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EVALUATION OF ANTIPYRETIC ACTIVITY OF *ZIZYPHUS JUJUBA* LAM. LEAVES ON ALBINO RATS

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Abstract:

Objective*: The objective of the study was to evaluate antipyretic activity of crude methanol extract of Zizyphus jujuba leaves. Z.jujuba commonly called, Red date or Chinese date or Bera (Pushto), belonging to family Rhamnaceae, is used primarily for its fruits. Jujube, a delicious fruit, is an effective herbal remedy improving stamina and muscular strength and aids weight gain, strengthens liver function and increases immune system resistance.*

Methodology: *The anti-pyretic activity of methanolic extract of Zizyphus jujuba Lam leaves was evaluated to Brewer's yeast induced pyrexia in rats with respect to control group.*

Results: *In the first hour, the antipyretic effect of methanol extract of Zizyphus jujuba (200 and 400 mg/kg) was significant ($p<0.05$, and $p<0.01$ respectively). The results suggests that Zizyphus jujuba at a dose of 200mg/kg caused a highly significant reduction at third hour ($p<0.001$). However, the effect increases significantly at the dose of 400 mg/kg having ($p<0.01$) at first, second and fourth hour. The antipyretic effect was comparable with that of a standard Paracetamol.*

Conclusion: *The results of the study indicate that the MEZJ has better potential against Pyrexia which supports the traditional claims in folklore medicine. Phytochemical investigation suggests the presence of saponin in the leaves which may be responsible for the anti-ulcer activity.*

Key words: *Zizyphus jujuba, Antipyretic activity, Brewer's yeast, Methanolic extract*

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INTRODUCTION:

Fever or pyrexia is may be due to infection, inflammation, tissue damage, graft rejection, and any disease states[1] Pyrexia is one of the most common medical signs. Antipyretics are the agents which reduce the elevated body temperature. They act centrally on the temperature regulation centre in the brain and also act peripherally through vasodilatation by promoting heat loss. Most of the antipyretic drugs act by inhibiting cyclooxygenase (COX)-2 expression, which inhibits prostaglandin PGE2 biosynthesis. As synthetic COX inhibitors are toxic to hepatic, brain cells, cortex, glomeruli, and heart muscles[2] natural antipyretic agents with less or no toxicity are essential. In spite of the newer advancements in synthetic drug development, plants are the major sources for raw materials in drug development. Herbal formulations are not known to cause any notable adverse effects[3] and are readily available at cheaper prices. *Zizyphus jujuba* Lamk is also called as Badar, Baer, Bogari, Barihannu belonging to family Rhamnaceae. The plant is distributed throughout India, Iran, and Afghanistan and in china. It is a small sub deciduous tree with dense spreading crown, commonly 0.6m girth and 6m high. Leaves 3-6.3 by 2.5-5 cm oblong or ovate, usually minutely serrulate or apex distinctly toothed, obtuse, base oblique and 3-nerved, nerves depressed on the glabrous shining upper surface, densely clothed beneath with white or buff tomentum.[4-5]A survey of literature on *Zizyphus jujuba* lam. revealed a few pharmacological reports on the plant like antioxidant and antilisterial effect[6]antisteroidogenic activity [7] antiobesity activity [8] sedative and hypnotic [9] anxiolytic[10] anticancer [11]The plant is reported to contain alkaloid jubanine-E [12]

It contains three flavones- C glucosides-6"sinapoylspinosin,6"-feruloylspinisin and 6-"p-coumaroylspinosin. The leaves and stems of *ziziyphus jujuba* lam contains saponins 3-o-[2-α-L-fucopyrnosyl-3-o-β-Dglucopyranosyl-α-L-arabinopyranosyl] jujubogenin. The fruits of Zizyphus jujuba lamk contain zizyphus saponins I, II, III and jujuboside B [13] jujuboside D [14] and jujuboside [15] Antipyretic action of *z.jujuba* was well studied using yeast-induced hyperpyrexia method [16] As PGE1-induced hyperpyrexia models are very few in the literature, we followed this method.

MATERIALS AND METHODS:

Plant material *Ziziphus jujuba* leaves were collected from in and around chembarambakkam, Chennai, India and authenticated by Dr.P.Jayraman, Director of Plant Anatomy Research Centre, Chennai. The fresh leaf of *Ziziphus jujuba* was identified and deposited at Department of Pharmacognosy, Sree Sastha Pharmacy College, Chembarambakkam, Chennai with the voucher number SSCPDPCOG/03/2020. The fresh leaf was separated and kept for shade drying. Dried leaf material was powdered using a mechanical grinder and passed through 60 mesh sieve to get the powder of desired coarseness. Powdered material was preserved in an airtight container.

Extraction of Plant material

The leaves of *Z.jujuba* were washed thoroughly in water to remove foreign matter and allowed to shade dry with a relative humidity of 40–45%. Then, leaves were powdered in roller grinder and passed through a sieve (No. 60). Then, the fine powder (Approx. 150 gm) was defatted with petroleum ether and extracted with water and 1 litre of Methanol at room temperature by using Soxhlet apparatus for 72 hours. The resultant extract was filtered and concentrated in a rotary evaporator under reduced pressure to obtain a brownish black colour residues. was stored at −20°C until required. The yield of the extract was found to be 7.2 %w/w. The methanol extract was collected and used for the present study.

Animals

Albino Westar rats of either sex weighing between 150-250 gm maintained in the Animal house facility of the Department of Pharmacology, Sree Sastha Pharmacy College were used in these experiments. The animals were maintained on standard small animal feeds (Excel feed, Ilorin) and water ad libitum. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) under the reference no. 1332/DPCG//20 /CPCSEA and CPCSEA guidelines adhered to during the maintenance and experiment. This research was carried out in accordance with the rules governing the use of laboratory animals as accepted internationally. The experiment was conducted between the hours of 900 h and 1600 h. The experimental groups consisted of six animals. They were maintained at constant room temperature (22° ± 1 °C) and submitted to12 h light/dark cycle with free access to food and water.

EXPERIMENTAL PROCEDURE

Acute oral toxicity study

Acute oral toxicity was conducted as per OECD guidelines (Organisation of Economic Cooperation and Development) 423 (Acute toxic class method). The acute toxic class method is a stepwise procedure of three animal of a single-sex per step. Depending on the mortality and/or moribund status of animals, on the average 2-4 steps may be necessary to allow judgment on the acute toxicity of the test substance. This

procedure results in the use of a minimal number of animals while allowing for the acceptable data-based scientific conclusion. The method uses defined doses, (5, 50, 300, 2000 mg/kg body weight) and the results allow a substance to be ranked and classified according to the globally harmonized system (GHS) for the classification of chemicals which causes acute toxicity. The method previously described by Lorke was adopted [17]

Antipyretic Activity:

The antipyretic activity was evaluated with fever induced by Brewer's yeast following the established method. [18-19] in rats with some modifications. At zero hour, the basal rectal temperature of each rat was recorded using clinical digital thermometer. Pyrexia was induced by subcutaneous injection of 15% w/v suspension of Brewer's yeast in distilled water at a dose of 10 mL/kg body weight. After 18 hr of Brewer's yeast injection the rise in rectal temperature was recorded and only animals showing an increase in temperature of at least 0.6°C (or 1°F) were selected for the study.

The animals were randomly divided into four groups, each group containing six rats.

Group I received 1% Tween-80 in normal saline orally.

Group II was given standard drug Paracetamol at the dose of 150 mg/kg per orally.

Groups III received Methanolic extract of *Z.jujuba* at oral dose of 200 mg/kg orally.

Groups IV received Methanolic extract of Z.jujuba at dose of 400 mg/kg orally.

After the treatment, the temperature of all the rats in each group was recorded at 0 hr, 1 hr, 2 hr, 3 hr, and 4 hr.

Statistical Analysis

All values were expressed as the mean ± standard error of the mean (SEM) and the results were analyzed statistically by one-way analysis of variance (ANOVA) for analgesic activity and multivariate analysis of variance (MANOVA) for antipyretic effect through time followed by Dennett's post hoc multiple comparison test by using SPSS ver. 16. For MANOVA, Levene's test of equality errors of variance was performed. $p<0.05$ was considered to be statistically significant.

RESULTS:

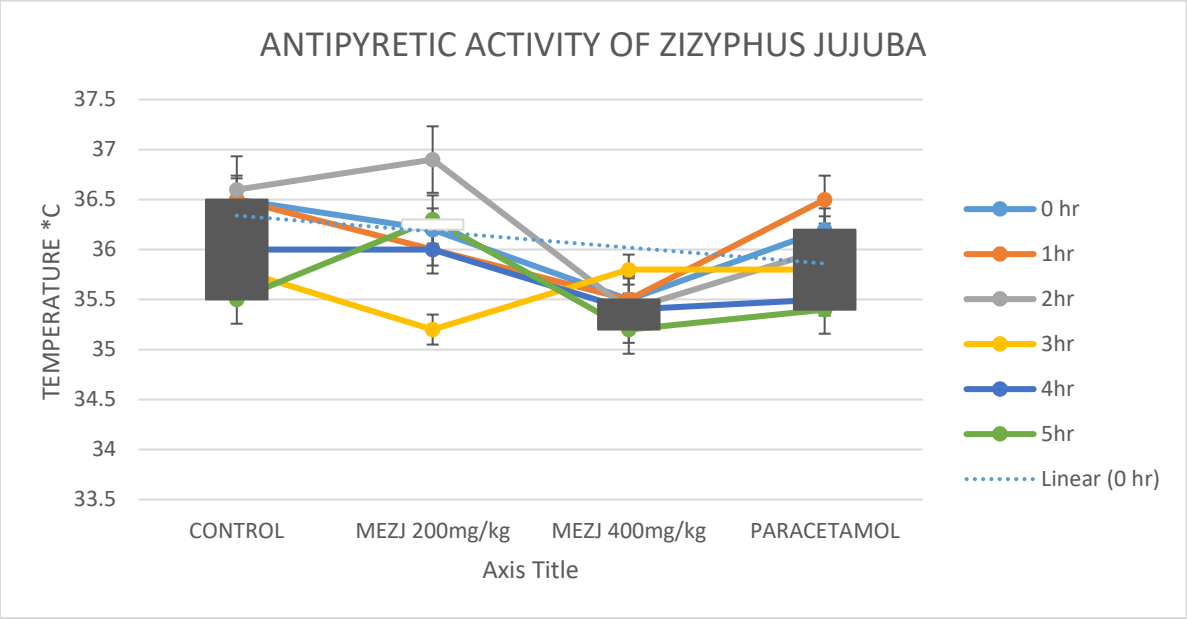
The experimental rats showed a marked increase in rectal temperature 18 hours after Brewer's Yeast injection. In the first hour, the antipyretic effect of methanol extract of *Zizyphus jujuba* (200 and 400 mg/kg) was significant ($p<0.05$, and $p<0.01$ respectively). The results suggest that *Zizyphus jujuba* at a dose of 200mg/kg caused a highly significant reduction at third hour ($p<0.001$). However, the effect increases significantly at the dose of 400 mg/kg having ($p<0.01$) at first, second and fourth hour. The antipyretic effect was comparable with that of a standard paracetamol.

Table 1: Antipyretic Activity of MEZJ Leaves

Rectal temperature in ºC at time(h)							
Drug	**18hr after yeast injection**	**0 hour**	**1 hour**	**2 hour**	**3 hour**	**4 hour**	**5 hour**
Control (5ml/kg)	36.4±0.03	36.5±0.05	36.5±0.10	36.6±0.04	35.8±0.03	36.0±0.04	35.5±0.02
MEZJ (200mg/kg)	35.8±0.04	36.2±0.08	36.±0.10***	36.9±0.07*	35.2±0.02**	36 ±0.14	36.3±0.11*
MEZJ (400 mg/kg)	35.4±0.02	35.5±0.14	35.5±0.06*	35.4±0.02**	35.8±0.01***	35.4±0.11*	35.2±0.20***
Paracetamol (150 mg/kg)	36.4±0.04*	36.2±0.02	36±0.08	36 ±0.02*	35.8±0.02**	35.5±0.1*	35.4±0.09

Values are the mean ± S.E.M. of 6 rats / treatment, Significant *P < 0. 05,P < 0.01, ***P < 0.001, compared with Control. MPZJ-Methanolic extract of *Ziziphus jujube***

Fig 1: Antipyretic Activity of MEZJ Leaves



DISCUSSION:

The mid-brain reticular formation, anterior hypothalamus, and posterior hypothalamus are considered to be the PGE1 febrile sensitive sites involved in the thermoregulatory function[20] One more study also indicated same that the site of PGE1, febrile sensitivity resides in the area of the anterior hypothalamus[21] This concludes that pyrogen activity in the production of fever is mediated through PGE1. There is a remarkable similarity in the mode of action of PGE1 and pyrogen in the production of fever except in the onset of action which is rapid with PGE1. Hence, pyrogen may be considered as a precursor which produces PGE1 in the brain tissue to affect the febrile response. Therefore, PGE1 coming one step closer to the production of fever would act more rapidly than pyrogen.

Ziziphus jujuba contains Flavonoids, Saponins, tannins, Vitamin A, Vitamin B, sugars, mucilage, calcium, phosphate & iron. The pulp contains moisture, protein, fat, carbohydrate, calcium, phosphorus, iron, carotene, thiamine, riboflavin, Vitamin C.

Many of these compounds inhibit the PGs and leukotriene synthesis[22] Thus, these active compounds of *Z.jujuba* may possess anti-inflammatory and antipyretic activity[23] by reducing the secretion of pro-inflammatory cytokines and tumor necrosis factor alpha[24] From our study, we can say that *Z.jujuba* in high doses reduces temperature very fast, whereas moderate doses reduces temperature slowly. Methanolic extract of *Zizyphus jujuba* developed to have therapeutic effects in antipyretic activity, or in the disease associated with increase in temperature. One such disease is arthritis, which include cartilage destruction with increase in temperature surrounding the joints and sometimes whole body. Various parts of *Zizyphus jujuba* have been used for hundreds of years and their safety and efficacy are well established through a long history of human use. The scientific research of this plant is currently more focussed on the identification, isolation and characterization of active principle(s) from crude extracts. The fact that strong synergism of several constituents in the crude drug may prove more potent and effective than any single purified compound, is always overlooked. Moreover, this may help to nullify the toxic effects (if any) of individual constituents. Taking consideration of these facts, the antipyretic activity was performed.

CONCLUSION:

The methanol extract of *Z.jujuba* displayed significant antipyretic property. The central antinociceptive activity was absent. Since this is a pioneer work further studies are necessary to validate this result and other detailed studies on compound identification and isolation and underlying mechanism for the observed effect are essential to guarantee its clinical use.

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Conflict of interests:
Author have declared that no conflict of interests exist.

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