

**Pharmacological Actions of Methanol Leaf Extract of *Combretum paniculatum* Vent. (Combretaceae) on the Gastrointestinal System**Ikechukwu E. Peter<sup>1</sup>, Chiamaka M. Aroh<sup>1</sup>, Uchenna G. Shere<sup>1</sup>, Njideka I. Ani<sup>2</sup>, Ifeyinwa C. Adaka<sup>3</sup>, Felix K. Asogwa<sup>2</sup>, Ogechukwu N. Isiogugu<sup>1</sup>, Collins U. Abonyi<sup>1</sup>, Akachukwu M. Onwuka<sup>1\*</sup><sup>1</sup>Department of Pharmacology & Toxicology, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka 410001 Enugu, Nigeria.<sup>2</sup>Department of Pharmacology & Toxicology, Faculty of Pharmaceutical Sciences, Enugu State University of Science and Technology, Enugu, Nigeria.<sup>3</sup>Department of Pharmaceutical and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka 410001 Enugu, Nigeria.

## ARTICLE INFO

## ABSTRACT

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*Combretum paniculatum* Vent. (Combretaceae) is used widely in ethnomedicine in the treatment of chronic diarrhea and dysentery, flatulence, vomiting, colic, and enlarged spleen and liver. The study evaluated the potentials of *C. paniculatum* in the treatment of gastrointestinal disorders using diarrheal and ulcer models in Swiss mice and Wistar rats. The anti-diarrheal effect of methanol extract of *C. paniculatum* was investigated using gastrointestinal motility test in mice, castor oil-induced diarrhea and castor oil-induced enteropooling in rats. Antiulcer effect was evaluated using indomethacin-, absolute ethanol-induced ulcer models and acid neutralizing capacity. The extract (100, 200 and 400 mg/kg), atropine (10 mg/kg), loperamide (2.5 and 3 mg/kg) and omeprazole (20 mg/kg) were administered. The methanol extract of *C. paniculatum* (MECP) leaves showed dose-dependent inhibition of intestinal motility. There was significant ( $P < 0.001$ ) reduction in the number of diarrheic droppings at all administered doses and the volume of intestinal content was significantly ( $P < 0.01$ ) reduced. MECP exhibited significant ( $P < 0.05$ ) ulcer protection at 400 mg/kg similar to omeprazole against indomethacin-induced ulcer. There was also significant ( $P < 0.05$ ) ulcer protection at 200 mg/kg against absolute ethanol-induced ulcer while exhibiting concentration-dependent increase in acid neutralization. The results obtained revealed that the extract possess antidiarrheal and antiulcer activities in Swiss mice and Wistar rats. This justified the folkloric use of *C. paniculatum* leaves in the treatment of diarrhea and ulcer.

**Keywords:** Antidiarrheal, *Combretum paniculatum*, enteropooling, gastrointestinal tract motility, indomethacin.

**Introduction**

Diarrhoea is characterized with frequent passage of liquid faeces and it involves both an increase in the motility of the gastrointestinal tract, along with increased secretion and decreased absorption of fluid, and thus a loss of electrolytes (particularly sodium) and water.<sup>1</sup> It is one of the main causes of infant mortality in developing countries,<sup>2</sup> causing about 5 to 8 million deaths a year, mainly among children under five years of age.<sup>3</sup> The use of antimotility agents, antibiotics, electrolyte and fluid replacement therapies are currently the mainstay in acute diarrhea management. Gastric ulcer is a common ailment throughout the world, in which the gastric mucosa becomes damaged and perforations lead to bleeding which affects about 10% of the world population.<sup>4</sup> Some endogenous and exogenous factors, including acid, pepsin, stress, and noxious agents such as non-steroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori* infection, smoking, and alcohol consumption are known to cause or aggravate gastric ulcer.<sup>5</sup>

Despite advances, adequate remedy for the gastrointestinal disorders

especially diarrhea and ulcer are still lacking. Thus, there is a growing interest in the scientific community to sought for remedies and possible drugs from plant origin, which may be easily available and accessible, particularly to the rural people in the developing countries. African ethnomedical systems employed numerous plant extracts for the treatment of diseases, including gastrointestinal disorders to give a therapeutic choice to the population.<sup>6</sup>

*Combretum paniculatum* Vent. (Combretaceae) is a shrub with deep root system and vivid scarlet flowers attaining 15 m in length. It is widely spread in tropical Africa. *C. paniculatum* is used widely in ethnomedicine in the treatment of chronic diarrhea and dysentery, flatulence, vomiting, colic, and enlarge spleen and liver.<sup>7</sup> It has been reported to show significant cytotoxic activity against breast cancer cells,<sup>8</sup> antimicrobial activity,<sup>9</sup> and efficacy in the treatment of ringworm and wounds.<sup>10</sup> Despite the traditional use of this plant against a wide range of diseases, there is a limited scientific report on the effect of the leaf extract on the gastrointestinal system. The study aimed to ascertain the effects of the methanol leaf extract of *C. paniculatum* on the gastrointestinal system using diarrheal and ulcer models.

**Materials and Methods****Animals**

Adult Wistar rats (120 - 180 g) and Swiss albino mice (19 - 25 g) of either sex were used. The animals were obtained from the Laboratory animal facility of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka. Animals were housed in steel cages within the facility under standard conditions (temperatures: 25-34°C, humidity 30-70%, adequate light and ventilation) and allowed free

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access to standard pellets (Mega feed, Nasarawa, Nigeria) and water. Prior to their use, they were allowed two weeks for acclimatization within the experimental environment. The experimental protocols were approved by the ethics committee of Faculty of Pharmaceutical Sciences, University of Nigeria (FPSRE/UNN/19/00015) and were in conformity with the ethical guidelines of the National Code of Conduct for Animal Research Ethics (NCARE).

#### Solvents, chemicals and reagents

The solvents, chemicals and reagents were of analytical grades. Methanol (JHD Chemical Reagent Co., Guangzhou, China), Tween 80 (Xilong Scientific Co., Guangdong, China), chloroform (JHD Chemical Reagent Co., Guangzhou, China).

#### Drugs

Loperamide (CLIMAX® Impulse Pharma. Ltd., Mumbai, India), Castor oil (Bells, Southport, England), atropine (Embassy Pharmaceutical Limited, Lagos, Nigeria), omeprazole Capsules BP 20 mg (Mancare Pharmaceuticals, Maharashtra, India), indomethacin capsule 25 mg (Maxheal Pharmaceuticals, Maharashtra, India), Gelusil tablets (250 mg magnesium trisilicate. B.P and dried aluminum hydroxide B.P 120 mg Dana Pharmaceutical Ltd, Lagos, Nigeria), acetylcholine (Sigma Aldrich, Darmstadt, Germany), histamine (Sigma Aldrich, Darmstadt, Germany).

#### Collection and preparation of plant material

Fresh leaves of *C. paniculatum* were collected in March, 2019 from Ajuona Obukpa in Nsukka Local Government Area, Enugu State, Nigeria. The plant was identified and authenticated by Mr. Nwafor Felix of the Department of Pharmacognosy and Environmental Medicine, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka, Nigeria. The voucher herbarium sample was prepared and deposited in the institutional herbarium and voucher number PCG/UNN/0321 was assigned. The plant material was cleaned, shade-dried for five days and pulverized using a milling machine.

#### Extraction of plant material

Pulverized plant material (2.5 kg) was extracted with 5 L of methanol by cold maceration for 48 h with intermittent agitation and thereafter filtered using sieve cloth and No. 1 Whatmann filter paper. The plant material was repeatedly washed with fresh solvent mixture until the filtrate became clear. The filtrate was transferred into a stainless tray and allowed to air-dry to obtain the methanol extract of *C. paniculatum* (MECP) as 164.2 g (8.21%), after which the extract was collected, weighed, transferred into an amber-coloured bottle and preserved in a refrigerator. The greenish coloured extract yielded 164.2 g (8.21%). The percentage yield of the extract was determined using the formula:

$$\% \text{ Yield} = \frac{\text{Weight of extract}}{\text{Amount of dry powder extracted (g)}} \times 100$$

#### Phytochemical screening of extract

The powdered leaves was subjected to various phytochemical screening for the identification of constituents using standard methods.<sup>11</sup>

#### Pharmacological tests

##### Acute toxicity studies

The acute toxicity test of the methanol extract of *C. paniculatum* (MECP) was determined in mice using the method of Lorke.<sup>12</sup> Briefly, the tests involved two phases. The first phase was the determination of the toxic range. The mice were placed in three groups (n = 3) and were given MECP (10, 100 and 1000 mg/kg; p.o.) solubilized in a solution of 3%, v/v Tween 80. The treated mice were observed for 24 h for the number of deaths. The death pattern in the first phase determined the doses used for the second phase. Since there were no deaths recorded in the first phase, a fresh batch of 4 mice received 1000, 1600, 2900, and 5000 mg/kg MECP orally. The treated animals were observed for lethality or signs of acute intoxication intermittently for 24 h. The

LD<sub>50</sub> is the geometric mean of the highest non-lethal dose and the least toxic dose.

#### Anti-diarrheal activity

##### Gastrointestinal motility test

Twenty-five (25) Wistar rats were divided into five groups of five animals each and were fasted for 18 hours with free access to water. The animals were given 0.3 mL each of castor oil orally, one hour later, extract at 100 mg/kg, 200 mg/kg and 400 mg/kg body weight were administered orally to Groups 2, 3 and 4, respectively, Groups 1 and 5 received 2.5 mL/kg of 3% v/v Tween 80 and the standard drug, atropine, at 1 mg/kg per oral. After one hour, each animal was given 0.2 mL of freshly prepared charcoal meal via the oral route. One hour later, all the animals were sacrificed by chloroform anesthesia, the stomach dissected and the entire intestine excised. The total length of the intestine from the pylorus to the ileocaecal junction and the distance travelled by the charcoal meal were measured and the percentage of transit inhibition calculated.<sup>13</sup> The percentage transit inhibition was determined using the formula:

$$\% \text{ of transit inhibition} = \frac{T_0 - T_1}{T_0} \times 100$$

Where T<sub>0</sub> = Total length of intestine

T<sub>1</sub> = Charcoal distance of test group

##### Castor oil-induced enteropooling assay in rats

The assay was carried out following the method described by Robert.<sup>14</sup> Rats were fasted for 12 h but allowed free access to water. They were divided into the following five groups of five animals each. Group 1 received vehicle (2.5 mL/kg), Group 2 received loperamide (3 mg/kg), and Groups 3 to 5 received MECP (100, 200 and 400 mg/kg), respectively 1 h prior to the oral administration of castor oil (1 mL/rat). One hour later, the rats were euthanized with chloroform, the small intestines were removed after tying the pylorus and ileocaecal junction. The entire intestine with the content were weighed, the intestinal contents were collected into a graduated tube, and the volume determined.

##### Castor oil-induced diarrhea in rats

Twenty-five rats were fasted for 18 hours and divided into five groups of 5 animals each and labeled groups 1 to 5. The plant extract at doses of 100, 200 and 400 mg/kg body weight was administered orally to Groups 2, 3 and 4, respectively. Groups 1 and 5 received 2.5 mL/kg of 3% v/v Tween 80 and the standard drug, loperamide at 2.5 mg/kg orally, respectively. One hour after the pre-treatment, all animals received 2 mL of castor oil orally. The animals were kept in separate metabolic cages with a white paper beneath the cage to collect faeces.<sup>15</sup> The severity and consistency of diarrhea was monitored at 1, 2, 3 and 4 hours after the castor oil administration. The total number of diarrheic faeces and non-diarrheic faeces in the groups treated with the extract was recorded. The total diarrheic faeces for the control group were considered to be 100%. The results were expressed as a percentage of inhibition of diarrhea.<sup>16</sup>

$$\text{Inhibition of defecation (\%)} = \frac{\text{NFeC} - \text{NFeT}}{\text{NFeC}} \times 100$$

Where NFeC = Mean number of faeces of control group

NFeT = Mean number of faeces of treated group

$$\text{Inhibition of diarrheic faces (\%)} = \frac{\text{NDFc} - \text{NDFt}}{\text{NDFc}} \times 100$$

Where NDF<sub>c</sub> = Mean number of diarrheic faeces of control group

NDF<sub>t</sub> = Mean number of diarrheic faeces of treated group

##### Antiulcer activity

Rats used were fasted for 24 h prior to the experiment and there were 25 rats for each model allotted into 5 groups of 5 rats each. Groups 1 to 3 received 100, 200 and 400 mg/kg MECP while Groups 4 and 5

represented 3% Tween 80 (5 mL/kg) (negative control) and omeprazole (20 mg/kg) (positive control), respectively.

#### Indomethacin induced ulcer

The method as described by Urishidani,<sup>17</sup> was used in this study. Indomethacin (50 mg/kg) was administered orally to all the animals 1 h after the various treatments. The animals were sacrificed by using chloroform 8 h after the indomethacin treatment.

#### Absolute ethanol induced ulcer

Animals were allotted to five groups and pre-treated as described above. One hour later, each animal was administered with absolute ethanol (5 mL/kg). The animals were sacrificed 1 h after the administration of absolute ethanol.<sup>18</sup>

#### Measurement of ulcer index

In each of these study models, the stomach of the sacrificed rats was removed, opened along the greater curvature, and then rinsed under a stream of tap water. The stomach was pinned flat on a corkboard and was observed using a hand lens ( $\times 10$  magnification). Erosions formed on the glandular portions of the stomach were counted and each given a severity rating on a 0-3 scale based on the diameter of ulcer (0, no ulceration; 1, ulcers  $\leq 1$  mm; 2, ulcers  $> 1$  mm  $\leq 2$  mm; 3, ulcers  $> 3$  mm). The total ulcer score for each stomach divided by a factor of 10 was calculated for each animal and expressed as ulcer index (U.I.) and the average taken as mean ulcer index for each group.<sup>19-21</sup> The degree of ulcer protection for each treatment group was calculated as a percentage for the mean ulcer index of the negative control group.<sup>22</sup>

#### Acid neutralizing capacity

The acid neutralizing capacity value for MECP (500, 1000, 1500 and 2000 mg/5 mL) was compared with the standard antacid Danacid [Aluminium hydroxide (250 mg) + Magnesium hydroxide (120 mg)/5 mL]. To the mixture, water was added to make up the total volume of 70 mL and then mixed for 1 min. Thereafter, 0.1N HCl (30 mL) was added into standard and test preparation and stirred for 15 min after which 2 drops of phenolphthalein was added and mixed. The excess HCl was immediately titrated with 0.5N sodium hydroxide solution dropwise until a pink colour was obtained.<sup>23</sup> The moles of acid neutralized was calculated by:

$$\text{Moles of acid neutralized} = (\text{Vol. of HCl} \times \text{Normality of HCl}) - (\text{Vol. of NaOH} \times \text{Normality of NaOH})$$

$$\text{Acid neutralizing capacity (ANC) per gram of antacid} = \frac{\text{Moles of HCl neutralized}}{\text{Grams of antacid/extract}}$$

#### Statistical analysis

Data obtained was analyzed by One-way ANOVA followed by Dunnett's multiple comparisons post-hoc test using GraphPad Prism version 7.0. The values are expressed as mean  $\pm$  standard error of mean (SEM).  $P < 0.05$  was considered statistically significant.

## Results and Discussion

Phytochemical screening of the leaf of *Combretum paniculatum* revealed the presence of numerous constituents such as flavonoids, saponins, tannins, phytosterols, reducing sugars and phenolic compounds (Table 1). Antidiarrheal properties of medicinal plants have been found to be due to tannins, flavonoids, alkaloids, saponins, reducing sugar, sterol and terpenes.<sup>24,25</sup> Hence tannins, reducing sugars and sterols may have contributed to the observed antidiarrheal and antiulcer activities of MECP established in this study.

Oral administration of the extract up to the dose of 5000 mg/kg caused no death of the mice and no severe signs and symptoms of overt toxic effect in the mice. This suggests that its median dose is above 5000 mg/kg. MECP is therefore, considered safe as postulated by Lorke (1983).<sup>12</sup>

The MECP exhibited dose-dependent reduction in intestinal charcoal meal propulsion in rats. There was a 36.42% inhibition of intestinal motility at 400 mg/kg, while 100 and 200 mg/kg MECP produced 30.29% and 32.74% inhibitions, respectively. However, these inhibitions were not statistically significant. The standard drug, atropine, showed a significant inhibitory effect of 49.79% on intestinal motility as presented in Figure 1. Atropine is known to inhibit intestinal transit probably due to its anticholinergic effect<sup>26</sup> and drugs which inhibit intestinal motility can also possess anti-diarrheal activity. MECP inhibited intestinal motility dose-dependently, however, it was not significant, hence, antimotility effect may not be the major contributor to the antidiarrheal effect of the extract.

Table 2 showed that MECP significantly ( $P < 0.01$ ) reduced diarrhea induced by castor oil. The percentage inhibition of defecation of MECP at 400 mg/kg was 54.39% while loperamide caused 59.65% inhibition. There was also similar percentage inhibition of diarrheic dropping between MECP (80.00%) and loperamide (83.64%). Castor oil, or its active metabolite ricinoleic acid, which produces irritation and inflammation of the intestinal mucosa, thus leading to prostaglandins release, stimulates intestinal motility and diminishes  $\text{Na}^+$ ,  $\text{Cl}^-$ , and water permeability in the intestine.<sup>27</sup> The MECP also showed a non-dose-dependent reduction in intestinal volume (Figure 2). At 400 mg/kg, MECP produced the highest (65.90%) reduction, while 100 mg/kg exhibited the least reduction (48.28%) in the volume of intestinal contents, respectively. Values for the extract treated groups were significant relative to the control. This suggests that MECP may decrease water and electrolyte secretion to the intestinal lumen while promoting their absorption, which in turn could decrease intestinal overload and distension. In addition, this could lead to a decrease in intestinal motility (giving a longer time for absorption) and water contents of the fecal drops and hence overall reduction in the total number of defecation. This is consistent with the mechanism of action of loperamide for its antidiarrheal effect.<sup>28</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin have been reported to damage gastric mucosa by decreasing prostaglandin (PG) synthesis through inhibition of cyclooxygenase (COX) enzymes and COX-independent mechanisms, thereby inducing ulceration.<sup>29</sup> MECP showed a non-dose-related gastric mucosal protection against indomethacin-induced ulcer. Pre-treatment of rats with MECP showed there was significant ( $P < 0.05$ ) ulcer protection at 400 mg/kg (55.81%) and omeprazole (53.49%) when compared to negative control (Figure 3) indicating that MECP could be valuable in the prophylaxis of gastric ulcer.

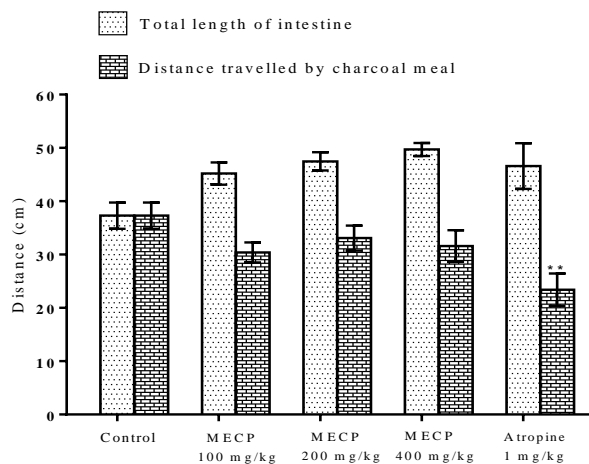
**Table 1:** Phytochemical constituents of the methanol extract of *C. paniculatum*

Constituents	Relative presence
Alkaloids	+
Resins	+
Tannins	+
Flavonoids	+
Saponins	+
Reducing sugar	+
Antraquinone glycosides	-
Antracene glycoside	-
Sterols	+
Terpenoids	+
Acidic compounds	Neutral
Proteins	+
Starch	-
Carbohydrate	-
Cardiac digitoxose	-
Fat and oil	-
Hydrolysis for glycosides	+
Cynogenetic glycosides	-

Key: - = Absent; + = Present

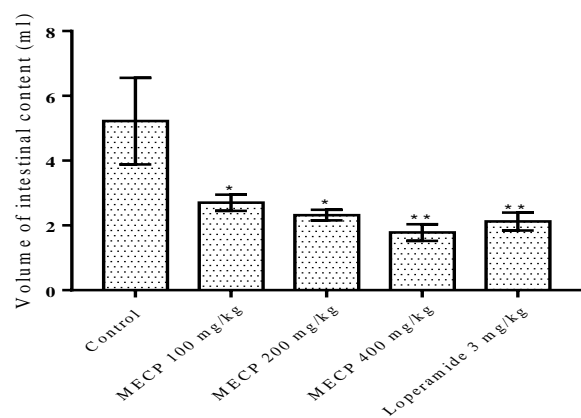
Oral administration of absolute ethanol in the animal model is destructive to the stomach tissue, since it penetrates rapidly and easily into the gastric mucosa, producing gastric lesions.<sup>30</sup> Such lesions are characterized by extensive submucosal edema, hemorrhage, desquamation of epithelial cells and infiltration of inflammatory cells, which are typical characteristics of alcohol injury in humans.<sup>31</sup> One hour after the administration of absolute ethanol to the different animal groups, the rats developed ulcer. MECP showed varying degree of ulcer protection but significance ( $P < 0.05$ ) was seen at 200 mg/kg dose (68.52%) relative to the negative control (Figure 4). Pretreatment with MECP decreased ulcer index and also increased

percentage protection. These results indicate that MECP possesses antiulcerogenic effect related to cytoprotective activity. Antacids have been effective in accelerating healing of duodenal and gastric ulcers.<sup>32</sup> The ulcer healing action of antacids is believed to be due to the neutralization of gastric luminal acid.<sup>32</sup> The extract produced a concentration-dependent increase in acid neutralizing capacity as compared with the standard. At a concentration of 2000 mg/mL, the MECP exhibited a significant increase in acid neutralizing capacity similar to the standard, danacid as presented in Table 3. This suggests that the acid neutralizing action may contribute to its gastroprotective effect.



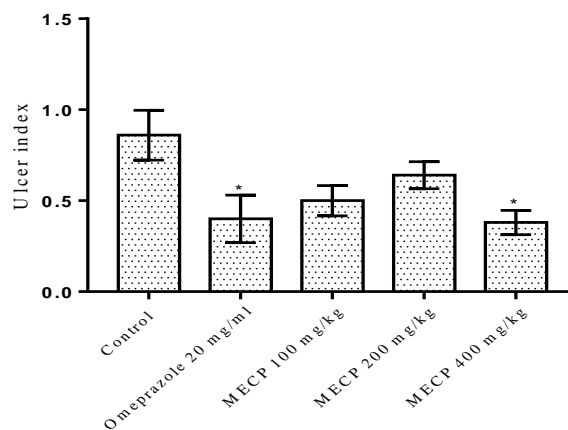
**Figure 1:** Effect of methanol extract of *C. paniculatum* on gastrointestinal motility

Values are expressed as mean  $\pm$  S.E.M.; n = 5; \*\*P < 0.01 relative to negative control



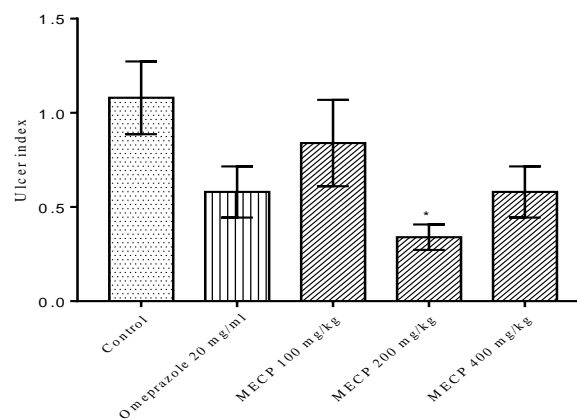
**Figure 2:** Effect of methanol extract of *C. paniculatum* on castor oil induced enteropooling in rats

Values are expressed as mean  $\pm$  S.E.M.; n = 5; \*, \*\* P < 0.05, P < 0.01 relative to negative control



**Figure 3:** Effect of methanol extract of *C. paniculatum* on indomethacin induced ulcer in rats

Values are expressed as mean  $\pm$  S.E.M.; n = 5; \* P < 0.05 relative to negative control



**Figure 4:** Effect of methanol extract of *C. paniculatum* on absolute ethanol induced ulcer in rats

Values are expressed as mean  $\pm$  SEM; n = 5; \*P < 0.05 relative to negative control

**Table 2:** Effect of MECP on castor oil induced diarrhea

Treatment	Dose (mg/kg)	NFe	NDF	Inhibition of defecation (%)	Inhibition of diarrheic dropping (%)
Control	-	11.40 $\pm$ 1.12	11.00 $\pm$ 1.18	-	-
Loperamide	2.5	4.60 $\pm$ 1.21**	1.80 $\pm$ 0.86***	59.65	83.64
MECP	100	11.20 $\pm$ 1.86	5.80 $\pm$ 1.32**	1.75	47.27
	200	9.60 $\pm$ 1.44	4.20 $\pm$ 1.02***	15.79	61.82
	400	5.20 $\pm$ 1.24*	2.20 $\pm$ 0.92***	54.39	80.00

Values are mean  $\pm$  SEM., n = 5, \*, \*\*, \*\*\* Significant difference from negative control ( $P < 0.05$ ,  $P < 0.01$  and  $P < 0.001$ ), respectively. MECP = methanol extract of *C. paniculatum*, NDF = mean number of diarrheic feces; NFe = mean number of feces.

**Table 3:** Effect of MECP on acid neutralizing capacity

Test substances	Concentration (mg/5 mL)	Volume of NaOH consumed (mL)	mEq of HCl consumed	ANC per gram of antacid
MECP	500	8.10	2.19	1.27
	1000	5.05	2.50	1.73
	1500	4.65	2.60	2.50
	2000	4.00	2.54	4.38
Danacid [(Aluminium hydroxide + Magnesium hydroxide)]	[(250 mg) + (120 mg)]	6.57	2.34	6.33

MECP = methanol extract of *C. paniculatum*; ANC = acid neutralizing capacity; mEq = milliequivalent

## Conclusion

The findings in this study, suggests that the methanol extract of *C. paniculatum* leaves has antidiarrheal and antiulcer activities, thus, justifying its traditional use in the treatment of diarrheal and ulcer. However, further studies are needed to identify the exact mechanisms and chemical compounds that are responsible for these pharmacological actions.

## Conflict of interest

The authors declare no conflicting interest

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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