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Evaluation of the anti-ulcer property of aqueous extract of unripe *Musa paradisiaca* Linn. peel in Wistar rats

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This study investigated the antiulcer activity of aqueous extract of unripe *Musa paradisiacal* (plantain) peels in rats using ethanol, aspirin, indomethacin and pyloric ligation-induced ulcer models. Fresh peels of *M. paradisiaca* were extracted in hot water and the yield lyophilised. Distilled water, standard drugs and extract were injected intraperitoneally before inducing ulcer. Lethality test and quantitative phytochemical analyses were also carried out using standard techniques. Results showed that the extract at 50, 100 and 200 mg/kg wt offered 73.87, 80.18 and 81.98% protection, respectively against ethanol-induced ulcer, whereas cimetidine (50 mg/kg) produced 72.07% ulcer protection. There was no significant difference ($p > 0.05$) between the various groups. The extract also inhibited aspirin-induced ulcer whereas omeprazole (20 mg/kg) significantly enhanced aspirin-induced ulcer. Similar to cimetidine, the extract did not inhibit indomethacin-induced ulceration. Extract (50, 100, and 200 mg/kg) and cimetidine (50 mg/kg) inhibited pyloric ligation-induced ulcer by 100 and 75%, respectively. Findings suggest antiulcerogenic potentials of the extract, thereby supporting its ethnomedicinal use as antiulcer agent. Up to 5000 mg/kg of extract did not cause mortality of the animals, indicating safety of the extract. The extract was rich in flavonoids (1.40 ± 0.02 mg/100 g).

Key words: *Musa paradisiaca*, peptic ulcer, antiulcerogenesis, aspirin-induced ulcer, medicinal plants, flavonoids.

INTRODUCTION

Ulcer is amongst the common defects of the gastric or intestinal walls, clinically presented as abdominal stress, most often in the upper part of the abdomen and epigastric region. It may manifest as superficial, deep or perforated erosions of the mucosal lining of the stomach (a gastric ulcer), or the small intestine (a duodenal ulcer). Both types of ulcerations are commonly known as peptic ulcer (Dhasan et al., 2010). Peptic ulcer, which is a non-malignant type of ulceration, arises as a result of the distortion of the balance between the endogenous aggressive factors (HCl, pepsin, bile, reactive oxygen species, etc) and the intestinal cytoprotective components (prostaglandins, nitric oxide, mucus bicarbonate system, surface active phospholipids, endogenous antioxidants, some growth factors, etc) (Raju et al., 2009; Wasman et al., 2010).

Epidemiological evaluations indicate that gastric and peptic ulcers are high ranking global health challenges

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effecting approximately 8 to 10% of the population (Kelly et al., 2009). Factors that predispose to the development of this disorder include stress, alcohol consumption, smoking, use of non-steroidal ant-inflammatory drugs (NSAIDS), *Helicobacter pylori* infections and drugs that stimulate the secretion of gastric acid and pepsin (Bandyopadhyay et al., 2001). A wide range of synthetic anti-ulcer agents commonly employed in the treatment of ulcer such as the H_2 – blockers (cimetidine, ranitidine, etc), M_1 – blockers (pirenzepine, telenzepine, etc) and proton pump antagonists (omeprazole, lansaprazole etc) decrease gastric acid secretion, whereas sucralate, carbenoxolone and like-drugs enhance mucosal defences. Although these drugs have improved ulcer therapy, the problems associated with their use (side actions), tolerance and possible incidence of relapse are still a great concern.

Medicinal plants, on the other hand, have equally contributed tremendously in the management of diseases and maintenance of health. This could be as a result of their availability, higher safety margin, and cheaper cost. Several herbal preparations have reportedly been employed in ulcer treatment. Included in this list are extracts of *Momordica* species (Vijayakumar et al., 2011; Dhasan et al., 2010; Alam et al., 2009), extracts of *Moringa oleifera* (Devaraj et al., 2007; Kansara and Singhal, 2013), extracts of the bark and leaves of *Sesbania* species (Bhalke et al., 2010; Sertie et al., 2001). Different parts of *Musa paradisiaca* Linn. (*Musaceae*) such as fruits, leaves, peels, roots and stalks have been reported to possess haemostatic effect (Obadomi and Ochuko, 2002), antidiabetic activity (Ojewole and Adewunmi, 2003), antihypertensive effect (Mohammad and Saleha, 2011; Jaiprakash et al., 2006), and hypolipidaemic activity (Mohammad and Saleha, 2011). In addition, Prabha et al. (2011) reported the antiulcer activity of the edible part of *Musa sapientum* on peptic ulcer, whereas Surabhi, (2011) reported the antiulcer potential of the aqueous leaf extract of *M. paradisiaca*. The thrust of this study is to evaluate the efficacy of the peels of unripe *M. paradisiaca* as a remedy against peptic ulcer using various experimentally-induced ulcer models.

MATERIALS AND METHODS

Plant

Freshly cut bunches of unripe plantain (*M. paradisiaca* Linn.) were harvested from Nanka, Orumba North Local Government Area of Anambra State, Nigeria, in February, 2012. The plant was identified and authenticated by Mr. P.O. Ugwuozor of The Department of Botany, Nnamdi Azikiwe University, Awka, Nigeria.

Animal

Apparently healthy male Wistar albino rats weighing between 100.0 to 112.0 g were used for the studies. All the rats were purchased from the Animal house of the Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka and were housed in standard animal cages in The Department of Applied Biochemistry, Nnamdi Azikiwe University, Awka. The animals were kept on animal pellet diet (Guinea Feeds Limited, Ewu, Edo State, Nigeria) and drinkable water *ad libitum* for one week before the experiments, to allow for acclimatization.

METHODOLOGY

Preparation of the aqueous extract

The fresh unripe *M. paradisiaca* fingers were washed and peeled, avoiding the edible part, and the peels cut into very small pieces. Known quantities (1.0 kg) of the peels were boiled in distilled water at the ratio of $1:2^{w}/_{v}$ for $1^{1}/_{2}$ h. The extract was filtered using cheese cloth and a membrane filter paper of 47.0 mm diameter and pore size approximately 0.45 µm, with the aid of a suction pump. The filtrate was concentrated using rotary evaporator, and the extract stored in the refrigerator prior to use.

Ethanol-induced ulcer study

The effect of *M. paradisiaca* extract on ethanol-induced ulcer was investigated using the method of Mbagwu et al. (2011). Thirty rats (100 to 110 g body wt.) were starved for 18 h and grouped into five groups (A to E) of six rats each based on their body weights. One hour before ethanol administration, animals in group A received distilled water, 2.0 ml/kg body wt. whereas rats in group B received cimetidine (50.0 mg/kg wt.). The extract-treated rats in groups C, D, and E received 50.0, 100.0 and 200.0 mg/kg body wt. doses of the extract, respectively. One millitre per kilogramme weight of ethanol (90%) was then administered to all the animals. Distilled water, cimetidine, extract and ethanol were all given intraperitoneally (i.p). Cimetidine and extract were dissolved in distilled water. One hour after ethanol injection, the rats were anaesthetized with chloroform and dissected. The stomachs were excised and carefully opened along the line of greater curvature to expose the walls. The stomachs' contents were then washed off and the stomach walls viewed with the aid of hand lens to determine the ulcer scores using the method of Raju et al. (2009). The ulcerative lesions were counted and scored as follows: Normal stomach – 0; spot ulceration – 1.0; haemorrhagic streaks – 1.5; ulcer – 2.0; and perforations - 3.0.

Aspirin-induced ulcer study

The effect of the extract on aspirin-induced ulcer model was studied according to the method of Ubaka et al. (2010). Thirty rats (100 to 110 g) were sorted into five groups (n = 6) according to their weights. Group A (negative control) received 2.0 ml/kg body wt. of distilled water, while group B (positive control) received the reference drug, omeprazole (20.0 mg/kg body wt.). Animals in the test groups C, D, and E received *M. paradisiaca* peel extract (50.0, 100.0, and 200.0 mg/kg body wt., respectively). Distilled water, omeprazole and the extract were administered intraperitoneally (i.p). After 1 h, all the animals were given aspirin (200.0 mg/kg body wt.) injection (i.p). Four hours later, the animals were anaesthetized with chloroform and dissected. Their stomachs were removed and treated as mentioned and the ulcers scored.

Indomethacin-induced ulcer study

The method of Ubaka et al. (2010) was adopted. Thirty male Wistar rats (105 to 115 g) were starved for 18 h and grouped into five groups (n = 6) according to their weights. Groups A, B, C, D and E received intraperitoneal injections of distilled water (2.0 ml/kg body wt.), cimetidine (50.0 mg/kg body wt.), extract (50.0 mg/kg body wt.), extract (100.0 mg/kg body wt.), and extract (200.0 mg/kg body wt.), respectively. Distilled water and cimetidine served as negative and positive controls, respectively. One hour later, indomethacin injection (i.p) was given to all the rats at a dose of 40.0 mg/kg body wt. Cimetidine, extract and indomethacin were solubilized in distilled water. Eight hours after indomethacin injection, the rats were anaesthetized with chloroform and dissected. The stomachs were isolated and treated as previously mentioned and the ulcer scores determined.

Pyloric ligation – induced ulcer study

Anti-ulcerative effect of the extract was also studied using the pyloric ligation method of Raju et al. (2009). Thirty male Wistar albino rats used were subjected to a 24 h – fast and grouped into five groups A to E (n = 6). Their abdomen were slightly opened under mild chloroform anaesthesia, and their pylorus carefully lifted and ligated, avoiding any damage to the vascular tissues. After ligation, the stomachs were quickly replaced and the abdomen sutured. Immediately after suturing, the animals in groups A, B, C, D and E received intraperitoneal injections of distilled water (2.0 ml/kg body wt.), cimetidine (50.0 mg/kg body wt.), extract (50.0 mg/kg body wt.), extract (100.0 mg/kg body wt.) and extract (200.0 mg/kg body wt.), respectively. Cimetidine and extract were dissolved in distilled water. Distilled water and cimetidine served as negative and positive references, respectively. Four hours after treatment, the animals were anaesthetized with chloroform, their abdomen dissected and duodenal portion ligated. The stomachs were then opened along the line of greater curvature and gastric content extracted. Gastric volumes were determined after centrifuging the gastric content at 4000 rpm for 20 min. Ulcer scores were also estimated as mentioned previously.

Calculation of ulcer index and percentage inhibition

Ulcer index (UI) = Mean of ulcer scores per rat

Percentage ulcer inhibition = UI (control) – UI (treated) × 100 /UI (control)

Acute toxicity study

Lorke (1983) method was adopted for the determination of the median lethal dose (LD_{50}) of the aqueous *M. paradisiaca* extract. In the pilot study, nine male Wistar rats weighing between 80 to 85 g were used. The rats were randomly divided into three groups (A, B, and C) of three rats each and were administered *M. paradisiaca* extract (i.p) 10.0, 100.0 and 1000.0 mg/kg body wt., respectively. The animals were then observed for behavioural changes and mortality for 24 h. When no death was observed in any of the groups, five other groups (I to V) were given 1250, 1500, 2000, 2500 and 5000 mg/kg body wt. of the extract (i.p) and monitored for 24 h for changes in behaviour and mortality. The LD_{50} is usually calculated as the geographic mean of the least lethal dose that killed a rat and the highest dose that did not kill a rat.

Analysis of phytochemical constituents

The amount of phenolic constituents present in the extract was determined using the method of Kahkonen et al. (1997).
Total alkaloids, cyanogenic glycosides, saponins, tannins and phytates were determined according to the method of AOAC (1984), whereas the quantity of flavonoids present was estimated using the method of Bohamam and Kocepal (1974).

Statistical analysis

All the data presented are means ± standard errors of means. Comparative analysis between the various groups was performed using analysis of variance (ANOVA).

RESULTS AND DISCUSSION

The pathogenesis of peptic ulcer is the distortion of the equilibrium existing between the aggressive factors (gastric acid, pepsin, etc) and the gastrointestinal components responsible for the maintenance of the integrity of gastrointestinal mucosal membrane (Raju et al., 2009; Wasman et al., 2010). Consequently, any agent that possesses the capacity to restore the equilibrium by enhancing the activity of the cytoprotective agents or diminishing the secretion of gastric acid could serve as an antiulcerative agent. Mbagwu et al. (2011) reported that ethanol induces ulceration due to the stimulation of lipid peroxidation resulting to increased generation of reactive oxygen species which cause serious damaging effect on the cells and cellular membranes of the mucosal epithelium.

The results from our studies indicate that intraperitoneal administration of ethanol produced severe ulcers and haemorrhagic streaks on the gastric mucosa of the experimental animals. Pre-treatment of the animals with 50.0 mg/kg body wt. of aqueous peel extract of *M. paradisiaca* prior to ethanol injection protected against ulcerogenesis by 73.87% (from UI of 1.11 ± 0.31 to 0.29 ± 0.05). Higher doses of the extract, 100.0 and 200.0 mg/kg body wt. inhibited ulcer formation by 80.18% (that is, 1.11 ± 0.31 to 0.22 ± 0.05) and 81.98% (1.11 ± 0.31 to 0.20 ± 0.07), respectively (Table 1). The differences between the groups were not statistically significant at $p < 0.05$. These observations also validate the ethnomedical use of concoctions containing *M. paradisiaca* extracts as effective antiulcerogenic ingredients (Swathi et al., 2011; Vadilevan et al., 2006; Mbagwu et al., 2011).

Results also show that 11.25% of the damage caused by ethanol appeared as red colouration of the gastric mucosa. The implication of this is that all the lesions (perforations, ulcers, or haemorrhagic streaks) developed as a result of the disruption of the vascular tissues of the gastric mucosal endothelium (Nagaraju et al., 2012). The *M. paradisiaca* extract effect was not statistically different ($p > 0.05$) from that of the standard antiulcer agent, cimetidine

Table 1. Effect of aqueous *M. paradisiaca* peel extract on ethanol-induced ulcer in rats.

Treatment	Ulcer Index	Percentage ulcer inhibition
Distilled water, 2.0 ml/kg	1.11 ± 0.31	-
Cimetidine, 50.0 mg/kg	0. 31 ± 0.09	72.07
M. paradisiaca, 50.0 mg/kg	0.29 ± 0.05	73.87
M. paradisiaca, 100.0 mg/kg	0.22 ± 0.05	80.18
M. paradisiaca, 200.0 mg/kg	0.20 ± 0.07	81.98

Results are presented as means ± standard errors of means, n = 6. *M. paradisiaca* extract protected against ethanol-induced ulceration of rat stomach. No significant difference at $p<0.05$ was observed between groups.

Table 2. Effect of aqueous *M. paradisiaca* peel extract on aspirin – induced ulcer in rats.

Treatment	Ulcer index	Percentage ulcer inhibition
Distilled water, 2.0 ml/kg	0.10 ± 0.05	-
Omeprazole, 20.0 mg/kg	0. 52 ± 0.09*	+420.00
M. paradisiaca, 50.0 mg/kg	0.10 ± 0.03**	0.00
M. paradisiaca, 100.0 mg/kg	0.00 ± 0.00**	100.00
M. paradisiaca, 200.0 mg/kg	0.01 ± 0.01**	90.00

Results are presented as means ± standard errors of means, n=6. * is significant at $p < 0.05$, when compared with the control group. ** is significant at $p<0.05$, when compared with omeprazole. **+**represents increase in ulcer index. *M. paradisiaca* peel extract (≥ 100.0 mg/kg) decreased the incidence of aspirin – induced ulcer in rats.

(50.0 mg/kg body wt.), which offered 72.07% protection. The non-steroidal anti-inflammatory drugs (NSAIDs), otherwise known as aspirin and aspirin-like drugs, such as indomethacin, adversely affect the gastroduodenal mucosa causing ulcerative lesions on the mucus membrane. This may result through several mechanisms, including suppression of the synthesis of gastric cyto-protective prostaglandin E_2 (via cyclooxygenase enzyme inhibition), decreased blood supply to gastric mucosa, increased gastric acid secretion, as well as inactivation of the growth factors involved in mucosal defence and repair (Wallace, 2000).

Results presented in Table 2 also revealed that the extract at all doses tested inhibited aspirin-induced ulcer in rats. Maximal inhibition (100%) was recorded at 100.0 mg/kg body wt. of extract, although this observation was not statistically significant at $p < 0.05$. Conversely, the reference drug, omeprazole (20.0 mg/kg body wt.) significantly ($p < 0.05$) aggravated aspirin-induced ulcer by 420% when compared with the negative control. This effect of omeprazole was statistically ($p<0.05$) different from that of *M. paradisiaca* extract at all the doses tested. The extract may have countered the effect of aspirin by reactivating prostaglandin synthesis that was inhibited by aspirin, or the processes essential for the regeneration of gastrointestinal mucosa. On the other hand, omeprazole could be blocking gastric ulcers through a mechanism or mechanisms different from the cyclooxygenase pathway. In an earlier report (Biswas et al., 2003), omeprazole inhibited gastric ulcer by virtue of its antioxidant property (the scavenging of hydroxyl radicals).

Result of the investigation of the effect of *M. paradisiaca* extract on indomethacin-induced ulcer is presented in Table 3. It indicates that extract at 50.0, 100.0, and 200.0 mg/kg body wt. did not offer any protection against gastric ulcer induced by indomethacin admini-stration. Rather, the extract (100.0 mg/kg body wt.) increased the severity of the ulcer by 159.26%. The effect of the extract was similar to that of cimetidine (50.0 mg/kg body wt.) which promoted ulcer formation by 97.0%. Differences between the various groups were non-significant ($p > 0.05$). This result corroborates earlier report by Kauffman et al. (1979), that cimetidine did not inhibit indomethacin-induced bowel ulceration. The results also suggest that the extract, just like cimetidine, synergized with indomethacin in the enhancement of mucosal damage. This synergistic combination could be between indomethacin and any of the phytochemicals present in the extract. Moreover, Clayton et al. (2006) had reported that cimetidine and ranitidine (short-acting inhibitors of acid secretion) were very much weaker at inhibiting indomethacin-induced ulcers.

Table 3. Effect of aqueous *M. paradisiaca* peel extract on indomethacin – induced ulcer in rats.

Treatment	Ulcer index	Percentage ulcer inhibition
Distilled water, 2.0 ml/kg	0.54 ± 0.22	-
Cimetidine, 50.0 mg/kg	1.51 ± 0.26	+97.00
M. paradisiaca, 50.0 mg/kg	1.04 ± 0.26	+92.59
M. paradisiaca, 100.0 mg/kg	1.40 ± 0.20	+159.26
M. paradisiaca, 200.0 mg/kg	0.96 ± 0.18	+77.78

Results are presented as means ± standard errors of means, n=6. +represents increase in ulcer index. Like cimetidine, *M. paradisiaca* extract enhanced indomethacin – induced ulceration of rat stomach. No significant differences at p<0.05 were observed between groups.

Table 4. Effect of *M. paradisiaca* peel extract on pyloric ligation – induced ulcer in rats.

Treatment	Ulcer index	Gastric juice Vol. (ml/100 g)	Percentage ulcer inhibition
Distilled water, 2.0 ml/kg	0.50 ± 0.14	1.60 ± 0.30	-
Cimetidine,50.0 mg/kg	0.10 ± 0.02	1.00 ± 0.04	75.00
M. paradisiaca,50.0 mg/kg	0.00 ± 0.00	0.10 ± 0.01	100.00
M. paradisiaca,100.0 mg/kg	0.00 ± 0.00	0.17 ± 0.03	100.00
M. paradisiaca,200.0 mg/kg	0.00 ± 0.00	0.13 ± 0.08	100.00

Results are presented as means ± standard errors of means, n=6. Like cimetidine, *M. paradisiaca* extract inhibited pyloric ligation – induced ulceration of rat stomach. No significant difference at p<0.05 was observed between groups.

The reference drugs, omeprazole, and cimetidine, used in this study, are conventional antisecretory drugs (gastric acid pump inhibitors) that are employed in the treatment of peptic ulcer. Pyloric ligation stimulates the secretion of gastric juice in experimental animals, though the mechanism is still unclear. The antisecretory effect of the extract was then studied using pyloric-ligation-induced ulcer model. As shown in Table 4, the extract remarkably prevented pyloric ligation-induced gastric ulcer, at all the tested doses. Doses of the extract above 50.0 mg/kg body wt. were more efficacious (produced 100.0% protection, that is UI 0.50 ± 0.14 to UI 0.00 ± 0.00) than the standard drug, cimetidine (50.0 mg/kg body wt.), which decreased the ulcer index by 75.0%. At 50.0 mg/kg body wt., the extract non-significantly ($p > 0.05$) reduced the volume of gastric secretion from 1.60 ± 0.30 to 0.10 ± 0.10. The effect of the extract increased with the dose. However, it is quite obvious from the results presented, that unripe *M. paradisiaca* peel extract mimics the actions of cimetidine in ameliorating experimental ulcers.

Findings from the 24 h–acute toxicity testing in rats showed that doses of *M. paradisiaca* peel extract as high as 1000.0 mg/kg body wt. did not cause any behavioural change or mortality in the animals. Phytochemical screening of the constituents of the extract showed that it contained phenolic substances (281.00 ± 0.82 mg/100 g), flavonoids (1.40 ± 0.02 mg/100 g), alkaloids (0.09 ± 0.01 mg/100 g), cyanogenic glycosides (6.25 ± 0.58 mg/100 g), saponins (0.73 ± 0.01 mg/100 g), tannins (1.25 ± 0.01 mg/100 g) and phytates (3.51 ± 0.02 mg/100 g). The antiulcer effect of *M. paradisiaca* extract could be ascribable to the presence of any of the detected chemical agents. Since plant flavonoids have been found to demonstrate gastroprotective and gastric ulcer healing properties (Kelly et al., 2009), these natural products may also play a role in the antiulcer activity of the aqueous, flavonoid-rich, unripe *M. paradisiaca* peel extract. Furthermore, screening for active antiulcer agents in *M. paradisiaca* extract using high performance liquid chromatography (HPLC), Lewis and Shaw (2001) reported the presence of a monomeric flavonoid, leucocyanidin, which protected the gastric mucosa from aspirin-induced erosions by increasing mucus thickness.

Conclusion

Findings from our studies indicate that the aqueous peel extract of *M. paradisiaca* Linn. protected against ulcerative lesions induced by ethanol, aspirin and pyloric ligation. Similar to the action of cimetidine standard, the extract exacerbated indomethacin-induced ulcer. *M. paradisiaca* peel extract mimics the actions of cimetidines in ameliorating ulcers in all the experimental models adopted, therefore it may possess an antisecretory property.

CONFLICT OF INTEREST

The author(s) have not declared any conflict of interests.

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