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## Anti-Diarrhoeal Activity of *Blighia sapida* (Sapindaceae) in Rats and Mice

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**Abstract:** The anti-diarrhoeal activity of the ethanolic and aqueous extracts of *Blighia sapida* (Sapindaceae) stem bark on castor oil-induced diarrhoea and enteropooling and gastrointestinal motility in rats and mice were investigated. Doses of the ethanolic and aqueous extracts of *B. sapida* (265, 530 and 1060 mg kg<sup>-1</sup> body weight) or loperamide (3 mg kg<sup>-1</sup>) were administered (p.o.) to rats and mice 4 h before castor oil challenge and the numbers of diarrhoeal defaecations or weight of faecal matter in intestines noted. In another study, animals were administered with charcoal meal or tragacanth and similar doses of extracts (p.o.) or 0.1 mg kg<sup>-1</sup> atropine (i.p.) or tragacanth administered immediately thereafter and the distance moved by the charcoal meal from the pylorus measured. The results indicate that both extracts of *B. sapida* caused significant ( $p < 0.001$ ) dose-dependent inhibitions of the castor oil-induced diarrhoea (39.7-93.2%) and intestinal motility (31.9-77.5%) with the highest dose (1060 mg kg<sup>-1</sup>) showing inhibitions (70.4-93.2%) comparable to loperamide (89-100%) and atropine (72.8-100%), respectively. However, castor oil-induced enteropooling was significantly ( $p < 0.05$ ) inhibited by the ethanolic and aqueous extracts in rats (23.8-25.9 %) and mice (58.4-59.0%) at the highest dose compared to 41.6-46.8% for loperamide. These results indicate that there were no significant differences between the ethanolic and aqueous extracts of *B. sapida* in the reduction or prevention of castor oil-induced diarrhoea and that *B. sapida* may act through the inhibitions of intestinal motility and enteropooling.

**Key words:** Castor oil, intestinal motility, enteropooling, atropine, loperamide

### INTRODUCTION

Diarrhoea is a major health challenge especially in children under 5 years of age in most developing countries. It is one of the leading causes of childhood morbidity and mortality in these countries. Annual death estimates from diarrhoeal diseases in children stands at over 6 million (Fauci *et al.*, 1998; Park, 2000).

About 70% of the populations in developing countries rely on traditional medicine for their primary health care needs. Thus the use of medicinal plants for the treatment/management of disease is a significant alternative to allopathic medicines which are sometimes expensive and with some untoward effects. Many medicinal plants have been well documented to have anti-diarrhoeal properties (Agunu *et al.*, 2005) but there is little scientific evidence validating their use as such. One of such medicinal plants is *Blighia sapida*, which has been used by the Centre for Scientific Research into Plant Medicine (CSRPM) for the treatment of diarrhoea for over twenty years.

*Blighia sapida* belongs to the family Sapindaceae and is commonly called ackee, akee apple, or vegetable brain. It is an evergreen tree more widely known for the edible part of its fruit and is indigenous to Africa. It has a trunk of up to 1.8 m in circumference and a dense crown of spreading branches making it suitable as a shade tree (Aderinola *et al.*, 2007). The root of *B. sapida* is also used

in combination with *Xylopia aethiopica* to terminate unwanted pregnancies and it is also a good source of phosphorus, magnesium and calcium (Abolaji *et al.*, 2007).

The immature fruit arils of *B. sapida* are poisonous. This is due to the presence of hypoglycins A and B, which have a potent hypoglycaemic causing clinical symptoms termed toxic hypoglycaemic syndrome (Joskow *et al.*, 2006). The most toxic hypoglycin A, is a water-soluble liver toxin shown to produce hypoglycaemia in rabbits, monkeys, rats and mice upon intravenous injection (Chen *et al.*, 1957) through the inhibition of gluconeogenesis. The LD<sub>50</sub> of hypoglycin A is 90 mg kg<sup>-1</sup> for adult rats (Hassall *et al.*, 1954). The fruit also contain saponins which are haemolytic (Abolaji *et al.*, 2007). The seeds contain hypoglycin B, which is approximately half as toxic as hypoglycin A (Hassall *et al.*, 1954).

Despite the use of *B. sapida* in the treatment of diarrhoea, there is no empirical pre-clinical scientific data to validate its clinical use. The present work sought to determine the anti-diarrhoeal activity of ethanolic and aqueous extracts of *B. sapida* in rodent diarrhoeal models with the view to validating its clinical use and the anecdotal claims for its use.

## MATERIALS AND METHODS

### Reagents and Chemicals

Castor oil, tragacanth, loperamide, activated charcoal and atropine were obtained from Sigma Chemical Co. (St. Louis, MO, USA). All other chemicals were purchased in their purest form available from British Drug Houses (BDH) Ltd. (Poole, UK).

### Plant Raw Material

Mature stem bark of *Blighia sapida* was collected from the Plant Development Department (PDD) of the Centre for Scientific Research into Plant Medicine (CSRPM), Mampong-Akuapem in the Eastern Region of Ghana. The plant was authenticated by Dr. Yaw Ameyaw, a botanist of the PDD, CSRPM. The stem bark was air dried and milled into a powdered form.

### Preparation of Ethanolic and Aqueous Extracts of *Blighia sapida*

For the ethanolic extract, 5 L of 70% ethanol was added to 1 kg of the powdered *B. sapida*. The mixture was left to stand for three days with periodic stirring. The preparation was sieved with a fine mesh and the ethanol evaporated using a rotary evaporator. The concentrated extract was then freeze dried to obtain the ethanolic extract of *B. sapida*. The dried extract obtained was 3.0 g, representing 3% (w/w) yield from the plant raw material. In the case of the aqueous extract, 3 L of warm water (80°C) was added to 1 kg of the powdered *B. sapida*. The mixture was kept at 80°C for 3 h with periodic stirring and then sieved as before. The filtrate was freeze-dried to obtain 43.8 g of dry aqueous extract of *B. sapida* equivalent to 4.38 % (w/w) yield from the plant raw material.

### Phytochemical Screening of *B. sapida* Extracts

The powdered *B. sapida* was screened for the presence or absence of groups of phytochemicals such as saponins, reducing sugars, phenolics, cyanogenic glycosides, polyamides, phytosterols, triterpenes, anthracenosides, flavonoids and alkaloids (Sofowora, 1982; Harborne, 1983).

### Animals

Male Sprague-Dawley rats (200-250 g) and male ICR mice (25-30 g) were obtained from the Animal Unit of the Centre for Scientific Research into Plant Medicine (CSRPM), Mampong-Akuapem, in the Eastern Region of Ghana. The animals were fed on powdered feed obtained from Ghana Agro Food Company (GAFCO) Tema, Ghana. They were allowed free access to sterilized distilled water. The research was conducted in accordance with the internationally accepted principles for laboratory animal use and care.

### **Acute Toxicity Studies**

A single oral dose (2 mL rat<sup>-1</sup> and 0.5 mL mice<sup>-1</sup>) of the ethanolic and aqueous extracts was administered at 5000 mg kg<sup>-1</sup> body weight to six rats and six mice each with an oral gavage needle. Mortality and general behavior of the animals were observed over a 48 h period. Surviving animals were observed for a further period of 12 days for toxic symptoms such as pilo-erection, condition of eyes, movement and breathing of animals.

### **Castor Oil-Induced Diarrhoea and Enteropooling**

In the castor oil-induced diarrhoea studies, male rats and mice were fasted overnight and placed singly in metal cages lined with A4 sheets. They were separated into two sets of 8 groups of 6 animals; one set each for the rats and mice. Groups 1-3 of the rat or mice set received oral administrations of the ethanolic extract of *B. sapida* at doses of 265 mg kg<sup>-1</sup> (therapeutic dose), 530 and 1060 mg kg<sup>-1</sup>, representing 2x and 4x the therapeutic dose. Groups 4-6 received equivalent doses of the aqueous extract. The seventh group, which served as the positive control, received 3 mg kg<sup>-1</sup> of loperamide (Venkatesan *et al.*, 2005; Kouitcheu *et al.*, 2006) and the eighth group, which served as the normal control, received 2% aqueous tragacanth suspension (Pulok *et al.*, 1995). One hour after treatment, each rat and mouse received 2 and 0.75 mL of castor oil, respectively by oral gavage. The numbers of wet defecations over a period of 4 hours were recorded and the mean number of diarrhoeal defecations was determined for each group.

In the castor oil-induced enteropooling studies, rats and mice were fasted overnight and placed in metallic cages in 8 groups of 6 rats or mice. Groups 1-3 of the rats or mice set received oral administrations of the ethanolic extract of *B. sapida* at doses of 265, 530 and 1060 mg kg<sup>-1</sup>. Groups 4-6 received equivalent doses of the aqueous extract. The seventh group received 3 mg kg<sup>-1</sup> of loperamide (p.o.) as positive control whilst the eighth group served as the normal control and received sterilized distilled water. Castor oil (2 mL rat<sup>-1</sup> and 0.75 mL mouse<sup>-1</sup>) was administered to all groups one hour after drug/extract administration. Two hours after castor oil challenge, the rats and mice were euthanized and the whole length of the intestine from the pylorus to the caecum was taken and weighed. The contents of the intestine were then collected and the empty intestine weighed to obtain the weight of intestinal content.

### **Intestinal Motility**

The experimental method in which normal control animals received aqueous tragacanth was used (Pulok *et al.*, 1995). Briefly, male rats and mice were fasted overnight and separated into 8 groups of 6 rats or mice. Each animal was administered orally with 1 mL and 0.5 mL charcoal meal (3% activated charcoal in 10% aqueous tragacanth) for rats and mice, respectively. Groups 1-3 of the rats or mice set received oral administrations of the ethanolic extract of *B. sapida* at doses of 265, 530 and 1060 mg kg<sup>-1</sup>. Groups 4-6 received equivalent doses of the aqueous extract. The seventh group received 0.1 mg kg<sup>-1</sup> atropine (i.p.) as positive control (Venkatesan *et al.*, 2005; Kouitcheu *et al.*, 2006) whilst the eighth group served as the normal control and received 2% aqueous tragacanth suspension. Thirty minutes after treatment, each rat or mouse was killed and the intestinal distance moved by the charcoal meal from the pylorus was measured and expressed as a percentage of the distance from the pylorus to the caecum.

### **Statistical Analysis**

One-way analysis of variance (ANOVA) and independent sample t-test was conducted between control and test to determine statistical significance. The 5% level of probability was used as criterion of significance in all instances. All statistical tests were performed with SPSS statistical software version 11.0.

## RESULTS

### Acute Toxicity Studies of *Blighia sapida* Extracts

The effect of a single oral dose of the ethanolic or aqueous extract of *B. sapida* (5000 mg kg<sup>-1</sup>) administered to six rats and six mice showed no deaths in both animal species with the ethanolic extract but deaths of two mice with the aqueous extract within 48 h. Autopsy of dead mice indicated that the deaths, within minutes of dosing, were caused by choking of animals by accidental entry of the aqueous extract into their lungs on oral gavage rather than the systemic effects of the extract. There were no physical signs of toxicity as evidenced by normal breathing and movement and the absence of bulging eyes and pilo-erection. These observations suggest that the oral LD<sub>50</sub> of both extracts is greater than 5000 mg kg<sup>-1</sup> for both mice and rats. Observations of animals over the next 12 days showed no adverse effects of treatment.

### Effect of Extracts on Castor Oil-Induced Diarrhoea

The effects of varying doses of ethanolic and aqueous extracts of *B. sapida* and loperamide on the number of diarrhoeal defaecations 4 h after castor oil challenge in rats and mice are shown in Fig. 1a and b. In the rats, the ethanolic and aqueous extracts caused dose-dependent inhibitions of diarrhoeal defaecations of (23.6-62.9%) and (44.4-60.7%), respectively whilst the positive control, loperamide,

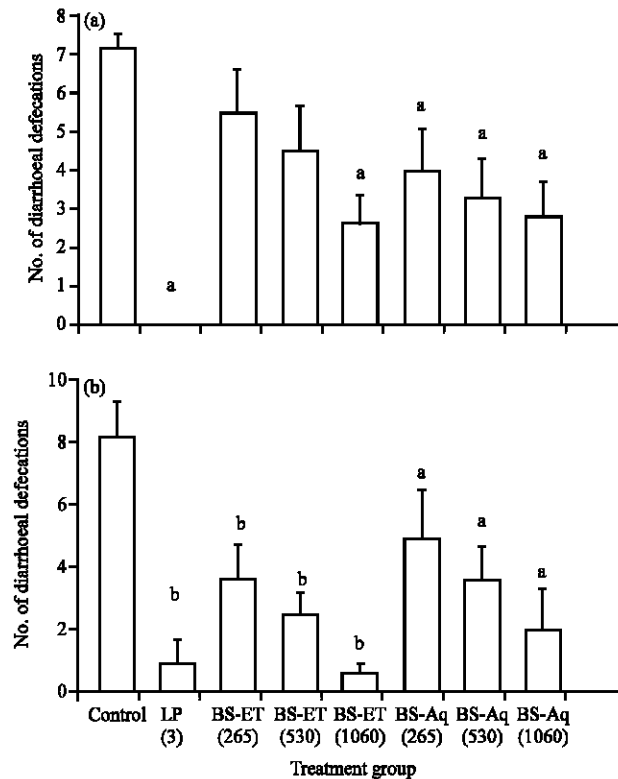


Fig. 1: Effect varying doses of ethanolic (Et) and aqueous (Aq) extracts of *Blighia sapida* (BS) and loperamide (LP) on castor oil-induced diarrhoea in (a) rats and (b) mice. Results are expressed as Mean±SEM (n = 5). Values in parenthesis represent dosage in mg kg<sup>-1</sup>. <sup>a</sup>Value significantly different from control; p<0.05. <sup>b</sup>Value significantly different from control; p<0.001

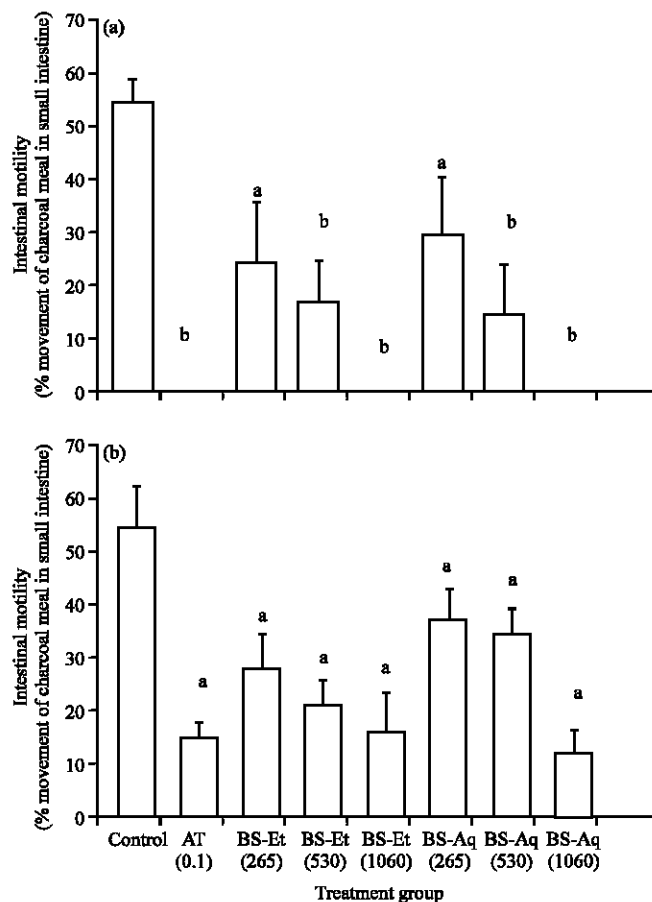


Fig. 2: Effect of varying doses of ethanolic (Et) and aqueous (Aq) extracts of *Blighia sapida* (BS) and atropine (AT) on castor oil-induced gastrointestinal motility in (a) rats and (b) mice. Results are expressed as Mean±SEM (n = 5). Values in parenthesis represent dosage in mg kg<sup>-1</sup>. <sup>a</sup>Value significantly different from control; p<0.05. <sup>b</sup>Value significantly different from control; p<0.001

caused a 100% inhibition of diarrhoeal defaecations when compared to untreated control (Fig. 1a). The inhibition of the ethanolic extract was significant at the 1060 mg kg<sup>-1</sup> dose whilst that of the aqueous extract was significant at all three doses (p<0.05). In mice, there were significant (p<0.05; p<0.001) dose-dependent inhibitions of diarrhoeal defaecations (Fig. 1b) with the ethanolic (68.1-93.6%) and aqueous (48.6-82.9%) extracts as well as loperamide (92.9%). Furthermore, the inhibition of diarrhoeal defaecations by the 1060 mg kg<sup>-1</sup> dose of *B. sapida* extracts (60.7-93.6%) was comparable to that of loperamide.

#### Effect of Extracts on Intestinal Motility

Figure 2a and b are graphical representations of the effects of increasing doses of *B. sapida* and atropine on intestinal motility in rats and mice. Results in rats show that there was a dose-dependent reduction in intestinal motility for both the ethanolic (55.4-100%) and aqueous (45.8-100%) extracts (Fig. 2a). The reductions by the 530 and 1060 mg kg<sup>-1</sup> doses of *B. sapida* were significantly different from untreated control (p<0.05; p<0.001) with the 100% reductions by the highest dose of the extracts

(1060 mg kg<sup>-1</sup>) being similar to atropine (0.1 mg kg<sup>-1</sup>), the positive control (100%). In mice, the reduction of intestinal motility by the ethanolic extract (48.1-70.4%) was directly dose-dependent whilst that of the aqueous extract (31.9-77.5%) was not (Fig. 2b). However, the effects of the varying doses of each extract and atropine were significantly different from untreated control (p<0.05). The reductions (70.4-77.5%) in intestinal motility in mice at the highest dose of extracts (1060 mg kg<sup>-1</sup>) were comparable to that of atropine (72.8%) as in rats.

### Effect of Extracts on Castor Oil-Induced Enteropooling

The effects of varying doses of *B. sapida* extracts and loperamide on castor oil-induced enteropooling in rats and mice are shown in Fig. 3a and b. In rats, there were significant (p<0.05) inhibitions in castor oil-induced enteropooling by the ethanolic (23.8%) and aqueous (25.9%) extracts of *B. sapida* at the highest dose (1060 mg kg<sup>-1</sup>) compared to the marked significant (p<0.05) inhibition by loperamide (46.8%). The 265 and 530 mg kg<sup>-1</sup> doses of the two extracts, however, showed no significant (p>0.05) effect on castor oil-induced enteropooling (Fig. 3a). Although in mice there was a direct dose-dependent effect on enteropooling by the aqueous extract (26.3-59%) this was not so in the case of the ethanolic extract (2.1-58.4%). The effects of the normal dose (265 mg kg<sup>-1</sup>) of *B. sapida* extracts (2.1-26.3%) and loperamide (41%) were not significantly different (p>0.05) from untreated

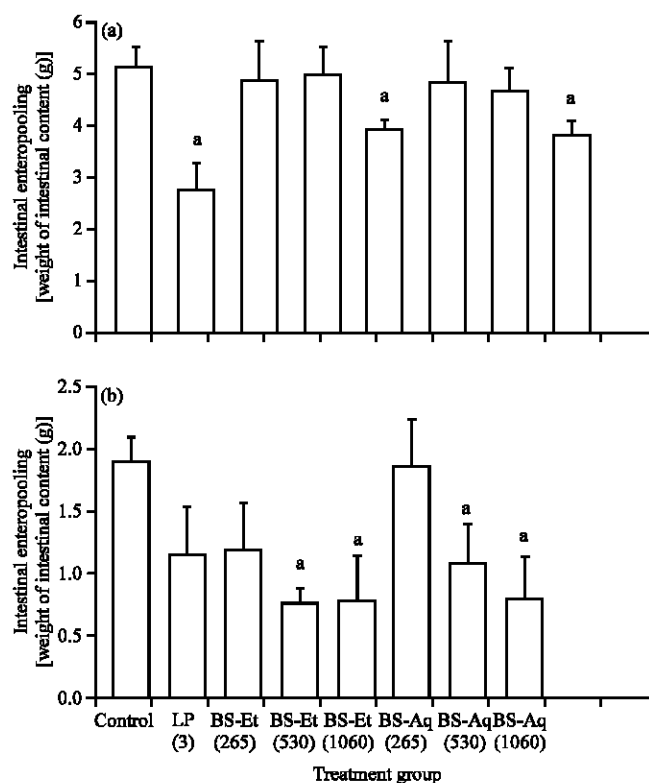


Fig. 3: Effect of varying doses of ethanolic (Et) and aqueous (Aq) extracts of *Blighia sapida* (BS) and loperamide (LP) and atropine (AT) on castor oil-induced enteropooling in (a) rats and (b) mice. Results are expressed as Mean±SEM (n = 5). Values in parenthesis represent dosage in mg kg<sup>-1</sup>. <sup>a</sup>Value significantly different from control; p<0.05

Table 1: Phytochemical screening of extracts of *Blighia sapida*

Groups of phytochemicals	Characterization test results	
	Ethanollic extract	Aqueous extract
Saponins	+	-
Reducing sugars	+	+
Phenolics	-	-
Cyanogenic glycoside	-	-
Polyamide	+	+
Triterpenes	-	-
Phytosterols	+	-
Anthracenosides	-	-
Flavonoids	-	-
Alkaloids	-	-

+: Present; -: Absent

control. However, the inhibitory effects of the two extracts at 530 and 1060 mg kg<sup>-1</sup>, were significant compared to untreated control (p<0.05), though slightly higher or similar to that of loperamide (Fig. 3b).

#### Phytochemical Composition of Extracts

The results of the screening of the groups of phytochemicals present in the ethanolic and aqueous extracts of *B. sapida* are shown in Table 1. Both extracts showed the absence of alkaloids, flavonoids, anthracenosides, phenolics and cardiac glycosides, but the presence of reducing sugars and polyamides. However, only the ethanolic extract contained both phytosterols and saponins.

### DISCUSSION

The powder of *B. sapida* root is used in our clinic with anecdotal evidence for its use in the treatment of diarrhoea. Scientific evaluation of the effects of the ethanolic and aqueous extracts of *B. sapida* in rodent diarrhoea models indicate that these extracts significantly inhibited castor oil-induced diarrhoea in rats and mice in a dose-dependent fashion (Fig. 1) with the highest dose (1060 mg kg<sup>-1</sup>), representing 4x the therapeutic dose, showing the highest anti-diarrhoeal activity (76-93.2%), which was comparable to 3 mg kg<sup>-1</sup> of the standard anti-diarrhoeal drug, loperamide (89-100%). Results further indicate that *B. sapida* has an LD<sub>50</sub> >5000 mg kg<sup>-1</sup> in rats and mice when compared to 90 mg kg<sup>-1</sup> for hypoglycin A, a toxic chemical constituent present in the fruit of *B. sapida*, in adult rats (Hassall *et al.*, 1954). The highest dose of *B. sapida* used in this study (1060 mg kg<sup>-1</sup>) may, therefore, be of no toxicological consequence. Recent studies on the anti-diarrhoeal activity of methanolic extract of root bark of *Securinega virosa* at 100 mg kg<sup>-1</sup> caused inhibition of castor oil-induced diarrhoea in rabbits to the same degree (100%) as 5 mg kg<sup>-1</sup> loperamide (Magaji *et al.*, 2007) whilst studies in mice showed a 31.7% inhibition by ethyl acetate extract of *Cylicodiscus gabunensis* at 750 mg kg<sup>-1</sup> compared to 76.8% by 3 mg kg<sup>-1</sup> loperamide (Kouitcheu *et al.*, 2006).

Studies of the effects of the extracts of *B. sapida* on intestinal motility and castor oil-induced enteropooling in rats and mice (Fig. 2, 3) indicate that the extracts generally appear to cause a significant dose-dependent reduction in intestinal transit of charcoal meal resulting in increased reabsorption of water from the intestines as evidenced by significant inhibitions of enteropooling at the highest dose of *B. sapida* extracts. Earlier studies with aqueous and ethanolic root extracts of *Asparagus racemosus* suppressed the propulsion of charcoal meal, thereby increasing the absorption of water and electrolytes (Venkatesan *et al.*, 2005). These effects on intestinal motility and enteropooling shown by the *B. sapida* extracts were comparable to the standard drugs atropine (0.1 mg kg<sup>-1</sup>) and loperamide (3 mg kg<sup>-1</sup>), respectively. Loperamide is known to slow down small intestinal transit and colon activity (Theoderau *et al.*, 1991) whilst atropine reduces



intestinal transit time possibly through its anticholinergic effects (Brown and Taylor, 1996) or reduction in gastric emptying (Izzo *et al.*, 1999).

The degree of anti-diarrhoeal activities shown by the ethanolic and aqueous extracts of *B. sapida* in rats and mice appears to be similar, indicating no significant species differences in the expression of activity. Phytochemical screening (Table 1) showed that whilst both extracts contained reducing sugars and polyamides only the ethanolic extract contains phytosterols and saponins. Thus one or more of these groups of phytochemicals might be responsible for the anti-diarrhoeal activity of *B. sapida*. Previous studies have suggested that the anti-diarrhoeal activity of medicinal plants may be due to flavonoids (Galvez *et al.*, 1991, 1993; Di Carlo *et al.*, 1993), alkaloids (Gricilda Shoba and Molly, 2001), tannins (Mukherjee *et al.*, 1998), saponins, sterols and reducing sugars (Otshudi *et al.*, 2000). Some patented polyamides such as polycoproamide, polyundecanamide and polyhexamethylene adipamide have been used as components of anti-diarrhoeal agents ([www.wikipatents.com/gb/1197079.html](http://www.wikipatents.com/gb/1197079.html)).

In conclusion, it may be said that *B. sapida* has anti-diarrhoeal properties which may be attributable to its inhibition of intestinal motility and enteropooling. These findings, therefore, support its ethnomedical use and the anecdotal claims for its use in the treatment of diarrhoea. Further studies are under way in our laboratory to determine the chemical constituent(s) responsible for its observed anti-diarrhoeal activity.

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