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Evaluation on Pharmacological and Toxicological Studies of *Cassia Fistula* for Antidepressant Activity in Mice

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Abstract: The present study was designed to perform evaluate antidepressant activity of ethanolic extract of cassia fistula leaf. Leaf of cassia fistula was extracted using ethanol as solvent by soxhlet apparatus. The evaluation of antidepressant activity was done using tail suspension test, and locomotor activity induced antidepressant models in wistar albino rats. The work entitled evaluation of anti-depression activity of leaf of cassia fistula was to determine the efficacy and safety in experimental animals. Both aqueous and alcoholic extract of leaf of cassia fistula (linn.) have shown significant reduction in depression of CNS as compared to tail suspension animals and locomotor activity confirming their anti-depression property. The aqueous and alcoholic extract of leaf of cassia fistula (linn.) has shown significant decrease in brain seratonin levels, increase in norepinephrine levels.

Keywords: Anti-Depression, Cassia Fistula, Serotonin, Norepinephrine, Alcoholic Extract.

INTRODUCTION

Depression is one of the most common psychiatric disorders with high mortality, morbidity and economic burden worldwide (1). Depression is considered as syndrome referring to a constellation of depressive symptoms and nosological category is a combination of misery and lethargy (2). Depression is heterogeneous disorder that affects ones mood, physical health and behaviour. Patients with major depression have symptoms that reflect changes in brain monoamine neurotransmitters, specifically norepinephrine, serotonin and dopamine (3). According to International Classification of Diseases-10 (ICD-10) and Diagnostic and Statistical Manual-IV (DSM-IV) depression episodes are recognized as individual suffering from depressed or sad mood, showing loss of energy and diminished activity (Patel, 2001). Theoretical

explanation of depression includes loss of interest, virtually in all activities, a significant reduction in productivity and negative impact on health (4).

Major depressive disorders have been traditionally considered as a neurochemical disorder etiologically. For decades depression has been linked particularly to disturbance in serotonergic and noradrenergic neurotransmitters. Major depression involves disturbance in emotional, cognitive, immune, autonomic and endocrine functions (5). Assessment of cerebrospinal fluid (CSF) chemistry, neruo-endocrine response to pharmacological challenge, neuroreceptor and transporter binding revealed that depressive patients show abnormalities in serotonergic, noradrenergic and dopaminergic system. Emotional, cognitive, immune, autonomic and endocrine system shares neurotransmitters, peptides, hormones and cytokines as well as their receptor as a common language to communicate with each other (6). This interplay is important during stress response. Stressful events are the precipitating factors for the onset of depression (7).

Depression is a state of low mood and aversion to activity that affects person's thoughts, behavior, feelings and physical well-being. Depressed people feel sad, anxious, empty, hopeless, helpless, worthless, guilty, irritable, or restless. They may lose interest in activities that once were pleasurable, experience loss of appetite or overeating, or problems concentrating, remembering details or making decisions; and may contemplate or attempt suicide. Insomnia, excessive sleeping, fatigue, loss of energy, or aches, pains or digestive problems that are resistant to treatment may be present (8). Depressed mood is not necessarily a psychiatric disorder. Depressed mood is a normal reaction to certain life events, a symptom of some medical conditions, and side-effect of some medical treatments. Depressed mood is also a main or common feature of certain psychiatric syndromes such as clinical depression (9).

Depressed mood can be the result of a number of infectious diseases and physiological problems including Addison's disease, Lyme disease, sclerosis, sleep and disturbed circadian rhythm. It is often one of the early symptoms of hypothyroidism (reduced activity of the thyroid gland). A number of psychiatric syndromes feature depressed mood as a main symptom. The mood disorders are a group of disorders considered to be primary disturbances of mood. These include major depressive disorder (MDD), commonly called major depression or clinical depression, where a person has at least two weeks of depressed mood or a loss of interest or pleasure in nearly all activities; and dysthymia, a state of chronic depressed mood, the symptoms of which do not meet the severity of a major depressive episode. Another mood disorder, bipolar disorder, features one or more episodes of abnormally elevated energy levels, cognition and mood, but may also involve one or more depressive episodes. Outside the mood disorders, borderline personality dis order commonly features depressed mood, and adjustment disorder with depressed mood is a mood disturbance appearing as a psychological response to an identifiable event or stressor, in which the resulting emotional or behavioral symptoms are significant but do not meet the criteria for a major depressive episode (APA, 2000) neurotransmitter levels result in the systemic effect with hyper activation of hypothalamic pituitary adrenal axis (HPA) besides psychological and behavioral consequences (10) which result in hypercortisolemia causing a

wide array of organ and immune changes (11). One among the affected part is hippocampus which expresses high number of steroid receptors, has key role in declarative memory tasks and many other cognitive functions (12). Depression is usually treated with the antidepressant drugs, which cascade serious side effects. So, currently and globally there is greater interest in herbal remedies.

Herbal medicines are an important part of the culture and traditions. Today, most of the population is reliant on herbal medicines for their health care needs. Apart from their cultural significance, this is because herbal medicines are more accessible and affordable (13). There is an increasing trend worldwide, to integrate traditional medicine with primary health care. Renewed interest in traditional pharmacopoeias has meant that researchers are concerned with determining the scientific rationale for the plant's usage. Traditional knowledge help scientists to target plants that may be medicinally useful (14).

Herbs have been highly valued and used regularly for thousands of years by the world as the medicine of the masses. Man has always searched for herb that heals the body and soothes the mind and there has never been a shortage of vegetation to investigate with some 20,000 species that have been used by various cultures. Medicinal plants have been used to treat psychotropic and behavioral conditions as anxiety, depression, seizures, memory impairment, dementia, insomnia, and drug intoxication. A new study published in Germany has found that St. John's Wort, a medicinal herb is more effective than a popular antidepressant drug in treating depression.

MATERIALS & METHOD

Collection of Plant Material

The leaves of the Cassia Fistula plant were collected from a nearby region in Madhya Pradesh based on geographic availability, and they were then cleaned with tab water and let too dry at room temperature. The materials were crushed and put through a 20-mesh filter once they had dried. The powdered drugs were kept out of direct sunlight and kept in sealed containers until needed.

Extraction of Plant Material

The powdered root was extracted with petroleum ether (40-60°) to remove lipids and then again extracted with ethanol in soxhlet extractor. The extract was concentrated under vacuum to get the residue. The residue was dried in vacuum desiccators. The extractive yield of ethanol was found to be more, and it was selected for antidepressant activity. All the test suspensions (200 mg/ml) were prepared in the vehicle, i.e., 5% w/v acacia mucilage and were administered in the dose of 200 mg/kg orally. Each time before extracting with alcohol, petroleum ether treated drug was air dried. For aqueous extract fresh untreated drug was taken. (15)

After the effective extraction, solvent was concentrated at room temperature in reduced pressure using a rotary evaporator and water was removed by heating on water bath. The color and

consistency of the extract was noted. Extract were subjected to chemical investigation and pharmacological screening for its anti depressant activity.

Table-1. Results of preliminary phytochemical analysis

Sr. No.	Name of the Test	Observation	
		Alcoholic Extract	Aqueous Extract
I.	**Tests for sterols**		
	1. Salkowski's Test	+	-
	2. Libermann Burchard's Test	+	-
II.	**Test for glycosides**		
	1. Baljet's Test	+	+
	2. Keller–Killiani Test	+	+
	3. Legal's Test	+	+
III.	**Tests for saponins**		
	1. Foam Test	+	+
	2. Haemolysis Test	+	+
IV.	**Test for carbohydrates**		
	1. Molish's Test	+	+
	2. Barfoed's Test	+	+
	3. Benedict's Test	+	+
V.	**Tests for alkaloids**		
	1. Mayer's Test.	-	-
	2. Wagner's Test.	-	-
	3. Dragendorff's Test	-	-
	4. Hager's Test	-	-
VI.	**Tests for flavonoids**		
	1. Ferric chloride Test.	+	+
	2. Shinoda Test.	+	+
	3. Alkaline Reagent Test.	+	+
	4. Lead Acetate Test.	+	+
VII.	**Tests for tannins**		
	1. Ferric chloride Test.	-	-
	2. Gelatin Test	-	-
VIII.	**Test for amino acid and protein**	-	-
	1. Million's Test	-	-
	2. Ninhydrin's Test		
IX.	**Test for fixed oils and fat**	-	-

(+) indicate positive result (-) indicate negative result.

Pharmacological study: - Evaluation of anti-obesity activity

Selection of animals: - (Animal care and handling)

Wistar albino rats of either sex weight (75-175 g) were selected respectively, procured from institute's animal breeding house. The animals were acclimatized to the standard laboratory conditions in well cross ventilated animal house at temperature 25±2°C relative humidity 44-56% and light and dark cycles of 10 and 14 hours respectively for 1 week before and during the experiments. The animals were fed with standard diet and water *adlibitum*. The experiments were approved by CPCSEA and the institutional ethics committee.

In-Vivo antidepressant studies

Animals

Adult healthy Swiss Albino mice of either sex (20-30g) were used. The animals were acclimatized for the laboratory conditions for a period of ten days i.e. room temperature (27±3^{o}C), relative humidity (65±10%), and 12h light/dark cycle. All animals were fed with rodent-pellet diet and water was allowed *ad libitum* under strict hygienic conditions.

Acute toxicity study

The acute toxicity study was conducted as per the OECD guidelines 423 (16) where the limit test dose of 2000 mg/kg was used (17). Observations were made and recorded systemically 1, 2, 4 and 24 h after dose administration for skin changes, morbidity, and aggressiveness, sensitivity of the sound and pain, as well as respiratory movement.

Behavioral parameters

Test for locomotor activity

The locomotor activity was measured using Acto photometer. It consists of cage which has 30 X 30 X 30 cm, and at the bottom six lights and photocells were placed in the outer periphery of the bottom in such a way that a single mouse blocks only one beam. Photocell is activated when the rays of light falls in photocells, the beam of light is interrupted as and when animal crosses the light beam, the number of interruptions were recorded for a period of 5 minutes (18).

Tail suspension test

The total duration of immobility by tail suspension was measured according to the method of (19). Mice both acoustically and visually isolated and suspended 50cm above the floor by adhesive tape placed approximately 1cm from the tip of the tail, immobility time was recorded during a 15minutes test for animals of all groups.

Experimental protocol for antidepressant activity

Mice were randomly divided into IV groups with six animals in each group.

Group I received only vehicle (1% tween 80 solution p. o, daily) and served as control;
group II received standard antidepressant drug- Imipramine (25mg/kg p.o, daily);
group III group received Cassia fistula 250mg/kg Aq. extract (p.o, daily) in 1% tween 80 respectively, group
IV received Cassia fistula250mg/kg methanolic extract in 1% tween 80 respectively, p.o, daily,
At the end of experimental period (7 days of treatment) the animals were fasted overnight and sacrificed by cervical dislocation. The brains were excised immediately and the brain tissue was homogenized and used for further analysis.

RESULT & DISCUSSION

Effect of hydroalcoholic extract of Cassia Fistula on Spontaneous motor activity

The results of the effect of hydroalcoholic extract of Cassia Fistula on spontaneous motor activity were summarized in Figure 45 and showed that there is no significant change in the spontaneous motor activity of Cassia Fistula at lower and higher doses when compared to control group.

Effect of hydroalcoholic extracts of Cassia Fistula on immobility time in TST

The results of the effect of hydroalcoholic extract of Cassia Fistulaon tail suspension test (TST) were summarized in Figure 46. Imipramine at a dose of 25 mg/kg showed significant decrease in immobility time ($P<0.001$) as compared to control group. Cassia Fistula showed significant decrease in immobility time ($P<0.001$) in a dose dependent manner as compared to control group.

Effect of hydroalcoholic extract of Cassia Fistula on immobility time in FST

The results of the effect of hydroalcoholic extract of Cassia Fistula on immobility time in FST were summarized in Figure 47 and imipramine at a dose of 25 mg/kg showed significant decrease in immobility time ($P<0.001$) as compared to control group. Cassia Fistula showed significant decrease in immobility time ($P<0.001$) in a dose dependent manner as compared to control group.

Table 2: Reducing power assay of Cassia Fistula

S.no	Concentration of *Ascorbic acid*, Cassia Fistula, (µg/mL)	Percentage of inhibition	
		Ascorbic acid	*Cassia Fistula*
1	40	20.87± 0.01	61.67 ±0.11

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2	80	34.46± 0.02	69.87 ±0.34
3	120	53.40± 0.02	70.73 ±0.06
4	160	85.92± 0.01	77.24 ±2.73
5	200	99.03± 0.01	83.01 ±0.60
	IC_{50}	**112.5µg/mL**	**34.57µg/mL**

Values are expressed as Mean ± SEM (N=3 Readings)

CONCLUSION

Cassia fistula were found to have potent antioxidant activity, as evident from invitro antioxidant studies against DPPH radical scavenging, Nitric oxide radical scavenging, Hydrogen peroxide radical scavenging activities, Reducing power assay, Total antioxidant capacity indicating that *Cassia fistula* were effective in scavenging the ROS generated during major depressive disorder *Cassia fistula* showed decreased immobility in FST and TST indicating their antidepressant activity.*Cassia fistula* showed the involvement of serotonergic system in their antidepressant activity, & also involvement of adrenergic system.

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