To Evaluate the Antidepressant Activity on Limonia Acidissima (leaves)

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ABSTRACT

Introduction: - Depression is a heterogenous disorder that affects a person's mood, physical health and behavior. It is caused not only by changing lifestyle as perceived by the general public but also by some of the allopathic drugs for example, anti-hypertensive drugs, reserpine that depletes neuronal storage granules of norepinephrine, serotonin and dopamine, causes clinically significant depression in more than 15% of patients. Patients with major depression have symptoms that reflect changes in brain monoamine neurotransmitters, specifically norepinephrine, serotonin and dopamine. The prevalence of depression in the general population worldwide is estimated to be about 5%. Among patients it ranges from 9% in ambulatory medical patients to 30% in hospitalized patients. According to a world health report about 450 million people suffer from a mental or behavioral disorder, yet only a small proportion of them receive even that basic treatment.Depression accounts for about 12% of the global burden of disease which is expected to rise to 15% by 2020. The major problems of existing allopathic antidepressant drugs include delayed clinical benefit, serious increase the synaptic concentration of at least two of these neurotransmitters, side effects, and a response rate of less than 50%. Commonly used drugs for depression are monoamine oxidase inhibitors and tricyclic antidepressants (TCAs). They namely 5-HT, NE and dopamine (DA). The combined effect of serotonin selective reuptake inhibitor (SSRI) and serotonin reuptake transporter (SERT) inhibitor increases synaptic concentration of 5-HT and its duration of action. Therefore, identification and validation of plant derived substances for the treatment.

Keywords-Forced swim Test, Limonia acidissima (leaves)

INTRODUCTION

Antidepressants are a category of drugs used to treat that symptoms or depressive disorder by correcting chemical imbalances of neurotransmitters within the brain. Chemical imbalances could also be chargeable for changes in mood and behavior. Antidepressants are available in a range of forms, however all of the them work by impacting bound neurotransmitters in brain, like serotonin and norepinephrine. [1]

Antidepressants play a major role in the treatment for those with moderate or severe depression. Though antidepressant might not cure depression, they will cut back the symptoms. The primary antidepressant drugs attempt to fit well during the initial stage of treatment. However, if it does not relieve the symptoms, it causes adverse effects on the individual. So first we have to find the right antidepressant based on the symptoms and the patient health condition. Spectrophotometric and chromatographic methods have been developed for determination of the antidepressant drug sulpiride in pharmaceutical formulation and plasms.[3]

An important theory to explain the cause of depression is the monoamine hypothesis which suggests that there is impairment of monoaminergic functions and the decrease of serotonin, norepinephrine and dopamine levels. At present there are several types of antidepressants used in clinical practice, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective reversible inhibitors of monoamine oxidase (RIMAs), and specific serotonin-norepinephrine reuptake inhibitors. (SNRIs), however, the adverse effects and cost limits their uses. Hence, there is justifiable need to search for therapeutic agents relatively potent, safe, low price, easily available and natural' in origin. Moreover, most of the patients respond to a single drug (most commonly a SSRI or a TCA) but only about 30% achieve remission (complete normalization of symptoms). Thus, combination therapy of antidepressants with different mechanism of action or those having mixed effects on serotonin (5HT) and catecholamines i.e., norepinephrine (NE) and dopamine (DA) levels in brain are often required. This also adds up to the adverse effects of individual drugs. [4]

CLASSIFICASION OF ANTIDEPRESSANT

- Tri cyclic Antidepressants Drugs(**TCA**)

- Monoamine Oxidase Inhibitors**(MAOIs)**

- Reversible Inhibitors of Monoamine Oxidase**(RIMA)**

- Selective Serotonin Reuptake Inhibitors**(SSRI)**

- Noradrenergic and Specific Serotonergic Antidepressants**(NASSA)**

- Nor adrenaline Reuptake inhibitors**(NARI)**

- LithiumSalts

MECHANISM

Neurotransmitters are endogenous chemicals that treatment signals across a synapse from one neuron to another „target neuron. Brain neurotransmitters might not be secreted in adequate amounts to alleviate mood disorders. The chemicals like serotonin, melatonin, and dopamine are the most important in brain for sense. Once the nerves are robbed of those neurotransmitters, they can't send messages to different nerves which leads to depression. The messages that are passed through the neurons are exhibited as emotions, behavior, temperature, appetite, or several alternative functions. The information sent depends on that neurons area unit activated and what a part of the brain isexcited.

Low levels of serotonin and norepinephrine within the conjunction area leads to depression. Hence medications like antidepressant used to treat this work by increasing the number of bound neurotransmitters in that particular part of the brain which leads to transmit the message.

Each type of antidepressant works on brain with little difference, all antidepressant medications influence the neurotransmitter how to work in the brain especially serotonin and norepinephrine, thus controlling the balance of the neurotransmitters.

SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin norepinephrine reuptake inhibitors) have difference mechanism of action. SSRI has three different serotonin reuptake inhibitors those are fluoxetine, paroxetine and sertraline. These have selective effect for both citalopram and fluvoxamine on the serotonin reuptake pump. It leads to primary increase in serotonin at the cell body and dendrites. So, SSRIs act by blocking the serotonin reuptake pump (5-HTT). Whereas SNR is presumably block both 5-HTT and the norepinephrine transporter (NET). Blocking these transporters prevents the neuron from vacuuming up excess neurotransmitters, permitting a lot of to stay within the synapse and stimulate postsynaptic receptors. SSRIs have important effects on NE as well and the SNRIs behave much more like SSRIs.

Tricyclic and tetracyclic antidepressants ease depression by affecting naturally occurring chemical messengers. Cyclic antidepressant usually blocks the results of 2 neurotransmitters known as serotonin and norepinephrine these are available in the brain. This looks to assist brain cells send and receive messages. The roles these chemicals have treat the depression.

Serotonin receptor modulators utilized in the treatment of irritable intestine syndrome. Serotonin plays a major role within the initiation of peristaltic and humor reflexes, and in modulation of visceral sensations.

- SIDE EFFECT

Nausea,Increased appetite and weight gain.Fatigue and drowsiness, Insomnia,Blurred vision,Constipation

- MAIN ADVERSE EVENTS RELATED TO USE OF NEWER GENERATION ADS

Hyponatremia, Sexualdysfunction, Osteoporosis andfractures, Bleeding, Sweating,Sleepdisturbances

- USES

Agitation,childhood enuresis, orbedwetting, generalized anxiety disorder,insomnia

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PLANT PROFILE

FIGURE 5 (Limonia Acidissima)

Limonia acidissima a moderate sized deciduous tree grown throughout India. It is an aromatic, slow increasing up to 9m tall, grows all over India trendy dry and warm areas up to 450m elevation, Often polygamomonoecious tree through rough, spiny bark. The spines stand axillary,short,straight, 2-5 cm long on some of the zigzag twigs.

The leaves are deciduous, alternative, dark-green, leathery,3 to 5-inch-long. Often minutely toothed, blunt or notched at the apex, dotted with oil glands and to some extent lemon- scented when crushed. Flowers small numerous, cloudy- red or greenish, born in small, loose, terminal or cross panicles. The fruit is berry, round toward oval, globose, large, 2 to 5-inch-wide, by a hard, woody rind, which is grayish-white, scurfy rind about 6 mm thick. The pulp remains sticky brown, aromatic odorous, resinous, astringent, acid before sweetish, white seeds scattered through it9, 7. Feronia remains a monotypic genus in the family Rutaceae. There are 2 forms, one with large, sweet pods and the other with small, acid fruits.

SYNONYMS

- Feroniaele phantum Correa
- Feronia Limonia (L.) Swingle
- Schinus Limonia L.

❖ BIOLOGY

Flowers are normally bisexual. In India, the fruits ripen from early October through March. Seedlings resolve not bear fruit until at least 15 years old.

❖ PHARMACOLOGICAL ACTIVITY

• Anti diarrhoeal activity

• Antidiabetic activity

•   Anticancer activity

• Anti diarrhoeal activity

•   Antidiabetic activity

• Anticancer activity

Material & Methods:

Experimental animal

Albino mice of either sex weighing between 25-30gm were used in this study. The animals were procured from animal house of Swami Vivekananda College of Pharmacy Indore M.P. and are acclimatized for 7 days and were housed under standard laboratory condition of temperature (25±2˚C) and relative humidity (55±5%) and were fed with standard pellet diet and water ad libitum. The study was approved by institutional Animal Ethics Committee and conducted as per rules and regulations in accordance to the guidelines of CPCSEA registration no. 1839/PO/ERe/S/15/CPCSEA.

Drugs

Imipramine, Normal saline and another chemical were of analytical grade.

Collection of the plant material

Plant *Limonia acidissima* was collected from Localmarket Indore. Leaves of the plant stood washed with running water, dried in shade at room temperature, ground to powder then stored in air tight bag in dry at low temperature.

Phytochemical evaluation

The phytochemical evaluation of methanolic extract of *Limonia acidissima* seeds are carried out as per standard methods .The presence of flavonoids will determined by lead acetate test, tannins by acetic acid test, saponins by foam test and steroids will determine

❖ **Preparation of extract**

Soxhlet Extraction

The shade dried leaves (600g), was extracted with Ethanol (90%) and water in a Soxhlet extractor. The concentrated material obtained was reduced to a thick mass at room temperature and water was removed by placing it in a desiccator. The weight of the dried mass was recorded and used for experimental studies. The various extracts obtained from the above procedure were used in the form of suspension.[46]

❖ **Experimental protocol**

Overnight fasted animals were selected randomly on the day of experiment for administration of vehicle, standard drug and study drug. The animals remained acclimatized one hour before for behavioral tests. 30 minutes and 1hour time interval between drug administration and behavioral tests were maintained in case of intraperitoneal and oral administrations respectively. The animals were divided into 4 groups of 4 animal each as follows:

Group I (n=4) – Control, received normal saline 2ml/kg, i.p.

Group II (n=4) – (Standard) Imipramine (forced swim test) 10mg/kg.

Group III (n=4) – Limonia Acidissima, 250mg/kg, i.p.

Group IV (n=4) – Limonia Acidissima 500mg/kg i.p.

The antidepressant activity was carried out using two different model.

Percentage Yield

$$\% \text{ Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

$$= \frac{4.26}{50} \times 100 = 8.52 \%$$

Test for antidepressant activity

Behavioral tests:

Forced swim test (FST)

Forced swim test, the most frequently used behavioral model for screening antidepressant-like activity in rodents. The procedure was same as followed previously. Mice were individually forced to swim in open glass chamber (25 ×15 × 25cm) containing fresh water to a height of 15 cm and maintained at 26°±1°C. At this height of water, animals were not able to support themselves by touching the bottom or the side walls of the chamber with their hind-paws or tail. Water in the chamber was changed after subjecting each animal to FST because "used water" has been shown to alter the behavior. Each animal showed vigorous movement during initial 2 min period of the test. The duration of immobility was manually recorded during the next 4 min of the total 6 min testing period. Rat were considered to be immobile when they ceased struggling and remained floating motionless in water, making only those movements necessary to keep their head above water. Following swimming session, mice were towel dried and returned to their housing conditions.

RESULT:

Table 1. Phytochemical analysis of *Limonia acidissima* Leaves Extract

S.NO.	Phytochemical constituents	Methanolic Extract Of *Limonia acidissima*
1.	Alkaloids	+
2.	Flavonoids	+
3.	Phenols	+
4.	Glycosides	+
5.	Saponins	-
6.	Steroids	+
7.	Carbohydrates	+
8.	Terpenoids	+
9.	Proteins and Amino Acids	+

Note- += Positive, -= Negative

Table 2. Effect of *Limonia acidissima* immobility time in Forced Swimming Test:

Group	Drug	Dose	Immobility period (secs)
1	NORMAL SALINE	2ml/kg i.p.	135
2	IMIPRAMINE	10mg/kg i.p.	98
3	Limonia acidissima (test I)	250mg/kg	115
4	Limonia acidissima (test II)	500mg/kg	133

Graph 1 : Effect of Limonia acidissima on immobility period (secs) of mice using Force Swim Test:
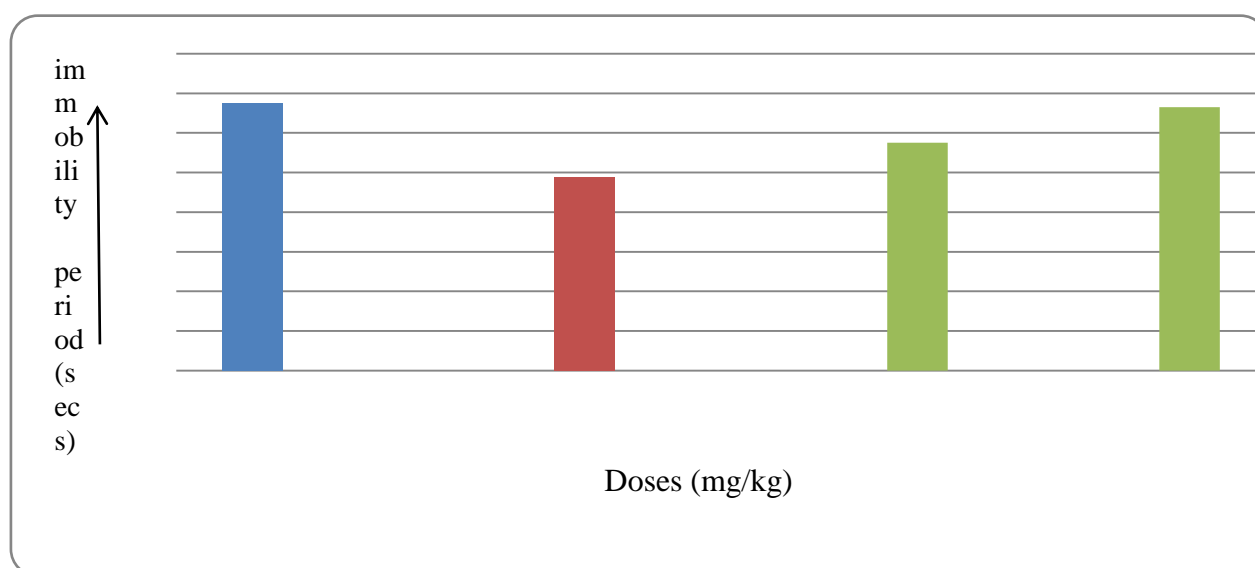
CONCLUSION

Hence Limonia acidissima leaf extract possesses antidepressant effect in animal models of depression which was comparable to that of Imipramine as demonstrated in this study. The phytochemical examination, departure of active ingredients and further investigation in this line is essential to establish its more effective therapeutic benefits.

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