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Gastro-Protective Properties of the Leaf Extracts of *Ocimum gratissimum* L. Against Experimental Ulcers in Rat

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Abstract: Methanol leaf extract of *Ocimum gratissimum* L. (Lamiaceae) was investigated for gastroprotective properties. The anti-ulcer effect was evaluated in three experimental ulcer models induced by ethanol, indomethacin and hypothermic-restraint stress in rats. Anti-ulcer related properties of the extract such as gastrointestinal transit and the activity on isolated gut tissue preparations of guinea pig and rabbit were also determined. The extract (ME) administered orally at doses of 200, 400 and 800 mg kg^{-1} significantly ($p<0.05$) reduced the ulcer indices in a dose-related manner. The extract showed higher gastroprotection against indomethacin and ethanol-induced ulcers than the stress-induced ulcer. Gastrointestinal motility was significantly ($p<0.05$) reduced by the extract in mice. On the rabbit jejunum, ME produced a concentration-dependent relaxation and inhibited ACh contractile responses. The extract, ME had no effect on guinea-pig ileum but inhibited the contractions produced by histamine. At doses above 3 g kg^{-1} (p.o.), ME caused no signs of acute toxicity or deaths in mice. Flavonoids, tannins, saponins, carbohydrate, steroids, alkaloids, terpenes and volatile oils were found present in the methanol extract of *O. gratissimum* leaf. The results show that the methanol leaf extract of *O. gratissimum* offers protection against ulcers induced by different ulcerogens and could justify the folk use of the plant in peptic ulcer diseases. Cyto-protection and antispasmodic activities may be the likely mechanisms for the anti-ulcer property of this plant.

Key words: *Ocimum gratissimum*, methanol leaf extract, anti-ulcer activity, gastro-protection

INTRODUCTION

Peptic ulcers are focal lesions of gastric or duodenal mucosa, occurring at sites where the mucosal epithelium is exposed to acid and pepsin and are characterized by gnawing or burning sensation in the abdomen (Dhuley and Naik, 1998). The life time prevalence of Peptic Ulcer Disease (PUD) is about 10% (Brunton, 1996). Despite the availability of many orthodox medications for PUD, the morbidity and mortality toll is still very high. In the United States, for example, a study estimated about 6500 deaths each year on ulcer-related complications (Sonnenberg, 1994). Moreover, the available therapeutic tools for the treatment of ulcers are associated with high relapse rates (Howden *et al*., 1988) and some cause limiting side effects. The prevalence of PUD has been reported to be on the increase in the developing countries (Shayne, 2002).

Medicinal plants are reservoirs for drugs and lead compounds for many therapeutic agents. There are avalanche of scientific support on the efficacy of medicinal plants in the management of ulcers of different aetiologies (Al-Harbi *et al*., 1997; Antonio and Souza-Brito, 1998; Anandan *et al*., 1999; David *et al*., 1999; Akah *et al*., 2001; Austin and Jegadeesan, 2000; Nwafor and Akah, 2003; Nwafor and Okoye, 2005).

The plant, *Ocimum gratissimum* is a shrub of versatile use in folk medicine and is commonly called teabush, fever plant or scent leaf. It is used traditionally by the Ibos of south eastern Nigeria in the treatment of a variety of stomach problems. *Ocimum gratissimum* is an erect perennial herb growing up to 2.5 m high (Dalziel, 1937). The leaves, usually 5-13 cm long and 3-9 cm wide, are simple ovate or obovate, toothed margins, with acute or acuminate apex (Wagner *et al*., 1990). The plant is cultivated in homes and garden and is widely found in the tropics (Dalziel, 1937). The plant is reputed for a number of therapeutic properties including hypoglycaemic (Mahabir and Gulliford, 1997; Aguiyi *et al*., 2000), antimutagenic activity (Obaseki-Ebor *et al*., 1993), antibacterial activity (Orafidiya *et al*., 2000), antihelminthic effects (Njoku and Asuzu, 1998), antifungal properties (Njoku and Asuzu, 1998), anti-diarrhoea effects (Offiah and Chikwendu, 1999;

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Orafidiya *et al.*, 2000) and anti-convulsant activities (Adesina, 1982). This research on the gastroprotective properties of the leaf extracts of *Ocimum gratissimum* L. (Lamiaceae) was motivated by the high efficacy claim in the folk use of the plant for peptic ulcer diseases.

MATERIALS AND METHODS

Collection and identification of plant material: The leaves of *O. gratissimum* were collected around Idu, Abuja, Nigeria in the month of September, 2005. The plant material was identified and authenticated by Mallam Ibrahim Muazzam of the Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria where voucher specimen (No. 3812) has been deposited.

Extraction: The fresh leaves were cleaned, air-dried and crushed into coarse powder using pestle and mortar. The powdered leaf (350 g) was macerated in 2.5 L of methanol for 24 h and was agitated intermittently. The filtrate was concentrated *in vacuo* at 40°C using a rotary evaporator to give a solid residue (ME), 22.75 g. The extract was subjected to phytochemical tests according to the methods of Evans (2004).

Animals: Adult Wistar rats (180-200 g), adult Swiss albino mice (28-32 g) of both sexes, adult guinea pigs (350-400 g) and New Zealand rabbits (1.5-3.0 kg) obtained from the Animal Facility Centre of National Institute for Pharmaceutical Research and Development (NIPRD), Abuja, Nigeria. The animals were acclimatized for 5 days and housed under standard conditions of temperature (25±2°C) and 12 h light/dark cycle. The rats and mice were fed with standard pellets (Ladokun Feeds, Ibadan, Nigeria) and the guinea-pig and rabbit fed with a local grass, *Panicum maxima* Jacq. (Poaceae). All animals were allowed unrestricted access to clean drinking water.

Acute toxicity test: The Methanol Extract (ME) was tested orally for acute toxic effect in mice using the method described by Miller and Tainter (1944). Six groups (n = 6) of Swiss albino mice (of either sex) were fasted for 24 h prior to test but were allowed free access to water. Different doses of ME (10, 100, 1000, 2000, 2500 and 3000 mg kg^{-1}) was administered to each group of mice and the number of deaths recorded over a 24 h period.

Effect of ME on isolated intestinal tissue: The effects of the methanol leaf extract on isolated guinea pig ileum and rabbit jejunum was studied. Segments of the intestinal tissue, 2-3 cm long, were suspended in 20 mL organ bath filled with Tyrode solution of composition (mM): NaCl-136.7, KCl-2.7, CaCl-1.8, $NaHCO_3$-11.9, MgCl-1.0, $NaHPO_4$-0.4 and glucose-5.5 maintained at 37±1°C and aerated with air. The preparation was set up under a resting tension of 0.5 g and allowed to equilibrate for 60 min during which the bathing fluid was changed every 10 min. At the end of equilibration, the direct effects of ME (0.05-0.4 mg mL^{-1}) on the tissue preparations were determined. On the guinea-pig ileum preparation, the effect of ME (0.2 mg mL^{-1}) and mepyramine (2.5×10^{-9}) on histamine (4.5×10^{-7}-7.2×10^{-6} M) -induced contractions were determined. On the rabbit jejunum preparations, the effects of ME (0.2 mg mL^{-1}) on rhythmic contraction and on ACh (2.5×10^{-9}-1.0×10^{-7} M) -induced contractions were also investigated. The contact time for each treatment is 30 sec with a tissue recovery period of 1 min. Responses was determined in triplicate and was recorded on Ugo Basile Unirecorder (7050) through an isometric transducer (7004).

Anti-ulcer tests: The methanol leaf extract (ME) was suspended in 3% Tween 85 and tested orally for anti-ulcer activities using three models of experimental gastric ulcers. Three dose levels of each sample (200, 400 and 800 mg kg^{-1}) were tested in each model. All the rats were allowed free access to water. Cimetidine (100 mg kg^{-1}) and 5 mL kg^{-1} of 3% Tween 85 were used as the reference and as the negative control treatments, respectively.

Indomethacin-induced ulcer test: In this model, one hour after the various treatments with ME (200, 400 and 800 mg kg^{-1}), cimetidine or vehicle, indomethacin (100 mg kg^{-1}) was administered orally to the rats which were randomized into five groups (n = 5) in order to induce ulcers. The animals were sacrificed 8 h later (Urishidani *et al.*, 1979).

Ethanol-induced ulcer test: Ethanol (1 mL of 96%, v/v) was administered orally to five groups (n = 5) of adult Wistar rats 1 h after the treatments with ME (200, 400 and 800 mg kg^{-1}), cimetidine or vehicle. The animals were sacrificed 30 min later (Morimoto *et al.*, 1991).

Hypothermic restraint-stress ulcer test: The rats were placed into groups (n = 5) and treated with ME (200, 400 and 800 mg kg^{-1}), cimetidine or vehicle. One hour later, they were immobilized individually in a restraining cage and put in a refrigerator maintained at 4±1°C. The rats were sacrificed 1 h later (Langason *et al.*, 1994).

For each of these models, the stomach of the sacrificed animals was removed and opened along the greater curvature. They were rinsed under a stream of tap water, pinned flat on a corkboard and were then observed with a hand lens (×10). 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 = 1 mm; 2, ulcers > 1 mm = 2 mm; 3, ulcers > 3 mm) (Main and Whittle, 1975; Nwafor and Okoye, 2005). The total ulcer score for each stomach divided by a factor of 10 was calculated for each animal and expressed as Ulcer Index (UI). The degree of ulcer protection for each treatment group was calculated as a percentage with respect to the mean ulcer index of the negative control group.

Effect of extract on gastrointestinal transit: Swiss albino mice (of either sex) were fasted for 24 h prior to the experiment, but were allowed unrestricted access to clean water. They were randomized into four groups (n = 5) and the ME (200, 400 and 800 mg kg^{-1}) was administered orally to the first three groups while the fourth group received the vehicle and served as the negative control. After 1 h of treatment, each mouse received 0.5 mL of charcoal meal (5% charcoal in 10% tragacanth mucilage) orally. The mice were killed with chloroform, 30 min later and the intestine carefully removed and displayed. 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 ileocaecal junction for each animal (Nwafor *et al.*, 2000).

Statistical analysis: The results were expressed as mean±standard error of mean. The test results were compared to the control values using Student's t-test and differences in paired mean observations were regarded as significant at $p<0.05$.

RESULTS

The phytochemical constituents of methanol extract of *O. gratissimum* include saponins, tannins, flavonoids, terpenes, alkaloids, carbohydrates, steroids and volatile oil. After 48 h of oral administration, the ME at a dose up to 3000 mg kg^{-1} did not cause death or sign of acute intoxication in mice.

Oral administration of ME (200, 400 and 800 mg kg^{-1}) and cimetidine (100 mg kg^{-1}) to rats significantly ($p<0.05$) inhibited the appearance of gastric mucosal lesions induced by ethanol, indomethacin and stress in a dose dependent manner (Table 1). At a dose of 200 mg kg^{-1}, the extract produced an ulcer protection comparable to the effect of cimetidine (100 mg kg^{-1}) in both the ethanol and indomethacin-induced ulcer models. At does greater than 400 mg kg^{-1}, the extract was more effective than cimetidine (100 mg kg^{-1}) in the ethanol and indomethacin ulcer models. In the stress ulcer model, the extract at 800 mg kg^{-1} was not as effective as cimetidine (100 mg kg^{-1}). Generally, the extract showed a higher

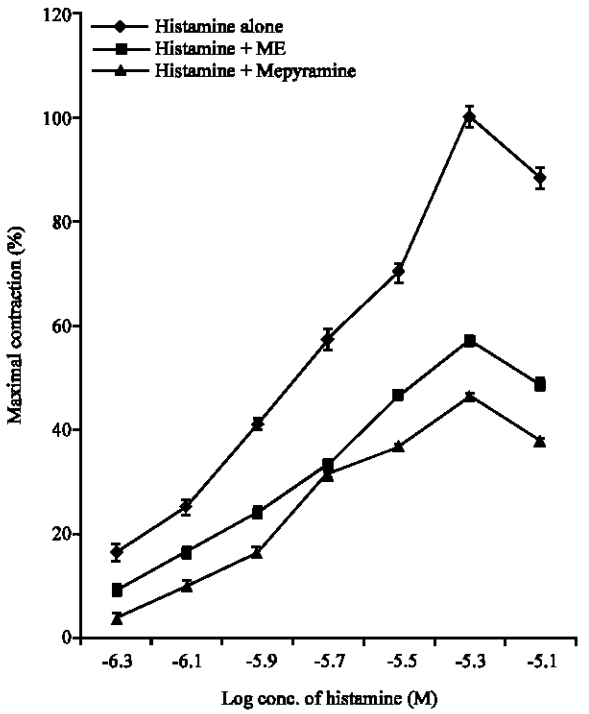

Fig. 1: The effect of ME (0.2 mg mL^{-1}) on contractions induced by histamine

Table 1: The effect of methanol extract of *O. gratissimum* extract on ulcers induced by different ulcerogens

	Ulcer index (percentage protection in parenthesis)				
Ulcerogenic agents	Tween 85	Cimetidine (100 mg kg^{-1})	ME (200 mg kg^{-1})	ME (400 mg kg^{-1})	ME (800 mg kg^{-1})
Ethanol (1 mL of 96%, p. o)	27.95±1.02	17.39±0.68* (37.78)	15.00±2.22* (46.33)	6.48±1.88* (76.82)	2.05±1.02* (92.67)
Indomethacin (30 mg kg^{-1}, p. o)	27.46±2.37	14.92±1.36* (45.67)	7.46±0.68* (72.83)	6.44±0.34* (76.55)	42.54±2.03* (90.75)
Stress (hypothermic-restraint)	27.61±2.56	0.00* (100)	22.50±0.68* (18.51)	12.61±1.02* (54.33)	5.11±1.70* (81.49)

*: Significant $p<0.05$; n = 5

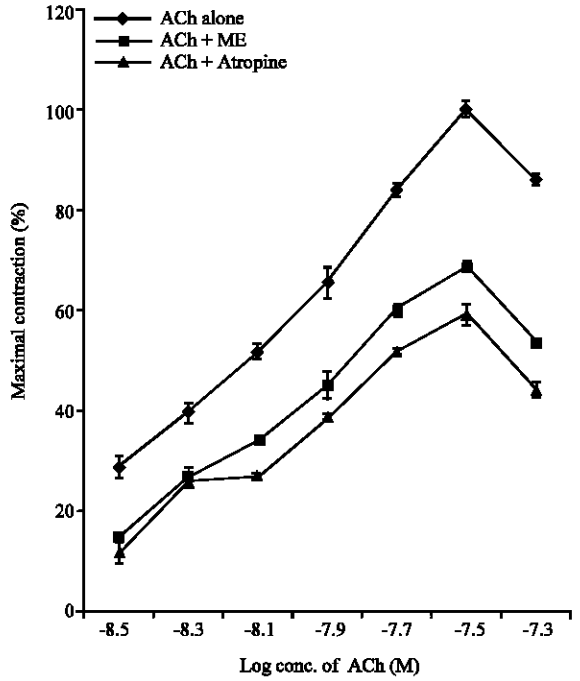

Fig. 2: The effect of ME (0.2 mg mL^{-1}) on contractions induced by ACh

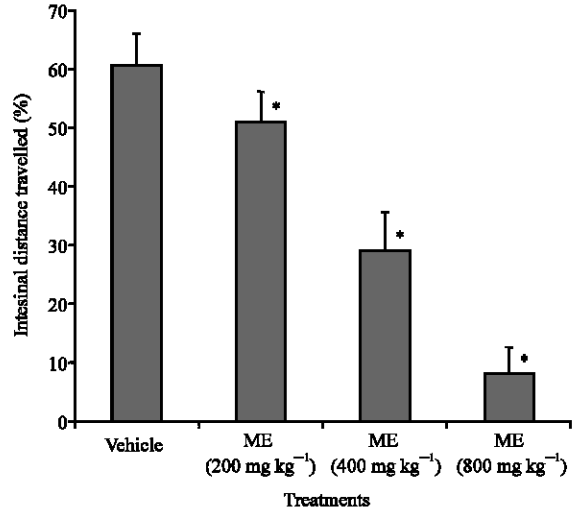

Fig. 3: The effect of ME on gastrointestinal motility *$p<0.05$; n = 4

protection of indomethacin and ethanol-induced ulcers than to the hypothermic-restraint stress ulcer (Table 1).

Administration of the extract reduced gastrointestinal propulsion in mice significantly ($p<0.05$) in a dose-related manner. In the control group treatment, the charcoal meal head traversed 60.57% of the length of the intestine while the 3 doses of ME inhibited this intestinal propulsion by 16.03±8.49, 51.89±10.38 and 86.79±7.54%, respectively (Fig. 3).

The methanol extract elicited no effect on isolated guinea pig ileum, but inhibited the contractile responses to histamine (4.5×10^{-7}-7.2×10^{-6} M) similar to the effect of mepyramine (2×10^{-9} M) (Fig. 1). On the isolated rabbit jejunum preparation, ME produced a concentration-dependent decrease in spontaneous contractility. The extract at 0.2 mg mL^{-1} also attenuated ACh-evoked contractions of the isolated rabbit jejunum preparations, similar to the effect of atropine (5×10^{-9} M) (Fig. 2).

DISCUSSION

The goals of therapy in the treatment of ulcers are to relief the patient from pain, to promote complete healing, to prevent reoccurrence and to prevent the development of complications (Afifi *et al.*, 1997). The therapeutic strategies are aimed at balancing the mucosal aggressive factors against mucosal protective factors. The different therapeutic agents available for the treatment of ulcers are either used to inhibit gastric secretions or to boost the mucosal defense mechanisms (Afifi *et al.*, 1997; Dhuley and Naik, 1998). The search for a safe anti-ulcer drug that optimizes these properties is continuing and part of the search is the evaluation of medicinal plants for gastro-protective properties (Afifi *et al.*, 1997; Akah *et al.*, 1998; Asuzu and Onu, 1990; Akah and Nwafor, 1999; Akah *et al.*, 2001; Nwafor and Akah, 2003; Nwafor and Okoye, 2005). Because *O. gratissimum* is widely used in folk medicine for the treatment of stomach problems including peptic ulcer diseases, we investigated the gastro-protective properties of the leaf extract of the plant using three experimental ulcer models.

The use of three models of ulceration is to cover the various possible therapeutic targets and multiple aetiologies of peptic ulcer disease. Different mechanisms are involved in the formation of gastric mucosal lesions in these experimental models. In the study, the extract of *O. gratissimum* significantly ($p<0.05$) inhibited ethanol-induced ulcer in rats. It is possible that the extract may be acting by promoting any of the mucosal defensive mechanisms since ethanol-induced gastric mucosal lesions are known to be caused by direct toxic action of ethanol, reduction in bicarbonate secretion and depletion of gastric wall mucous (Marhuenda *et al.*, 1993). Ethanol reduces endogenous glutathione and prostaglandin (PG) levels while the release of histamine, influx of calcium ions and generation of free radicals are increased (Galvin and Szabo, 1992). Research has also demonstrated that ethanol-induced gastric mucosal lesions are not inhibited by anti-secretory agents but by agents that enhance mucosal defensive factors (Morimoto *et al.*, 1991).

The methanol extract of *O. gratissimum* also showed a significant ($p<0.05$) protection of the rats against

indomethacin-induced ulcers. Non-steroidal anti-inflammatory agents such as indomethacin cause ulceration mostly at the glandular part of the stomach (Nwafor *et al.*, 1996) which is related to inhibition of endogenous prostaglandin synthesis. This inhibition is associated with over production of leukotrienes which induces mucosal vaso-constriction thereby reducing local blood flow (Dajani and Agrawal, 1995). This activity of the extract suggests cytoprotective mechanisms of action. Prostaglandins has been demonstrated to serve useful gastro-protective functions which involve maintaining gastric microcirculation, stimulation of mucous and bicarbonate secretions and inhibition of gastric acid secretions (Konturek *et al.*, 1988).

Hypothermic restraint ulcer model is associated with increase in gastric acid secretion and a decrease in pH (Murakami *et al.*, 1985). Although the extract offered significant protection against hypothermic-induced stress ulcers, the degree of protection was lower when compared to the effects on the ethanol and the indomethacin-induced ulcers. Studies have shown that histamine has an essential role in the pathogenesis of stress ulcer since it is a potent stimulator of gastric acid secretion (Ibu, 1985). It is therefore not surprising that cimetidine at 100 mg kg^{-1} offered a 100% protection in the stress ulcer model.

The methanol extract of *O. gratissimum* appear to act in a non-specific manner since it showed activity against different ulcerogens acting through different mechanisms. It is possible that this activity may be due to the combined effects of different bioactive constituents of the plant. In addition to other phyto-constituents, flavonoids, saponins and tannins were found to be abundantly present in the methanol extract of *O. gratissimum*. These constituents are known to possess anti-ulcer and gastro-protective properties. In different studies, flavonoids have shown anti-secretory and cytoprotective properties (Guaraldo *et al.*, 2001) and have also been reported to increase capillary resistance and improve microcirculation which renders the cells less injurious to ulcer aggressive factors (Hashizume *et al.*, 1978). Saponins have equally been shown to exhibit anti-ulcer properties through the formation of protective mucous on the gastric mucosa and by selectively inhibiting PGF2α (Lewis and Hanson, 1991; Aguwa and Okunji, 1986). Tannins are astringent and have vaso-constrictive and protein precipitating effects. Precipitate of protein at ulcer sites forms impervious protective pellicle rendering it less permeable to toxic substances and more resistant to attack of proteolytic enzymes (Nwafor *et al.*, 2000).

In ulcer patients, reduction in gut motility helps to ameliorate the ulcer pain and hasten the healing of ulcer wounds (Mersereau and Hinchey, 1988). The extract also showed a significant ($p<0.05$) and dose-related reduction in gastrointestinal motility. This activity was also corroborated in the *in vitro* studies where the extract inhibited the rhythmic contractions of isolated rabbit jejunum preparations. The inhibition of the spontaneous pendular movements of the jejunum by the extract is desirable since antispasmodic activity have been found useful in peptic ulcer diseases (Offiah and Chikwendu, 1999; Brunton, 1996). Although the extract inhibited the contractile responses to both histamine and acetylcholine on isolated tissue, we may not be able to conclusively associate the anti-ulcer properties of *O. gratissimum* to the antagonism of these mediators which are important in the pathology of ulcer.

CONCLUSION

The methanol leaf extract of *O. gratissimum* protected rats against ulcers induced by indomethacin, ethanol and hypothermic stress. We have postulated that antispasmodic and non-specific cyto-protection through enhanced mucosal defense mechanisms may be responsible for the gastroprotective properties. The result of this study could explain the successes claimed in the use of this plant in traditional practices for peptic ulcer diseases. Further studies will be necessary to characterize the active principle(s) responsible for the gastroprotective effects of *Ocimum gratissimum* leaf extracts.

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