



EFFECT OF LEAF EXTRACT OBTAINED FROM *FICUS LINGUA* (MORACEAE) ON GASTRIC ULCER HEALING IN RATS

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ABSTRACT

Ficus genus is typically tropical plants and is among the earliest fruit trees cultivated by humans. The species *Ficus* genus is commonly used in traditional medicine for a wide range of diseases and contain rich secondary metabolites. The present study was initiated to investigate the healing effects and to understand potential underlying mechanism of leaf extract obtained from *Ficus lingua*. Anti-ulcer activity was studied on chronic gastric ulcers induced by injection of 0.05 ml of acetic acid (AA) into the stomach wall. Ulcer index, percentage of healing, mucus secretion, histological, inflammatory cytokines marker and oxidative stress parameters were evaluated. *Ficus lingua* protected the gastric mucosa from AA ulceration, as revealed by the improved macroscopic and histological appearance. *Ficus lingua* significantly increased the gastric homogenate content of SOD. *Ficus lingua* inhibited the lipid peroxidation as revealed by the reduced gastric content of

MDA. Analysis of serum cytokines indicated that *Ficus lingua* pretreatment obviously elevated the decrease of interleukin-10 (IL-10) level, while markedly mitigated the increment of IL-6 and tumor necrosis factor-alpha (TNF- α) secretions in AA-induced rats. These results strongly indicate that *Ficus lingua* could exert a gastro-healing effect, and the underlying mechanism might be associated with the stimulation of secretion of mucus, improvement of antioxidant and anti-inflammatory status.

KEYWORDS: Gastric ulcer, *Ficus lingua*, antioxidant, anti-inflammatory.

INTRODUCTION

Peptic ulcers are pathological lesions in the gastrointestinal tract that usually occur in the stomach and duodenum.^[1,2] Peptic ulcer disease affects 10% of the world population,^[3,2] and is characterized by a deep necrotic injury due to the destruction of mucosal and submucosal layers, infiltration of neutrophils, reduction in blood flow, induction of oxidative stress, and secretion of inflammatory mediators.^[4-6]

Generally, gastric ulcers develop when an imbalance occurs in the equilibrium between protective (e.g. mucus layer) and aggressive factors (e.g. HCl and pepsin) of the gastric mucosa.^[7,8] Excessive drinking habits, poor diets, stress, smoking, *Helicobacter pylori* and excessive ingestion of non-steroidal anti-inflammatory drugs (NSAIDs) all contribute to peptic ulcer disease.^[9-11]

To date, a great number of synthetic drugs have been used for the treatment of gastric ulcers, such as anti-acids, proton pump inhibitors, anticholinergics and histamine receptor antagonists.^[12,13] However, many of these drugs not only can produce undesirable adverse effects, but also involve high cost in gastric ulcer patients.^[14,15,13] Natural products of plant origin that may present fewer side effects are emerging as a promising therapeutic resource for the development of new drugs in the management of gastrointestinal diseases.^[16] To this extent, we look into natural medicinal plants for drug discovery.

Among the pharmacological properties demonstrated for the compounds present in genus *Ficus* are anticonvulsant, anti-inflammatory, analgesic, antimicrobial, antiviral, hypolipidemic, antioxidant, immunomodulatory, antiasthmatic, parasympathetic modulatory, estrogenic, antitumor, antiulcer, antianxiety, antihelmintic, analgesic, tonic, anti-diabetic, antipyretic, anti-inflammatory, antitussive, hepatoprotective activities etc.^[17-23] For all these

reasons, plants belonging to the genus *Ficus* could be considered a priori as a good source of new natural compounds to treat and prevent many diseases including gastric ulcers. Therefore, our present study aimed to evaluate the antiulcer potential of aqueous extract of *Ficus lingua* using the acetic acid-induced gastric chronic ulcers in rats as an experimental model, as well as to determine the effects of aqueous extract of *Ficus lingua* on gastric biochemical parameters and to elucidate its mechanisms of action.

MATERIALS AND METHODS

Collection of plant material and preparing plant extract

The leaves of *Ficus lingua* were collected from Ambam subdivision in the south region of Cameroon. The identity of the plant species was confirmed at the National Herbarium in Yaoundé, Cameroon, where a voucher sample was deposited under the registration number of 5706 /HNC.

The fresh leaves of *Ficus lingua* were collected, dried and ground to a powder. Nine hundred grams (900 g) of the dried material was boiled in 9 liters of water for 20 minutes. The extract solution was filtered through Whatman filter paper No 3. The resulting solution was lyophilized to obtain 74.97 g of solid (8.33 % yield). The extract dissolved readily in distilled water was used as the vehicle in the subsequent experiments.

Experimental Animals

Adult male Wistar rats weighing between 150-200 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).

Acetic acid-induced chronic ulcers

The method described by Pillai et Santhakumari (1984) was used.^[24] Briefly, laparotomia was performed under ether anesthesia on experimental rats after a 24h fasting. Fifty microlitres of 30% glacial acetic acid were injected into the wall of the stomach corpus at the region of the lesser curvature and the stomach wall wiped using cotton wool soaked in a 9‰ NaCl solution. The abdominal incisions were stitched up and feeding was resumed. A disinfectant (Betadine) was applied daily to avoid infection. Four days after the operation, a control group

(control 1) was sacrificed using ether and their stomach was opened to establish the degree of ulceration prior to the onset of treatment. The remaining rats were divided into six groups: the longitudinal group (control 2) and normal (group 3) (treated rats sacrificed water to 14 days after induction of ulcers) received 1 ml/200 mg of distilled water daily by gavage for 10 days, while groups 4, 5 and 6 were given 100 mg/kg, 200mg/kg and 400 mg/kg of the extract respectively. Group 7 rats were given 50 mg/kg of sucralfate. 24 hours after the last administration, laparotomy was performed under light ether anesthesia and the pylorus of each rat was tied followed by the closure of the abdominal incisions. All rats were euthanized 6h later and the blood samples were obtained with no addition of anticoagulants and centrifuged at 2400 rpm for 15 min. The gastric juice produced by each was collected, centrifuged, and the volume measured to obtain serum for biochemical analysis.

Meanwhile, their stomachs were removed rapidly and opened along the greater curvature and rinsed with cold saline to remove the gastric contents and blood clots. The flattened stomach samples were photographed, and the ulcer area (mm²) was measured.

Ulcer healing rates were calculated by comparing the ulcer status of extract- and sucralfate-treated rats with those of the ulcerated untreated controls. The degree of auto-healing was evaluated by comparing the untreated controls with the rats sacrificed four days after induction. The stomachs were fixed and stored in formaldehyde awaiting histological studies. Gastric tissue samples were also taken, prepared and preserved frozen until the measurement of different oxidative stress parameters.

Measurement of gastric acidity

Samples of centrifuged gastric juice (1 mL) were analyzed for hydrogen ion concentration by pH-metric titration with 0.1N NaOH solution.

Histological analysis

Stomach tissues from each group were fixed in 10% formalin solution for 24 h, dehydrated, and embedded in paraffin. Tissue sections (5 µm) were cut and stained with hematoxylin and eosin (H&E) solution. Histopathological changes in the stomach, including edema, blood vessel changes, white blood cell infiltration, and glandular damage, were analyzed under a light microscope at 400× magnification.^[25]

Measurement of glutathione (GSH), superoxide dismutase (SOD), malonaldehyde (MDA) level, and catalase (CAT) activity

After photographing, oxidative stress parameters were measured in gastric tissue samples. Superoxide dismutase (SOD) activity was measured using a standard method and expressed in mmol/g of protein.^[26] Catalase (CAT) was determined and expressed as μmol of $\text{H}_2\text{O}_2/\text{min}/\text{mg}$ of protein.^[27,28] Reduced glutathione (GSH) was measured based on the reaction between 2,2-dithio-5, 5-dibenzoic acid and the thiol (SH) groups of glutathione to yield a complex whose absorbance was read at 412 nm and expressed as U/mg of protein.^[29,30] Lipid peroxidation was assessed by measuring malondialdehyde levels in gastric tissue samples (MDA), expressed as pmol/mg of wet stomach tissue.^[31] Tissue protein was measured using the Biuret method of protein assay.^[32]

Cytokines evaluations

The levels of cytokines (IL-6, IL-10 and $\text{TNF-}\alpha$) in the serum were evaluated using commercial enzyme-linked immunosorbent assay (ELISA) kits (eBioscience, USA) as per the manufacturer's instructions.^[33] The absorbance was read at 450 nm with a microplate spectrophotometer (Multiskan GO, Thermo Fisher Scientific, USA).

Statistical analysis

The values were expressed as mean $\pm$ SEM. Statistical analysis was performed by one way analysis of variance (ANOVA) followed by dunnett's tests. p values < 0.05 were considered as significant.

RESULTS

Anti-ulcer activity

Effects of *Ficus lingua* on chronic gastric ulcers parameters

Table 1. Shows the effects of *Ficus lingua* on some ulceration parameters in rats with chronic gastric ulcers. The stomach of rats in the control group1 (rats sacrificed 4 days after injection of acetic acid) presented an ulcer index of 51.00. The administration of distilled water for 10 days (longitudinal control group 2), resulted in a reduction of this ulcer index from 51.00 to 26.67, corresponding to an auto healing rate of 53.00 %. Treatment with *Ficus lingua* at doses of 100, 200 and 400 mg/kg for 10 days, resulted in a significant decrease ($p < 0.001$) in the ulcerated surface, with ulcer index of 8.00; 0.00 and 0.00 respectively with the extract doses of 100, 200 and 400 mg/kg, compared to the longitudinal control (control 2) (26.67). This healing was accompanied by a significant increase ($p < 0.05$) in mucus production which

increased from 58.25 mg in the control 2 to 81.00 mg in animals treated with *Ficus lingua* at maximal dose of 400 mg/kg. As for rats treated with Sucralfate for 10 days, the ulcer index decreased significantly ($p < 0.001$) compared to the longitudinal control (26.67 mg).

Table 1: Effects of *Ficus lingua* on chronic gastric ulcers parameters.

Treatment	Doses(mg/kg)	N	Ulcer Index	(%) US	(%) Healing	Mucus produced (mg)
Normal rats	—	5	—	—	—	39.00 ± 1.73
Control 1	—	5	51.00 ± 5.19	5.00	—	34.33 ± 4.33
Control 2	—	5	26.67 ± 4.41 ^{###}	4.00	53.00	58.25 ± 2.32 [#]
<i>Ficus lingua</i>	100	5	8.00 ± 1.15 ^{###**}	1.00	70.33	63.00 ± 1.73 [#]
<i>Ficus lingua</i>	200	5	0.0 ± 0.0 ^{###***}	0.0	100.0	73.00 ± 4.04 ^{##}
<i>Ficus lingua</i>	400	5	0.0 ± 0.0 ^{###***}	0.0	100.0	81.00 ± 10.97 ^{###*}
Sucralfate	50	5	2.33 ± 0.17 ^{###***}	0.33	87.33	54.00 ± 0.57

Control 1 (ulcerated rats sacrificed 4 days after acetic acid injection); Control 2 (ulcerated rats receiving distilled water : spontaneous healing) ; N = number of rats; (%) U.S = Percentage of Ulcerated Surface; (%) Healing = Healing Percentage; the values in the table represent the means ± SEM; ^{###} $p < 0.001$: statistically significant compared to the control 1; ^{*} $p < 0.05$; ^{**} $p < 0.01$ and ^{***} $p < 0.001$: statistically significant compared to the control 2.

Effect of the aqueous extract of *Ficus lingua* leaves on the stomach mucosa

Figure 1. Shows macroscopic aspects of the stomachs of rats with 30% acetic acid ulcers induced and treated with the aqueous extract of *Ficus lingua* leaves. The stomachs of rats in the control group 1, killed 4 days after acetic acid injection (Fig. 1B) exhibit a large crater in the mucosa. The stomachs of rats in the control group 2 that received water (Fig. 1C) exhibit a smaller crater than the one of control group 1. The stomach of rats in the groups treated with the extract at a dose of 100 mg/kg (Fig. 1D) and sucralfate showed a smaller crater compared to that of the controls 1 and 2. In animals treated with the aqueous extract of *Ficus lingua* leaves at the respective doses of 200 (Fig.1E) and 400 mg/kg (Fig. 1F), no crater was observed, and the stomach appeared similar to that of the normal rats group (Fig. 1A).

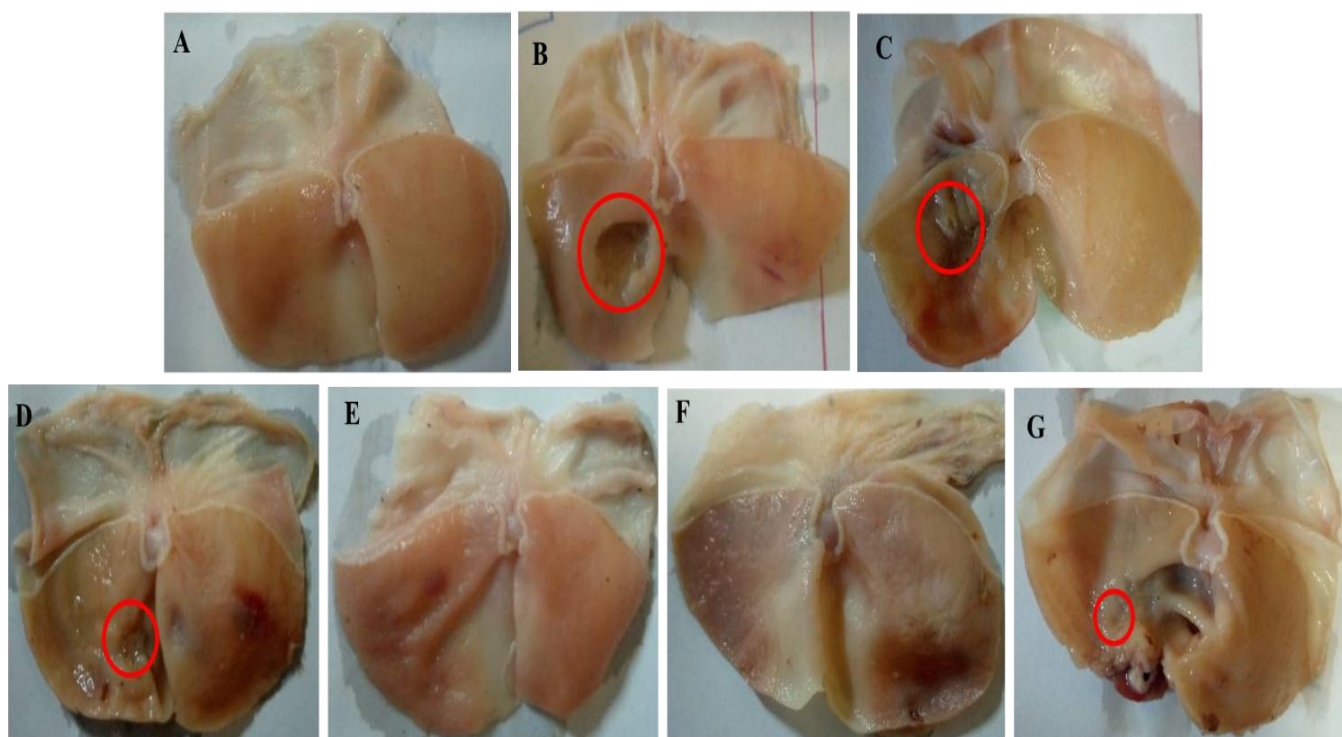


Figure 1: Effects of *Ficus lingua* aqueous extract on chronic gastric lesions induced by 30% acetic acid.

A= Normal rat stomach; B= control 1 stomach: rats sacrificed on day 4 after ulcer induction; C= control 2 stomach (negative): rats receiving distilled water; D= 100 mg/kg extract; E= 200 mg/kg extract; F= 400 mg/kg extract; G= Positive control: rats receiving sucralfate.

Histological sections showed that the injection of 30% acetic acid caused epithelial destruction as observed with control 1 (Fig. 2B). Some parts of the destruction of gastric mucosa are still presents in control 2 (Fig. 2C). However, rats receiving the aqueous extract of *Ficus lingua* at doses of 100, 200 and 400 mg/kg and Sucralfate (50 mg/kg) showed a better protection of the gastric mucosa by glandular regeneration with an almost normal appearance of the mucosa (Fig. 2D, 2E, 2F, 2G).

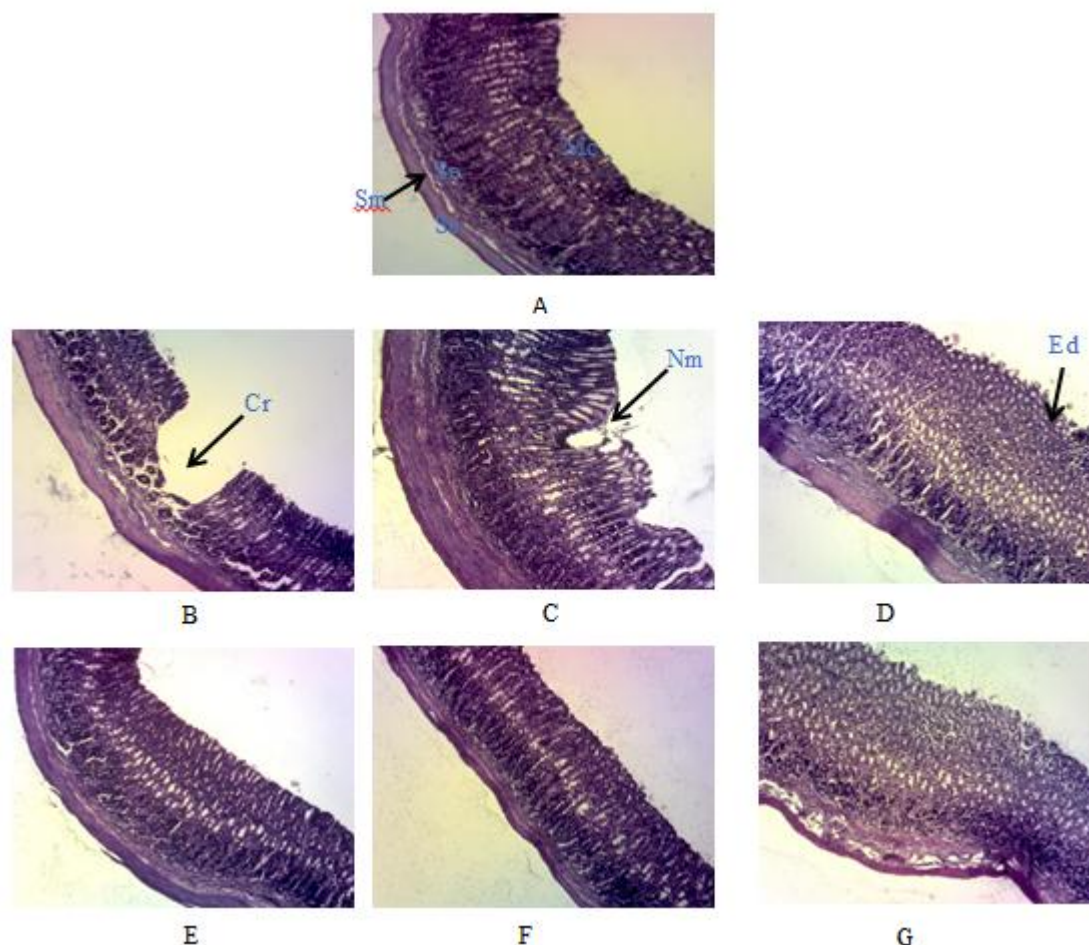


Figure 2: Histological presentation of stomach tissue after acetic acid induced ulcers and treatment with aqueous extract of *Ficus lingua*.

Sm: submucosa; **Nm:** Necrotic mucosa; **Se:** Serosa; **Ed:** Épithélial destruction; **Cr:** Ulcer crater; A= Normal rat stomach; B= control 1 stomach: rats sacrificed on day 4 after ulcer induction; C= control 2 stomach (negative): rats receiving distilled water; D= 100 mg/kg extract; E= 200 mg/kg extract; F= 400 mg/kg extract; G= Positive control: rats receiving sucralfate.

Effect of the aqueous extract of *Ficus lingua* on gastric acidity

The extract of *Ficus lingua* decreased significantly gastric acidity ($P < 0.001$), dropped from 42.96 mEq/l in the control 2 to 27.21, 25.33 and 21.95 mEq/l, respectively, for the 200 and 400 mg/kg doses of extract, and Sucralfate (Fig. 3).

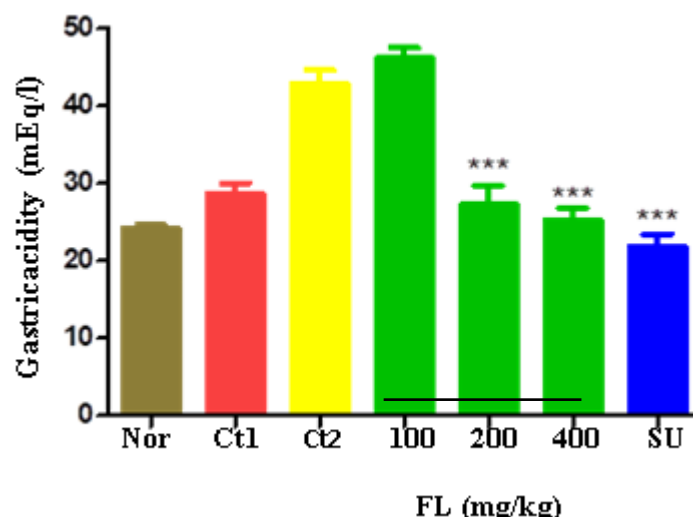


Figure 3: Effects of sulcrafate (50mg/kg) and *Ficus lingua* (100, 200 and 400 mg/kg) on the gastric acidity (mEq/l) in rats. The results were expressed as mean $\pm$ SEM and analyzed by ANOVA followed by Dunnett's test,; *** $p < 0.001$: statistically significant compared to control 2. Nor= Normal rat stomach; Ct1= control; Ct2= control 2; SU= sucralfate.

Effects of *Ficus lingua* on oxidative stress parameters

The antioxidant activity results presented in Table 2 shows that the aqueous extract of *Ficus lingua* caused an increase/decrease in certain parameters of oxidative stress in the gastric tissue of rats with chronic gastric ulcers. SOD levels increased significantly ($p < 0.001$) in rats treated with the aqueous extract of *Ficus lingua* with the extract doses of 200, and 400 mg/kg compared to the control 2. MDA levels decreased significantly ($p < 0.001$) in animals treated with *Ficus lingua* at the various doses, compared to control 1 and 2.

Table 2: Effects of *Ficus lingua* on tissue oxidative stress parameters.

Traitement	Doses (mg/kg)	N	SOD (U/mg protein $\times 10^1$)	Catalase(μ mol H_2O_2 /min/mg protein)	GSH (mol/g tissu $\times 10^{-6}$)	MDA (mmol/g tissu $\times 10^{-7}$)
Normal rats	—	5	0.83 ± 0.45	11.41 ± 0.32	3.81 ± 0.41	6.95 ± 0.22
Control 1	—	5	3.20 ± 0.34	3.18 ± 0.32	3.07 ± 0.33	13.01 ± 0.61
Control 2	—	5	2.08 ± 0.13	$5.88 \pm 0.68^{\#}$	2.66 ± 0.29	$17.02 \pm 1.62^{\#}$
<i>Ficus lingua</i>	100	5	2.75 ± 0.30	$7.38 \pm 0.81^{###}$	3.6 ± 0.21	$2.98 \pm 0.037^{###***}$
<i>Ficus lingua</i>	200	5	$4.67 \pm 0.73^{**}$	$7.01 \pm 0.32^{###}$	4.19 ± 0.16	$8.36 \pm 0.22^{###***}$
<i>Ficus lingua</i>	400	5	$4.50 \pm 0.40^{**}$	$7.37 \pm 0.65^{###}$	2.98 ± 0.51	$7.70 \pm 0.74^{###***}$
Sucralfate	50	5	$0.87 \pm 0.20^{**}$	$7.17 \pm 1.10^{###}$	3.49 ± 0.53	$4.07 \pm 0.85^{###***}$

Control 1 (ulcerated rats sacrificed 4 days after acetic acid injection); Control 2 (ulcerated rats receiving distilled water: spontaneous healing); N = number of rats; the values in the table represent the means $\pm$ SEM; #p < 0.05; ###p < 0.001: statistically significant compared to the control 1; **p < 0.01; ***p < 0.001: statistically significant compared to control 2.

Effects of *Ficus Lingua* on the Production of Pro- and Anti-inflammatory Cytokines in Stomach Homogenates

Analysis of the pro- and anti-inflammatory cytokine assays (Table 3) showed that the higher concentration of proinflammatory cytokines in control 2 receiving distilled water considerably decrease in groups treated with *Ficus lingua* extract. Concentration of TNF α significantly decrease (p < 0.05) with the maximal dose of 400 mg/kg and IL6 concentration significantly (p < 0.001) decrease, in a dose dependent manner. The decrease in IL 10 anti-inflammatory cytokine concentration in control 2 (52.16 $\pm$ 2.54 pg/mL) compared with the one of control 1 (75.71 $\pm$ 8.89 pg/mL) and the one of normal rats group (92.21 $\pm$ 3.96 pg/mL), significantly increased with the aqueous extract of *Ficus lingua* and Sucralfate (50 mg/kg). The higher concentration was obtained with the maximal concentration of 400 mg/kg (111.7 $\pm$ 5.26 pg/mL).

Table 3: Concentration of pro and anti-inflammatory cytokines.

Traitement	Doses (mg/kg)	N	TNF α (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)
Normal Rats	—	5	255.9 $\pm$ 30.16	154.7 $\pm$ 15.43	92.21 $\pm$ 3.96
Control 1	—	5	358.0 $\pm$ 59.34	248.3 $\pm$ 22.65	75.71 $\pm$ 8.89
Control 2	—	5	564.8 $\pm$ 57.90	473.7 $\pm$ 21.78 ^{###}	52.16 $\pm$ 2.54
<i>Ficus lingua</i>	100	5	492.4 $\pm$ 46.44	338.7 $\pm$ 18.15 ^{**}	86.46 $\pm$ 2.65 ^{**}
<i>Ficus lingua</i>	200	5	363.5 $\pm$ 29.94	276.5 $\pm$ 17.05 ^{***}	107.6 $\pm$ 6.29 ^{###***}
<i>Ficus lingua</i>	400	5	289.3 $\pm$ 52.70 [*]	257.1 $\pm$ 10.89 ^{***}	111.7 $\pm$ 5.26 ^{###***}
Sucralfate	50	5	256.2 $\pm$ 27.89 ^{**}	267.5 $\pm$ 25.04 ^{***}	106.2 $\pm$ 7.94 ^{###***}

Control 1 (ulcerated rats sacrificed 4 days after acetic acid injection); Control 2 (ulcerated rats receiving distilled water : spontaneous healing);N = number of rats; values in the table represent means $\pm$ SEM; #p < 0.05; ##p < 0.01 and ###p < 0.001: statistically significant compared to the control 1; *p < 0.05; **p < 0.01 and ***p < 0.001: statistically significant compared to the control 2.

DISCUSSION

The method of induction of chronic gastric ulcers by injecting acetic acid into the gastric wall produces ulcers pathologically and therapeutically similar to human gastric ulcers. This model easily produces characteristic circular and deep ulcers in the stomach.^[34] These ulcers are produced mainly due to the increased secretion of acid by the parietal cells that cause mucosal necrosis.^[35]

The increased gastric secretion causes a backscattering of H^+ ions through channels present in the mucus, to the internal layers of the gastric mucosa. This results in necrosis, transformation of superficial lesions into deeper wounds and inactivation of growth factors which are important for maintenance mucosal integrity and repair.^[36] The tissue necrosis causes the release of arachidonic acid metabolites which attract leukocytes (polymorphonuclear neutrophils and macrophages). These leukocytes phagocytize necrotic tissue and release pro-inflammatory cytokines and growth factors that activate fibroblasts, endothelial cells and epithelial cells. This activation is at the origin of the formation of granulation tissue as part of the healing process.^[37] Elevated value of ulcer percentage and ulcer index (5 ± 0.57 and 51 ± 5.19 respectively) observed with the transversal control sacrificed four days after acetic acid injection are due to the physio-pathological mechanisms of acetic acid that lead to the formation of these chronic gastric ulcers. A decrease in ulcer index and an increase in mucus production was observed with the longitudinal control (negative control) that received only water for 10 days in comparison with the transversal control (control sacrificed 4 days after acetic acid injection). The aqueous extract of *Ficus lingua*, after 10 days of treatment, significantly reduced ($p < 0.001$) ulcer index in groups receiving extract doses of 100, 200 and 400 mg/kg, compared with the negative control that received only water. This reduction of ulcer index was accompanied by a dose dependent increase in mucus production compare with the longitudinal control (negative control) that received only water, with a significant production obtained with the maximal dose of 400 mg/kg. Mucus production with sucralfate (50 mg/kg) was lower than the one obtained with the different doses of extract. These observations suggest that mucus production in the normal process of healing as observed with the longitudinal control (negative control) was amplify by *Ficus lingua* aqueous extract. This mean that the plant extract could act in the process of gastric ulcers healing by stimulating the production of mucus, thus contributing not only in the reinforcement of the muco-bicarbonate barrier, but also to the amplification of the cicatrization. The mucus covering of the entire gastrointestinal mucosa serves as the first

line of the defense against physical damage and back diffusion of hydrogen ions.^[11,38] This mucus is a viscous, elastic adherent and transparent gel formed by water and glycoproteins. Its protective effects depend not only on the gel structure but also on the amount or thickness of the layer covering the mucosal surface. Thus the ability of the gastric mucosa to resist injury caused by endogenous secretions (acid, pepsin and bile) and by ingested irritants such as alcohol, aspirin and NSAIDs can be attributed to a number of factors that have been generally referred to as mucosal defense.^[39]

It has been observed in this study a significant ($p < 0.001$) decrease of gastric acidity with the extract doses of 200 and 400 mg/kg, compared with the longitudinal control. In the process of gastric secretion regulation, histamine striggers, through the activation of its receptors H_2 , the secretion of chlorhydric acid by the parietal cells and pepsin by chief cells.^[40] Thus, all H_2 antihistaminic substances like sucralfate inhibit chlorhydric acid secretion, hence the decrease in gastric acid observed in this study with sucralfate.^[40] This mechanism is probably the same with the aqueous extract of *Ficus lingua*.

On the other hand, organisms per se have enzymatic and non-enzymatic defenses, including GSH, SOD and CAT against the ROS-induced lipid peroxidation.^[41] GSH and SOD are known to be able to scavenge superoxide, hydrogen peroxide, hydroxyl and lipid peroxy radicals, with a consequence of attenuating the tissue damage. CAT as preventive antioxidant triggers the rapid conversion of peroxy radical into biologically safe substances, like water.^[42] MDA, an index of lipid peroxidation, can usually quantify to identify lipid peroxidation.^[43] Thus, to address the role of oxidative stress in our model, we assessed several oxidant–antioxidant parameters in the gastric tissues of rats. The experimental results showed that of Acid acetic increased MDA level, accompanied by a decrease of GSH, CAT and SOD activities, all of which are endogenous antioxidants. Our data support a critical role of oxidative stress in the pathogenesis of the gastric ulcer. Nevertheless, pretreatment with aqueous extract of *Ficus lingua* resulted in significant increases in the activities of SOD, as well as a decrease in MDA formation, indicating its antioxidant activity. Our experimental results indicate that aqueous extract of *Ficus lingua* potentially exerted gastroprotective effect via an antioxidant mechanism.

Gastric ulceration is accompanied by acute inflammation. Pro-inflammatory cytokines like TNF-Alpha play an important role in the production of acute inflammation.^[44] An increase in TNF- α and IL-6 was observed in control group 1 killed 4 days after acetic acid induction,

compare with the normal group. This was probably due to the stimulation of macrophage to release these cytokines after acetic acid injury. An increase of macrophages and polymorphonuclear cells at the ulcerated area led to an increase in proinflammatory cytokines, hence the high concentration of TNF- α and IL 6 (564.8 ± 57.90 pg/mL and 473.7 ± 21.78 pg/mL respectively) in control 2 receiving distilled water during 10 days, compared with control 1 (358.0 ± 59.34 pg/mL and 248.3 ± 22.65 pg/mL respectively). Antiinflammatory cytokines like IL10 can be produced by macrophage and T Lymphocyte and are capable of inhibiting proinflammatory cytokines.^[45] The aqueous extract of *Ficus lingua* leaves significantly ($p < 0.001$) decrease the concentration of proinflammatory cytokines, TNF-Alpha and IL6, and on the other hand significantly ($p < 0.001$) increase the concentration of anti-inflammatory cytokine IL-10, suggesting that this extract play an antiinflammatory role, through the regulation of inflammatory parameters.

Histological analysis revealed destruction of the mucous layer down to the mucosal muscle, proving the effectiveness of chronic gastric ulcers instalment. The destruction was more severe in the control rats sacrificed four days after injection of acetic acid. In comparison with this later, the longitudinal control presented a beginning of muscular mucous layer reparation. This is the auto healing process put in place by the organism to restore the initial state of stomachal tissue in replacement of the damage tissue.^[46] The aqueous extract of *Ficus lingua* caused a gradual improvement of the gastric mucosal state with different extract doses (100, 200 and 400 mg/kg). A better protection of the gastric mucosal by glandular regeneration and an almost normal aspect of the mucosal has been noticed. Protection of the gastric mucosal has also been observed with sucralfate (50 mg/kg). All these observations suggest that the aqueous extract of *Ficus lingua* enable a rapid healing, and the efficacy of this extract could be due to the reinforcement of the muco-bicarbonate barrier and the acceleration of the mechanisms of gastric ulcer cicatrization.

The effects of leaves aqueous extract of *Ficus lingua* on different parameters that were evaluated, namely ulcer area percentage, ulcer index, mucus, gastric juice acidity favorize healing and cicatrization of gastric ulcers.^[47,13] Results obtained with the percentage healing confirm this hypothesis. The negative control presented an auto healing rate of 53%. This autohealing can be justified by coordinated cellular reactions to restore the integrity of the gastric mucosa. Tissue necrosis leads to the release of arachidonic acid metabolites, thus attracting leukocytes (neutrophils and macrophages). These leukocytes phagocyte the

necrotic tissue and release pro-inflammatory cytokines and growth factors that activate fibroblasts, endothelial cells and epithelial cells. This activation is responsible for the formation of the granulation tissue.^[46] The aqueous extract of *Ficus lingua* leaves caused a significant increase in the healing percentage of chronic gastric ulcers ranging from 70.33 to 100% compared with the negative control.

CONCLUSION

The present study demonstrates that the aqueous extract of *Ficus lingua* have an antiulcer effect, which may probably be related to the antisecretory, mucosal protecting, anti-inflammatory, or antioxydant activity. Indeed, the aqueous extract of *Ficus lingua* administration not only significantly increased the mucus production, SOD activities and decreased MDA level in gastric tissue, but also reduced the secretions of proinflammatory mediators such as IL-6 and TNF- α and raised the level of anti-inflammatory cytokine IL-10 in serum in rats exposed to acetic acid. The experimental findings render the aqueous extract of *Ficus lingua* as a promising chemical constituent for the treatment of gastric ulcer. Moreover, the elucidation of the underlying mechanisms of action also helps put the traditional use of *Ficus lingua* Herba for gastrointestinal diseases on a solid scientific footing.

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