IJPSR (2013), Vol. 4, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 26 October, 2012; received in revised form, 05 December, 2012; accepted, 22 January, 2013

ANTIDIARRHEAL ACTIVITY OF *DILLENIA INDICA* BARK EXTRACT

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Keywords:
Diarrhea, flavonoid, antibacterial, *Dillenia indica*

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ABSTRACT

The present study was designed to investigate the antidiarrheal potential of the methanolic extract of *Dillenia indica* bark (MDIB). The extract studied for antidiarrheal property using castor oil and magnesium sulphate induced diarrheal model and charcoal induced gastrointestinal motility as well as PGE_2-induced enterolooping test in mice. In addition, activities against some causative diarrheal pathogenic bacteria were also determined. At the doses of 100 and 200 mg/kg body weight, MDIB extract significantly reduced the frequency and severity of diarrhea in test animals throughout the study period and also showed a significant ($p<0.001$; $p<0.05$) reduction in the gastrointestinal motility in charcoal meal test as well as PGE_2-induced intrafluid accumulation. MDIB extract also displayed strong antibacterial effect against some diarrhoic pathogenic bacteria and highest activity was found against Escherichia coli. Altogether, these results suggest that the *Dillenia indica* bark extracts could be used as a potential antidiarrheal agent.

INTRODUCTION: Diarrhea is an alteration in the normal bowel movement, characterized by increased frequency of bowel sound and movement, wet stool, and abdominal pain [1]. Regardless of the understanding causes, treatment and prevention of diarrheal diseases, an estimated 4.6 million people, with 2.5 million children, die from diarrhea every year, particularly in developing countries [2].

Diarrhea, may be acute or chronic. With acute diarrhea being the most common is usually caused by an infectious agent, even though drugs, poisons or acute inflammatory reactions can contribute a lot [3]. Now a days, rotavirus is the major causative agent for infectious diarrhea, particularly in young children, however, other viral (adenovirus, enterovirus and norovirus), bacterial (*Escherichia coli, Salmonella sp. Shigella sp. Camphylobacter* and *Vibrio cholerae*) and parasitic (*Cryptosporidium* and *Giardia*) agents are important pathogens [4]. Oral rehydration therapy (ORT) has been identified as a key factor in the decline of child mortality rate due to diarrhea, although it does not reduce the volume or duration of diarrhea [5]. Likely, antibiotics and gut motility suppressing agents bid the other treatment option, wherein reverse dehydration, shorten the length of illness and reduce the period of time when an individual is infected [6]. Treatment with pharmacological agents that are pathogen specific or that suppress severe symptoms would be of benefit to patients suffering from prolonged diarrhea [7]. Medicinal herbs constitute an indispensable component of the traditional medicine practiced worldwide due to their economical viability, accessibility and ancestral experience.

Despite the availability of a vast spectrum of approaches for diarrheal management, a vast majority of the people of Bangladesh have been known to treat diarrhea with a variety of medicinal plants one of which being *Dillenia indica* [8]. The genus *Dillenia* has sixty species, of which *Dillenia indica* Linn., belongs to the family Dilleniaceae, is the most common edible species. Originated from Indonesia, this evergreen tropical tree is now found from Bangladesh, India, and Nepal to China.

The leaf, bark and fruit of this plant are used as traditional medicine. The juice of *D. indica* leaves, bark and fruits are mixed and given orally (5-15ml, two to five times daily) in the treatment of cancer and diarrhea [9]. The fruit juice of this plant has anti-leukemic effect [10], cardiotonic effect, used as cooling beverage in fever and also employed in cough mixture. The leaves and bark are used as a laxative and astringent. Bruised bark is applied as a cataplasm for patients with arthritis [11].

The solvent extracts of fruits and leaves of *D. indica* are reported to have antioxidant activity [12]. CNS depressant activities [13] and anti-inflammatory activity [14] in mice were found from the alcoholic extract of the leaves of *D*. *indica*. As a part of our ongoing research [15, 16] on Bangladeshi medicinal plants, the present study aimed to evaluate the antidiarrheal activity of peel and pulp extracts of *Dillenia indica* bark.

MATERIALS AND METHODS

Plant Materials: The bark of the plant of *Dillenia indica* Linn was collected from the botanical garden of Pharmacy department, Jahangirnagar University, Bangladesh during January 2011. The plant material was taxonomically identified by the National Herbarium of Bangladesh whose voucher specimen no. JU/32234 is maintained in our laboratory for future reference.

Preparation of Plant Extract: The plant material was shade-dried with occasional shifting and then powdered with a mechanical grinder, passing through sieve #40, and stored in a tight container. The dried powder material (1.5 kg) was refluxed with MeOH for three hours. The total filtrate was concentrated to dryness, *in vacuo* at 40^0C to render the MeOH extract (490 g).

Chemicals: Folin-chiocaltu phenol reagent, were purchased from E. Merck (Germany). Galic acid and quercetin, were purchased from Sigma Chemical Co. Ltd, (St. Louis, MO, USA). All other chemicals and reagents were of analytical grade.

The amount of Phenolic Compounds and Flavonoids: The total phenolic content of extract was determined using Folin–Ciocalteu reagent[17]. Extracts (100 µl) were mixed with the Folin–Ciocalteu reagent (500 µl) and 20% sodium carbonate (1.5 ml). The mixture was shaken thoroughly and made up to 10 ml with distilled water. The mixture was allowed to stand for 2 h. Then the absorbance at 765 nm was determined with a Shimadzu UV-160A spectrophotometer (Kyoto, Japan). These data were used to estimate the phenolic contents using a standard curve obtained from various concentration of gallic acid.

The flavonoids content was determined by aluminium chloride colorimetric method[18]. The different concentration of extracts (0.5 ml) were separately mixed with 95% ethanol (1.5 ml), 10% aluminum chloride (0.1 ml), 1M potassium acetate (0.1 ml) and distilled water (2.8 ml). After incubation at room temperature for 30 min, the absorbance of the reaction mixture was measured at 415 nm. The amount of 10% aluminum chloride was substituted by the same amount of distilled water in blank. All the determinations were carried out in duplicates. These data were used to estimate the flavonoid contents using a standard curve obtained from various concentration of quercetin.

Acute Toxicity Study: Animals were divided into groups of five mice each. The test was performed using increasing doses of both test extracts, given orally, in a 10 ml/kg volume to different groups serving as test groups[19]. Another group of mice was administered saline (10 mL/kg, p.o.) as negative control. The mice were allowed food *ad libitum* during the 24 h test and kept under regular observation for mortality.

***In vivo* anti-diarrheal activity:**

1. **Castor oil-induced Diarrhea:** The experiment was performed according to the method described by Shoba & Thomas [20]. Briefly, mice fasted for 24 h were randomly allocated to four groups of five animals each. The animals were all screened

initially by giving 0.5 ml of castor oil. Only those showing diarrhea were selected for the final experiment. Group I received 1% CMC (10 ml/kg, *p.o.*), groups III-IV received orally MDIB extract (100 and 200 mg/kg), respectively. Group II was given Loperamide (3 mg/ kg, *p.o.*) in suspension. After 60 min, each animal was given 0.5 ml of castor oil, each animal was placed in an individual cage, the floor of which was lined with blotting paper which was changed every hour, observed for 4 h and the characteristic diarrhoeal droppings were recorded.

2. **Magnesium sulphate-induced Diarrhea:** Diarrhoea was induced by oral administration of magnesium sulphate at the dose of 2 g/kg to the animals 30 min after pre-treatment with vehicle (1% Tween 80 in water, 10 ml/kg, *p.o.*) to the control group, loperamide (3 mg/kg) to the positive control group, and the methanol extract (MDIB) at the doses of 100 and 200 mg/kg to the test groups[21].

3. **Effect on Gastrointestinal Motility:** Animals were divided into four groups of five mice each and each animal was given orally 1 ml of charcoal meal (5% activated charcoal suspended in 1% CMC) 60 min after an oral dose of drugs or vehicle. Group I was administered 1% CMC (10 ml/kg) and animals in groups III-IV received extract of MDIB at the dose of 100 mg/kg and 200 mg/kg body weight, respectively. Group II received atropine sulfate (0.1 mg/kg,) as the standard drug.

   After 30 min, animals were killed by light ether anaesthesia and the intestine was removed without stretching and placed lengthwise on moist filter paper. The intestinal transit was calculated as a percentage of the distance travelled by the charcoal meal compared to the length of the small intestine [22].

4. **PGE_2-induced Enteropooling:** The method of Robert et al.[23] was applied. Overnight fasted mice were divided into five groups of 5 animals each. Group I was given 2% gum acacia and kept as a control. Group III-IV received 100 and 200 mg/kg p.o. of MDIB extracts, respectively. Group II served as a vehicle control and received 2% gum acacia plus PGE_2 (0.5 ml of 100µg/kg, i.p.). Group V received loperamide and kept as a positive control. Immediately afterwards, diarrhea was induced by 0.5 ml of 100µg/kg, i.p., dose of PGE_2 (Sigma Aldrich, USA). After 30 minutes, the animals were sacrificed, small intestine was removed, and intestinal contents were collected and measured in a syringe. The percentage inhibition in intestinal fluid was determined by comparing the values with vehicle control.

5. **Antimicrobial activity:** Sterile 6.0 mm diameter blank discs (BBL, Cocksville, USA) were impregnated with test substances of MDIB at the dose of 500µg/disc. This disc, along with standard discs (Ciprofloxacin, Oxoid Ltd, UK) and control discs were placed in petri dishes containing a suitable agar medium seeded with the test organisms using sterile transfer loop and kept at 4^oC to facilitate maximum diffusion.

   The plates then kept in an incubator (37^0C) to allow the growth of the bacteria. The antibacterial activities of the test agents were determined by measuring the diameter of the zone of inhibition in terms of millimeter. Antimicrobial activity was tested against *Staphylococcus aureus*, *Escherichia coli, Pseudomonus aeruginosa, Salmonella typhi, Shigella boydii, Shigella flexneri and Shigella dysenteriae* were obtained from International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B)[24].

Statistical analysis: All values were expressed as the mean ± standard error of the mean (SEM) of three replicate experiments and were analyzed using the GraphPad program (GraphPad, San Diego, CA, USA). The analysis was performed by using student's t test. $p<0.001$ and $p<0.05$ were considered to be statistically significant.

RESULTS:

Total Phenolic and Flavonoid contents: The total extractable phenolic contents of MDIB were 83.23 ± 0.81 mg/g plant extract (in GAE). In case of flavonoid, MDIB also displayed the highest flavonoid content (30.34 ± 0.39 mg/g plant extract in QA) (**Table 1**).

TABLE 1: YIELD, TOTAL AMOUNT OF PLANT PHENOLIC COMPOUNDS AND FLAVONOIDS OF METHANOLIC EXTRACT OF *DILLENIA INDICA* BARK

Sample	Yield (%)	Total phenols mg/g plant extract (in GAE)[a]	Total flavonoids mg/g plant extract (in QA)[b]
MDIB	15.0%	83.23 ± 0.81	30.34 ± 0.39

[a] Gallic acid equivalents (GAE, mg/g of each extract) for the total phenolic content. [b] Quercetin equivalents (mg/g of each extract) for the total flavonoid content. The GAE and QA are expressed as means ± SEM of triplicate experiments.

Acute Toxicity studies: Methanolic extract of *Dillenia indica* bark (MDIB) (500 – 5000 mg/kg, body weight) given orally did not cause any death in the different dose groups. The LD_{50} values for oral administration of the plant extracts were found to be greater than 5000 mg/kg in both cases.

Effect on castor oil-induced Diarrhea: The extracts significantly reduced the number of diarrheal episodes in a dose dependent manner when compared with the untreated controls. At 200 mg/kg doses, MDIB showed 53.39% reduction in the number of fecal episodes, whereas loperamide offered 81.55% protection (**Table 2**).

TABLE 2: EFFECT OF *DILLENIA INDICA* BARK EXTRACTS ON CASTOR OIL-INDUCED DIARRHEA IN MICE.

Group	Dose (mg/kg)	Onset of diarrhea (min)	Animals with diarrhea	No. of faeces in 4 h	% inhibition of defaecation
Group I	Vehicle	28.45 ± 1.19	5/5	20.6 ± 0.68	-
Group II	100	39.67 ± 2.73	4/5	18.2 ± 1.05	11.65
Group III	200	54.23 ± 3.03*	3/5	9.6 ± 0.29*	53.39
Group IV	10	130 ± 0.13**	1/5	3.8 ± 0.58**	81.55

Values are presented as mean ± SEM, (n=5); *,** p<0.001; <0.05, respectively, compared to control by student's *t*-test. Group I received vehicle (1% CMC), Group II and III received MDIB 100 and 200 mg/kg p.o., respectively, and Group IV received Loperamide 10 mg/kg p.o.

Effect on Magnesium sulphate-induced Diarrhea: MDIB extracts exhibited significant antidiarrheal activity against magnesium sulphate-induced diarrhea (**Table 3**). The extracts at both dose levels significantly (p< 0.001, p< 0.05) reduced the extent of diarrhea and also notably delayed the onset of diarrhea in a dose dependent manner.

TABLE 3: EFFECT OF *DILLENIA INDICA* BARK EXTRACTS ON MAGNESIUM SULPHATE-INDUCED DIARRHEA IN MICE.

Group	Dose (mg/kg)	Onset of diarrhea (min)	Animals with diarrhea	No. of faeces in 4 h	% inhibition of defaecation
Group I	Vehicle	35.05 ± 1.09	5/5	21.2 ± 1.68	-
Group II	100	28.67 ± 1.73	4/5	13.4 ± 1.05	36.79
Group III	200	49.93 ± 1.03*	3/5	7.7 ± 0.49*	63.67
Group IV	10	110 ± 0.10**	1/5	4.8 ± 0.51**	77.35

Values are presented as mean ± SEM, (n=5); *,** p<0.001; <0.05, respectively, compared to control by student's *t*-test. Group I received vehicle (1% CMC), Group II and III received MDIB 100 and 200 mg/kg p.o., respectively, and Group IV received Loperamide 10 mg/kg p.o.

Effect on Gastrointestinal Motility: With the gastrointestinal transit experiment, the treated groups showed significant difference compared with control (p< 0.001, p< 0.05). The intestinal transit of charcoal meal was 71.88% in the control group, but at 200 mg/kg b.wt. dose 32.35% in MDIB (**Table 4**).

TABLE 4: EFFECT OF *DILLENIA INDICA* BARK EXTRACTS ON CHARCOAL MEAL STIMULATED GASTROINTESTINAL TRANSIT IN MICE

Treatment	Dose (p.o.)	Mean intestinal length (cm)	Mean distance traveled by charcoal (cm)	% GI transit
Vehicle	0.4 mL/mouse	62.6 ± 0.91	45.0 ± 1.08	71.88 ± 1.57
Atropine	0.1 mg/kg	60.0 ± 1.19	15.4 ± 0.79**	25.67 ± 0.80**
MDIB	100 mg/kg	64.8 ± 1.11	31.6 ± 1.06	48.76 ± 2.32
	200 mg/kg	61.2 ± 1.51	19.8 ± 2.02*	32.35 ± 3.82*

Values are presented as mean ± SEM, (n=5); *,** p<0.001; <0.05, respectively, compared to control by student's *t*-test.

PGE_2 – induced Enteropooling: The plant extract reduced the intestinal fluid accumulation induced by PGE_2 in a dose dependent manner (**Figure 1**). At 200 mg/kg b.wt. dose, MDIB showed a good reduction (29.60%) compared with the vehicle control.

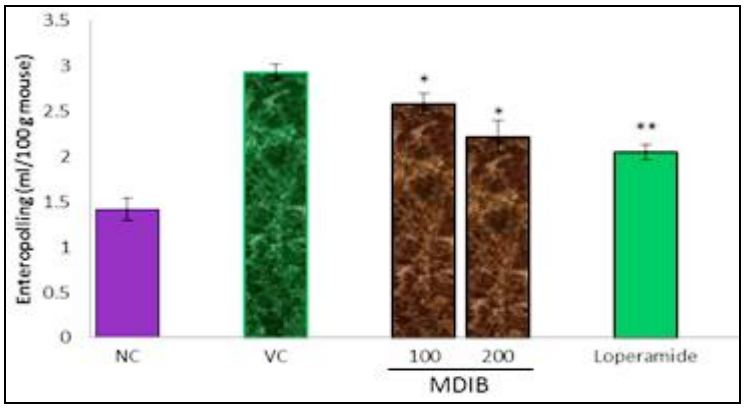

FIGURE 1: EFFECT OF THE METHANOLIC EXTRACT OF *DILLENIA INDICA* BARK ON PGE_2-INDUCED ENTEROPOOLING IN MICE. Values are presented as mean ± SEM, (n=5); **,* $p<0.001$; <0.05, respectively, compared to vehicle control by student's *t*-test. NC: Normal Control; VC: Vehicle control.

Antibacterial activity: Table 5 expressed the antibacterial activity (zone of inhibitions) of the MDIB extracts. The MDIB extract showed significant to moderate activity against *Staphylococcus aureus, Salmonella typhi, Shigella dysenteriae, Pseudomonas aeruginosa and Escherichia coli.* MDIB extracts have not shown any activity against *Shigella flexneri* and *Shigella boydii*. The highest zone of inhibition was found against *Escherichia coli* (zone of inhibition 11.09 ± 0.22 mm).

TABLE 5: ANTIBACTERIAL ACTIVITY OF THE METHANOLIC EXTRACTS OF *DILLENIA INDICA* BARK

Bacterial strain	Diameter of zone of inhibition (mm)	
	Ciprofloxacin	MDIB
Staphylococcus aureus	28.03 ± 0.12	11.09 ± 0.14
Pseudomonas aeruginosa	29.13 ± 0.21	9.82 ± 0.04
Salmonella typhi	25.41 ± 0.11	8.09 ± 0.12
Shigella flexneri	27.34 ± 0.12	NA
Shigella dysenteriae	28.01 ± 0.11	9.02 ± 0.62
Shigella boydii	29.39 ± 0.14	NA
Escherichia coli	30.23 ± 0.18	10.59 ± 0.22

Assay was performed in triplicate and results are the mean of three values ± Standard Deviation. NA- Zone of inhibition < 5 mm consider as no activity.

DISCUSSION: Plants or plant derived preparations are used abundantly by mass population against diarrheal disorders without any scientific explanation. Imbalance between absorptive and secretary mechanisms in the GIT accompanied by intestinal hurry results in frequent loose stools or diarrhea [25]. Use of medicinal plants against diarrhea have been validated by several studies i.e. antispasmodic effects, delay intestinal transit, suppress gut motility, stimulate water adsorption, or reduce the intraluminal fluid accumulation [26, 27].

Those experimental procedures were therefore employed to judge the antidiarrheal efficacy of *Dillenia indica* bark in the current study.

In the present investigation, MDIB at large dose (200 mg/kg, b.wt.) exhibited significant antidiarrheal effects in one or the other experimental models. With respect to the castor oil induced diarrhea model, the results revealed that MDIB showed better protection from diarrhea in the animals as compared with vehicle control and so was the case in PGE_2 induced enteropooling. It is likely that the extracts bring out the aforementioned action either through their proabsorbtive property that promotes faster fluid absorption in the intestine or through an anti-secretory mechanism.

Our first speculation gains support from the fact that castor oil, which was used as a diarrhea inducing agent in the experimental protocol. Several mechanisms have been previously proposed to explain the diarrhoeal effect of castor oil including inhibition of intestinal Na^+, K^+- ATPase activity to reduce normal fluid absorption [28], activation of adenylate cyclase or mucosal cAMP mediated active secretion [29], stimulation of prostaglandin formation [30], platelet activating factor and recently nitric oxide has been claimed to contribute to the diarrhoeal effect of castor oil [31].

However, it is well evident that castor oil produces diarrhea due to its most active component recinoleic acid which causes irritation and inflammation of the intestinal mucosa, leading to release of prostaglandins, which results in stimulation of secretion [32]. The prostaglandins of the E series are considered to be good diarrheogenic agents in experimental animals as well as in human beings [33]. The inhibitors of prostaglandins biosynthesis are therefore considered to delay the castor oil induced diarrhea [34].

On the other hand, magnesium sulphate has been reported to induce diarrhea by increasing the volume of intestinal content through prevention of reabsorption of water. It has also been reported that it promotes the liberation of cholecystokinin from the duodenal mucosa, which increases the secretion and motility of small intestine and thereby prevents the reabsorption of sodium chloride and water [35].

MDIB extracts were found to improve the diarrheal condition in this model. The extracts may increase the absorption of water and electrolyte from the gastrointestinal tract, since it delayed the gastrointestinal transit in mice as compared to the control. The delay in the gastrointestinal transit prompted by the extract might have contributed, at least to some extent, to their antidiarrheal activity by allowing a greater time for absorption.

In the small intestinal transit test, both extracts suppressed the propulsion of charcoal marker in a dose dependent manner. This finding suggests that the extracts act on all parts of the intestine. A decrease in the motility of gut muscles increases the stay of substances in the intestine [36]. This allows better water absorbtion. It is therefore presumed that the reduction in the intestinal propulsive movement in the charcoal meal model may be due to antispasmodic properties of the extracts. Salah *et al.,* [37] has reported that flavonoids inhibit the intestinal motility in experimental induced diarrhea in rats.

Flavonoids and sugars obtained from selected traditional medicinal plants in Bangladesh were reported by Rahman and Wilcock having antidiarrheal properties [38]. Longanga Otshudi *et al.,*[39] screened a number of medicinal plants and showed that antidiarrheal activity of those plants were due to tannins, alkaloids, saponins, flavonoids, sterols, triterpenes and reducing sugars contained in them. The flavonoids presence of these types of compounds, such as kaemferol, myricetin, apigenin, and leucocyanidin in *Dillenia indica* is likely to contribute to its grastrointestinal effects [40].

Also some plants show antidiarrheal properties by their antimicrobial activities [41]. MDIB was shown to exhibit good antibacterial activity when tested against *Escherichia coli, Shigella dysenteriae, Pseudomonas aeruginosa* and *Staphylococcus aureus* and also supported to the previous study [42]. Phytoconstituents such as saponin, phenolic compounds, flavonoids and glycosides have been reported to inhibit bacterial growth and to be protective to plants against bacterial and fungal infections. In the present study this possibility is supported by the estimation of total polyphenols and flavonoids [40], which was found to be present in high concentration and was found to be 84.23±0.81 *mg* equivalent of gallic acid/*g* plant extract. Moreover, Mokbel *et al*.,[43] isolated various anti-bacterial compound viz. ß-sitosterol, malic acid, succinic acid, palmatic acid, 12-hydroxystrearic acid, glycoside, the d-malic and 12- hydroxystrearic acid. So the antibacterial activity showed by the extract may be due to the presence of those compounds.

CONCLUSION: The results obtained in the present study suggest that *Dillenia indica* bark extracts have beneficial effect in controlling the diarrhea in experimental animals. The antidiarrheal property of *Dillenia indica* is mediated through inhibition of hypersecretion, gastrointestinal motility and increase of gastric transit time. The *Dillenia indica* could be used in the treatment of diarrhea.

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How to cite this article:
Islam MM, Pia RS, Jahan KSE, Chowdhury J, Akter F, Parvin N and Akter S: Antidiarrheal activity of *Dillenia indica* bark Extract. *Int J Pharm Sci Res*. 2013; 4(2); 682-688.