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The effect of *Aloe vera* A. Berger (Liliaceae) on gastric acid secretion and acute gastric mucosal injury in rats

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Abstract

The effect of varying doses of ethanol extract of *Aloe vera* (Liliaceae) on acute gastric mucosal lesions induced by 0.6 M HCl and acid output was studied in the pylorus ligated and lumen perfuse rats, respectively. Acid secretion was determined by titration of the collected gastric juice to pH 7.0. Intraperitoneal injection of *Aloe vera*, dose dependently inhibited gastric acid secretion. The plant was more active as a gastroprotective agent at lower concentration against mucosal injury induced by 0.6 M HCl. In conclusion, *Aloe vera* is endowed with gastric acid anti-secretory activity and could protect the gastric mucosa at low concentrations against injurious agents.

Keywords: *Aloe vera*; Gastric acid secretion; Gastroprotection; Pyloric ligation

1. Introduction

Gastroduodenal ulceration is a common disease in both developed and developing countries (Pavo et al., 2000). The presence of acid is still considered a factor in the development of acute and chronic gastric mucosa lesions in the occurrence of the disease. As a result, suppression of gastric acid by surgical and a variety of pharmacological means (Morrissey and Barrease, 1974; Rabon and Michael, 1990; Walsh and Peterson, 1995) provides effective and rapid healing of ulcer (Bastaki et al., 2000). Owing to the persistence problem of recurring ulcer after treatment, new drug approaches are constantly being pursued.

Members of the genus Aloe, especially *Aloe vera* A. Berger (family: Liliaceae) commonly known as Barbados aloe or Curaçao aloe have been used over the years to treat various ailments and have been referred to as the miracle plant (James et al., 1992; David, 1997; Blumenttal et al., 1998). It has been suggested that the extract of the plant promotes healing of diseases through the complex synergistic interaction of many substances, including alkaloids, saponins, fatty acid materials, glycoproteins, resins, sterols, gelonins, minerals, Vitamins (A, C, and E) amino acids, enzymes, and other small constituent molecules (James et al., 1992). Although *Aloe vera* emulsion (sap and gel mixed with mineral oil) has been used to treat patients with peptic ulcer (Hennessee and Cook, 1994), the role of the extract on gastric acid secretion and its influence on experimental lesions in the gastric mucosa has been relatively unexplored. In the present study, we have investigated the effect of ethanol–H_2O extract of *Aloe vera* on gastric acid secretion and 0.6 M HCl induced gastric mucosa damage in the rat.

2. Materials and methods

2.1. Animals

Wistar rats of both sexes weighing between 180 and 200 g were purchased from the Veterinary Research Institute, Vom, Plateau State, Nigeria. The animals were housed in large cages in environmentally controlled room (25 ± 2 °C, 12-h light/12-h dark cycles) with free access to standard laboratory chow. Tap water was supplied ad libitum. The animals were randomly distributed into different experimental groups. Each control and experimental group consists of five rats each. The animals were deprived of food but not water 18 h before the experiment.

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2.1.1. Plant material

Fresh *Aloe vera* was obtained from the Botanical Garden of Ahmadu Bello University, Zaria, Nigeria. Identification of the plant was done by the herbarium keeper (Mr Musa Mohammed) of the Department of Biological Sciences, Ahmadu Bello University. Voucher no. 1115 is available at the same herbarium.

Some 300 g of the clean fresh plant material was ground using an electrical grinder. The extraction was carried out using 70% ethanol. The mixture was agitated over the mechanical shaker for 12 h. The resulting mixture was filtered and the filtrate concentrated into a residue over water bath (Brian and Turner, 1975). The yield was 11.5% (w/w). Consequently the residue from the extract was dissolved in saline and used in the study.

2.1.2. Chemicals

Urethane, sodium hydroxide (NaOH), sodium chloride (NaCl), histamine dihydrochloride, and hydrochloric acid (HCl) were purchased from Sigma Chemical Co. (St. Louis, MO, USA). The dose of cimetidine was prepared from ampoules containing 200 mg/2 ml (Smith Kline and Beecham, London, England), by diluting with distilled water. Sucralfate was a kind gift from Dr A.J. Nok of the Department of Biochemistry, Ahmadu Bello University.

2.2. Experimental procedures

The effect of *Aloe vera* on gastric acid was investigated in anaesthetized rat with lumen perfused stomach. The gastroprotective activity of the plant extract was assessed against 0.6 M HCl induced gastric lesions in the conscious rat.

2.2.1. Secretory studies

The technique described by Greenwood and Mantle (1992) was essentially followed. After an overnight fast, the animals were anaesthetized by a single intraperitoneal (i.p.) injection of urethane (0.2 ml/100 g body weight of a 50% solution). A trachea catheter was inserted to provide a clear airway, the esophagus was canulated and attached to a syringe pump. After a midline incision, the stomach was exteriorized and the pylorus canulated with polyethylene tube. The laparotomy was then sutured closed to prevent desiccation and heat loss. For the duration of the experiment the stomach was perfused from the esophageal end with prewarmed (37 °C) isotonic saline at the rate of 0.7 ml/min. After 30 min of equilibration period post surgery, the perfusate was collected from the distal cannular at 10 min interval for a total period of 120 min. Changes in the acid concentration of the perfusates were determined by titration to pH 7.0 against 0.1 M NaOH.

The study evaluated the effect of 25, 50, and 100 mg/kg of ethanol–H_2O extract of *Aloe vera* or 100 mg/kg of cimetidine, a histamine H_2-receptor antagonist (positive control) administered i.p. after two 10 min basal collection. The control animals received the vehicle solution (normal saline) alone. In another series of experiments, animals received *Aloe vera* or cimetidine (100 mg/kg) 20 min before administration of histamine (4 mg/kg). Again perfusate was collected and treated as described for basal controls. The concentration of the gastric acid secreted was calculated for each animal and expressed as mEq./10 min.

2.2.2. Gastroprotective activity

After an overnight fast, pyloric ligation was done through a midline abdominal incision under ether anesthesia. The abdomen was sutured close and *Aloe vera* extract was dissolved in saline and administered intragastrically (25, 50, and 100 mg/kg) in a 10 ml/kg volume. Control animals received normal saline. In one experiment group, 2 ml of sucralfate (500 mg/kg), an aluminum salt of sucrose octasulfate, which is known to protect the gastric mucosa against many type of acute experimental injury (Harrignton et al., 1981; Nagashima et al., 1983; Okabe et al., 1983), was administered intragastrically. This group serves as the positive control. Thirty minutes after pretreatment with either *Aloe vera* or sucralfate, 0.6 M HCl was given intragastrically (1 ml/rat). The animals were allowed to recover from anesthesia and they were killed 3 h after HCl administration by ether overdose. The stomachs were removed and opened along the lesser curvature, rinsed, laid out on a flat surface, and examined for the presence of mucosal lesions. A 2× hand lens was used to locate and score the lesions according to the method of Ohara et al. (1995). Severity of the gastric mucosal damage was graded as follows: grade 0, no lesion; grade 1, hemorrhagic erosions (less than five); grade 2, hemorrhagic erosions (more than five); grade 3, many small linear ulcers (shorter than 2 mm) or single linear ulcer of marked ulcer (larger than 2 mm); grade 4, multiple linear ulcer of marked size. The ulcer index for each group was calculated by multiplying the number of rats in each grade by the number of grade divided by the number of rats in each group.

2.3. Statistical analysis

Results are presented as mean ± S.E.M. Data were analyzed using one way analysis of variance (ANOVA) or in the case of the effect of *Aloe vera* or sucralfate on gastric mucosa damage, Kruskal–Wallis test followed by Tukey's multiple comparison test was used. Results were considered significant if $P < 0.05$.

3. Results

3.1. Secretory studies

Basal acid output varied among rats; however, acid secretion from individual animals did not fluctuate significantly over the course of 120 min (Fig. 1) in the control animals. Dose-dependent inhibition of basal gastric acid secretion was produced by the extract and the reference drug

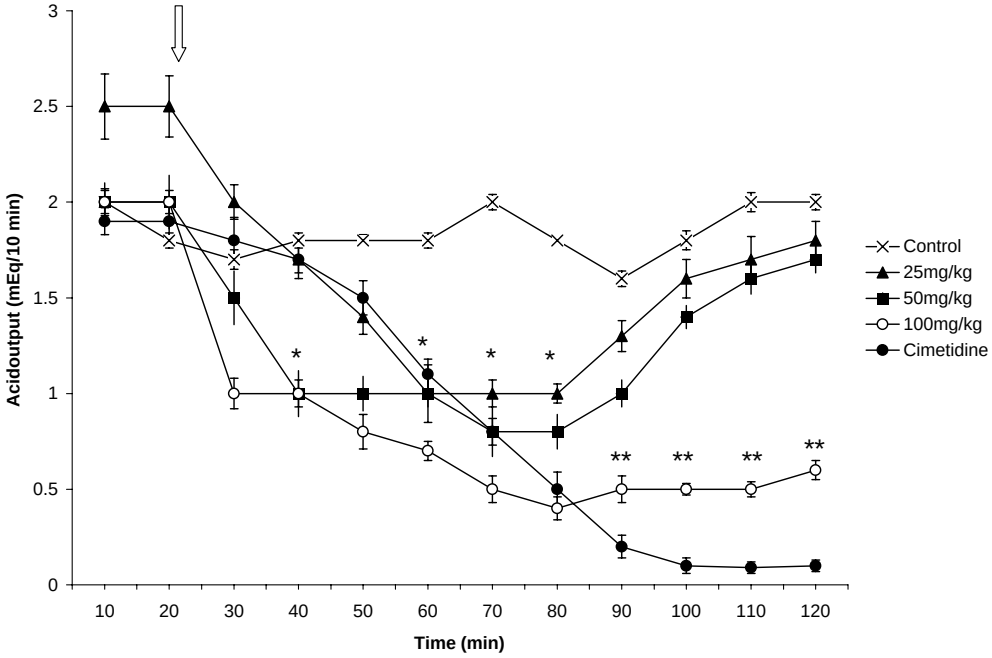

Fig. 1. Effect of *Aloe vera* and cimetidine (arrow) on gastric acid secretion in urethane anaesthetize rat. Control animals received normal saline (i.p.). Rats were prepared as described in Section 2.2.1. After a 30-min equilibration period, gastric perfusate was collected at 10-min interval and analyzed for gastric acid concentration. Data shown represent the mean ± S.E.M. for a total of five rats per treatment group. Significance difference from the respective control group is given as $^{*}P < 0.05$, $^{**}P < 0.001$.

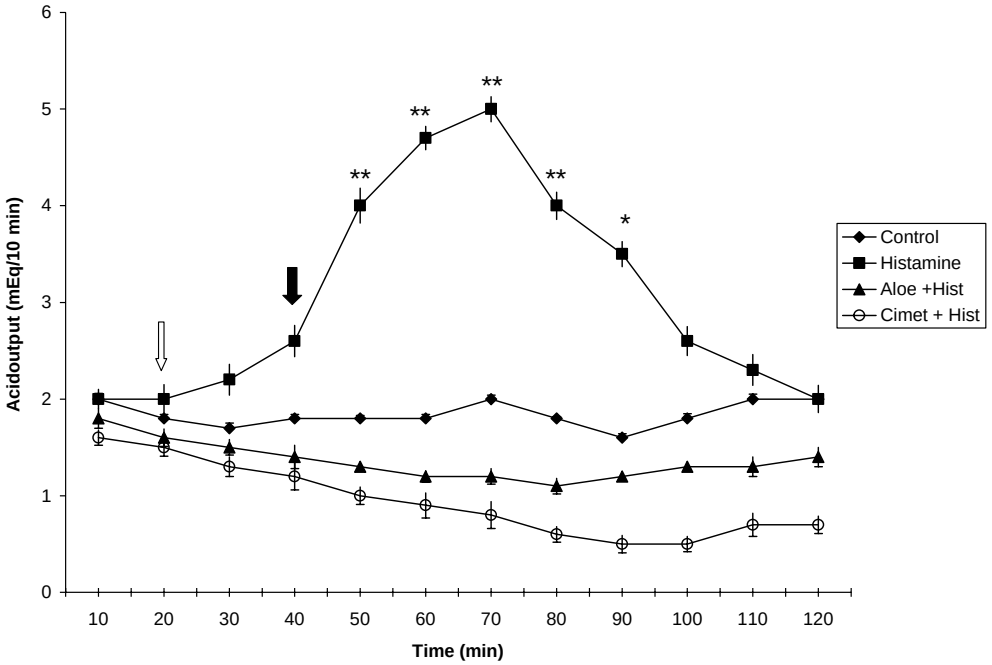

Fig. 2. Effect of *Aloe vera* (100 mg/kg) or 100 mg/kg cimetidine (open arrow) on histamine induced acid secretion (filled arrow) in the rat stomach. Rats were prepared as described in Section 2.2.1. After a 30-min equilibration period, *Aloe vera* and cimetidine were administered i.p. 20 min before histamine. Gastric perfusate was collected at 10-min interval and analyzed for gastric acid concentration. Control animals received the vehicle (normal saline) only. Each value represents the mean ± S.E.M. for a total of five rats per treatment group. Significance difference from the respective control group is given as $^{*}P < 0.05$, $^{**}P < 0.001$.

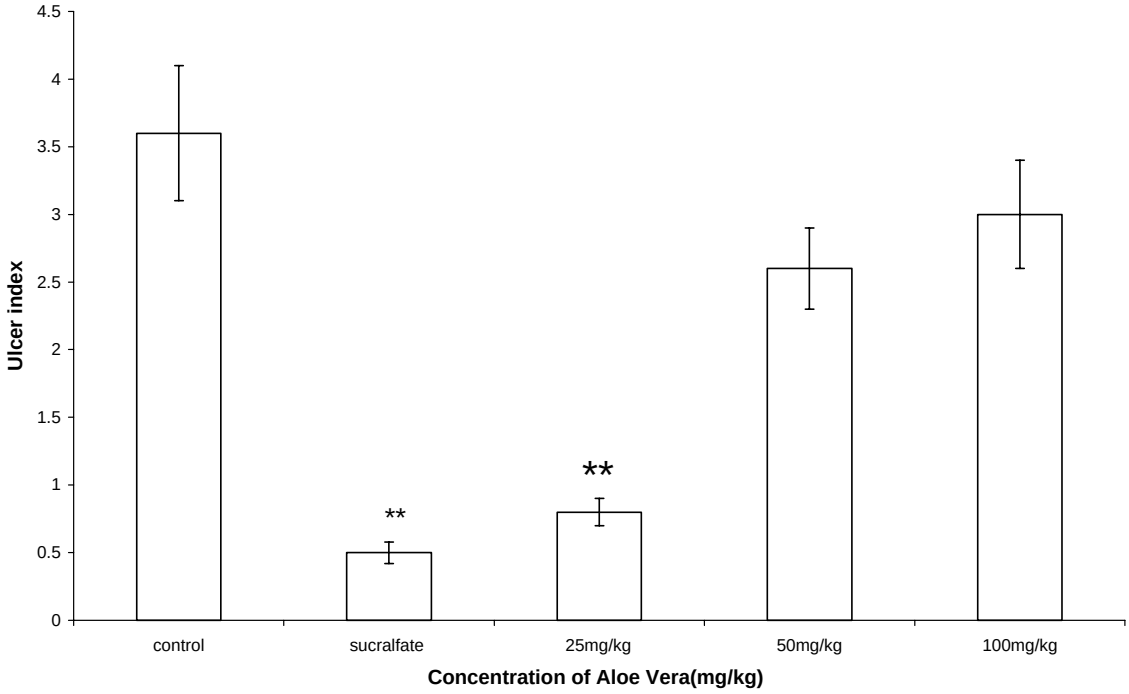

Fig. 3. Effect of *Aloe vera* and sucralfate (500 mg/kg) on gastric mucosa lesions induced by intragastric administration of 0.6 M HCl (1 ml/rat intragastrically). Control animals received the vehicle (normal saline) before challenge with 0.6 M HCl. Rats were prepared as described in Section 2.2.2. Results shown are the mean ulcer index assessed 3 h after HCl challenge. Values are mean ± S.E.M. from five rats per group. $^{**}P < 0.001$ compared to vehicle-treated groups.

(cimetidine). A maximum inhibition relative to control values was noted with all the doses used. This was achieved 60 min after administration of various doses of the extract (Fig. 1). Statistical analysis showed all the doses of the extract differed significantly from the controls in terms of acid output ($P < 0.05$). Treatment with cimetidine (a histamine H_2-receptor antagonist) and *Aloe vera* (100 mg/kg) prevented the increase in gastric acid output induced by histamine but *Aloe vera* was less potent than the reference H_2-receptor antagonist, cimetidine (Fig. 2).

3.2. Gastroprotective activity

The intragastric administration of 0.6 M HCl produced macroscopically visible hemorrhagic lesion in the glandular portion of the stomach. The ulcer index of the control animals was 3.6 ± 0.5 (Fig. 3). Lesion formation was not significantly modified by higher doses of the extract (50 and 100 mg/kg). By contrast HCl induced gastric lesion was significantly reduced by the reference drug, sucralfate (500 mg/kg) and 25 mg/kg of the extract (Fig. 3). In this group (25 mg/kg), the ulcer incidence was 40% as compared to 100% in the other groups (50 and 100 mg/kg).

4. Discussion

Results obtained in this study showed that *Aloe vera* extract inhibit gastric acid secretion and do not posses gastroprotective activity against HCl induced damage at higher doses in the rat. Like sucralfate, the extract provided gastric protection at a lower dose of 25 mg/kg. This may suggest that, at this dose, the plant possesses cytoprotective activity. Because "cytoprotection" means protection against mucosal injury by a mechanism different from inhibition or neutralization of gastric acid (Robert, 1979), it is plausible to consider the extract as a putative cytoprotective agent. This assumption is made based on the observation that the total amount of acid secreted in response to this dose at the end of 120 min was minimal when compared to the other doses. The mechanism of cytoprotection is presently unknown. Several hypotheses have been proposed, such as increased mucus synthesis (Bolton et al., 1978; Kauffman et al., 1980), bicarbonate secretion (Garner and Heylings, 1979), increased mucosal blood flow (Konturek and Robert, 1982), and increased phospholipids mucosal coating (Lichtenberger et al., 1983), among others (D'Souza and Dhume, 1991). The effect of this plant on some of these parameters will be reported in a forthcoming paper.

The failure of the plant extract to protect the gastric mucosal at 50 and 100 mg/kg maybe due to the presence of significant amount of salicylic acid (Blitz et al., 1963), an aspirin like compound that inhibit cycloxygenase enzyme which is responsible for the synthesis of prostaglandin. Presence of prostaglandins leads to increase mucosal blood flow, bicarbonate secretion, and mucus production, thus protecting the gastric mucosa against injury (Hollander, 1994; Wallace et al., 1995; Linder et al., 2000). Salicylic acid

may also cause mucosal injury by inhibiting mucosal cell proliferation (Levi et al., 1990).

The anti-ulcer effect of *Aloe vera* (Hennessee and Cook, 1994) maybe due to its acid reducing properties. This property is shared with other anti-ulcer drugs (Muller et al., 1983; Sewing et al., 1983; Barr et al., 1983; Rabon and Michael, 1990). The observation that *Aloe vera* extract inhibits acid secretion may be due to the presence of lectins in the plant (Blitz et al., 1963). Lectins are proteins/glycoproteins which are capable of recognizing and binding to carbohydrate moieties (Bardocz et al., 1995). It has been shown that lectins inhibit aminopyrine uptake by parietal cells (Healey et al., 1998). Thus, the ability of the extract to inhibit gastric acid output maybe as a result of direct action on the acid producing cells. Histamine has been reported to augment the acid secretory response in normal rats (Mehta et al., 1993). This response was substantially inhibited by *Aloe vera* (100 mg/kg) just like the H_2-receptor antagonist, cimetidine (Fig. 2). This suggests that the plant may interact with H_2-receptors on the parietal cells to reduce acid output.

In conclusion, the present study demonstrated that the extract possesses gastric acid inhibitory properties in addition to gastroprotective activity at lower concentrations which may explain its usage in peptic ulcer treatment. However, the cellular mechanisms for these actions remain to be established.

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