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Effect of *artocarpus heterophyllus* phenolic seed extract in animal models of depression: A preclinical study

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Abstract

Background: The jackfruit (*Artocarpus heterophyllus* Lam.) is an integral part of common Indian diet. The present study was carried out to elucidate the possible antidepressant activity of jack fruit in Swiss albino mice.
Objective: To evaluate the possible antidepressant activity of *Artocarpus heterophyllus* seed extract in *Swiss albino* mice.
Methodology: A total of 30 (n=30) Male Swiss albino mice weighing 25-35 g, divided into five groups of six animals each was used for the study. *Artocarpus heterophyllus* (Jackfruit) collected grinded and crushed well and uniformly. Powder was subjected to solvent extraction with phenol in a soxhlet apparatus. Antidepressant activity of phenolic extract of *A. heterophyllus* seeds was evaluated by using two models –Forced Swimming Test (FST) and Tail Suspension Test (TST).
Results: One way ANOVA was used for multiple comparisons followed by post hoc (bonferroni test) for comparison between groups. *Artocarpus heterophyllus* (Jackfruit) at the dose of 200 mg/kg significantly reduced the immobility time in both the tests (TST and FST) compared to the control. The reduction in duration of immobility at the dose of 200 mg/kg was comparable to the standard drug Imipramine.
Conclusion: The phenolic extract of seeds of *Artocarpus heterophyllus* has significant antidepressant activity in both the animal models of depression (FST and TST).
Keywords:-*Artocarpus heterophyllus,* anti-depressants, Forced Swimming Test and Tail Suspension Test

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1. Introduction

Depression is considered as an affective disorder characterized primarily by change of mood. It is associated with significant socioeconomic problems, morbidity and mortality. According to the World Health report approximately 450 million people suffer from a mental or behavioral disorder [1], yet only a small minority of them receives even the most basic treatment. Various drugs are available for the treatment of depression. They include monoamine oxidase inhibitors, selective and non-selective monoamine reuptake inhibitors and selective serotonin reuptake inhibitors [2]. These medications work by normalizing the levels of neurotransmitters, notably serotonin and nor-epinephrine. Approximately two-thirds of the depressed patients respond to the currently available treatments but the magnitude of improvement is still disappointing. More over these drugs have unusual side effects like. The medical need for newer, better-tolerated and more efficacious treatments remains high. Oxidative stress as a patho-physiological mechanism in depression [3]. The antioxidant properties of natural products are suggested to have a role in reversing the deleterious effect of aging on neuronal communication and behaviour. The jackfruit (*Artocarpus heterophyllus* Lam.) is an integral part of common Indian diet. The results of different in vitro

antioxidant activity assays indicated that seed extracts possessed appreciable free radical scavenging effects and metal ion chelating activity in a concentration-dependent manner [4] So the present study carried out to elucidate the possible anxiolytic and potentiating activity of *Artocarpus Heterophyllus* phenolic seed in Swiss albino mice.

1.1 Objective

To evaluate the possible antidepressant activity of *Artocarpus Heterophyllus* seed extract in Swiss albino mice.

2. Materials and methods

2.1 Animals:

Institutional Animal Ethical clearance was obtained before conducting the study. Male Swiss albino mice weighing 25-35 g. were used for the study. The mice were housed in the central animal house of the Department of Pharmacology, Yenepoya Medical College, Yenepoya Deemed to be University, Mangalore, Karnataka, India under suitable conditions of housing, temperature, ventilation and nutrition. The study was conducted in accordance with standard CPCSEA guidelines.

2.2 Collection of plant material:

Artocarpus heterophyllus (Jackfruit) was collected from the places around the Mangalore, Karnataka, India**.** *A. heterophyllus* seeds were cleaned and sliced with around 2mm thickness and sun dried for 7 days without removing the thin brown spermoderm covers the fleshy white cotyledons. The dried seeds were grinded uniformly for 10 minutes with highest precaution to avoid any contamination and made them as particle-sized powder (<0.5mm). The powdered material was packed in plastic pouch and stored in normal room temperature until use. The procedure for jackfruit seed powder extraction was followed based on previous reports in the literature [5]. Powder was subjected to solvent extraction with phenol in a soxhlet apparatus. After exhaustive extraction, the phenolic extract was dried at low temperature under reduced pressure in a rotary evaporator to obtain greenish-black colored residue which was used for anxiolytic studies.

2.3 Drugs: The standard antidepressant drug Imipramine tablet 5mg was purchased from institutional pharmacy store.

2.4 Inclusion criteria:

- Male Swiss albino mice weighing between 25-35g.
- Age 3-4 months.
- Healthy with normal behavior and activity.

2.5 Exclusion criteria:

- Mice <25g and >35 and age <3 months and > 4 months.
- Female mice were excluded
- Animals previously used in other experiments.

A total of 30 animals (n=30) were used. Mice were divided into five groups of six animals each.

2.6 Acute oral toxicity test

The acute toxicity study is done to find out the therapeutic index, i.e. the ratio between the pharmacologically effective dose and lethal dose on the same strain and species. The extract of *Artocarpus heterophyllus* was safe up to the dose of 2000mg/kg (p.o) body weight. Mice were administered the phenolic extract of *Artocarpus heterophyllus* in a dose of 5, 50, 300 and 2000 mg/kg per orally to find out safe dose range in animals. Mice were observed for 48 hours from the time of drug administration and looked for general behavior and mortality.

Behaviour of the animals was closely observed for the first 3 h then at an interval of every 4 h during the next 48h. The extract did not cause mortality in the mice during 48h observation but some behavioural changes were noted. There was no significant difference in food and water intake among the animal groups studied. Then the results of the LD_{50} study performed on mice were expressed using Karber's method. It can be concluded that there is no mortality and toxicity symptoms for the phenolic extract.

Acute oral toxicity test was carried out in male *Swiss albino* mice according to Organization of Economic Co-operation and Development (OECD) guidelines, ANNEX-423 [6].

Antidepressant activity of phenolic extract of *A. heterophyllus* seeds was evaluated by using two models – Forced Swimming Test (FST) [7] and Tail Suspension Test (TST) [8]. The experiment was conducted in Ethanopharmacology laboratory of the Department of Pharmacology, Yenepoya Medical College, Yenepoya University, between 8:00 A.M. to 2:00 P.M. The food and water was removed during study period. Animals were weighed and appropriate dose of drug was given per orally (p.o) to the different groups. The experiment was conducted sixty minutes after the administration of the drug.

2. Forced Swim Test:

Mice will be housed in individual cages one day prior to experiment. Mice will be individually forced to swim inside a vertical Plexiglass cylinder (40 cm x 18cm and containing 15 cm of water at 25^{o}C) and were observed for 6 minutes. Evaluation was initiated after 2 minutes. Initially mice will be hyperactive vigorously swimming in circles, trying to climb the wall or diving to the bottom. After 2-3 min this activity will get subsided and there will be a period of immobility or floatation of increased duration. Duration of immobility will be noted for each mice. Antidepressant activity will be described by increase in the duration of mobility or decrease in the duration of immobility. After the test, animals will be allowed to dry and returned to their home cages.

2.8 Tail Suspension Test

Mice will be rendered immobile by suspending the mice from tail to induce behavioural despair. In this situation animal shows two types of behaviour: Agitation (mobile) and immobility. The total time of immobility spent by mice is the time of helplessness (depression). In this experiment, mouse will be hung upside down by its tail such that its nostril touches the water surface kept in a container. Initially the mouse tries to escape by making vigorous movement but fails to escape and becomes immobile. The total time of immobility in 5 min duration will be recorded.

Table 1: Groups of animals

Groups	Dose
Group 1	Control 0.05ml/10g of Normal Saline
Group 2	15 mg/kg b.w Imipramine
Group 3	Phenolic extract of *AH* seeds extracts 100 mg/kg b.w
Group 4	Phenolic extract of *AH* seeds extracts 200 mg/kg b.w
Group 5	Combination of imipramine 15 mg/kg+ AH 200 mg/kg b.w

3. Results

One way ANOVA was used for multiple comparisons followed by post hoc (bonferroni test) for comparison between groups.The results are expressed in Mean ± SD.[9]

Table 2: Effect of AH on immobility time in mouse forced swim test (FST)

Group No.	Treatment	Immobility time (day 15)
1	Vehicle control (10 ml/kg)	128±2.73
2	Imipramine (15 mg/kg)	85.67±4.27
3	AH (100mg/kg)	101.33±3.71
4	AH (200mg/kg)	86.33±3.74
5	AH (100mg/kg) + Imipramine (15 mg/kg)	87.67±1.58

Table 3: Effect of AH on immobility time in mouse tail suspension test (TST)

Group No.	Treatment	Immobility time (day 15)
1	Vehicle control (10 ml/kg)	194±6.18
2	Imipramine (15 mg/kg)	149.67±4.33
3	AH (100mg/kg)	161.67±8.12
4	AH (200mg/kg)	147.33±10.27
5	AH (100mg/kg) + Imipramine (15 mg/kg)	163.07±4.60

Forced swim test

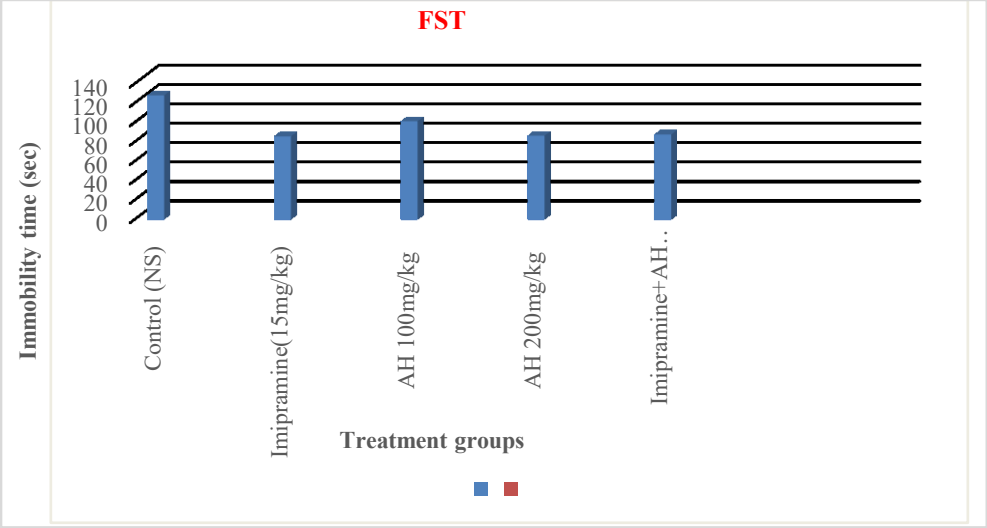

Figure 1: Assessment of immobility;

AH treatment (200 mg/kg b.w) significantly decreased immobility time when compared to the control group; P<0.05 considered as statistically significant, values were expressed as Mean±SD

Tail suspension Test

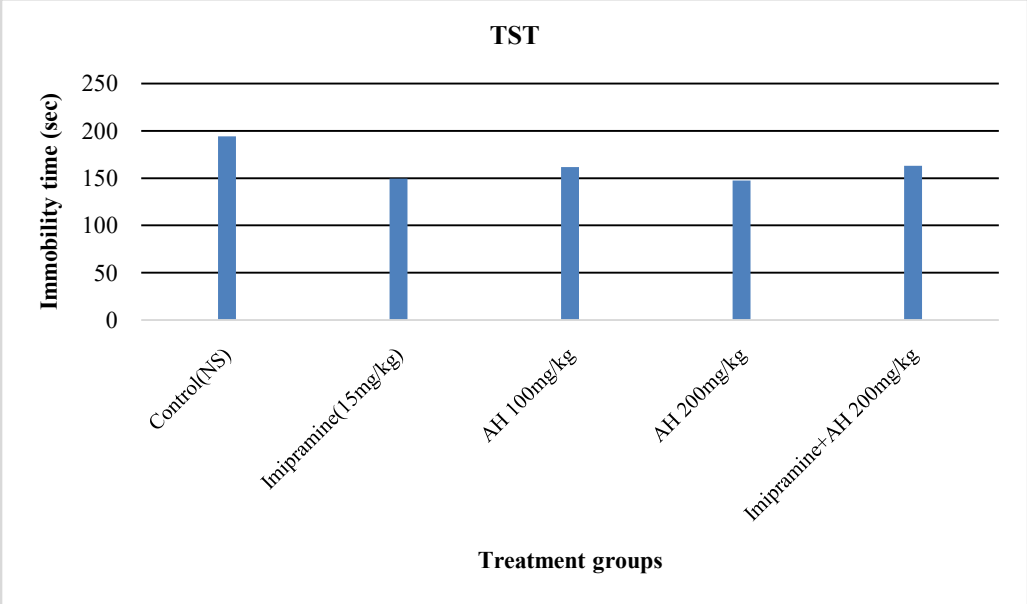

Figure 2: assessment of immobility

AH treatment (200 mg/kg b.w) significantly decreased immobility time when compared to the control group; $P<0.05$ considered as statistically significant, values were expressed as Mean±SD

4. Discussion

Mood disorder is one of the most common mental illnesses. Prevalence of depression alone in general population is estimated to be around 5% with suicide being one of the most common outcomes [10]. Most of the drugs which are being used now in the treatment of depression have adverse effects that affect the quality of life of the patient. This may leads to patient's non-compliance to medication, which further worsens the problem.

The present study evaluated the anti-depressant activity of Phenolic extract of *Artocarpus Heterophyllus* (AH) seed extract in 2 models of depression (FST and TST). Both AH 100 mg and 200 mg showed significant reduction in the immobility time when compared to the control AH 200 mg showed significant reduction in the immobility time when compared to the control, standard drug imipramine and AH 100mg. AH 100 mg and combination of AH 200 mg+ imipramine showed equal efficacy as that of standard drug (imipramine). Oxidative stress is one of the mechanism involved in the neuropsychiatric problems [11].

Exact mechanisms underlying the antidepressant action cannot be concluded at the moment due to the presence of large number of phytochemicals in the AH. However, the antidepressant activity may be attributed to the presence of saponins, alkaloids, polyphenols, flavanoids and sterols in the extract.[12]

Literature survey reveals AH has free radical scavenging activity and antioxidant property [13]. Previous studies have done on fruits, roots and leaves extract of AH.[12] This is the first anti-depressant study done using seed extract of Artocarpus Heterophyllus.

5. Conclusion

Herbal medicines have a prime importance in the health care system of our country. Many known and unknown plants may be a potential source to make novel compounds with medicinal values. But appropriate measures are to be taken to test the safety, efficacy and superiority of these herbal products over non-herbal medicines. The products should not be recommended without proper preclinical and clinical studies.

From this study it can be concluded that the phenolic extract of seeds of *Artocarpus heterophyllus* has significant antidepressant activity in both the animal models of depression (FST and TST) in the doses of 100mg/kg and 200mg/kg. It can be presumed that the presence of flavonoids, saponins and alkaloids in the *Artocarpus heterophyllus* may be responsible for the anti-depressant effect.

However this is just a preliminary study .Further studies has to be carried out to find the exact mechanism responsible for the anti-depressant effect by isolating the active constituents.

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