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Antiulcer activity of the stem bark aqueous extract of *Croton oligandrum* (Euphorbiaceae) against Ethanol/HCl-induced gastric mucosal injury in rats

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Abstract

Gastric ulcer is an alteration of the lining of the stomach with destruction of mucus-producing cells. Many factors are contributing to the development of peptic ulcer such as phygiological stress, high production of acid, non-steroidal anti-inflammatory drugs (NSAIDs) and alcohol consumption. *Croton oligandrum* is traditionally used to treat many diseases including gastric ulcers. This study aims to investigate the cytoprotective activity of *Croton oligandrum.* To assess the gastroprotective potential of *Croton oligandrum* ulcer models were established using ethanol and indomethacin. Sucralfate was used as reference anti-ulcer drugs. Rats were treated with *Croton oligandrum* before induction of gastric ulceration by ethanol/HCl or HCl-ethanol-Indomethacin. The area and ulcer index appearance of ulcers were quantified, and mucus was measured. Pretreatment with *Croton oligandrum* showed a remarkable decrease in ulcer area when compared with control groups. *Croton oligandrum* (50, 100 mg/kg and 200 mg/kg of body weight) exhibited gastroprotective activity and prevented both gastric lesions induced in rats.

Keywords: Medicinal Plant; Gastric Ulcer; Cytoprotection; *Croton oligandrum*

1. Introduction

Gastric ulcer (GU) is one of the most common digestive system diseases with a high morbidity of about 5–10 % during human lifetime, being a major public health burden in the present century [1].

Although the etiology and pathogenesis of GU remains controversial, numerous studies have revealed that it is caused by the critical imbalance between mucosal invasive factors such as *H. pylori* infection, hypergastrinemia, stress, cigarette smoking, nutritional deficiencies and the use of non-steroidal anti-inflammatory drugs (NSAIDs) for a long period of time and the protective factors of gastric mucosa (especially prostaglandins level and antioxidant enzymes activity), resulting in disruption of the gastric mucosal defensive barrier thus leading to gastric ulcer [2-5].

Several medications such as antibiotics, antacids, proton-pump inhibitors (omeprazole) and H_2 receptor antagonists are readily available for the treatment of ulcers [6,7]. However, these agents are facing major problems due to their limited efficacy against gastrohelcosis and severe side effects, for instance, gynecomastia, hypoacidity, impotence, osteoporotic bone fracture, hypergastrinaemia and cardiovascular disease risks [8-11]. Thus, new drug candidates which could provide high efficacy and low toxicity are needed valuable for the prevention and treatment of GU.

The genus Croton belongs to the Euphorbiaceae family, and contains approximately 1300 species of trees, shrubs, and herbs, which are widely distributed throughout tropical and subtropical regions f the world. Many Croton species have

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been used as folk medicines in Africa, south Asia, and south America, for the treatment of many diseases such as stomachache, abscesses, inflammation, and malaria [12-14]. Due to their great structural diversity and broad relevant bioactivities, Croton species have attracted increasing research attention [15]. *Croton oligandrum* is a tree (5–10 m high), commonly found in Western and Central African forests, especially in Cameroon and Gabon [16-19]. The stem bark decoction of *C. oligandrum* is taken orally in Cameroon to treat anaemia, pneumonia, and splenomegaly [17, 20,21]. Previous phytochemical analyzes revealed the presence of alkaloids, anthocyanins, flavonoids, sterols and terpenoids [22].

The objective of the present study was to investigate the antiulcer activity of *C. oligandrum* in rats.

2. Material and method

2.1. Plant Material

The stem barks of *C. oligandrum* were harvested in Ambam village in the Ntem valley Department in the South region of Cameroon. The identification of the plant species was confirmed at the National Herbarium in Yaoundé, Cameroon, where a voucher sample was deposited under the registration number of N°65776 HNC.

2.2. Preparation of Plant Extract

One thousand gram (1000 g) of powder was macerated in 5 liters of distilled water for 48 hours. After filtration using Whatman Paper No. 4, the solution was lyophilised at medicinal research institute and medicinal plant study, resulting in 29 g of extract (2.9 % yield).

2.3. Experimental Animals

Adult male Wistar rats weighing between 150-240 g were used in this study. Animals were maintained under standard conditions in the animal house of the Animal Physiology Laboratory, Faculty of Science, University of Yaoundé I. The animals were fed with all a standard laboratory diet and given freshwater ad libitum. All animal care and experimental procedures were carried in agreement with a protocol approved by the Cameroon National Ethics committee (Reg. No FWAIRB00001954).

2.4. HCl/ethanol-induced gastric lesions

HCl/ethanol was used to induce gastric ulcer according to the method described Hara and Okabe [23]. The rats subjected to a non-water fast for 48 hours before the experiment, received a dose of the plant extract (50; 100 and 200 mg / kg, p.o) for the test groups and sucralfate (100 mg/kg) or distilled water (1 mL) for the control groups. One hour later, HCl/ethanol (1 mL) was administered. All rats were sacrificed 1 hour later with ether and the ligated stomach at the esophagus and pylorus of each rat was removed. 10ml of 2% formalin was injected into each stomach. Ten minutes later, each stomach was opened and rinsed. Ulcers were measured and mucus was collected and weighed. Ulcer index (UI), percentage inhibition (%I) and percentage ulcerated area (%SU) were calculated, and ulcer scores were assigned according to the method described by Tan et al [24].

2.5. HCl/ethanol-induced gastric lesions in rats pre-treated with indomethacin

All rats were pretreated with indomethacin (20 mg/kg) intraperitoneally [25]. 1 hour later, the experimental rats received a dose of the plant extract (50, 100 and 200 mg/kg) while the control rats received sucralfate (100 mg/kg) or 1 mL distilled water. respectively orally. One hour later, all animals were orally administered 1 mL of HCl/ethanol solution and were sacrificed after 1 hour using ether. 10ml of 2% formalin were injected into each stomach (ligated at the cardia and pylorus). Ten minutes later, each stomach was opened and rinsed. Ulcers were measured and mucus was collected and weighed. Ulcer scores were assigned according to the method described by Tan et al [24].

2.6. Ulcerated Surface, Ulcer Index and Measurement of Mucus Contents

The stomach of each rat was removed and opened along the greater curvature. Then, the stomach was gently rinsed with water to remove the gastric contents, for subsequent scanning and measurement of the ulcerative lesion index (IU). Ulcerated area and ulcer index were calculated as described by Ndji et al [26]. Ulcerated area: length x width. Ulcer scores were allotted as follows: no ulcer = 0.0; ulcer surface ≤0.5mm^2 =1; ulcer surface > 0.5 ≤ 2.5mm^2 = 2; ulcer surface >2.5 ≤ 5mm^2 = 3; ulcer surface >5 ≤10mm^2 = 4; ulcer surface >10 ≤15mm^2 = 5; ulcer surface >15 ≤ 20mm^2 = 6; ulcer surface >20 ≤ 25mm^2 = 7; ulcer surface >25 ≤ 30mm^2 = 8; ulcer surface >30 ≤ 35mm^2 = 9; and ulcer surface >35mm^2 =10. The ulcer index (UI) was calculated with the following formula:

$$UI = \frac{1}{n}\sum_{1}^{n} \text{score} \pm \text{SEM}$$

The percentage of ulcerated area in relation to the total stomach was calculated using the following equation:

$$\%\ \text{Ulcerated area} = \frac{\text{total ulcerated area}}{\text{total stomac area}}\ \text{X}\ 100$$

The percentage of inhibition was calculated using the following equation:

$$\text{Inhibition}\ (\%) = \frac{\text{Ulcer index control group} - \text{Ulcer index test group}}{\text{Ulcer index control group}}\ \text{X}\ 100$$

The stomach of each rat was untied alongside the greater curvature. Then, the mucus covering of each stomach was gently scraped using a glass slide and the collected mucus was weighed carefully using a sensitive digital electronic balance [27].

2.7. Statistical Analysis

Data were presented as mean ±SEM. The data were analyzed by one way analysis of variance (ANOVA) followed by Dunnett's post-hoc test using Graphpad Prism 8.0 Software. Values of $P < 0.05$ were considered as statistically significant.

3. Results

3.1. Effects of the aqueous extract of the stem bark of *C. olingadrum* on gastric ulcers induced by the HCl/Ethanol in rats

Administration of the HCl/ethanol solution produced dark band-shaped lesions in the glandular portion of the stomach in rats (Figure 1). Ulcerated area and ulcer index were significantly reduced by the aqueous extract of *C. olingadrum* (Figure 2A and 2B). The weight of mucus, on the other hand, showed no significant variation compared to the control (Figure 2C). Sucralfate induced a significant decrease ($p<0.001$) in ulcer surface area and a non-significant variation in ulcer index and mucus weight compared to the control.

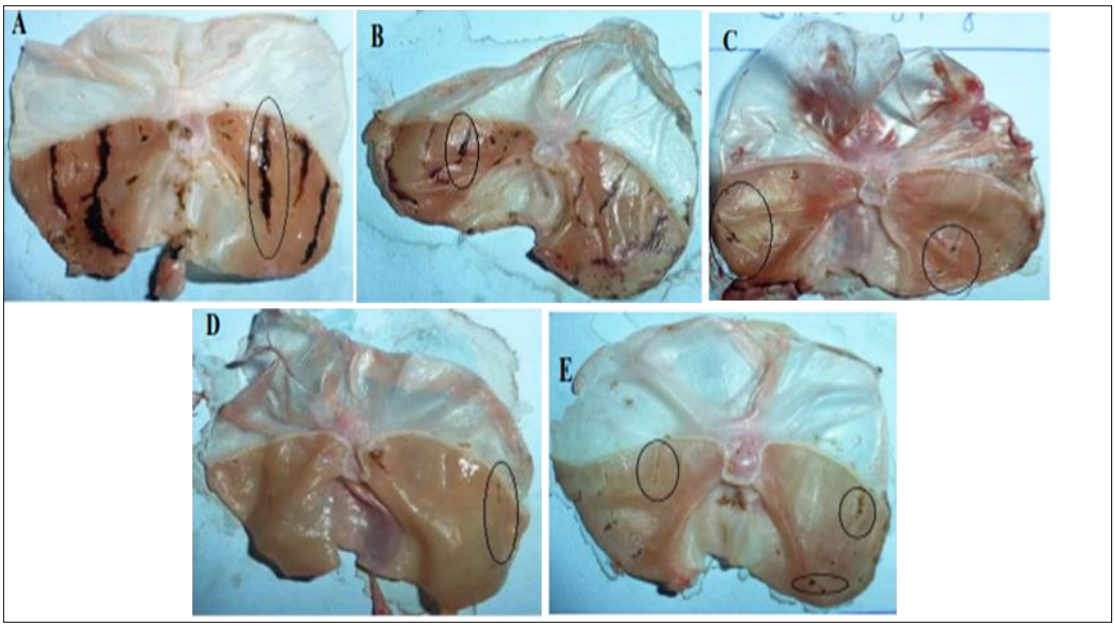

Figure 1 Effects of the aqueous extract of the stem barks of *C. olingadrum* on the stomachs of rats whose ulcers were induced by the HCl/ethanol. (A) control, (B) extract at a dose of 50 mg/kg, (C) extract at a dose of 100 mg/kg, (D) extract at a dose of 200 mg/kg, (E) sucralfate at a dose of 100 mg /kg

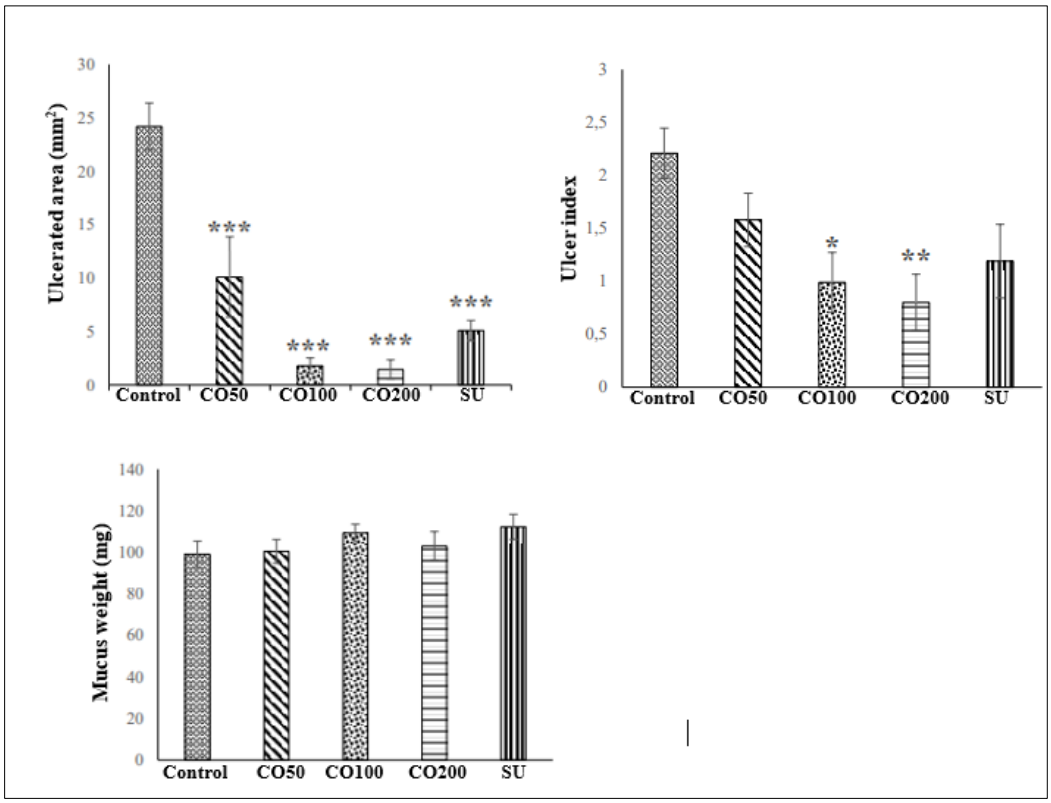

Figure 2 Effects of the aqueous extract of the stem barks of *C. olingadrum* on the ulcerated area, ulcer index and mucus weight in rats whose ulcers were induced by the HCl/ethanol.

Each bar represents the mean ± SEM; * P < 0.05, ** P < 0.01, *** P < 0.001 significant difference compared to the control; CO: extract at a dose of 50 mg/kg, 100 mg/kg, and 200 mg/kg; SU: sucralfate at a dose of 100 mg/kg

3.2. Effects of the aqueous extract of the stem bark of *C. olingadrum* on HCl/ethanol-induced gastric lesions in rats pre-treated with indomethacin

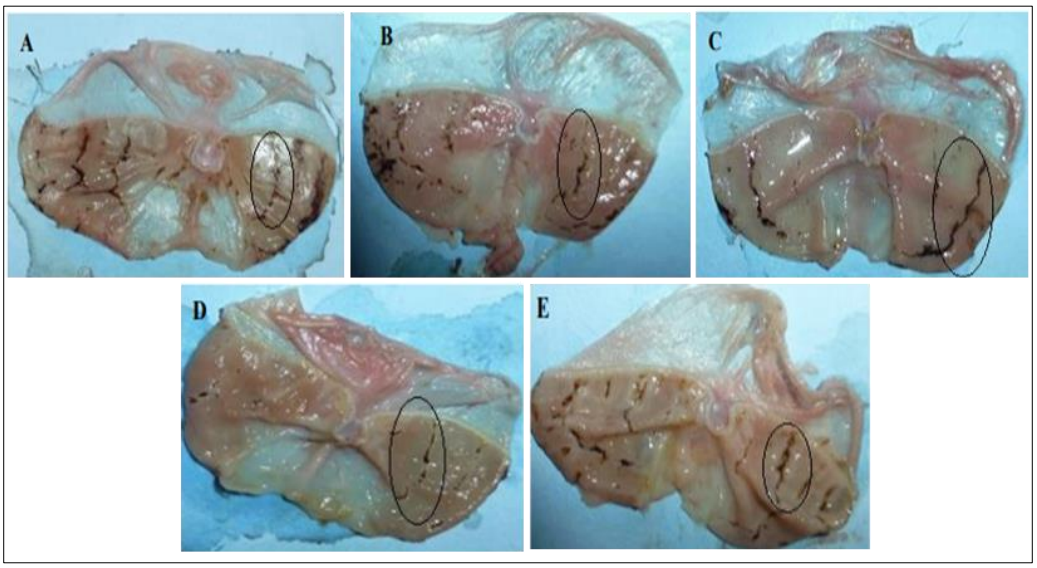

Figure 3 Effects of the aqueous extract of the stem barks of *C. olingadrum* on the stomachs of rats whose ulcers were induced by the HCl/ethanol with indomethacin pretreatment. (A) control, (B) extract at a dose of 50 mg/kg, (C) extract at a dose of 100 mg/kg, (D) extract at a dose of 200 mg/kg, (E) sucralfate at a dose of 100 mg/kg

The glandular surface of the stomach of rats treated with HCl/Ethanol and indomethacin presents lesions in the form of dark bands whose size and number are more accentuated in the control (Figure 3). Ulcerated area and ulcer index were significantly reduced by the aqueous extract of *C. olingadrum* (Figure 4A and 4B). The weight of mucus, on the other hand, showed no significant variation compared to the control (Figure 4C). Sucralfate induced a significant decrease in ulcer surface area and a non-significant variation in ulcer index and mucus weight compared to the negative control.

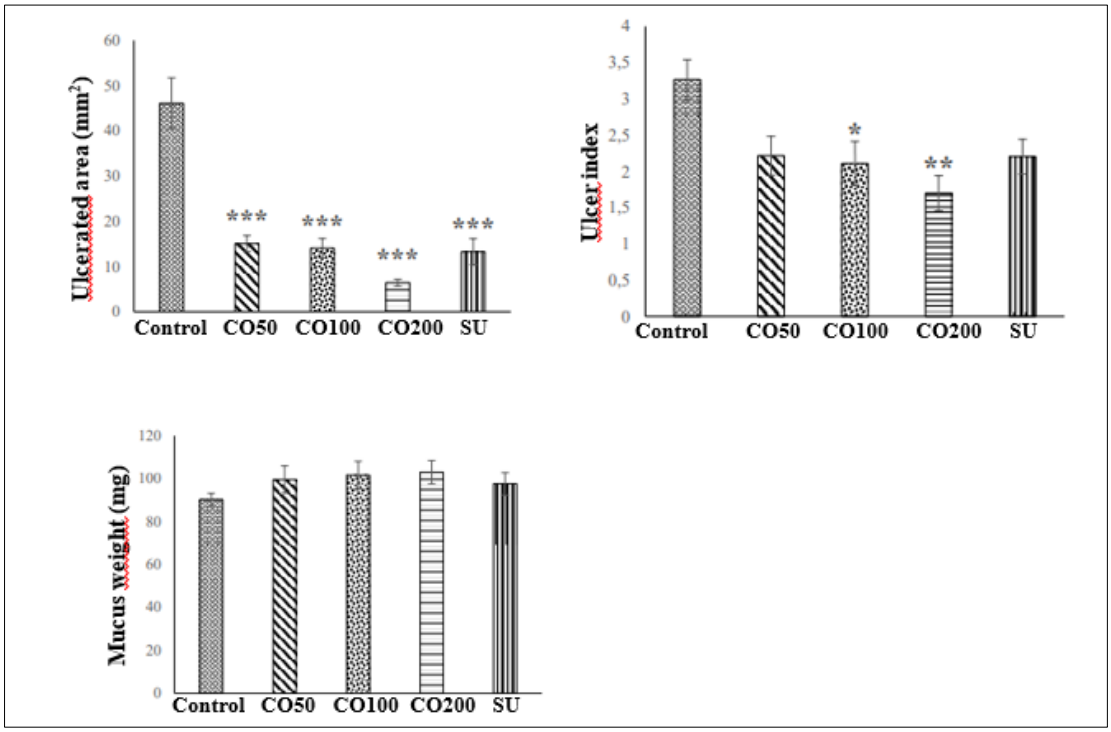

Figure 4 Effects of the aqueous extract of the stem barks of *C. olingadrum* on the ulcerated area, ulcer index and mucus weight in rats whose ulcers were induced by the HCl/ethanol pretreated with indomethacin.

Each bar represents the mean ± SEM; * P < 0.05, ** P < 0.01, *** P < 0.001 significant difference compared to the control; CO: extract at a dose of 50 mg/kg, 100 mg/kg and 200 mg/kg, SU: sucralfate at a dose of 100 mg/kg

4. Discussion

Under normal conditions, the integrity of the gastric mucosa is maintained by mucus-producing cells which are found throughout the stomach [28]. when mucosal defense is impaired, mucosal injury can occur, resulting in the appearance of a gastric ulcer [29]. Several methods of experimental study of antiulcer activity can be used. HCl/ethanol is one of the most used models to evaluate antiulcer activity in rats [30]. Hydrochloric acid and alcohol are among the few elements that the stomach absorbs [31]. These substances erode the muco-bicarbonate barrier, reduce the resistance of the mucosa, and cause its congestion and cellular necrosis [32]. The effect of HCl/ethanol results in the appearance of significant lesions in the form of dark bands on the glandular surface of the stomach. HCl/ethanol pretreated with indomethacin is a model used to determine the mechanisms of action by which the extract promotes mucus secretion. Pretreatment with indomethacin amplifies the irritant effect of the HCl/ethanol mixture on the mucosal barrier [33]. Indomethacin is a non-steroidal anti-inflammatory drug which has the property of inhibiting cyclooxygenase (COX), an enzyme which leads to the synthesis of prostaglandins from arachidonic acid. COX 1 is a constitutional enzyme which governs the synthesis of prostaglandins involved in gastric cytoprotection and COX 2 is responsible for the synthesis of prostaglandins during inflammatory reactions [34]. Inhibition of prostaglandins reduces the secretion of bicarbonate ions and that of mucus, thus predisposing the gastroduodenal mucosa to ulcerations induced by irritant substances [35]. Indomethacin increases the risk of developing an ulcer [36]. The results obtained show that the extract administered 1 hour before the induction of ulcers led to a significant reduction in the ulcerated surface area and the ulcer with HCl /ethanol and with HCl/ethanol pretreated with indomethacin, and a non-significant variation in mucus production unlike the control batch negative in both cases.

Mucus covers the surface of the gastric mucosa and represents the first line of defense of the gastric mucosa against irritant agents [37]. The luminal surface of the mucus gel is covered by a phospholipid film which imparts hydrophobic

properties to the mucus layer [38]. In the HCl/ethanol test with indomethacin pretreatment, the ulcerated area and ulcer index were elevated, and mucus secretion was reduced compared with HCl/ethanol induction. These differences would be because indomethacin (20 mg/kg) administered amplifies the irritant effect of the HCl/ethanol mixture by reducing the secretion of prostaglandins and then the blood flow of the gastric mucosa. In view of the action of indomethacin and the results obtained, it would be important to point out that the aqueous extract of *C. olingadrum* would not act through endogenous prostaglandins to protect the stomach mucosa by secretion of mucus but by other mechanisms.

5. Conclusion

The results showed that *Croton oligandrum* at a concentration of 50, 100 mg/kg and 200 mg/kg have significant antiulcerogenic effects against hydrochloride ethanol.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed

Statement of ethical approval

The experimental protocols were approved by the University's Animal Care Ethics Committee.

Author Contributions

- Research project: A. Conception, B. Organization, C. Execution.
- Manuscript: A. Writing of the first draft, B. Review and Critique.
- Mezui Christophe: 1A,1B,1C,2B; Ndji Otto: 1A,1B,1C,2A,2B; Ambassa:1C, 2B; Nkouendazem: 1C; Emakoua: 1C, 2B; Tan: 2B.

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