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Review Article

Neuro-pharmacology of Phytoceuticals: A Brief Review on Depression

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Abstract: Depression is a life-threatening chronic illness that affects people around the world. The medicines used to treat this disease have several side effects and can cause drug or drug-food interactions. In addition, only 30% of patients respond appropriately to existing medications and the rest do not fully recover. Therefore, it seems necessary to find an effective treatment that is reasonably effective, has few side effects, and is low in cost. The purpose of this study was to review animal and double-blind clinical studies on the antidepressant potential of herbs.

Keywords: Depression, Neuropharmacology, Phytoceuticals & botanicals.

INTRODUCTION

Depression is the leading source of disability and affects an estimated 121 million People all over the world. Depression can lead to suicide, a tragic death associated with loss of about 850,000 lives per year. As per World Health Organization survey, in 2020, depression will reach 2nd place in the Handicap chart The Adjusted Life Year (DALY) is calculated for all ages, both sexes. Today depression is was the 2nd causes of DALY in the 1544 age group for both sexes combine [1].

Depression is one of the most commonly observed mental illnesses and affects our way of thinking, feelings, behaviors, and personal well-being. As per WHO, it is forecasted to be the leading cause of various other diseases by 2030. Clinically, depression is treated with various types of artificial drugs that have some limitations, including side effects, slow onset of action, poor remission, and path physiological response rates to complications of depression. .. In addition, treatment cannot be given clinically to patients unless it is harmful to work or family life. In addition, synthetic drugs are usually a single target drug. Unlike synthetic drugs, there are many plants that have flavonoids, have effects on multiple molecular targets, and exhibit antidepressant effects by affecting multiple neurotransmissions or pathways, including: B. Noradrenalinergic, serotonergic, GABAergic and dopaminergic; inhibition of monoamine oxidase and tropomyosin receptor kinase B; simultaneous increase in nerve growth and brain-derived neurotrophic factors.

As per Oxford Dictionary (2008) depression defined as "*A mental condition characterized by harsh feelings of hopelessness and insufficiency, typically accompanied by a lack of energy and interest in life*."

Mental depression, which afflicts a person's mood, thoughts, physical health, and behavior, is a chronic illness. Biological and emotional factors are associated with the symptoms of depression. Delayed thoughts, behaviors, and appetite are biological symptoms, and emotional indicators include mystery, indecision, pessimism, guilt, inadequacy, low self-esteem of ugliness, indecision, and loss of motivation [2].

There are two main types of depression, specifically unipolar depression and bipolar depression. In unipolar depression, mood swings are consistently on the same track and are non-familially associated (about 75% of cases), clearly accompanied by traumatic life events, complemented by indicators of anxiety and agitation. The following types are bipolar depression (about 25% of cases), sometimes referred to as endogenous depression, that exhibit familiar patterns,

differ from external stressors, and often appear in early adult life, resulting in a period of Depression and mania are fluctuating over time few weeks [3].

Epidemiology

Major depression is considered the fourth most common cause of loss measured in disability-adjusted life years (DALYs) and ranks higher than ischemia and cerebrovascular disease. The DALY Diagnosis and Treatment of Depression (Index Words: Depression, Anti-Depression, Medical Education, Diagnosis, Treatment) Typical Symptoms Depression Mood Loss of Interest and Joy in Activities That You Usually Enjoy Loss of Energy or Fatigue Increased Other Symptoms Decreased Concentration and Attention Self-Pessimism and Confidence Sinfulness and Valueless Thoughts Future Pessimistic and Pessimistic Perspectives Self-injurious or suicide thoughts or actions Sleep Difficulty Mild Depression Episode: At least 2 Typical Symptoms and 2 Other Symptoms Moderate Depression Episodes: At least 2 Typical Symptoms and 3 (Preferably 4) Other Symptoms Major Depression Episodes: All 3 Typical Symptoms and 4 other symptoms panel. The lifetime risk of major depressive disorder is 1025% for women and 512% for en. The reason for this difference is not clear, but it is important that women are twice as likely to be depressed as men. Most people with depression go into primary care and the prevalence of major depression in adult's ranges from 5% to 10%. Patients with depression often present with pain, nonspecific musculoskeletal symptoms, and medically unexplained symptoms. Many people with depression show vague symptoms. In one study, up to 70% of depressed patients who reported to their doctor reported only physical symptoms. Up to 50% of depressed patients are undiagnosed despite the high prevalence of primary care [4].

ICD-10 guidelines for identifying a depressive episode

Typical symptoms	Other symptoms
Depressed mood„	Reduced concentration and attention„
Loss of interest and enjoyment of activities that are normally pleasurable„	Reduced self-esteem and self-confidence„
Decreased energy or increased fatigue	Ideas of guilt and unworthiness„
	Bleak and pessimistic views of the future„
	Ideas or acts of self-harm or suicide„
	Disturbed sleep„
	Loss of appetite

Prevalence –*Indian scenario*

Depression is a serious illness and a serious public health problem. While the development of depression can be caused by a combination of factors, understanding the impact, possible triggers, and treatment of the disorder is essential to promoting well-being of those affected. There is also a need to study the current history of depressive disorders worldwide to determine the need and duration of continued treatment. Studies should also evaluate cost-effective treatment models that can be readily used in primary care to effectively treat depression. Depression is the most frequently reported mental disorder in most community studies. It is also reported to be one of the most common psychiatric disorders in the outpatient population and among subjects seen in a diversity of medical and surgical settings. It is also reported to be the most common psychiatric disorder among older adults in a variety of settings. Indian studies have also shown that life events in the period before the onset of depression play an important role in depression. Studies of women also had shown the importance of identifying risk factors such as interpersonal conflict, marital discord, and sexual coercion [5].

Symptoms [6]

- **Depressed mood most of the day**
- **loss of interest in pleasurable activities**
- **decreased or increased appetite**
- **weight loss or gain**
- **difficulty concentrating**
- **insomnia or hypersomnia -feeling of worthlessness or guilt**
- **psychomotor retardation or agitation fatigue -recurrent thought of death, suicide and or a suicide attempt.**

The degree of the depression is supplementary determined by the being there of the following symptoms (World Health Organization; 2004) [7]:

- Sleep disturubance
- Reduced concentration or indecision
- Low self-assurance
- Imbalance appetite
- Suicidal tendency
- Protest or slowing of movements
- fault or self-blame

Causes

Abuse	Past physical, sexual, or emotional abuse can lead depression later in life.
Certain medications	For example, a number of drugs used to treat high blood pressure, such as beta-blockers or reserpine, can increase your risk of depression.
Conflict	Personal conflicts or disputes with family members or friends may leads depression.
Death or a loss	Sadness or grief from the death or loss of a loved one, though natural, can also increase the peril of depression.
Genetics	A past family history of depression may increase the risk. It's consideration that depression is passed genetically from one generation to the next with unknown mechanism.
Major events	Even good events such as starting a new job, graduating, or getting married can lead to depression. So can moving, losing a job or income, getting divorced, or retiring.
Serious illnesses	Occasionally depression co-exists with a major illness or is a reaction to the illness.
Substance abuse	Almost 30% of people with substance abuse problems also have major or clinical depression.

Common symptoms of Depression

In female	In male	In teens
❖ irritability ❖ anxiety ❖ mood swings ❖ fatigue ❖ ruminating (dwelling on negative thoughts)	❖ To drink alcohol in excess ❖ Display anger, and engage in risk-taking as a result of the disorder. ❖ avoiding families and social situations ❖ working without a break ❖ having difficulty keeping up with work and family responsibilities	❖ withdrawing from friends and family ❖ difficulty concentrating on schoolwork ❖ feeling guilty, helpless or worthless ❖ restlessness

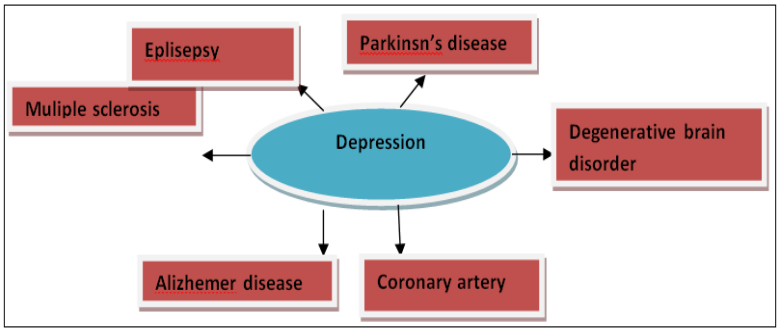
Complication

When left untreated, depression is emotional, behavioral, health, and even legal / financial problems, relationships difficult, social isolation. It can also cause serious complications such as suicide.

Prevention

Preventive measures include regular exercise, a healthy diet, and a stable relationship. They help keep stress low, thereby reducing the chances of feeling depressed again. Depression results are usually favorable. Prompt treatment allows people with depression to return to a happier lifestyle and a more balanced outlook on life [8].

Several of the physical illnesses commonly associated with depression



Pathophysiology of depression

The pathophysiology of depression is caused by a mechanical imbalance between the secretion and synthesis of neurotransmitters (monoamines, norepinephrine, and serotonin), causing brain dysfunction. The "catecholamine hypothesis" suggests that a deficiency of a neurotransmitter or norepinephrine at the synaptic level of the brain causes depression [9].

Disorders of the neurotransmitter system inactivate the monoamine, norepinephrine, and serotonin pathways, causing depressive symptoms.

Today, a variety of antidepressants and psychotherapies are used for the effective treatment of chronic depressive disorders [10].

Alterations of Serotonin in Depression	**Alterations of Norepinephrine in Depression**
• Short concentrations of the major metabolite of 5HT (5-hydroxyindole acetic acid) are found in the CSF of patients who are depressed and suicidal. • Augmented density of 5HT2 receptors has been reported in both blood platelets and brain postmortem tissue of patients with depression (a compensatory response to low synaptic 5-HT concentrations?). • Decreased 5HT transporter (SFRT) binding site density is seen in the midbrain and in blood platelets of patients with depression. • Decreased plasma concentrations of L-tryptophan, the precursor to 5HT, are found in patients with depression. • Depletion of SRI in depressed patients in remission provokes a rapid relapse in depressive symptoms. • Polymorphisms in the SERI gene mediate the depressogenic effects of child abuse and neglect. • Increased MAO-A activity is found in the CNS of depressed patients.	• In depressed case low level of NE metabolites are found in the urine and CSF. • Increased density of -adrenergic receptors is found in postmortem brain tissue in the cortex of depressed suicide victims. • Stress, which precipitates depression in susceptible individuals, increases activity of the NE circuits in the brain. • In depressed case increased MAO-A activity is seemed. • Depletion of NE in depressed patients in reduction treated with a NE reuptake inhibitor precipitates a relapse in depressive symptoms. • In depressed case a dull growth hormone response to the D2 adrenergic agonist clonidine is found NE reuptake inhibitors are effective antidepressants (desipramine,reboxetine& maprotiline).

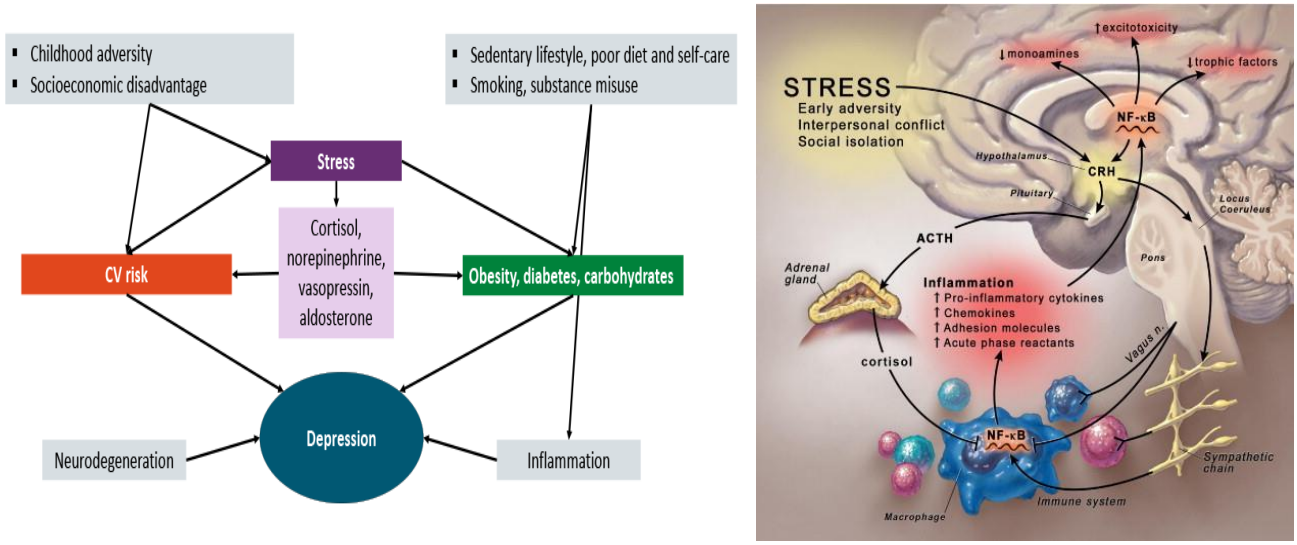


Fig 1: Pathophysiology of depression

Treatment approach towards depression [11]

Antidepressants	Psychological therapies
Tricyclic antidepressants and monoamine oxidase inhibitors **Specific serotonin reuptake inhibitors (SSRIs) includes; fluoxetine,fluvoxamine, sertraline, citalopram, escitalopram andparoxetine.** **Newer generations :** **Venlafaxine and duloxetine target multiple neurotransmittersystems (SNRIs – serotonin noradrenaline reuptakeinhibitors).** **Other antidepressants available includenefazodone, trazadone, mirtazapine, reboxetine & bupropion.**	Cognitive behavioral therapy Inter-personal therapy **Other: Electroconvulsive therapy** It indicated when a rapid response is required, such as in severe depression where food intake is poor, or in those with high suicidal risk. Patients with psychotic depression respond well to ECT. Elderly patients often develop side-effects to antidepressant medication and may find it difficult to tolerate a therapeutic dose. Such patients benefit by ECT as do patients with resistant.

Neuropharmacology of Phytoceuticals

Depression and anxiety are now the second and fifth leading causes of long-term disability worldwide and are intensifying the quest for new treatments. There is much research on herbal extracts and secondary metabolites from plants used in traditional medicine for antidepressant and antidepressant effects [12].

Phytoceuticals	Neuropharmacology
Terpenes	Although most terpenes have a GABAergic mechanism, their action may also occur through the serotonergic system, as confirmed in the study by Costa *et al.*, 2013 [13]
Flavonoids	Quercetin might engage inhibiting NMDA receptors to decrease intracellular calcium that, in turn, inhibits the protein calmodulin, thereby inhibits neuronal nitric oxide synthase to decrease nitric oxide levels (NO) Holzmann I *et al.*, 2015 [14]. On the other hand, neurosteroids and the serotonergic system have also been implicated in the anxiolytic effect of flavonoids, as in the case of puerarin, which increased 5-HT and allopregnanolone levels in the prefrontal cortex and hippocampus in male rats (Qiu ZK *et al.*, 2017) [15]. Rutin at doses of 300 and 562 mg/kg, i.p., or 16 nmol/site, in the basolateral amygdala of male rats tested in EPM. This engaged partial GABAergic neurotransmission that was not associated with BDZ binding in the GABAA receptors (Hernandez-Leon A *et al.*, 2017) [16].

Phytoceuticals	Neuropharmacology
	Viscosine treated male mice assessed in EPM and LDB was observed to exert its exploit through the α1β2γ2L and α2β2γ2L modulates of the GABAA receptors at a site distinct from the one classically associated with benzodiazepine (Karim N *et al.*, 2015) [17].
Alkaloids	Harman bonds to type 5-HT2A serotonergic receptors but shows no affinity to dopaminergic or BZ receptors (Glennon RA *et al.*, 2000) [18]. Punarnavine administered at doses of 20 and 40 mg/kg, v.o., for 14 days decreased immobility on FST, MAO-A activity, and corticosterone levels in both stressed and unstressed mice (Dhingra D *et al.*, 2014), while treatment with evodiamine at 10 and 20 mg/kg in rats exposed to CUMS reversed the decrease in their preference for sugared water and immobility time on FST, but increased 5-HT and NA levels and the protein expression of BNDF in the hippocampus. However, it reduced corticosterone levels, suggesting that it likely altered monoamines and BDNF-TrkB signaling in the hippocampus (Jiang ML *et al.*, 2015) [19, 20].
Sterols	Trevisan *et al.*, 2012 suggested that α-spinasterol has the ability to cross the BBB and exert an antagonistic effect on the transitory potential receptor V1 (TRPV1). When these receptors are expressed in a variety of areas of the brain—prefrontal cortex, amygdala, hypothalamus, and hippocampus—their activation augments the release of glutamate and, consequently, that of GABA, DA, or other catecholamines [21].

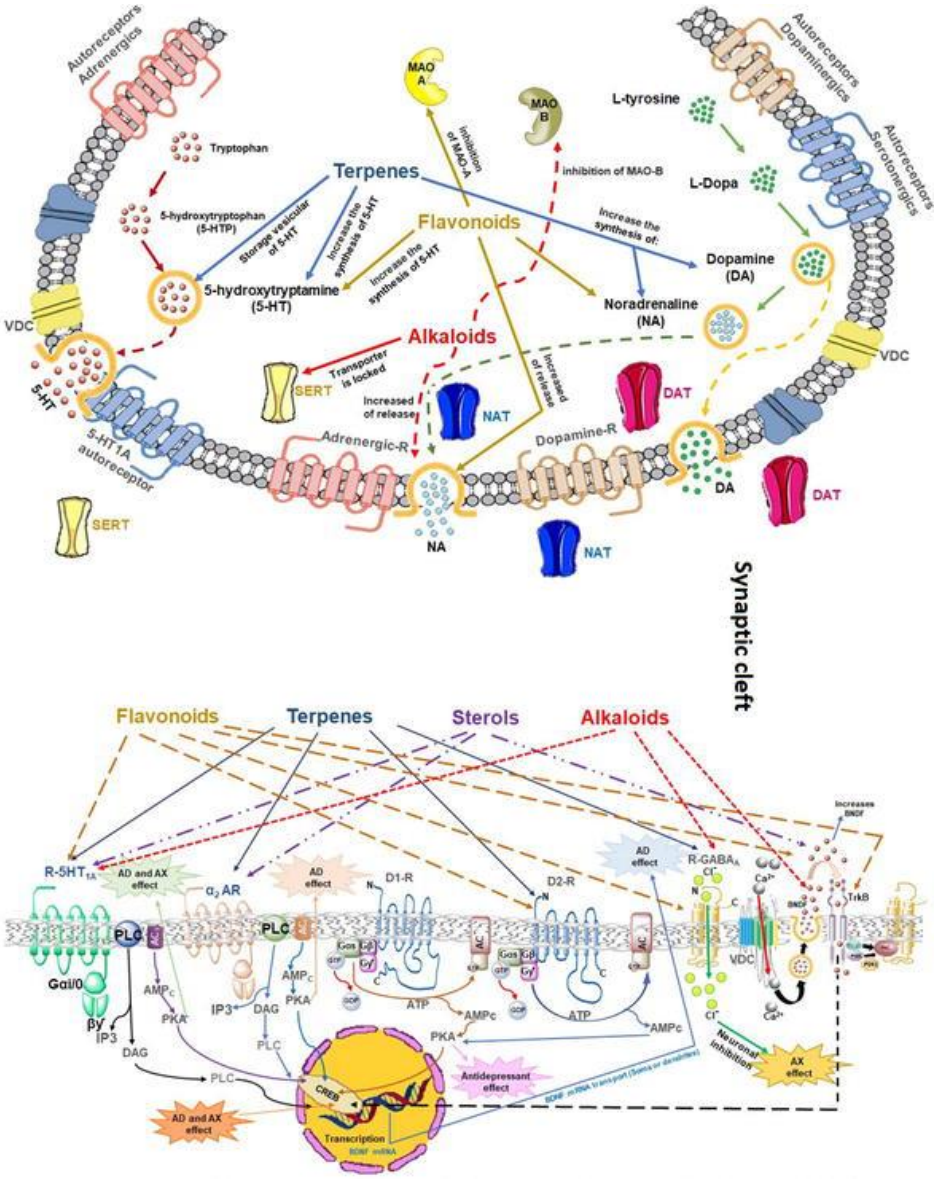
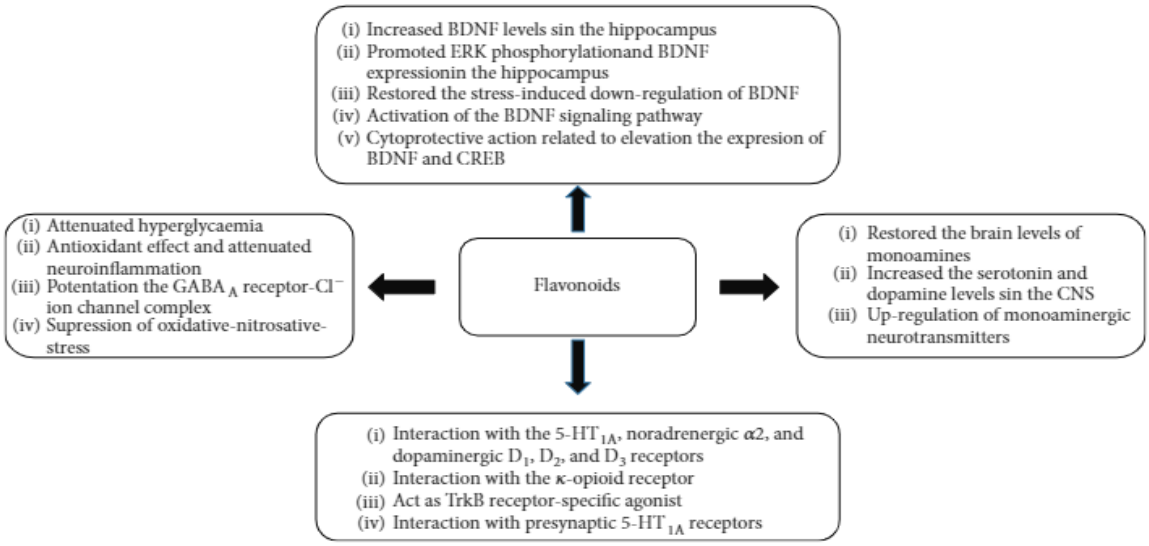
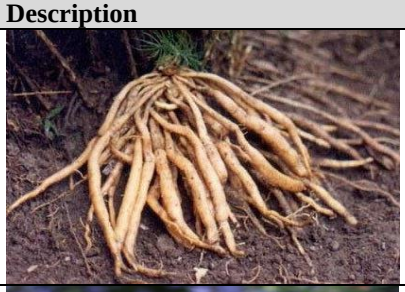


Fig 2: Neuropharmacology of Phytoceuticals

Emerging role of flavonoids as anti-depressant [22]



List of Botanicals used effective against depression

Plants	Description	
Asparagus racemosus (Shatavari) **Asparagaceae**		Root used against epilepsy and biliousness [23].
Rosemarinus officinalis **(Lamiaceae)**		Used to treat different diseases including depression, insomnia and arthritic pains [24].
Curcuma longa **(Zingiberaceae)**		Epidemiological analysis found that people taking curcumin in their daily lives have sharper brain and better cognitive abilities. Curcumin has many interesting properties that justify its use in intrinsic depression. Curcumin is an inhibitor of monoamine oxidase (MAO) enzymes, which regulate the amount of many neurotransmitters and promote hippocampal neurogenesis [25, 26].
Cucurbito pepo **(Cucurbitaceae)**		Pumpkin is a gourd like cucurbita squash and has high anti-oxidant, anti-depressant,anti-helmentitic and anti-microbial potential [27].

Plants	Description	
Dracocephalum moldavica **(Lamiaceae)**		Effective against blood pressure, angina, atherosclerosis, neuralgia, migraine and headache [28].

CONCLUSION

The World Health Balance shows that depression with mental illness affects most of the world's population and causes severe distress. As mentioned earlier, there are many more medicinal plants that have fewer side effects than synthetic drugs and produce alternative and effective treatment options for depression.

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