, M. R. M. (2016). *Poisonous Herbal Plants*: NA. Educreation Publishing. [This book provides information about poisonous nature of herbal plants]

Ekor, M. (2014). The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Frontiers in Pharmacology*, 4, 177. [This article provides information about the adverse reactions of medicinal plants and challenges in monitoring safety]

Bent, S., Goldberg, H., Padula, A., and Avins, A. L. (2005). Spontaneous bleeding associated with *Ginkgo biloba*. *Journal of General Internal Medicine*, 20(7), 657-661. [This article provides information about the adverse effect of *Ginkgo biloba*]

Piscitelli, S. C., Burstein, A. H., Chaitt, D., Alfaro, R. M., and Falloon, J. (2000). Indinavir concentrations and St John's wort. *The Lancet*, 355(9203), 547-548. [This article provides information about adverse effects of St john's wort]

Haller, C. A., and Benowitz, N. L. (2000). Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *New England Journal of Medicine*, 343(25), 1833-1838. [This article provides information about adverse effects of ephedra]

Stickel, F., Baumüller, H. M., Seitz, K., Vasilakis, D., Seitz, G., Seitz, H. K., and Schuppan, D. (2003). Hepatitis induced by Kava (*Piper methysticum* rhizoma). *Journal of Hepatology*, 39(1), 62-67. [This article provides information about adverse effects of kava]

Fugh-Berman, A. (2000). Herb-drug interactions. *The Lancet*, 355(9198), 134-138. [This article provides information about adverse drug interaction of *Ginkgo biloba*]

Izzo, A. A. (2005). Herb–drug interactions: an overview of the clinical evidence. *Fundamental and Clinical Pharmacology*, 19(1), 1-16. [This article provides information about adverse drug interaction of Psyllium seed]

Holstege, C. P., Mitchell, K., Barlotta, K., and Furbee, R. B. (2005). Toxicity and drug interactions associated with herbal products: ephedra and St. John's Wort. *Medical Clinics*, 89(6), 1225-1257. [This article provides information about adverse drug interaction of Ephedra]

Abebe, W. (2002). Herbal medication: potential for adverse interactions with analgesic drugs. *Journal of Clinical Pharmacy and Therapeutics*, 27(6), 391-401. [This article provides information about adverse drug interaction of feverfew]

El-Mallakh, R. S. (1983). The Na, K-ATPase hypothesis for manic-depression. II. The mechanism of action of lithium. *Medical hypotheses*, 12(3), 269-282. [This article is referred for the mechanism of action of electrolyte membrane hypothesis]

Jeon, S. W., and Kim, Y. K. (2016). Molecular neurobiology and promising new treatment in depression. *International journal of molecular sciences*, 17(3), 381. [This article speaks on the pathological basis of neuroendocrine mechanisms, immunity hypothesis and role of biomarkers mainly, the genetics of depression]

Kharade, S. M., Gumate, D. S., and Naikwade, D. (2010). A review: hypothesis of depression and role of antidepressant drugs. *Depression*, 15(16), 17. [This article speaks on the glucocorticoid receptor theory and sleep alterations in depression]

Strawbridge, R., Young, A. H., and Cleare, A. J. (2017). Biomarkers for depression: recent insights, current challenges and future prospects. *Neuropsychiatric disease and treatment*. [This article speaks about the role of biomarkers in the etiology of depression]

Whalen, K., Finkel, R., and Panavelil, T. A. (2015). *Lippincott illustrated reviews: Pharmacology* (6th ed.). Philadelphia, PA: Wolters Kluwer [This book was referred for the information on the mechanism of action of drugs and treatment approaches in depression]

Joyce, J., and Herbison, G. P. (2015). Reiki for depression and anxiety. *Cochrane Database of Systematic Reviews*. <https://doi.org/10.1002/14651858.CD006833.pub2> [reiki and depression]

Kinser, P. A., Goehler, L. E., and Taylor, A. G. (2012). How Might Yoga Help Depression? A Neurobiological Perspective. *EXPLORE*, 8(2), 118–126. <https://doi.org/10.1016/j.explore.2011.12.005> [Yoga in depression]

Embong, N. H., Soh, Y. C., Ming, L. C., and Wong, T. W. (2015). Revisiting reflexology: Concept, evidence, current practice, and practitioner training. *Journal of Traditional and Complementary Medicine*, 5(4), 197–206. <https://doi.org/10.1016/j.jtcme.2015.08.008> [importance of reflexology in depression]

Sánchez-Vidaña, D. I., Ngai, S. P.-C., He, W., Chow, J. K.-W., Lau, B. W.-M., and Tsang, H. W.-H. (2017). The Effectiveness of Aromatherapy for Depressive Symptoms: A Systematic Review. *Evidence-Based Complementary and Alternative Medicine*, 2017, 5869315. <https://doi.org/10.1155/2017/5869315> [aromatherapy in management of depression]

Haller, H., Anheyer, D., Cramer, H., and Dobos, G. (2019). Complementary therapies for clinical depression: An overview of systematic reviews. *BMJ Open*, 9(8). <https://doi.org/10.1136/bmjopen-2018-028527> [Effect of exercise in depression]

Massage Therapy for Psychiatric Disorders | FOCUS. (n.d.). Retrieved December 4, 2020, from <https://focus.psychiatryonline.org/doi/10.1176/appi.focus.20170043>

Mendelson, S. D. (2019). *Herbal Treatment of Major Depression: Scientific Basis and Practical Use*. CRC Press. [This book gives complete knowledge of which drugs and phytochemicals have been researched so far for depression]

Apoorva H A, Seema Mehdi, Krishna KI, and Nabeel K. (2019). Medicinal Herbs and Phytochemicals Used in the Treatment of Depression: a Review. *Asian Journal of Pharmaceutical and Clinical Research*, May 2020, 8–14. <https://doi.org/10.22159/ajpcr.2019.v12i5.32708> [introduction to mechanism of herbs and phytochemicals]

Gurib-Fakim, A. (2006). Medicinal plants: Traditions of yesterday and drugs of tomorrow. *Molecular Aspects of Medicine*, 27(1), 1–93. <https://doi.org/10.1016/j.mam.2005.07.008> [Introduction about mechanism of herb]

Progress, R., and Applications, F. (2020). Advances in Pharmaceutical Biotechnology. In *Advances in Pharmaceutical Biotechnology*. <https://doi.org/10.1007/978-9-81-15-2195-9> [Role of phytochemicals as antidepressant]

Chen, S. L., and Chen, C. H. (2015). Effects of Lavender Tea on Fatigue, Depression, and Maternal-Infant Attachment in Sleep-Disturbed Postnatal Women. *Worldviews on Evidence-Based Nursing*, 12(6), 370–379. <https://doi.org/10.1111/wvn.12122> [mechanism of lavender]

Hritcu, L., Cioanca, O., and Hancianu, M. (2012). Effects of lavender oil inhalation on improving scopolamine-induced spatial memory impairment in laboratory rats. *Phytomedicine*, 19(6), 529–534. <https://doi.org/10.1016/j.phymed.2012.02.002> [mechanism of lavender]

Gupta, J., Gupta, R., and Varshney, K. K. (2020). Emerging mechanisms and potential antidepressant action of medicinal plants. *International Journal of Pharmaceutical Sciences and Research*, 11(January), 1–13. [https://doi.org/10.13040/IJPSR.0975-8232.11\(1\).1-13](https://doi.org/10.13040/IJPSR.0975-8232.11(1).1-13) [Mechanism of green tea]

- Kulkarni, S. K., Bhutani, M. K., and Bishnoi, M. (2008). Antidepressant activity of curcumin: Involvement of serotonin and dopamine system. *Psychopharmacology*, 201(3), 435–442. <https://doi.org/10.1007/s00213-008-1300-y> [Mechanism and uses of curcumin]
- Kakkar, V., Modgill, N., and Kumar, M. (2016). Novel drug delivery systems for herbal antidepressants. In *Herbal Medicine in Depression* (pp. 529-556). Springer, Cham. [Mechanism and uses of St. john's wort]
- Lee, G., and Bae, H. (2017). Therapeutic effects of phytochemicals and medicinal herbs on depression. *BioMed Research International*, 2017. <https://doi.org/10.1155/2017/6596241> [Ferulic acid uses and mechanism]
- Hwang, D., Vasquez, I., Galvez, L., Do, H., Ana, A., Matta, S., Zhou, F., Chen, M., and Russo-Neustadt, A. (2017). Ashwagandha and Its Active Ingredient, Withanolide A, Increase Activation of the Phosphatidylinositol 3' Kinase/Akt Cascade in Hippocampal Neurons. *European Journal of Medicinal Plants*, 20(2), 1–19. <https://doi.org/10.9734/ejmp/2017/35355> [Ashwagandha mechanism]
- Sathyapalan, T., Beckett, S., Rigby, A. S., Mellor, D. D., and Atkin, S. L. (2010). High cocoa polyphenol rich chocolate may reduce the burden of the symptoms in chronic fatigue syndrome. *Nutrition Journal*, 9(1), 1–5. <https://doi.org/10.1186/1475-2891-9-55> [Mechanism of cocoa]
- Lokesh Pathak, Yadendra Agrawal & Ashish Dhir (2013) Natural polyphenols in the management of major depression, *Expert Opinion on Investigational Drugs*, 22:7, 863-880, DOI: 10.1517/13543784.2013.794783 [mechanism of quercetin]
- Melo, F. H. C., Moura, B. A., de Sousa, D. P., de Vasconcelos, S. M. M., Macedo, D. S., Fonteles, M. M. de F., Viana, G. S. de B., and de Sousa, F. C. F. (2011). Antidepressant-like effect of carvacrol (5-Isopropyl-2-methylphenol) in mice: Involvement of dopaminergic system. *Fundamental and Clinical Pharmacology*, 25(3), 362–367. <https://doi.org/10.1111/j.1472-8206.2010.00850.x> [Mechanism of carvacrol]
- Turner, R. S., and et al. (2015). placebo-controlled trial of resveratrol for Alzheimer disease. *Neurology*, 85, 1–10. [Uses of resveratrol]
- Vahdati Hassani, F., Naseri, V., Razavi, B. M., Mehri, S., Abnous, K., and Hosseinzadeh, H. (2014). Antidepressant effects of crocin and its effects on transcript and protein levels of CREB, BDNF, and VGF in rat hippocampus. *DARU, Journal of Pharmaceutical Sciences*, 22(1), 1–9. <https://doi.org/10.1186/2008-2231-22-16> [Mechanism of saffron]
- Gohari, A. R., Saeidnia, S., and Mahmoodabadi, M. K. (2013). An overview on saffron, phytochemicals, and medicinal properties. *Pharmacognosy Reviews*, 7(13), 61–66. <https://doi.org/10.4103/0973-7847.112850> [Mechanism and uses of saffron]
- Chang, S. C., Cassidy, A., Willett, W. C., Rimm, E. B., O'Reilly, E. J., and Okereke, O. I. (2016). Dietary flavonoid intake and risk of incident depression in midlife and older women. *American Journal of Clinical Nutrition*, 104(3), 704–714. <https://doi.org/10.3945/ajcn.115.124545> [Introduction to flavonoids]
- Samieri, C., Sun, Q., Townsend, M. K., Rimm, E. B., and Grodstein, F. (2014). Dietary flavonoid intake at midlife and healthy aging in women. *American Journal of Clinical Nutrition*, 100(6), 1489–1497. <https://doi.org/10.3945/ajcn.114.085605> [Action of flavonoids]
- Omar, H. A., Abboud, K., Cheng, N., Malekshan, K. R., Gamage, A. T., and Zhuang, W. (2016). Miean, K. H., and Mohamed, S. (2001). Flavonoid (myricetin, quercetin, kaempferol, luteolin, and apigenin) content of edible tropical plants. *Journal of Agricultural and Food Chemistry*, 49(6), 3106-3112., 18(4), 2315–2344. [Flavonoids]
- Guan, L. P., and Liu, B. Y. (2016). Antidepressant-like effects and mechanisms of flavonoids and related analogues. *European Journal of Medicinal Chemistry*, 121, 47–57. <https://doi.org/10.1016/j.ejmech.2016.05.026> [Mechanism of flavonoids]
- Gill, R., Tsung, A., and Billiar, T. (2010). Linking oxidative stress to inflammation: Toll-like receptors. *Free Radical Biology and Medicine*, 48(9), 1121–1132. <https://doi.org/10.1016/j.freeradbiomed.2010.01.006> [Mechanism of flavonoids]

Paul R. A., Chawki B., and Laurent D (2012). The neurobiology of depression—revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. *Philosophical transactions of the royal society B*, 367(1601): 2378–2381. doi:10.1098/rstb.2012.0190. [Explains about the cellular and molecular aspect of serotonin]

Georgina Rodríguez de L. A, and María Graciela L. O., Brain. (2014). Na⁺, K⁺-ATPase Activity In Aging and Disease *International Journal of Biomedical Science*. 10(2): 85–102. [Explains about electrolyte activity in brain emphasizing on brain sodium-potassium ATPase activity]

Andrea de Abreu Feijó de Mello, Marcelo Feijó de Mello, Linda L Carpenter and Lawrence H Price. Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis. *Rev Bras Psiquiatr* 2003;25(4):231-38[Explains about stress, HPA axis and impairment of serotonin]

Richard. N., and Osmaan. S., (2011). Complementary and alternative medicine for the treatment of major depressive disorder. *Canadian Family Physician*. 57:659-63. [Explains about the evidences supporting complementary and alternative treatment for depression]

Naseem A, Q., and Abdullah M, Al-Bedah. (2013). Mood disorders and complementary and alternative medicine: a literature review. *Neuropsychiatric Disease and Treatment*. 9 639–658. [Describes about complementary and alternative therapy in depression].

Biographical Sketches

Ms. Seema Mehdi is a full-time faculty in the department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher education and Research (JSS AHER), Mysuru, Karnataka, India. She started her career in academics and research from July 2013. She has completed Bachelors of Pharmacy in 2010 and Masters in Pharmacology in 2013, PG Diploma in Principles of Clinical Pharmacology online program by NIH, USA in 2012. PG diploma in Regulatory toxicology in 2018 and in 2019 she has done online certificate course in Drug Metabolism and Pharmacokinetics (DMPK) and pursuing her PhD from the same institution where she is presently working. To her credit, she has 8 years of teaching and research experience in area of Neuropsychopharmacology and Nutritional neuroscience, mainly focused on Depression. She is both diligent in her research practice and committed to the profession. She has 23 research and review publications and authored 4 Book chapters in the indexed national and international journals and books respectively. In 2018, she received a travel grant from JSSAHER to attend an international conference at Paris, France, as a speaker in Young research forum. She has guided 6 post graduate (M Pharm) students and serving as an Advisory board member, reviewer and editorial member for many national and international journals and presently, she is also carrying out a research project which is funded by the JSS AHER.

Dr. K L Krishna has done his post-graduation in Pharmacology from Delhi University and obtained doctoral degree in Pharmaceutical Sciences from Nirma University, Ahmedabad. He is presently working as Assistant Professor in the Department of Pharmacology, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India. He has more than 20 years of teaching as well as research experience in the research area of Neuropharmacology, Toxicity studies and has more interest in Phytopharmacological research. He has published more than 73 research and review papers in peer reviewed national and international journals with Google citations of more than 1000. He has visited Europe and Malaysia to present a scientific paper, for which he was awarded with UGC and JSSU Travel Grant award respectively. He has guided more than 47 M Pharm students and 1 PhD student, currently guiding 4 PhD Scholars. He is a member of many National professional bodies and technical editor/reviewer for many national and international journals. He has special concern to the societal works and currently looking after National Service Scheme (NSS) affairs of the University as JSS AHER NSS Co-ordinator. He has been recognized as CPCSEA nominee and representing CPCSEA at many institutions IAEC and actively involved in preclinical research. He is recognized as Pharmacy Council of India (PCI) Inspector to conduct the PCI Inspections of Pharmacy Colleges across India.

Dr M Kishor. MBBS MD, Associate Professor of Psychiatry, JSS Medical College and Hospital, JSS Academy of Higher Education and Research, Mysuru, Karnataka, India has been Awarded National Fellowship of the Dr. Ramachandra N Moorthy Foundation for Mental Health and Neurological Sciences also an Invited Guest Faculty: Faculty of Medicine, AIMST University, Kedah, Malaysia, JSSAHER delegate to Mayo Clinic, Rochester Minnesota USA, he is Awarded 11th International Neuropsychiatry

Association T S Srinivasan-Award. Editor and Founder Member: India's first monthly newsletter 'MINDS' for Doctors www.mindsnewsletter. Editor of 5 Books, Presented Paper at National and International Scientific conferences. Published papers in National and International Journals- more than 80 publications. Guided MD and PhD scholars. Currently he is involved in DST and DBT Funded Research on cognition. Conducted over 70 Seminars, Symposium and Workshops on Mental health and training for professionals and for educational institutions. He is an invited resource person to All India Radio. His Areas of Interest are Disorders of Mood, Undergraduate and Postgraduate Medical Education, Medical Student's Mental Health, Suicide Prevention, Addiction Medicine, Perinatal and Child Psychiatry. He is a Member-Secretary- JSS Brain Bank and Research Facility, Member JSSAHER Postgraduate Committee, Member of Special Interest Group Geriatrics, JSS University, Secretary of Minds United for Health Sciences and Humanity Trust, Mysuru. Life Fellow- IPS, Life Member IAPP, Life Member- IMA, Secretary IAPP Karnataka 2013-14, EC member IPS KC 2012-14, Convener Indian Psychiatric Society –National Combat Depression Task Force 2018-20 and Organising Chairperson - National Conference on Combating Depression. Co chairperson: Indian Psychiatry Society Faculty Training Task Force.