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Full Length Research Paper

Antinociceptive and neuropharmacological activities of ethanolic extract of the fruits of *Ficus hispida* Linn.

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The crude ethanolic extract of the fruits of *Ficus hispida* Linn. (Family: Moraceae) growing in southeast part of Bangladesh has been evaluated for its possible antinociceptive and neuropharmacological properties. The ethanolic extract of the fruits of *F. hispida* exhibited statistically significant ($p < 0.001$) writhing inhibition in acetic acid-induced writhing model in white albino mice (Swiss-webstar strain). The crude extract produced 30.41% inhibition of writhing at the dose of 250 mg/kg body weight and 62.84% inhibition of writhing at the dose of 500 mg/kg body weight, while the standard drug diclofenac inhibition was found to produce 75.68% at a dose of 25 mg/kg body weight. The extract of *F. hispida* fruits also potentiated the pentobarbital induced sleeping time in mice, decreased the open field score in open field test, decreased the number of hole crossed from one chamber in the hole cross test and decreased the head dip responses in hole board test. Acute toxicity test showed that the plant might be safe for pharmacological uses. Therefore, the obtained results tend to suggest the antinociceptive and neuropharmacological activities of the ethanolic extract of the fruits of *F. hispida* and thus, provide the scientific basis for the traditional uses of this plant part as a remedy for pain and depression. The obtained results provide a support for the use of this plant in traditional medicine and its further investigation.

Key words: *Ficus hispida*, antinociceptive, acetic acid-induced writhing model, neuropharmacological.

INTRODUCTION

Ficus hispida Linn. belongs to the Moraceae family. It is a moderate sized tree, grows up to 3.0 m, with spreading branches and many aerial roots. It is widely distributed throughout India, Sri Lanka, Myanmar, Southern region of the Republic of China, New Guinea, Australia and Andaman Islands in damp localities. It also grows in secondary forests, open lands and riverbanks up to 1200 m in altitude (Ripu et al., 2006). *F. hispida* is used by the maaiba indigenous medicine - man of Manipur, India as an indigenous traditional medicine (Manandhar et al., 1995). A new norisoprenoid, ficustriol, phenanthroindolizidine, alkaloid, O-methyltylophorinidine (Peraza Sánchez et al.,2002), palmitic oil, 9,12-octadecadienoic acid, hexadecanoic acid ethyl ester, linalool, 1-hydroxylinalol,1- hydroxylinalool and benzyl alcohol have been isolated so far from the plant (Song et al., 2001). The root and leaves are of particular interest from a medicinal numerous plants and polyherbal formulations claimed to point of view as an antidiarrhoeal activity (Subhash and Mandal, 2002). Furthermore, the plant has also been reported for antidiabetic (Ghosh et al., 2004), cardioprotective (Shanmugarajan and Arunsunda, 2008) effects. It shows anticonvulsant activities in different models like strychnine, picrotoxin and pentylenetetrazol (PTZ)-induced seizure models (Dhanasekarana et al., 2009). The extracts of all parts of the plant have been reported to be bitter, cooling, astringent and antidysenteric and to have activity against psoriasis, anemia, piles, jaundice, and hemorrhage

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(Nadkarni, 1976). The fruit acts as a coolant and tonic. The juice obtained from the fig is taken along with jaggery as a mild purgative. A mixture of honey and its juice is a good antihaemorrhagic (Sergio and Peraza, 2002).

However, there is no scientific proof justifying the traditional use of *F. hispida* fruits in the antinociceptive and neuropharmacological activities. Hence, the present study was undertaken to evaluate its potential antinociceptive and neuropharmacological efficacy in experimental models of depression and pain in mice, as part of ongoing investigations on local medicinal plants of Bangladesh. In this study, we reported antinociceptive and neuropharmacological potentiality of the fruits of *F. hispida*.

MATERIALS AND METHODS

Collection and identification of plant materials

The plant selected for present work was *F. hispida* (Family: Moraceae), which was collected from Pabna (Vill. Dipchar) district. The time of collection was December, 2009 at the daytime. The fruits were collected from the fresh plants. The fruits of *F. hispida* were collected for identification. The Bangladesh National Herbarium Dhaka identified the fruits (Herbarium Accession No. 31117).

Preparation of ethanolic extract

The fruits of *F. hispida* were freed from any of the foreign materials. Then the fruits were chopped and air-dried under shed temperature followed by drying in an electric oven at 40°C. The dried plant materials were then grounded into powder. About 500 g of powdered material was taken in a clean, flat-bottomed glass container and soaked in 1.4 L of 80% ethanol. The container with its contents was sealed and kept for a period of 4 days accompanying occasional shaking and stirring. The ethanolic extract was filtered by Buchner funnel and the filtrate was concentrated with rotary evaporator at bath temperature not exceeding 40°C to have gummy concentrate of extract (yield approximately 13.26%).

Animal

For the experiment, Swiss albino mice of either sex, weighing between 20 to 25 g, were collected from the animal research branch of the International Center for Diarrheal Disease and Research, Bangladesh (ICDDR, B). Animals were maintained under standard environmental conditions (temperature: 24.0 ± 1.0°C, relative humidity: 55 to65% and 12 h light/ dark cycle) and had free access to feed water and libitum. The animals were acclimatized to laboratory condition for 1 week prior to experiments. All protocols for animal experiment were approved by the ICDDR, B, Bangladesh. For acute toxicity test, male rats of Wister strain weighing 175 to 202 g were used.

Phytochemical screening

The freshly prepared crude extract was qualitatively tested for the presence of chemical constituents, by using the following reagents and chemicals, for example, alkaloids were identified by the Dragendorff's reagent, flavonoids with the use of Mg and HCl, tannins with ferric chloride and potassium dichromate solutions, steroids with Libermann-Burchard reagent and reducing sugars with benedict's reagent (Ghani, 1998; Evans, 1989; Harborne, 1984).

Antinociceptive activity

Antinociceptive activity of the crude extract fruits of *F. hispida* was tested using the model of acetic acid-induced writhing in mice (Whittle, 1964; Ahmed et al., 2004). The experimental animals were randomly divided into four groups, each consisting of five animals. Group I was treated as 'control group' which received 1% (v/v) Tween-80 in water at the dose of 10 ml/kg of body weight; Group II was treated as 'positive control' and was given the standard drug diclofenac sodium at dose of 25 mg/kg of body weight; Groups III and IV were test groups of ethanolic extract of fruits of *F. hispida* and were treated with the extracts at dose 250 and 500 mg/kg of body weight, respectively. Each mouse was weighed properly and the dose of the test samples, standard and control materials were adjusted accordingly. Control vehicle, standard drug and extracts were administered orally, 30 min prior to acetic acid (0.7%) injection in peritoneum. Then after an interval of 10 min, the number of writhes (squirms) was counted for 5 min.

Neuropharmacological activity

Pentobarbital-induced hypnosis

Pentobarbital-induced hypnosis test was carried out by the method of Williamson et al. (1996). The test animals were divided into four groups consisting of seven mice in each group. Group I was the control group, Group II was positive control, Groups III and IV were the experimental groups. The experimental groups were administered with the ethanolic extract of *F. hispida* at dose of 250 and 500 mg/kg body weight orally, while positive control was treated with diazepam (1 mg/kg p.o.) and control with vehicle (1% v/v Tween 80 in water). Each mouse was placed in an observation box (a rectangular open box composed of hardboard floor (36 × 36 cm^2) with a surrounding wall 30 cm height. 30 min later, pentobarbital (40 mg/kg, i.p.) was administered to each mouse to induce sleep. The total sleeping time were recorded for both control as well as for treated groups. The animals were observed for the latent period (time between pentobarbitone administration to loss of righting reflex) and duration of sleep (time between the loss and recovery of righting reflex).

Exploratory behaviour

This experiment was performed by: (1) Open field test (Gupta et al., 1971), (2) Hole cross test (Takagi et al., 1971) and (3) Hole board test (Nakama et al., 1972). The test animals were divided into four groups consisting of seven mice in each group. Group I was the control group, Group II was the positive control and Groups III and IV were the experimental groups. The experimental groups were administered with the ethanolic extract of fruits of *F. hispida* at dose of 250 and 500 mg/kg of body weight per orally (p.o.), while the animals of Group I (control) were supplied with 0.1% (v/v) Tween-80 (p.o.) at the dose of 10 ml/kg of body weight and Group II was treated as 'positive control' by giving diazepam intraperitoneally 1 mg/kg (i.p.). The observations were made on 0 min before injection and 30, 60, 90, 120,180 and 240 min after injections of the test samples and control.

Acute toxicity test

The acute toxicity of *F. hispida* ethanolic extract was determined in rats according to the method of Hilaly et al. (2004) with slight

Table 1. Results of different group tests of ethanolic extract of *F. hispida* fruits.

Plant extract	Alkaloid	Reducing sugars	Tannins	Flavonoids	Saponin	Steroid
EE	+	-	++	++	+	-

EE, Ethanol extract of *F.* hispida; +, positive result; -, negative result; ++, significantly positive.

Table 2. Antinociceptive effects of ethanolic extract of *F. hispida.* fruits.

Group	Treatment and dose	Number of writhes (% writhing)	% Writhing inhibition
I (Control)	1% Tween 80 solution 10 ml/kg, p.o.	29.6 ± 0.51 (100)	-
II (Positive Control)	Diclofenac Na 25 mg/kg, p.o.	7.20 ± 0.58** (24.32)	75.68
III (Test Group-I)	Et. Extract of fruit of *F. hispida* 250 mg/kg, p.o.	20.60 ± 0.51** (69.59)	30.41
IV (Test Group-II)	Et. Extract of fruit of *F. hispida* 500 mg/kg, p.o.	11.0 ± 0.45** (37.16)	62.84

Values are expressed as mean ±SEM (Standard error mean); Et., Ethanolic; * indicates P < 0.01 and **indicates P < 0.001; n, number of mice; p.o., per oral.

modifications. Rats fasted for 16 h and were randomly divided into groups of five rats per group. Graded doses of the extract (200, 400, 800 and 1600 mg/kg p.o.) were separately administered to the rats in each of the groups by means of bulbed steel needle. All the animals were then allowed free access to food and water and observed over a period of 48 h for signs of acute toxicity. The number of deaths within this period was recorded.

Statistical analysis

Data were presented as mean ± standard deviation (SD). Statistical analysis for animal experiment was carried out using one-way analysis of variance (ANOVA) followed by Dunnet's multiple comparisons using SPSS data editor for Windows, Version 11.5.0 (SPSS Inc., U.S.A.). The results obtained were compared with the control group. P-values < 0.05 were considered to be statistically significant.

RESULTS

Preliminary phytochemical analysis

Results of different chemical tests on the ethanol crude fruits extract of *F. hispida* showed the presence of tannin, flavonoid, saponin and alkaloid (Table 1).

Antinociceptive

The results of the test showed that ethanolic extract of fruits of *F. hispida* 500 mg/kg exhibit highly significant (P < 0.001) inhibition of writhing reflex by 62.84% and 250 mg/kg showed 30.41% inhibition, while the standard drug diclofenac inhibition was found to be 75.68% at a dose of 25 mg/kg body weight. The result is showed in Table 2.

From the observation made, it can be suggested that the ethanolic extract of fruits of *F. hispida* is an effective analgesic that supports the claim about the fruits being used as an analgesic in traditional practice. However, further study should be done for its isolated, purified active compounds.

Pentobarbital-induced hypnosis test

Statistical analysis of the data obtained in this test show that (Table 3) both 250 and 500 mg/kg dose of ethanolic extract of fruits of *F. hispida* prolong the duration of the pentobarbitone-induced sleeping time. The total sleeping time was about 75 and 61 min at dose of 500 and 250 mg/kg of body weight, respectively of the extract of fruit whereas, in positive control group it was about 93 min.

Exploratory behaviour test

Test for exploratory behaviour in mice was performed by: (1) Open field test (2) Hole cross test and (3) Hole board test. It was observed that the extract of fruits decreased the number of open field score (Table 4), caused decrease

Table 3. Effect of ethanolic extract of *F. hispida* fruits on pentobarbital-induced hypnosis in mice.

Animal group	Treatment	Time of onset Ofsleep (min)	Total sleeping time (min)
I (Control)	1% Tween 80 solution (10 ml/kg, p.o.) + Pentobarbital, i.p. (40 mg/kg)	15.69 ± 1.63	38.87 ± 3.48
II (Positive Control)	Diazepam (1 mg/kg,p.o.) + Pentobarbital, i.p. (40 mg/kg)	4.34 ± 0.16**	93.06 ± 1.20**
III (Test Group-I)	Et. *F. hispida* (250 mg/kg, p.o.) + Pentobarbital, i.p. (40 mg/kg)	7.36 ± 1.30**	60.80 ± 2.87**
IV (Test Group-II)	Et. *F. hispida* (500 mg/kg, p.o.) + Pentobarbital, i.p. (40 mg/kg)	6.25 ± 0.84**	75.31 ± 3.51**

Values are expressed as mean ±SEM; Et., Ethanolic; **indicates P < 0.001; p.o., per oral; i.p., Intraperitoneal.

Table 4. Effect of ethanolic extract of *F. hispida* fruits on open field test (Mean ± SEM).

Group	Movement on open field test before and after drug administration (Mean ± SEM)						
	0 min	30 min	60 min	90 min	120 min	180 min	240 min
Control	122.02 ± 2.30	83.08 ± 2.24	60.20 ± 1.19	55.55 ± 0.96	43.8 ± 1.43	34.51 ± 1.41	26.45 ± 1.40
Diazepam (1 mg/kg) (i.p.)	91.79 ± 1.50**	36.13 ± 1.07**	21.16 ± 1.23**	16.67 ± 1.38**	15.51 ± 1.33**	12.23 ± 1.38**	7.49 ± 1.13**
Et. fruits extract (250 mg/kg) (p.o.)	106.79 ± 3.48*	54.16 ± 2.94**	42.72 ± 3.35**	35.63 ± 2.64**	24.01 ± 1.52**	20.40 ± 1.56**	16.26 ± 1.58**
Et. fruits extract (500 mg/kg) (p.o.)	101.79 ± 1.98**	44.62 ± 2.26**	35.14 ± 1.69**	24.37 ± 1.35**	18.05 ± 1.77**	14.09 ± 1.33**	10.89 ± 1.57**

Values are Mean ± SEM; *, P < 0.01; **, P < 0.001 versus control, Student's t-test; Et., Ethanolic; p.o., per oral; i.p., intraperitoneal.

decrease in the number of hole crossed from one chamber to another chamber (Table 5), and also decreased head dip responses (Table 6) in mice at dose 250 and 500 mg/kg of body weight from 30 to 240 min.

Acute toxicity test

In acute toxicity study, oral administration of graded doses (200, 400, 800 and 1600 mg/kg p.o.) of the ethanol extract of *F. hispida* to rats did not produce any significant changes in behaviour, breathing, cutaneous effects, sensory nervous system responses or gastrointestinal effects during the observation period. No mortality or any toxic reaction was recorded in any group after 48 h

Table 5. Effect of ethanolic extract of *F. hispida* fruits on hole cross test (Mean ± SEM).

Group	Movement on hole cross test before and after drug administration (Mean ± SEM)						
	0 min	30 min	60 min	90 min	120 min	180 min	240 min
Control	20.31 ± 0.45	15.71 ± 0.54	14.40 ± 0.61	12.93 ± 1.02	11.80 ± 0.66	10.55 ± 0.56	9.77 ± 0.78
Diazepam (1 mg/kg) (i.p.)	9.90 ± 0.70**	8.79 ± 0.43**	7.10 ± 0.38**	6.30 ± 0.58**	5.66 ± 0.91**	5.12 ± 0.98**	4.42 ± 0.63**
Et. Fruit extract (250 mg/kg) (p.o.)	14.60 ± 0.51**	9.80 ± 0.55**	9.86 ± 0.28**	8.44 ± 0.23**	7.66 ± 0.39**	7.02 ± 0.32**	6.66 ± 0.24**
Et. Fruit extract (500 mg/kg) (p.o.)	13.61 ± 1.08**	9.41 ± 0.54**	9.00 ± 0.86**	7.75 ± 0.95*	7.08 ± 0.33**	6.87 ± 0.33**	6.18 ± 0.13**

Values are Mean ± SEM; *, P < 0.01; **, P < 0.001 versus control, Student's t-test; Et., Ethanolic; p.o., per oral; i.p., intraperitoneal.

Table 6. Effect of ethanolic extract of *F. hispida* fruits on hole board test (Mean ± SEM).

Group	Effect on hole board test (head dipping) before and after drug administration (Mean ± SEM)						
	0 min	30 min	60 min	90 min	120 min	180 min	240 min
Control	16.52 ± 0.64	19.15 ± 1.15	21.57 ± 1.05	22.57 ± 1.05	18.84 ± 0.69	16.0±0.84	14.0±0.84
Diazepam (1 mg/kg) (i.p.)	12.67 ± 0.63**	7.14 ± 0.23**	6.54 ± 0.48**	4.97 ± 0.38**	3.16 ± 0.31**	2.24 ± 0.57**	2.04 ± 0.45**
Et. fruits extract (250 mg/kg) (p.o.)	13.0 ± 0.54**	11.18 ± 0.37**	10.41 ± 0.51**	9.44 ± 2.58**	8.31 ± 0.4**	7.4 ± 3.813*	5.12 ± 0.31**
Et. fruits extract (500 mg/kg) (p.o.)	14.26 ± 0.82*	10.84 ± 0.69**	8.14 ± 0.64**	6.93 ± 3.03 **	5.18 ± 0.58**	3.87 ± 0.47**	2.45 ± 0.54**

Values are Mean ± SEM; *, P < 0.05; **, P < 0.001 versus control, Student's t-test; Et., Ethanolic; p.o., per oral; i.p., intraperitoneal.

of administering the extract to the animals. *F. hispida* was safe up to a dose level of 1600 mg/kg of body weight.

DISCUSSION

Our present study reveals that the fruits extract of *F. hispida* show dose-dependent central nervous system (CNS) depressant and analgesic activities. Oral administration of *F. hispida* fruits extracts produced significant peripheral antinociceptive effect in acetic acid-induced writhing test. Pain sensation in acetic acid-induced writhing method is elicited by triggering localized inflammatory response resulting in release of free arachidonic acid from tissue phospholipid via cyclooxygenase (COX), and prostaglandin (PG) biosynthesis (Ahmed et al., 2001; Duarte et al., 1988). In other words, the acetic acid-induced writhing has been associated with increased level of PGE_2 and $PGF_{2\alpha}$ in peritoneal fluids as well as lipoxygenase

product (Derardtet al., 1980). The increase in PG levels within the peritoneal cavity then enhances inflammatory pain by increasing capillary permeability (Zakaria et al., 2008). The acetic acid-induced writhing method was found effective to evaluate peripherally active analgesics. The agent reducing the number of writhing will render analgesic effect preferably by inhibition of PG synthesis, a peripheral mechanism of pain inhibition (Ferdous et al., 2008). The effect of the extracts against the noxious stimulus may be an indication that it depressed the production of irritants and hereby reduction in number of writhes in the animals. The significant pain reduction of the plant extract might be due to the presence of analgesic principles acting with the PG pathways. Phytochemical screening of the ethanol extract of *F. hispida* reveals the presence of steroid, tannin, reducing sugars, flavonoids, saponin and alkaloid. Flavonoids were reported to have a role in analgesic activity primarily by targeting prostaglandins (Rajnarayana et al., 2001). Inhibition of pain has been associated with presence of steroidal constituents (Miguel et al., 1996). Tannins have also been shown to play a role in antinociceptive and anti-inflammatory activities in some studies (Vanu et al., 2006). Because tannins inhibit PG synthesis by modifying the production of COX-1 and COX-2) and lipooxygenase (LOX) involved in the PG synthesis (Sreejayan, 1997; Yokozawa et al., 1998). The plant is also reported to contain saponins. There is growing interest in natural saponins due to both improved extraction and structural analysis techniques of these compounds, and also by the fact of their wide spectrum of pharmacological activities; for instance, bactericidal, antiviral, cytotoxic, analgesic, antiinflammatory, anti-cancer and antiallergic (Attele et al.,1999). Besides, alkaloids are well known for their ability to inhibit pain perception (Uche et al., 2008). So it is possible that these phytoconstituents may be responsible for its analgesic activity.

The most important step in evaluating drug action on the CNS is to observe the behaviour of the test animals. Substances that have CNS depressant activity either decrease the time for onset of sleep or prolong the duration of sleep or both. Both the doses of the crude extract produced a significant increase in the hypnotic effect induced by the pentobarbitone, in a dose-dependent manner, thus, suggesting a profound sedative activity. Like many other centrally acting drugs, barbiturates acts on the cerebral cortex to produce their actions (Bowman and Rand, 1980). Pentobarbital, a barbiturates class hypnotic drug by an allosteric modification of gamma-amino-butyric acid type A ($GABA_A$) receptor increases the chloride conductance and potentiates $GABA_A$ mediated postsynaptic inhibitors (Katzung, 2004). The extract potentiates pentobarbitone-induced sleeping time that may be attributed to an action on the central mechanism involved in the regulation of sleep (N'Gouemo et al., 1994; Chindo et al., 2003). The prolongation of pentobarbital-induced sleeping time may be attributed to an inhibition of pentobarbital metabolism (Kaul and Kulkarni, 1978). The extract prolongation of pentobarbital sleep suggests that barbital-induced hypnosis is a good index of CNS depressant activity (Fujimori et al., 1965).

Again, the extract significantly decreased the locomotor activity as shown by the results of the open field, hole cross and hole board tests. The locomotor activity is a measure of the level of excitability of the CNS (Mansur et al., 1980) and any decrease of this activity may be closely related to sedation resulting from depression of the CNS (Ozturk et al., 1996). Extracts of *F. hispida* decreased locomotor activity this indicates its CNS depressant activity. $GABA_A$ is the major inhibitory neurotransmitter in the CNS. Different anxiolytic, muscle relaxant, sedative-hypnotic drugs elicit their action through $GABA_A$, therefore, it is possible that extracts of *F. hispida* may act by potentiating GABAergic inhibition in the CNS via membrane hyperpolarization which leads to a decrease in the firing rate of critical neurons in the brain or may be due to direct activation of GABA receptor by the extracts (Kolawole et al., 2007).

Also, phytoconstituents like tannins, saponins, glycosides and triterpenes are reported to possess sedative effects (Khairnar et al., 2010; Kumar et al., 2012). Emamghoreishi et al. (2006) and Kolawole et al. (2007) also reported that many flavonoids and neuroactive steroids were found to be ligands for the $GABA_A$ receptors in the CNS, which led to the hypothesis that they act as benzodiazepine-like molecules (Fernández et al., 2006). This is supported by their behavioral effects in animal models of anxiety, sedation and convulsion (Johnston, 2005). The depressant effect may be due to action of alkaloids on the cerebral mechanism involved in sleep regulation (N'Gouemo et al., 1994).

From previously discussed, it can be suggested that the presence of different phytochemicals, as shown from the phytochemical investigation, may be responsible for both analgesic and depressant activity that may be complement to each other and may be used in variety of painful and excitatory conditions.

Conclusion

On the basis of results obtained from the present study, it can be concluded that the ethanolic fruits extract of *F. hispida* possesses remarkable analgesic and CNS depressant activities, thereby, lends support to the traditional use of the plant in painful disorders and central depressant effect and possible application in anxiety conditions. Again, no mortality was recorded in the acute toxicity test. Present work was a preliminary effort which will require further detailed investigation including characterization of active compounds and requires preformulation studies for development of a potential dosage form.

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