

Original Research Article

Ulceroprotective Potentials of Methanolic Extract of *Acacia ataxacantha* leaves in Indomethacin and Stress Induced Gastric Ulcer Models

ABSTRACT

Aims: This study was carried out to investigate the ulceroprotective activity of methanolic extract of *Acacia ataxacantha* leaves (MEAAL) against indomethacin and stress induced gastric ulcer in experimental rats.

Study design: Administration of MEAAL at the dose of 100 mg/kg body weight and 200 mg/kg body weight and evaluation of its ulceroprotective activity.

Place and Duration of Study: The experiments were conducted at the Department of Biochemistry, University of Ilorin, Ilorin, Nigeria. Performed between September 2012 – May 2013.

Methodology: In this study, *Acacia ataxacantha* leaves were extracted with 95 % methanol. MEAAL at the dose of 100 and 200 mg/kg body weights were administered to male albino rats 30 minutes before the administration of indomethacin and subjected to stress. Ranitidine was used as a standard antiulcer drug. Animals were then sacrificed and the various biochemical parameters assessed were gastric ulcer indices, gastric pH levels, gastric ulcer percentage inhibition, which were done in order to explore the ulceroprotective potential of the plant.

Results: Induction of ulcer by the intraperitoneal administration of indomethacin and forcing rats to undergo stress by swimming resulted in increased ulcer index and decreased pH. Rats pretreated with MEAAL (100 and 200 mg/kg body weights) showed significant reduction in ulcer index to indomethacin and stress induced ulcer models in a dose dependent manner when compared to the control group. Also, the significant decrease in the gastric pH levels of both ulcer models, were normalized by MEAAL. The various percentages of gastric ulcers inhibition were statistically significant ($P < .05$) in the groups pretreated with MEAAL. The overall effect of the extract was comparable to that of the standard drug (ranitidine) used.

Conclusion: These findings validated the potentials of *Acacia ataxacantha* leaves as an ulceroprotective agent and provides a scientific rationale for the use of *Acacia ataxacantha* in Senegalese folk medicine.

Keywords: *Acacia ataxacantha*, Ulceroprotective, Gastric ulcer, Indomethacin, Ranitidine.

1. INTRODUCTION

The term ulcer was first introduced by Quike in 1882 [1] and it is now regarded as the new "plague" of the 21st century [2]. A peptic ulcer is a benign lesion in the lining of the stomach or duodenum, where acid and pepsin bathes the surface. Gastric mucus is the highly hydrated viscoelastic gel that protects the epithelium from mechanical stress, as well as from erosion by acid and pepsin [3]. It is generally very common in people who keep themselves

in hurry, become worry and consume curry [4]. Factors such as stress, smoking, alcohol usage, nutritional deficiencies and frequent ingestion of non-steroidal-anti inflammatory drugs such as indomethacin (NSAIDs) have been shown to contribute to gastric ulcer incidences [5]. The massive intracellular accumulation of calcium represents a major step in the pathogenesis of gastric mucosal injury. This leads to cell death and exfoliation in the surface epithelium [6]. Gastric ulcers are also associated with considerable morbidity related to chronic epigastric pain, nausea, vomiting, and anemia [7]. Causes of gastric ulcer disease due to NSAIDs include factors that increase acid secretion, reduction of gastric mucosal blood flow, inhibition of prostaglandin synthesis, disruption of mucosal barrier, inhibition of mucus and bicarbonate secretion in the gastro intestinal mucosa [8, 9]. Although there is evidence to implicate *Helicobacter pylori* in the development of peptic ulcers, the proportion of ulcers not related to either *H. pylori* or NSAIDs have increased, and this particularly affects the management of peptic ulcer [10]. On rare occasions, a gastric ulcer may become malignant. Ulcer therapy has progressed from vagotomy to anticholinergic drugs, histamine H₂ receptor antagonists, antacids and to proton pump inhibitors [11]. A widely used drug associated with rare idiosyncratic hepatotoxicity is the histamine H₂ receptor antagonist ranitidine (RAN) [12]. It is available over the counter for oral administration or by prescription for parenteral administration for treatment of gastric ulcers, hypersecretory diseases, and gastroesophageal reflux disease. Idiosyncratic RAN occurs in few people taking the drug [13]. Most liver reactions are mild and reversible; however, extensive liver damage have occurred in individuals undergoing RAN therapy [14,15]. Thus, there is need for more effective and safe antiulcer agents. These needs have prompted researchers to investigate the pharmacological features of natural compounds with more effective, less side effects and less expensive for the treatment of gastric ulcer disease [16]. There are many plant extracts used in folk medicine for the treatment of gastric ulcer. Ethnobotanically, *Acacia ataxacantha* roots have been documented for its use in Kenya as a treatment for joint and back ache [17]. *Acacia ataxacantha* pods and seeds have also been documented to be used as a stomachic herbal drug and for dysentery in Abeokuta, southwestern Nigeria [18]. Some Senegalese herbal practitioners claim that the leaves are used in the treatment of gastric ulcer. In spite of its broad spectrum ethnomedicinal uses, there is a dearth of scientific information published in literature on its acclaimed medicinal potentials especially for gastric ulcer. The aim of the present study is to evaluate the ulcero-protective potential of MEAAL in indomethacin and stress induced gastric ulcer models. However, there are also several experimental models for evaluating ulcero - protective activity either for plant crude extracts or pure natural and synthetic compounds [19]. *Acacia ataxacantha* or Flame thorn is an African tree species with conspicuous red pods and numerous hooked prickles. It is widespread in sub-Saharan Africa from Senegal in the west to Sudan in the east, Namibia, Botswana, Zimbabwe, and in the Transvaal and Kwazulu-Natal and northern part of Nigeria. The genus *Acacia* belongs to the family Fabaceae [20].

2. MATERIAL AND METHODS

2.1 PLANT MATERIAL

Fresh leaves of *Acacia ataxacantha* were collected in September, 2012 from a farmland in Uruan, Kano State, Nigeria. The plant was identified and authenticated by Mr. Bolu, a taxonomist in the Department of Botany, University of Ilorin, Nigeria. Herbarium specimen voucher no 892 was deposited at Department of Botany of same institution for future references.

2.2 Extract Preparation

Fresh leaves (2kg) of the plant were dried under room atmospheric temperature for two weeks. The leaves were pulverized and grounded into fine powder. The powder was macerated in 95 % methanol (300ml/100g) for 72 hrs. The extract was cooled at room temperature, filtered and evaporated to dryness under reduced pressure in a rotary evaporator and kept under refrigeration at - 4° C till further use.

2.3 Ulcero-protective Study

2.3.1 Animal Subjects

Male albino rats (*Rattus norvegicus*) with average weight of (130 – 150) grams were obtained from the Animal Holding Unit of the Faculty of Science, University of Ilorin, Ilorin, Nigeria. The animals were housed in clean metabolic cages, placed in well-ventilated house conditions (Temperature: 28 - 31°C; photoperiod: 12 h natural light and 12 h dark; humidity: 50 - 55 %). They were also allowed free access to pelletized rat feeds (Bendel Feeds and Flour Mills Ltd., Kwara State, Nigeria) and water *ad libitum*. The cages were cleaned of waste once daily. All animals were carefully monitored and maintained in accordance with ethical recommendations and directives for animal experiments. Animals were allowed two weeks of acclimatization.

2.3.2 Indomethacin-induced Ulcer

Thirty male rats were randomized into five groups of six rats each. Food was withdrawn 24hrs and water 2hrs before the commencement of experiment [21]. Normal saline served as the vehicle of oral administration of MEAAL, indomethacin was administered intraperitoneally.

Animals in group I served as control and received 2 ml normal saline orally.

Animals in group II received indomethacin and served as ulcer control

Animals in group III received 100 mg/kg body weight of the extract orally.

Animals in group IV received 200 mg/kg body weight of the extract orally.

Animals in group V received the standard drug, ranitidine 20 mg/kg body weight orally.

After 30 minutes, indomethacin was administered at a dose of 20 mg/kg body weight to group III, IV and V. After 3 hrs, the animals were sacrificed with anaesthetic ether. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10 % formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored [22]. Ulcer index (UI) and gastric ulcer inhibition percentage of each of the groups pretreated with extract were calculated using standard methods [23, 24]. The pH of the gastric juice was recorded using a pH meter.

2.3.3 Stress induced Ulcer

Thirty male rats were randomized into five groups of six rats each. Stress ulcers were induced by forcing the male albino rats to swim in a glass cylinder containing water to the height of 35cm maintained at 25 °C for 3 hrs [25]. Animals were fasted for 24 hrs prior to the experiment. Normal saline served as the vehicle of oral administration of extract.

Animals in group I served as control and received 2 ml of normal saline orally

Animals in Group II served as ulcer control.

Animals in group III received 100 mg/kg body weight of the extract.

Animals in group IV received 200 mg/kg body weight of the extract.

Animals in group V received the standard drug, ranitidine 20 mg/kg body weight orally.

After 30 minutes, the animals in groups II, III, IV and V were forced to swim in a glass cylinder containing water. After this, the animals were sacrificed with anaesthetic ether. Each stomach was opened along the greater curvature and examined for gastric erosions under a dissecting microscope (10×). Gastric juice was collected into centrifuge tubes and centrifuged at 1000 r/min for 10 min. The pH of the gastric juice was recorded using a pH meter. The ulcer index (UI) and gastric ulcer percentage inhibition was determined. This was quantified by a scoring technique whereby normal gastric mucosa was scored 0, punctuate haemorrhage (pinpoint ulcers) was scored 0.5, one or two small hemorrhage ulcer was scored 1.0, and ulcer greater than 3 mm in diameter was scored 2.0 . Ulcer index: The number of ulcers was counted and scoring was undertaken according to the reported method [26]. The ulcer index was determined by using the formula:

$$\text{Ulcer index} = 10/X$$

Where: X = Total mucosal area/Total ulcerated area

125 2.4 STATISTICAL ANALYSIS

126 All the values were expressed as mean $\pm$ standard error of the mean (S.E.M) of six animals
127 each across the groups. Statistical analysis of data was carried out using one-way analysis
128 of variance (ANOVA) with the spss soft-ware (version 16) Duncan Multiple Range Test
129 (DMRT). P value $< .05$ was considered to be statistically significant.

130 3. RESULTS AND DISCUSSION

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132 3. RESULTS

133 3.1 Indomethacin-induced gastric ulceration

134 Intraperitoneal administration of indomethacin induced severe gastric ulceration. MEAAL
135 pretreatment and ranitidine groups showed significant reduction ($P < .05$) in the incidence
136 and severity of ulceration. MEAAL and ranitidine showed significant increase ($P < .05$) in pH
137 also a significant reduction ($P < .05$) in ulcer indices relative to the ulcer control group were
138 observed. The effect of MEAAL was comparable to that of the standard drug, ranitidine.
139 These results are shown in Table1.

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141 **Table 1:** Effect of MEAAL pretreatment on pH, ulcer indices and inhibition percentage in
142 indomethacin - induced gastric ulceration

Group	pH	Ulcer indices	Inhibition%
I (Control)	2.49 $\pm$ 0.21 ^a	—	-
II (Ulcer control)	1.98 $\pm$ 0.11 ^b	14.88 $\pm$ 1.20 ^a	-
III <i>A ataxacantha</i> (100mg/kg)	3.48 $\pm$ 0.21 ^c	1.89 $\pm$ 0.16 ^b	65
IV <i>A ataxacantha</i> (200mg/kg)	3.52 $\pm$ 0.11 ^c	1.87 $\pm$ 0.08 ^b	69
V Ranitidine	3.45 $\pm$ 0.23 ^c	1.92 $\pm$ 0.18 ^b	68

143 Data are mean $\pm$ SEM of six determinants. Values carry superscripts different from the ulcer
144 control for each parameter that are significantly different ($P < .05$).

145 3.2 Stress-induced gastric Ulceration

146 Forcing male albino rats to swim in a glass cylinder containing water for 3 hrs induced
147 severe gastric mucosal lesions. MEAAL pretreatment, at a dose of 100 mg/kg body weights
148 and 200 mg/kg body weights, showed significant ulcero-protective potencial against these
149 lesions ($P < .05$). Standard drug ranitidine at 20 mg/kg body weight included in the study
150 exhibited significant protection as well ($P < .05$). There was also a significant ($P < .05$) dose-
151 dependent increase and reduction in the pH and ulcer indices respectively relative to ulcer
152 control group in the MEAAL pretreatment groups. The effect of MEAAL was comparable to
153 that of the standard drug, ranitidine. These results are shown in Table 2.

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160 **Table 2:** Effect of MEAAL pretreatment on pH, ulcer indices and inhibition percentage in
161 stress-induced gastric ulceration

Group	pH	Ulcer indices	Inhibition%
I (Control)	2.51 ± 0.18 ^a	--	--
II (Ulcer control)	1.50 ± 0.14 ^b	32.88 ± 3.16 ^a	--
III MEAAL(100 mg/kg b.w)	2.69 ± 0.19 ^c	9.53 ± 0.76 ^b	52
IV MEAAL (200 mg/kg b.w)	2.76 ± 0.11 ^c	5.39 ± 0.31 ^c	71
V Ranitidine	2.79 ± 0.15 ^c	5.52 ± 0.18 ^c	85

Data are mean ± SEM of six determinants. Values carry superscripts different from the ulcer control for each parameter that are significantly different ($P < .05$).

4. DISCUSSION

Indomethacin is an indole derivative act not only as anti-inflammatory but also analgesic and antipyretic. This drug has better ulcerogenic potential than other NSAIDS [27]. Indomethacin reduces the prostaglandins PG by inhibiting both COX enzymes, that impares the mucosal barrier thus rendering gastric mucosa more susceptible to injury [28, 29]. In our study, indomethacin caused damage on the glandular mucosa of high ulcer index consequently leading to a fall in pH level by the induction of H^+/K^+ ATPase in gastric parietal cells. In contrast to it, pre-treatment with MEAAL at the dose of 100 mg/kg and 200 mg/kg body weights significantly decreased ($P < .05$) the ulcer index which was comparable to the effect exerted by standard antiulcerogenic drug ranitidine as evident in Table 1. The fall in pH levels in indomethacin induced gastric ulcer in albino rats, were increased with MEAAL pre-treatment at the dose of 100 mg/kg body weight and 200 mg/kg body weights as shown in Table 1. Suppression of acid remains the mainstay treatment for this disease, as maintaining a gastric pH over 3 for 18–20 h day ensures the healing of most of the gastric ulcers after 8 weeks of treatment [30,31]. The MEAAL protected in a dose-dependent manner, the gastric mucosa from indomethacin - induced ulcers with significant protection ($P < .05$). Ranitidine, substance orally used as a standard drug in this experiment, at a dose of 20 mg/kg, provided similar protection against the gastric ulcers induced by indomethacin. There was a significant increase ($P < .05$) in the gastric ulcer inhibition percentages relative to the ulcer control of the MEAAL pretreated and ranitidine groups as shown in Table 1. The mechanism by which the extract inhibited ulcerogenesis by indomethacin is not well understood because indomethacin inhibits cyclooxygenase and produces the well recognized prostaglandin cytoprotective deficiency[32], which contributes to the pathogenesis of gastric injuries. Forcing albino rats to swim in water is one of the best models in rats to induce ulcer. The model provides both emotional stress as well as physiological stress to the animal. Stress-induced gastric damage is generally considered to be the result of an imbalance between aggressive and defensive mucosal factors. The imbalance determines the outcomes of gastric lesions under the exposure to noxious etiologies represented with either a relative increase in aggressive factors or a considerable decrease in protective factors [33,34]. The stress model used here increases acid secretion and decreases gastric mucosal pH [35]. Brozozowski *et al.* [36] observed that exposure of rats to 3 hrs of stress induced by cold and restraint produced gastric lesions, and that this effect was accompanied by a decrease in prostaglandin (PGE_2) generation and a marked fall in gastric blood flow. In the present study, as shown in Table 2, MEAAL pre-treatment at the dose of 100 mg/kg and 200 mg/kg body weights increase the pH when compared to the ulcer control. MEAAL at the dose of 100 mg/kg and 200 mg/kg body weights have also shown significant ulcero-protective

activity in a dose dependent fashion, by decreasing the high ulcer index evident in the ulcer control group as shown in Table 2. This is also similar to the action of the standard ulcer drug ranitidine. This is also made evident, when MEAAL at a dose of 100 mg/kg and 200 mg/kg body weights also increase the gastric inhibition percentages when compared to the ulcer control. The results of the present study indicated that MEAAL pre-treatment displays a significant cytoprotective activity, since it significantly reduced gastric lesion induced by a non-steroidal, anti-inflammatory drug, Indomethacin and stress induced ulcers. The ulcero-protective potential of the extract is probably due to a reduction in gastric acid secretion since it caused an upsurge of gastric pH, thus, decreasing ulcer indices. The phytochemical analysis of MEAAL was carried-out separately but not included as part of the results in the current study. The preliminary phytochemical analysis indicated the presence of alkaloids, polyphenols, flavonoids, saponins, tannins, terpenoids. However, glycosides were completely absent. These secondary metabolite classes are related to ulcero - protective activity. There are many studies related to the antiulcerogenic properties of flavonoids [37,38]. Flavonoids are also reported to protect the mucosa by preventing the formation of lesions by various necrotic agents [39]. Saponins exhibit ulcer protective effect by selective inhibition of prostaglandin F_{2α} and by protection of gastric mucosa [40, 41]. Considering the presence of these secondary metabolites, the ulcero – protective activity elucidated by the *Acacia ataxacantha* leaves may be connected to the presence of these phytoconstituents.

5. CONCLUSION

In conclusion, this study validated the ulcero-protective potentials of *Acacia Ataxacantha* leaves in indomethacin and stress induced gastric ulcer using rat models. The result shed light and gives a scientific rationale on the reasons for its use in Senegalese folk medicine.

COMPETING INTERESTS

The author has declared that no competing interests exist.

CONSENT

Not Applicable

ETHICAL APPROVAL

All authors hereby declare that "principles of laboratory animal care" (nih publication no. 85-23, revised 1985) were followed, as well as specific national laws where applicable. all experiments have been examined and approved by the appropriate ethics committee"

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