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Antidiarrheal activity of aqueous leaf extract of *Ceratotheca sesamoides* in rats

Yakubu M. Toyin[1], Opakunle F. Khadijat[1], Salimon S. Saoban[1], Ajiboye T. Olakunle[2], Bamisaye F. Abraham[3] and Quadri A. Luqman[1]

[1]Phytomedicine, Toxicology and Reproductive Biochemistry Research Laboratory, Department of Biochemistry, Ilorin; [2]Antioxidants, Free Radicals and Toxicology Research Laboratory, Department of Chemical Sciences, Fountain University, Osogbo; [3]Department of Biochemistry, Joseph Ayo Babalola University, Ikeji-Arakeji, Osun State, Nigeria.

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Abstract

The antidiarrheal effects of the aqueous leaf extract of *C. sesamoides* at 25, 50 and 100 mg/kg body weight was evaluated in female rats using gastro-intestinal transit, diarrhea and enteropooling induced by castor oil models. The extract was positive for alkaloids, saponins, flavonoids and phenolics. The 25 mg/kg body weight of the extract significantly ($p<0.05$) prolonged the onset time of diarrhea, decreased the fecal parameters (number, water content, fresh weight, total number of wet feaces) with no episode in the animals treated with 50 and 100 mg/kg body weight. The activity of small intestine Na^+-K^+ ATPase increased ($p<0.05$) while the nitric oxide, volume and mass of intestinal fluid as well as the distance travelled by the charcoal meal decreased. The patterns of changes were similar to the reference drugs. Overall, the antidiarrheal activity of the aqueous leaf extract of *Ceratotheca sesamoides* may be due to alkaloids, phenolics, flavonoids and saponins present in the extract.

Introduction

Diarrhea is a disease in which waste matter most often in liquid form is emptied from the bowels much more frequently than normal. Diarrheal diseases are a major health concern in developing countries with an estimate of about 1.8 million deaths per annum (WHO, 2004). The disease may be caused by a wide array of agents such as entero-pathogenic microorganisms (*Shigella flexneri*, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* and *Candida albicans*), alcohol, irritable bowel syndrome, bile salts, hormones, secretory tumors and intoxication (Anne and Geboes, 2002; Teke et al., 2007; Brijesh et al., 2011).

Despite improvements in public health and economic well being, diarrhea remains an important clinical problem in developed and developing countries (Casburn-Jones and Farthing, 2004). Generally, the treatment of diarrheal is non-specific, and is usually aimed at reducing the discomfort and inconvenience of frequent bowel movements (Brunton, 2008; Suleiman et al., 2008). These approaches include maintenance of fluid and electrolyte balance, use of anti-infective agents, antidiarrheal agents, and most recently probiotics or microbial components which have a value in the treatment of rotavirus infections and post antibiotic diarrhea (Marcos and DuPont, 2007). In order to overcome the menace of diarrhea in developing countries, especially the discomfort and inconvenience of frequent bowel movements, the World Health Organization

(WHO, 2004) has introduced a program for diarrheal control, which involves the use of traditional herbal medicines due partly to their economical viability, accessibility and ancestral experience and perceived efficacy. A medicinal plant widely claimed to be effective in the management of diarrhea in Nigeria is *Ceratotheca sesamoides*.

Ceratotheca sesamoides (Pedaliaceae) is found in tropical Africa like the open savanna woodlands across the region from Senegal to Northern and Southern part of Nigeria. It is known by various names such as Eku (Yoruba-Western Nigeria), Tchabalaba (Guinea Bissau), Lalucaminho (Senegal) and (False Sesame-English) (Adegoke et al., 1968). It is an erect or sub-erect herb of about 60 cm tall. The fruits are laterally flatten-ed capsule with slender horns. The colour of the flower varies from pink, lilac, lip and throat cream with dark lines. The locally acclaimed medicinal uses of *C. sesamoides* include antidiarrheal, antimalarial antidiabetic and anti-inflammatory. Only a very few scientific studies are available on *C. sesamoides*. For example, Fasakin (2004) reported on the proximate compositions of the leaves and seeds of the plants. Despite the aforementioned claim of *C. sesamoides* leaves as an antidiarrheal agent, there has not been any scientific report, at least to the knowledge of the authors that has either substantiated or refuted this claim. Therefore, this study sets out to provide information on the acclaimed antidiarrheal activity of aqueous leaf extract of *C. sesamoides* with a view to ascertaining the claim.

Materials and Methods

Plant materials: The plant was obtained from a vegetable seller at a market (Ipata) in Ilorin, Nigeria. It was authenticated at the Herbarium Unit of the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria where a voucher specimen (I.U. 011) was deposited.

Drugs and chemicals: Loperamide hydrochloride, atropine sulfate, and castor oil were products of Richy Gold International Ltd., Nigeria, Laborate Pharmaceuticals, Punjab, India, and Bells Sons and Co. (Druggist) Ltd., Southport, England, respectively. Adenosine 5′-triphosphate (disodium salt) was a product of Sigma Chemical Co, St. Louis, MO, USA. Nitric oxide assay kit was a product of Assay Designs Stressgen, Ann Arbor, MI, USA.

Animals: Healthy, female albino rats (*Rattus norvegicus*) weighing 137.4 ± 4.0 g obtained from the Animal House of the Department of Biochemistry, University of Ilorin, Nigeria were used for this study. All the animals were housed in clean aluminum cages placed in a well-ventilated house conditions (temperature 25°C, photoperiod 12 hours natural light, 12 hours dark and humidity 45-50%). The animals were allowed free access to rat feeds (Premier Feed Mill Co. Ltd., Ibadan, Nigeria) and clean tap water except when fasting was required during the study. The cages were cleaned of wastes on a daily basis.

Preparation of extract: The leaves of *C. sesamoides* were separated from the stem, washed under running tap and oven dried (Uniscope Laboratory Oven, SM9053, Surgifriend Medicals, England) at 40°C for 48 hours. The dried materials were pulverized using an electric blender (Mikachi MX 1830, Shangai, China) and stored in an air-tight container prior to extraction. A portion (30 g) of the powder was extracted in 1500 mL of cold distilled water for 48 hours. The extract was filtered (Whatman No. 1 filter paper) and the resulting filtrate evaporated to dryness on a water bath (Uniscope Laboratory Water Bath SM801A, Surgifriend Medicals, England) to give a yield of 15 g which correspond to a percentage yield of 50%. This was reconstituted separately in distilled water to give the required doses of 25, 50 and 100 mg/kg body weight used in the present study. The doses of 25 and 50 correspond respectively, to "a pinch" and "a spoon" of the plant powder estimated to be consumed as a remedy for an adult 70 kg man. The 100 mg/kg body weight dose which is a quadruple-fold of the least dose was used to account for cases of 'abuse' by the user.

Phytochemical screening: Preliminary chemical tests were carried out on the extract to detect the presence of alkaloids, steroids, saponins, phenolics, flavonoids, cardiac glycosides, tannins, cardenolides and dienolides according to the procedures described by Sofowora (1993).

Castor oil-induced diarrhea in rats: Diarrhea was induced in the rats using a modified method of Bajad et al (2001). The test animals were fasted (without food, but water) for 18 hours prior to the commencement of the experiment. Each animal was placed in a cage, the floor of which was lined with blotting paper. Animals in the first group (negative control) were orally administered with 1 mL of distilled water while those in the second, third and fourth groups were respectively administered with the same volume (1 mL) of the extract corresponding to 25, 50 and 100 mg/kg body weight. The fifth group (positive control), was orally administered with same volume (1 mL) of loperamide hydrochloride preparation corresponding to 2.5 mg/kg body weight. At 30 min post treatment, each animal was again administered orally with 1 mL of castor oil and the time between the administration of the oil and the appearance of the first diarrheal drop was noted.

The severity of diarrhea was accessed every hour for a period of 6 hours by monitoring the diarrheal drops on the pre-weighed blotting paper placed beneath the individual rat cages. The total number of feces, diarrheal feces and total weight of feces excreted were expressed as average of six determinations and compared with the control groups. The percentage inhibition of diarrheal defecation in each group was also computed. At the end of the 6 hours of monitoring the diarrheal drops, the animals were sacrificed and small intestine homogenates prepared according to the procedure described by Akanji and Yakubu (2000). The assay of both the activity of Na^+-K^+ ATPase and nitric oxide concentration in the small intestine homogenates was done using the protocol described by Bewaji et al (1985) and Nathan (1992) respectively.

Castor oil-induced enteropooling, intestinal transit and intestinal fluid in rats: Intraluminal fluid was determined as described by Havagiray et al (2004). Briefly, fasted animals as previously described were randomly selected into five groups of six animals each. Animals in the negative control group received 1 mL of distilled water orally while those in the positive control group were orally administered with 1 mL of atropine sulphate corresponding to 0.6 mg/kg body weight. Animals in the test groups were administered with same volume of the extract corresponding to the doses of 25, 50 and 100 mg/kg body weight. Immediately after the administration, 1 mL of castor oil was also administered orally to each rat in all the groups. After 30 min, the rats were sacrificed using the procedure previously described by Akanji and Yakubu (2000). The small intestine was excised and the intestinal content was squeezed quantitatively into a measuring cylinder. The volume and mass of the intestinal content were obtained and the inhibition of intestinal content was also computed.

Gastrointestinal motility test: The method described by Teke et al. (2007) was adopted for the determination of the effect of the extract on gastrointestinal transit in the rats. Fasted animals (as previously described) were assigned into five groups of six rats each. The animals in the negative control group received 1 mL of distilled water orally while those in the positive control received 1 mL of atropine sulphate intramuscularly. Animals in the third, fourth and fifth groups received equal volume of the extract corresponding to 25, 50 and 100 mg/kg body weight. After 30 min, all the animals were again administered orally with 1 mL of charcoal meal (10% charcoal suspension in 5% agarose agar). At 30 min post administration of the charcoal meal, all the animals were sacrificed using the procedure described by Akanji and Yakubu (2000). The small intestine was removed and afterwards, the length of the small intestine and the distance travelled by charcoal meal through the organ was measured. The distance was expressed as a percentage of the length of the small intestine.

Statistical analysis: Data were expressed as the means ± SEM of 6 replicates. Statistical analysis was performed using One-way Analysis of Variance (ANOVA) and complemented with Student's t-test. The values were considered statistically significant at $p<0.05$.

Results

The aqueous leaf extract of *C. sesamoides* was positive for alkaloids, saponins, flavonoids and phenolics while tannins, cardiac glycosides, steroids, cardenolides and dienolides were not detected (Table I).

The 25 mg/kg body weight of the extract significantly ($p<0.05$) prolonged the onset time of diarrhea while there was no episode of diarrhea in the 50 and 100 mg/kg body weight extract treated animals (Table II). Compared with the distilled water treated animals, the extract significantly ($p<0.05$) decreased the number of feces in a dose related manner. While the total number of wet feces, fresh weight of feces and water content of feces decreased significantly in the animals administered with 25 mg/kg body weight of the extract in a manner similar to the loperamide treated animals, there was no episode in the animals administered with the 50 and 100 mg/kg body weight of the extract. Although there was increase in the computed percentage inhibition of defecation in all the treated groups when compared with the distilled water administered animal, it is worthy of note that the 50 and 100 mg/kg body weight of the extract produced 100% inhibition of defecation. The activity of Na^+-K^+ ATPase activity in the small intestine also increased

Table I

Some phytochemical constituents of aqueous leaf extract of *Ceratotheca sesamoides*

Phytochemical constituents	Result
Alkaloids	Present
Saponins	Present
Tannins	Not detected
Flavonoids	Present
Cardiac glycosides	Not detected
Steroids	Not detected
Phenolics	Present
Cardenolides and dienolides	Not detected

Table II

Effect of aqueous leaf extract of *Ceratotheca sesamoid* against castor oil induced-diarrheal rats

Parameter/doses	Loperamide (mg/kg body weight)	Water	Plant extract (mg/kg body weight)		
	2.5	0	25	50	100
Onset time (min)	233 ± 8.8[b]	63.5 ± 1.6[a]	194.5 ± 4.9[c]	Nil	Nil
Total number of feces	2.5 ± 0.6[b]	8.5 ± 0.6[a]	6.0 ± 0.0[c]	2.0 ± 0.0[d]	1.5 ± 0.0[e]
Number of wet feces	2.0 ± 0.0[b]	4.5 ± 0.6[a]	2.0 ± 0.0[b]	Nil	Nil
Fresh weight of feces (g)	1.3 ± 0.02[b]	1.7 ± 0.0[a]	1.0 ± 0.0[c]	Nil	Nil
Water content of feces (mL)	0.6 ± 0.02[b]	1.3 ± 0.03[a]	0.6 ± 0.0[c]	Nil	Nil
Inhibition of defecation (%)	55.6	0	55.6	100	100
Small intestine Na^+-K^+ ATPase activity (µmol Pi/ mg protein/hour)	1322.7 ± 12.2[a]	952.8 ± 15.1[b]	1210.1 ± 14.4[c]	1330.0 ± 11.9[a]	1509.1 ± 19.7[d]
Small intestine nitric oxide concentration (µmol/L)	88.2 ± 8.0[a]	274.4 ± 7.1[b]	86.1 ± 11.1[a]	87.2 ± 8.1[a]	89.0 ± 7.2[a]

Values are mean ± SD (n = 6); Values carrying different superscript along each rows are significant ($p<0.05$) different from each other

Table III

Effect of aqueous leaf extract of *Ceratotheca sesamoid* on castor oil-induced enteropooling in rats

Parameters/dose	Atropine sulfate (mg/kg body weight)	Water	Plant extract (mg/kg body weight)		
Parameters/dose	0.6	0	25	50	100
Mass of intestinal fluid (g)	1.2 ± 0.1[b]	3.3 ± 0.3[a]	1.3 ± 0.1[c]	0.5 ± 0.01[d]	0.6 ± 0.0[d]
Volume of intestinal fluid (mL)	1.4 ± 0.2[b]	3.3 ± 0.1[a]	2.8 ± 0.2[c]	1.9 ± 0.1[d]	1.0 ± 0.1[e]
Inhibition of intestinal content (%)	64.6	0	59.9	84.4	83.2

dose dependently in the extract treated animals in a manner similar to the positive control animals. In contrast, the concentration of nitric oxide was reduced significantly by the extract in this study in a similar fashion to the reference drug (Table II).

The extract significantly decreased the volume and mass of intestinal fluid of castor oil-induced entero-pooling in rats. While the reduction in the mass of intestinal fluid at 50 and 100 mg/kg body weight of the extract was more than the atropine sulphate, it was only the 100 mg/kg body weight of the extract that reduced the volume of the intestinal fluid more than the reference drug treated animals. Generally, the inhibition of intestinal fluid was higher in the extract and atropine sulphate treated animals (Table III).

Although, the length of the small intestine in all the experimental animals was not significantly different from each other, the extract significantly reduced the distance travelled by the charcoal meal. These values were lower in the extract and atropine sulphate treated animals than in the distilled water control animals (Table IV).

Discussion

The age long use of herbal medicines in the treatment of diarrheal disease is a common practice in many countries across the globe including Nigeria. Therefore, the need to substantiate or otherwise the folkloric claim of *C. sesamoides* as an antidiarrheal agent using several models of diarrhea cannot be overemphasized. The results shows that there has been statistically significant reduction not only on the onset of diarrhea but also on its severity as revealed by the castor oil-induced diarrhea and enteropooling as well as charcoal meal gastrointestinal transit models in the present study.

Castor oil has been widely used in diarrhea studies because it is capable of causing the body through its metabolite, ricinoleic acid, to produce autocoids and prostaglandins which are known inducers of diarrhea

Table IV

Effect of aqueous leaf extract of *Ceratotheca sesamoid* on castor oil-induced enteropooling in rats

Parameters	Atropine sulphate (mg/kg body weight)	Water	Plant extract (mg/kg body weight)		
Parameters	0.6	0	25	50	100
Length of intestine (cm^3)	85.0 ± 5.3[a]	84.1 ± 6.7[a]	86.0 ± 4.9[a]	85.2 ± 6.3[a]	85.2 ± 5.0[b]
Distance travelled by meal after 30 min (cm^3)	45.0 ± 3.3[b]	68.0 ± 0.0[a]	45.0 ± 0.0[c]	47.0 ± 1.1[d]	40.5 ± 0.0[e]
Distance travelled by meal to length of small intestine (%)	52.9	80.8	52.3	55.3	49.9

Values are mean ± SD (n = 6); Values carrying different superscript along each rows are significant ($p<0.05$) different from each other

in animals (Greenbargena et al., 1978). Ricinoleic acid initiates diarrhea via several mechanisms such as: I. causing irritation and inflammation of the intestinal mucosa, leading to the release of prostaglanding which stimulates motility and secretory diarrhea (Pierce et al., 1971; Mbagwu and Adeyemi, 2008); II. affecting electrolyte transports (by reducing active Na^+ and K^+ absorption) and smooth muscle contractility in the intestine via decreasing or inhibiting the activity of Na^+-K^+ ATPase in the small intestine and colon (Palombo, 2006); III. increasing the volume of intestinal content by preventing the reabsorption of water; IV. interfering with oxidative metabolism and thus an effect on adenylate cyclase or mucosal adenosine 3′, 5′-cyclic monophosphate content; and being cytotoxic to intestinal epithelial cells and causing histological abnormalities and mucosal permeability (Mascolo et al., 1993). These sequences of events may be related to the release of eicosanoids, prostaglandins, nitric oxide, platelet activating factor, cAMP and tachykinins by the intestinal mucosal, which consequentially could give rise to diarrhea.

Therefore, the significantly ($p<0.05$) prolonged time of induction of diarrhea, decreased frequency of stool and fecal parameters (total number of feces, fresh weight, water content and number of wet feces) following the administration of the extract suggest antidiarheal activity at this dose. This assertion was further corroborated with the increased inhibition of defecation. The same percentage of inhibition of defecation in the 25 mg/kg body weight of the extract and loperamide hydrochloride suggest that the antidiarrheal activity of the extract may proceed via the same mechanism as that of the reference drug, loperamide hydrochloride. The clinical effect of the extract as antidiarrheal agent was demonstrated at 50 and 100 mg/kg body weight where the typical parameters of diarrhea did not manifest in the animals. The extract might have exerted its antidiarrheal activity via secretory mechanism as evident from reduction in total number of wet faeces. Furthermore, this antidiarrheal activity could have resulted from the inhibitory activity of aqueous leaf extract of *C. sesamoides* on prostanglandins synthesis, nitric oxide and platelet activating factors production, as inhibitors of prostaglandins and nitric oxide syntheses are known to delay diarrhea induced by castor oil (Capasso et al., 1994; Adzu et al., 2003; Tangpu and Yadav, 2004). Similar effects were reported in several studies by Qnais et al (2005), Akindele and Adeyemi (2006) and Appidi et al (2010) following the administration of aqueous leaf extracts of *Juniperus phoenicia, Byrsocarpus coccineus* and *Hermania incana*, respectively.

Castor oil, the inducer of diarrhea in animals decrease or inhibit the activity of Na^+-K^+ ATPase in the small intestine and colon and thus affect electrolyte transports by reducing active Na^+ and K^+ absorption (Palombo, 2006). Similarly, study by Capasso et al (1994) have implicated elevated nitric oxide in the pathogenesis of diarrhea, a disease which was prevented by the intraperitoneal injection of nitric oxide synthase inhibitor, N^G-nitro-L-arginine methyl ester (2.5–50 mg/kg twice) to rats. Therefore, the increase in the activity of Na^+-K^+ ATPase as well as decrease in the concentration of nitric oxide in the small intestine of extract treated animals may be one of the mechanisms by which the extract exhibits its antidiarrheal effect.

The accumulation of intestinal fluids may be a resultant clinical effect of bowel function disturbance, in which case, there is impaired intestinal absorption, excessive intestinal secretion of water and electrolytes, and a rapid bowel transit (Gurgel et al., 2001; Mbagwu and Adeyemi, 2008). The reduction in the parameters of enteropooling and consequent increase in the percentage inhibition of intestinal content of the animals suggest that the extract might have inhibited or reduced the massive secretion of water into the intestinal lumen.

It is possible that the aqueous leaf extract of *C. sesamoides* may be explored in managing secretory diarrhea. This anti-enteropooling effect of *C. sesamoides* could be due to the presence of flavonoids in the extract, as the phytochemical have been reported to inhibit intestinal motility and hydroelectrolytic secretion (Perez et al., 2005).

Atropine sulfate is known to produce an anticholinergic effect on intestinal transit whereas activated charcoal can prevent the absorption of drugs and other chemicals into the body by absorbing them on the surface of the charcoal particles (Venkatesan et al., 2005). Thus, the suppression or reduction in the intestinal propulsive movement of the charcoal meal by all the doses of the extract in the present study suggest among others that the extract was able to increase the time for absorption of water and electrolytes in a manner similar to the reference drug, atropine sulfate (Teke et al., 2007). It may also indicate a reduction in peristaltic activity and ultimately reduction in the gastrointestinal motility (Nwiniyi et al., 2004). This effect which suggests antidiarrheal activity may be attributed to the flavonoids since it has been reported to be able to inhibit fluid secretion in the small intestine thereby reducing the rate of flow in the gut. The extract appears to have acted on all parts of the intestine producing inhibitory effect on both the gastrointestinal propulsion and fluid secretion. The findings in this study are similar to the report by Maridass (2011) following the administration of 500 mg/kg body weight of ethanolic tuber extract of *Eulophia epidendrae* to castor oil-induced diarrheal rats.

Previous studies have implicated a wide array of phytochemicals with antidiarrheal activity. These include tannins, alkaloids, saponins, flavonoids, sterols, terpenoids and reducing sugars (Galvez et al., 1993; Mukherjee et al., 1998; Otshudi et al., 2000; Shoba and Thomas, 2001; Havagiray et al., 2004; Venkatesan et al., 2005). Flavonoids and saponins are known to inhibit the release of autocoids and prostaglandins thereby reducing the motility and secretion induced by castor oil (Veiga et al., 2001; Perez et al., 2005). Because many of these compounds might have antidiarrheal effects, it is difficult to suggest which of them is responsible for the desired effect. However, we suggest that alkaloids, saponins and flavonoids present in the extract of *C. sesamoides* might be responsible for its antidiarrheal activity.

Conclusion

Aqueous leaf extract of *C. sesamoides* has antidiarrheal activity made possible by the alkaloids, phenolics, flavonoids and saponins via reduction or inhibition of typical indices of diarrhea such as the fecal parameters, enteropooling, gastrointestinal motility and stimulation/enhancement of Na^+-K^+ ATPase activity and reduction in the nitric oxide concentration of the small intestine.

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Ethical Issue

This study was carried out according to the guidelines of European Convention for the Protection of Vertebrate Animals and Other Scientific Purposes- ETS-123 (2005).

Conflict of Interest

Authors declare no conflict of interest.

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Author Info
Yakubu M. Toyin (Principal contact)
e-mail: tomuyak@yahoo.com