

Preliminary Evaluation of Anti-Diarrheal, Ulcer-Protective and Acute Toxicity of Aqueous Ethanolic Stem Bark Extract of *Ficus trichopoda* in Experimental Rodents

^{1,6,7}S.O. Balogun, ^{2,6}J.K. Tanayen, ^{2,6}A.M. Ajayi, ^{1,6}A. Ibrahim, ^{5,6}J.O.C. Ezeonwumelu, ^{3,6}A.A. Oyewale, ^{2,6}O.J. Oloro, ^{4,6}A.D.T. Goji, ^{5,6}D.M. Kiplagat and ^{5,6}B. Adzu

^{1,6}Department of Biochemistry,

^{2,6}Department of Pharmacology and Toxicology,

^{3,6}Department of Anatomy,

^{4,6}Department of Physiology,

^{5,6}Department of Clinical and Biopharmacy, School of Pharmacy,

⁶Kampala International University Complementary and Alternative Medicine Research (KIUCAMRES), Kampala International University - Western Campus,

P.O. Box 71 Bushenyi, Uganda

⁷Programa de pós-graduação em Ciências da Saúde, (Farmacologia), Faculdade de Ciências Médicas, Universidade Federal de Mato Grosso, Mato Grosso, Cuiaba, Brazil

Abstract: *Ficus trichopoda*, Baker, is a medicinal plant belonging to the Moraceae family used popularly as a 'multi-purpose' herb in Uganda. The aim of this study was to evaluate the anti-diarrheal, ulcer protective effects of 70% ethanolic extract of *Ficus trichopoda* stem bark (FTE) and its acute toxicity. The anti-diarrheal effect was evaluated using castor-oil induced diarrhea model while anti-ulcer effect was evaluated using ethanol-induced ulcer model using rats. Loperamide and misoprostol were used as standard drugs for diarrhea and ulcer studies respectively. The extract was administered orally at three different doses of 125, 250 and 500 mg/kg. Acute toxicity was evaluated by oral administration of the extract at 1000, 2000 and 4000 mg/kg body weight in mice. The extract exhibited a graded dose-dependent inhibition of the castor oil induced diarrhea. The onset-time and severity of diarrhea was significantly reduced ($p < 0.05$). Anti-diarrhea activity exerted was significant at 250 mg/kg (66.67% inhibition) and maximal at 500 mg/kg (88.89% inhibition). The inhibition at 500 mg/kg compared well with the standard drug, Loperamide which produced 100% inhibition of diarrhea in rats. Also, oral administration of FTE produces a dose-dependent inhibition of ethanol-induced gastric ulcer with maximal effect at 500 mg/kg (49.05%). The oral LD₅₀ value obtained was >4000 mg/kg in mice. Preliminary phytochemical screenings indicated the presence of reducing sugar, alkaloids, saponins, pyrocatecholic tannins and free amino acids/amines. This study confirmed the antidiarrheal properties of this plant as it is used in traditional medicine.

Key words: Acute toxicity, anti diarrheal, *Ficus trichopoda*, gastroprotective, loperamide, Uganda

INTRODUCTION

Genus *Ficus* belongs to Family Moraceae commonly referred to as fig trees. Forty-four species are known from Uganda (Berg and Hijman, 1989; Verdcourt, 1998). A number of *Ficus* sp. are used as food and for medicinal properties (Lansky *et al.*, 2008). Several ficus species are traditionally used in African folk medicine in the treatment of many illnesses such as convulsions and respiratory disorders (Wakeel *et al.*, 2004). The decoction of *Ficus rhynchocarpa*, *Ficus sycomorus*, *Ficus*

natalensis and *Ficus vasta* are used to treat various stomach disorders. Several other reports have demonstrated different biological activities of *Ficus* plants including peptic ulcer treatment (Kokwaro, 1993; Akah *et al.*, 1997; Mandal *et al.*, 2000; Chiang *et al.*, 2005; Kuetea *et al.*, 2008; Rao *et al.*, 2008; Singh *et al.*, 2009). The reported medicinal uses of these plants includes: treatment of various gastrointestinal disorders, infectious diseases, fertility treatment and induction of labor (Kamatenesi-Mugisha and Oryem-Origa, 2007; Ssegawa and Kasenene, 2007).

Gastrointestinal disorders are one of the most important causes of morbidity for the populations of non-industrialized countries (Borrelli and Izzo, 2000). Diarrhea, one of the gastrointestinal disorders, is a common disorder characterized by an increase in stool frequency and a change in stool consistency (Farthing, 2002). It remains one of the major health threats to populations in the tropical and subtropical poor countries. According to Heinrich *et al.* (2005), the World Health Organization (WHO) estimates that 3-5 billion cases occur each year (1 billion in children less than 5 years of age), and that approximately 5 million deaths are due to diarrhea annually (2.5 million in children less than 5 years of age).

Another medically important gastrointestinal disorder is peptic ulcer. It is dominant among the diseases that affect the world's population. It is now generally accepted that gastric lesions develop when the delicate balance between some gastroprotective and aggressive factors is lost (Hoogerwerf and Pasricha, 2001; Falcao *et al.*, 2008). Several pharmaceutical products have been employed for the treatment of gastroduodenal ulcer and peptic diseases, resulting in decreasing mortality and morbidity rates, but they are not completely effective and produce many adverse effects (Rates, 2001). These adverse effects include high incidence of hip fractures, non-steroidal anti-inflammatory drugs-induced gastropathy (Rates, 2001). Long-term use of some of these drugs may result into diarrhea (Kakei *et al.*, 1993), impotence, achlorhydria, hypergastrinemia and hyperplasia of enterochromaffin-like cells (Howden and Hunt, 1994).

Against numerous gastrointestinal diseases, the populations of developing countries have only medicinal plants as primary sources of medicine (Lima *et al.*, 2008). Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results for the treatment of gastric ulcer (Schmeda-Hirschmann and Yesilada, 2005). Furthermore, the herbal medicine practitioners are accessible, their products less expensive, and the population consider the traditional practice a part of their heritage (Elisabetsky *et al.*, 1995).

In Uganda, a large part of the population depends on traditional medicine for day-to-day health care needs (Kamatenesi-Mugisha and Oryem-Origa, 2007). In the light of these and as part of our research activities in validation of medicinal plants used in the popular medicine in the South-West of Uganda, we choose to work on *Ficus trichopoda* due to its widespread availability and usage among the local people for medical uses.

Despite the popular use of this plant, there is no literature on biological activities addressing its effects on the gastrointestinal tract. The present study was to assess the safety as well as the effects of an aqueous ethanolic extract of FTE on diarrhea and ulcer using castor oil induced diarrhea and ethanol induced ulcer model respectively.

MATERIALS AND METHODS

Laboratory animal acquisition and maintenance:

Animals used in these experiments were obtained from the animal house of pharmacology and toxicology department, Kampala International University-Western Campus. Animals were maintained under standard environmental conditions and had free access to standard rodent feed (Nuvita® feeds, Jinja Uganda) and tap water. Housing conditions and in vivo experiments were used according to the guidelines established by the Institute of Laboratory Animal Resources Commission on Life Sciences National Research Council, Washington, D.C. (1996).

Plant material collection and identification:

The stem bark and the leaves of *F. trichopoda* were collected in the month of June, 2009 in the morning. The plant was identified by a taxonomist at Makerere University Kampala and a voucher specimen deposited at Herbarium section of School of Pharmacy, Kampala International University. The stem bark was then ground into powder and was used for the subsequent experimentation.

Preparation of plant extract:

The powdered material was exhaustively extracted by cold aqueous ethanolic maceration for two days and the supernatant decanted. The entire process was repeated three times, and the extracts combined and filtered through Whatman No 1 filter paper. The crude extract was evaporated to dry powder at 40°C in an oven.

Preliminary phytochemical screening:

The aqueous ethanolic stem bark extract was subjected to qualitative phytochemical screening according to standard methods (Trease and Evans, 1989).

3Acute toxicity study:

Acute toxicity of the aqueous ethanolic extract of FTE was done following Lorke's (1983) method with slight modifications. Briefly, three groups of three mice were fasted overnight with access to water *ad libitum*. On the day of the experiment, the mice were administered via the oral route with 1000, 2000 and 4000 mg/kg body weight of the plant stem bark extract. Animals were observed for any signs of toxicity and mortality up to 72 h after the administration of the extract.

Castor oil-induced diarrhoea in rats and body weight decrease:

The method of Awouters *et al.* (1978) was adopted with slight modifications. Rats of either sex (120-200 g) were fasted overnight. The animals were divided into five groups (n = 5). Normal saline (10 mL/kg) was given to the first group orally while the second group received Loperamide (3 mg/kg). Graded doses of FTE (125-500 mg/kg, p.o.) were administered to the last three

Table 1: Effect of aqueous ethanolic extract of FTE on ethanol-induced ulceration (125-500mg/kg, p.o)

Treatment	Dose	Ulcer index (mm) ¹	Inhibition of ulceration ² (%)
<i>Ficus trichopoda</i>	125 mg/kg	80.90±17.23	1.63
<i>Ficus trichopoda</i>	250 mg/kg	58.80±18.68	28.50
<i>Ficus trichopoda</i>	500 mg/kg	41.90±19.23	49.05
Misoprostol	400 µg/kg	16.00±6.78	80.54
Distilled water	10 mL/kg	82.24±13.3	-

¹: Values expressed as mean±S.E.M. (n = 5); p<0.01 vs. control (One way ANOVA); ²: Compared with saline control

Table 2: Effect of ethanolic extract of FTE on castor oil-induced diarrhoea and loss in body weight (125-500mg/kg, p.o)

Treatment	Dose (mg/kg, p.o.)	Loss in B.W. ¹ (g)	Diarrhoea score			Total score	Inhibition ² (%)
			++	+	0		
<i>Ficus trichopoda</i>	125	11.22±3.14	3	1	1	7	22.22
<i>Ficus trichopoda</i>	250	9.98 ±3.17	0	3	2	3	66.67 ³
<i>Ficus trichopoda</i>	500	7.88 ±4.13	0	1	4	1	88.89 ³
Loperamide	3	6.84 ±4.67	0	0	5	0	100 ³
Distilled water	10ml/kg	7.04 ±1.70	4	1	0	9	-

¹: Values expressed as mean±S.E.M. (n = 5); ²: Compared with saline control; ³: Denotes statistical significance between treated groups and control. (One way ANOVA p<0.01); BW: body weight

groups. Thirty minutes after pre-treatment with these agents, the animals were challenged with 1 mL of castor oil. Thereafter, they were placed in cages lined with adsorbent papers and observed for 6 h for the presence of characteristic diarrhoeal droppings. The diarrhoea score of each rat was taken 6 h after the castor oil administration and recorded using a predetermined scoring index (Di Carlo *et al.*, 1994) as follows; (+ +) for copious, (+) for mild and 0 for lack of diarrhoea. The animals were reweighed once again, and changes in body weight taken (Yu *et al.*, 2000). The total score of each group were taken and activity expressed as % inhibition of diarrhoea.

Ethanol-induced gastric ulceration in rats: This was performed as described by Morimoto *et al.* (1991) with modification. Rats were distributed into five groups (n = 5). Rats were given an oral dose of the vehicle (distilled water 10 mL/kg body weight) and a gastroprotective agent misoprostol (400 µg/kg body weight) (Asad *et al.*, 2001) and graded doses of the plant extracts (125, 250, and 500 mg/kg body weight). After 1 h, the rats were treated orally with 1 mL/kg body weight of absolute ethanol. Three hours later, the rats were sacrificed by cervical dislocation, and the stomach removed and opened along the greater curvature. The stomachs were thoroughly rinsed with water to remove the gastric contents and blood clots if any. The extents of the ulceration were measured by adding up the length (mm) of the ulcers for each stomach (Arun and Asha, 2008). Mean scores for each group were calculated and expressed as ulcer index (UI). The group that received distilled water with ethanol alone served as the negative control group. From this data, the percentage inhibition of ulceration was determined for each group according to the formula:

$$\{UI = (\text{negative control}) - \text{treated}/UI (\text{negative control})\} \times 100$$

Statistical analysis: Data were expressed as mean values ± standard error of mean (S.E.M) and comparisons of data were done by one-way analysis of variance (ANOVA) with the use of software SPSS version 11.5.

RESULTS

Phytochemical analysis: The preliminary phytochemical analysis of the aqueous ethanolic extract of the stem bark of FTE revealed the presence of reducing sugars, alkaloids, saponins, pyrocatecholic tannins and free amines/ amino acids.

Acute toxicity evaluation: Oral administration of the aqueous ethanolic extract of FTE in doses up to 4000 mg/kg body weight did not produce any mortality and any visible signs of toxicity when observed up to 72 h after administration.

Effect on castor-oil induced diarrhea: Table 1 summarizes the results obtained in the experimental model of castor oil-induced diarrhea. The aqueous ethanolic extract of *Ficus trichopoda* significantly (p<0.05) inhibited the frequency as well as the severity of the diarrhea. On oral administration of castor oil and following the course of observation for 6 h, all the rats in the control group (distilled water 10 mL/kg, p.o.) produced copious diarrhea. Pretreatment of the rats with the aqueous ethanolic extract of FTE (125-500 mg/kg) caused a significant (p<0.05) dose dependent inhibition in severity of diarrhea (22.2-88.89 %) as shown in Table 2. There was no significant difference in the loss of body weight across all groups.

Gastroprotective effects on ethanol-induced gastric ulceration: Ulcer index are shown below (Table 1). Oral administration of 70% ethanol produced mucosal lesions in the rat stomach. Gastroprotective effects of 125, 250

and 500 mg/kg were in a dose-dependent manner (Table 1) although these differences were not statistically significant ($p < 0.05$).

DISCUSSION

The aim of the present study was to assess the effect of an aqueous ethanolic extract of FTE on diarrhea and ulcer using castor oil induced diarrhea and ethanol induced ulcer model respectively. Castor oil is known to cause diarrhea due mainly to the presence of ricinoleate which account for about 90% composition of the oil (Mckeon *et al.*, 1999). Ricinoleate is known to cause increases in peristaltic activity of the small intestine and thus alters the permeability of Na^+ and Cl^- in the intestinal mucosa (Palombo, 2006). Stimulation of the release of endogenous prostaglandin has also been found to be associated with ricinoleate found in castor oil (Zavala *et al.*, 1998).

Acute toxicity studies showed that the plant extract is relatively safe at high doses which may not necessarily be reached in human usage. The acute toxicity study on the FTE revealed that it is relatively safe. Figs as a fruit have a very high safety profile. Bafor and Igbinuwen (2009) demonstrated that the aqueous leaf extract of *Ficus exasperata* to be relatively safe in both 24 h and 14 days oral administration. However, research into the safety profile of ethanolic extract of *Ficus natalensis* administered orally at doses of 100 and 500 mg/kg body weight to rats for 14 days produces a significant toxicity to the liver (Kinyi and Balogun, 2009).

Ficus Pretreatment of the rats in this present study with FTE exhibited significant dose-dependent antidiarrheal activity. The effect observed was similar to the standard drug, Loperamide at 3 mg/kg. This is in concordance with findings by Mandal and Kumar, (2002), Ahmadua *et al.* (2007) who demonstrated anti-diarrheal effects of *Ficus hispida* and *Ficus sycomorus*, respectively. Studies have shown that antidiarrheal properties of many plants stem from the presence of tannins, alkaloids, saponins, flavonoids, sterol and/or triterpenes and reducing sugars (Longanga *et al.*, 2000; Adzu *et al.*, 2003). Tannins for example are known to reduce secretion and make the intestinal mucus resistant through the formation of protein tannate (Tripathi, 1994). We may plausibly explain that the anti-diarrheal effect observed may be due to the presence of these various phytochemicals in the extract.

However, pretreatment of the rats with FTE did evoke a dose dependent inhibition of ethanol-induced gastric erosion and hemorrhage (1.63, 28.5 and 49.05% for 125, 250 and 500 mg/kg, respectively), but these observations were not statistically significant as compared to the control. It should be noted also that although the standard drug had an inhibition of 80.54% but this

difference was not statistically significant either as compared to the control. The import of these findings is the need to assess the anti-ulcer activity of FTE using other *ulcer models*.

CONCLUSION

The current study revealed that FTE has antidiarrheal effect but no statistically significant ulcer protective effect and is relatively safe.

The findings help to support the claim by traditional healers who use this plant in the treatment of diarrhea and gastric ulcers in Uganda.

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