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Screening of Analgesic and Immunomodulator activity of *Artocarpus heterophyllus* Lam. Leaves (Jackfruit) in Mice

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Adaptability is probably the most distinct characteristics of life which may be defined as sum of all nonspecific response of the body to any demands made upon it; fundamentally it was a physiological response; primary object of which was to maintain life and to re-establish the normal state. Analgesic and Immunomodulator activity of leaves of *Artocarpus heterophyllus* Lam. was evaluated by using Eddy's hot plate method and Swimming endurance test at the dose levels of 250 and 500mg/kg in Swiss albino mice respectively. The methanolic and aqueous extracts of leaves of *A. heterophyllus* were administered to the experimental animals among which the methanolic extract of *A. heterophyllus* leaves have shown to be exhibit significant analgesic and immunomodulator effect by paw licking and increasing the swimming or survival time ($P < 0.001$) respectively in mice

Keyword: *Artocarpus heterophyllus* Lam., Eddy's hot plate, Swimming endurance test, Analgesic, Immunomodulator

1. Introduction:

Immunomodulatory agents are used to either suppress or stimulate the immune responsiveness of an organism against the invading antigens. Several plant products have been reported for immunomodulatory activity and many formulations of these plant products are available to enhance the immune system. Plants are the essential and integral part in complementary and alternative medicine. Plants have the ability of the formation of secondary metabolites like proteins, flavonoids, alkaloids, steroids and phenolic substances which are in turn used to restore health and heal many diseases^[1,2].

Ayurveda and other Indian literature mention the use of plants in treatment of various human ailments. There are many plants, which are having immunostimulatory where as other have immunosuppressant activity^[3]. The *Artocarpus*

heterophyllus Lam. is a species of tree of the mulberry family *Moraceae*, known by other names jackfruit. It is a large, evergreen tree, 10-15m in height, indigenous to the evergreen forests at altitude of 450-1,200m and cultivated throughout the hotter parts of India. *Artocarpus heterophyllus* Lam. is an important source of compounds like morin, dihydromorin, cynomacurin, artocarpin, isoartocarpin, cyloartocarpin, cycloheterophyllin ($C_{30}H_{30}O_7$), artocarpesin, oxydihydroartocarpesin, artocarpetin, norartocarpetin, cycloartinone, betulinic acid, artocarpanone and heterophylol^[4,5] which are useful in fever, boils, wounds, skin diseases, convulsions, diuretic, constipation, ophthalmic disorders and snake bite etc. The leaves are useful in fever, ulcers, boils wounds, skin diseases, antidiarrhoeal, analgesic and as immunomodulator. The ripe fruits are sweet,

cooling, laxative, aphrodisiac, and tonic. The seeds are sweet, diuretic, aphrodisiac and constipating^[6]. The plant is reported to possess antibacterial^[7], anti-inflammatory^[8], antidiabetic^[9], antioxidant^[10], antifungal^[11] and immunomodulatory properties^[12].

Artocarpus heterophyllus Lam. is used as a traditional medicine as analgesic and immunomodulator. Immunomodulator activity has been scientifically proved in fruits whereas analgesic activity is not scientifically proved. The aim of the present study is to investigate its analgesic and immunomodulator activity on leaves of *A. heterophyllus* in a scientific manner which has not been carried out so far.

2. Materials and Methods

2.1 Collection of Plant Materials

The leaves of *Artocarpus heterophyllus* Lam were collected from local area of Lucknow and authenticated from Taxonomic division of National Botanical Research Institute, Lucknow and a voucher specimen was deposited for future references (ref. no.: NBRI/CIF/Re./08/2008/32).

2.2 Preparation of Extracts

The leaves were washed with tap water and then with distilled water and dried in shade. Leaves were comminuted to powder and extracted with methanol and water. The extracts were concentrated under reduced pressure using rotavapour.

2.3 Animals

Adult male Swiss albino mice weighing 20 ± 5 g, six animals per group were used for the study. The animals were housed under standard laboratory conditions in polypropylene cages. Ambient temperature of $25 \pm 4^\circ\text{C}$, $55 \pm 2\%$ relative humidity and 12h dark and light cycle was maintained. They were supplied with food and water *ad libitum*. All groups of animals were treated with normal saline water, standard and test drugs for 21 days. Acute toxicity of all the extracts was determined by LD₅₀ values by staircase method which was more than 3000mg/kg b.w. for the methanol and the aqueous extracts of leaves^[13]. All

pharmacological activities were carried out as per CPCSEA norms, after obtaining the approval (Ethical committee No. BBDNITM/IAEC/Clear/03/2009) from the Institutional Animal Ethical Committee of Babu Banarasi Das National Institute of Technology & Management, Lucknow, India.

2.4 Analgesic Activity

a. Eddy's Hot Plate Method

The animals were divided into six groups of 6 animals each. Group I served as control. Group VI served as standard and were injected Diclofenac sodium (9.5mg/kg) intraperitoneally. Group II and III were treated orally with methanolic extract of 250 and 500mg/kg body weight respectively. Group IV and V were treated orally with aqueous extract at a dose level of 250 and 500mg/kg body weight respectively. The animals were individually placed on the hot plate maintained at 55°C , one hour after their respective treatments. The response time was noted as the time at which animals reacted to the pain stimulus either by paw licking or jump response, whichever appeared first. The cut off time for the reaction was 15 seconds^[14, 15].

2.5 Immunomodulatory Activity

a. Swimming Endurance Test

Swimming endurance test was carried out on a 21st days according to method described by standard monograph. Precaution was taken that mice should not be at rest at any particular place and should swim continuously. End point of the test is considered to be the point of exhaustion, when the animal remains floating passively in water in an upright position, making only small movements to maintain the head just above the water level^[16, 17].

3. Results and Discussion

The data reveals that the methanolic extract of *A. heterophyllus* leaves at a dose of 500mg/kg showed significant activity ($P < 0.001^*$, $P < 0.05^{**}$) after 60 minutes. The results showed significant analgesic activity against thermal stimuli. The analgesic studies revealed that the methanolic extract of *A. heterophyllus* leaves exhibited

potent analgesic (central analgesic activity) and also revealed that the extracts shows dose dependent analgesic effect. On the basis of swimming endurance test, the effect of methanolic and aqueous extract of *A. heterophyllus* Lam. leaves was compared respectively. It was concluded that the methanolic extract of leaves were having higher values with respect to aqueous extract in increasing swimming or survival time, hence methanolic

extract were found to exert more immunomodulator effect than aqueous extract. Thus, the results obtained in the present study suggested that *Artocapus heterophyllus* exhibited analgesic and immunomodulator activity and thus supports the folk usage, it is highly desirable to explore its mechanism of action further for pharmacological justification to the use of the plant extract by traditional medicine practitioners as analgesic and immunomodulator action.

Table 1: Effect of Extracts on Pain Induced By Hot Plate

S. No.	Groups	Eddy's hot plate, paw licking time in seconds after (Mean±SEM)				
		0 Min.	30 Min.	60 Min.	90 Min.	120 min
I.	Control (DMSO) 1 ml per oral	6.0±0.56	6.20±0.34	5.72±0.28	5.24±0.87	5.12±0.34*
II.	Methanolic extract (250mg/kg per oral)	6.2±0.36	12.55±0.34*	16.34±0.67*	15.44±0.18*	11.55±0.65*
III.	Methanolic extract (500mg/kg per oral)	6.0±0.58	19.67±0.86*	21.78±1.59*	20.53±0.78*	13.98±0.37*
IV.	Aqueous extract (250mg/kg per oral)	6.4±0.76	10.67±0.98*	11.56±0.34*	8.98±0.67*	6.59±0.45**
V.	Aqueous extract (500mg/kg per oral)	6.5±0.46	15.89±0.45*	15.34±0.27*	11.54±0.39*	8.72±0.70*
VI.	Diclofenac Sod. (9.5 mg/kg intra peritoneally)	5.5±0.89	23.45±0.98*	24.52±0.65*	21.26±0.64*	18.40±0.45*

Values are expressed as mean±SEM, (n=6) (compared to control group) by using One Way Analysis of Variance (ANOVA) followed by Newman-Keuls test P<0.001*, P<0.05**.

Table 2: Effect of Jackfruit Extracts (Methanolic and Aqueous) On Swimming Endurance

Treatment groups (oral)	Dose (on the basis of body weight) by oral route	Mean Swimming time (in min.)
Control (Normal Saline)	2 ml	280.60±1.39
Standard (AP-3000)	30 mg/kg	355.50±1.4**
Methanolic extract	250 mg/kg	318.70±0.88***
Methanolic extract	500mg/kg	329.0±0.97***
Aqueous extract	250 mg/kg	307.0±0.51***
Aqueous extract	500mg/kg	318.0±1.16***

Values are expressed as mean±SEM (n=6) One Way Analysis of Variance (ANOVA) followed by Newman-Keuls test P* <0.05, P**<0.01, P***<0.001.

4. Conclusion

The above studies indicate that the methanolic extract of the leaves of *Artocarpus heterophyllus* possess analgesic and immunomodulator activity up to significant level which is justified by Eddy's hot plate and Swimming endurance test. Further studies are desirable to isolate the active constituents responsible for this activity.

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