ORIGINAL ARTICLE

AQUEOUS LEAF EXTRACT OF *Ficus carica* L. INHIBITS HISTAMINE INDUCED GASTRIC ACID SECRETION, WHILE PROMOTING INTESTINAL MOTILITY IN SPRAGUE DAWLEY RAT

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ABSTRACT

Background: *Ficus carica is a plant belonging to the family Moraceae, popularly known as 'Opoto' in Southwest Nigeria. It is used in folk medicine as an emollient, demulcent, laxative and galactogogue. However, these claims need to be scientifically evaluated. In this study, the effects of oral administration of the aqueous leaf extract of Ficus carica L. on gastric acid acidity and intestinal motility were studied in laboratory rats.*

Objectives: *The objectives of this study are to evaluate the effect of aqueous leaf extracts of Ficus carica on gastric acid secretion and intestinal motility in the laboratory rats.*

Method: *The research was divided into two phase; gastric acid secretion and gastric motility studies. A total of forty-two male rats used for this study were divided into two groups; group for gastric secretion study (10 rats) and those rats for intestinal motility study (32 rats). The groups were further divided into control and extract treated group and the latter were gavaged with 2.0 mg/kg of the extract daily for three week prior to the assay while the control group received equal volume of distilled for the duration of the study. Animals were fasted overnight before the day of the test. The motility study was carried out using the activated charcoal method while the effect on gastric acid secretion was carried out by gastric effluent titration method at basal rate and after the administration of histamine and histamine receptor blocker respectively.*

Results: *Aqueous Ficus carica L. leaf extracts significantly reduced gastric acidity while reducing the gastrointestinal transit time with increased peristaltic index.*

Conclusion: *Aqueous leaf extract of Ficus carica reduced the acidity of the gastric secretion while increasing the motility. This extract may further be explored for possible development of drugs for treating gastric ulcer and constipation.*

Keywords: *Ficus carica, gastric acid secretion, intestinal motility, anti-ulceration*

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Citing this article
Awobajo, F.O., Ogbu, J.I., Olowe J.A., Fashina A.Y. and Sunmonu O.O. AQUEOUS LEAF EXTRACT OF Ficus carica L. INHIBITS HISTAMINE INDUCED GASTRIC ACID SECRETION, WHILE PROMOTING INTESTINAL MOTILITY IN SPRAGUE DAWLEY RAT. KIU J. Health Sci, 2023: 3(1);

Conflict of Interest: None is declared

INTRODUCTION

Gastrointestinal disorders, among which are peptic ulcer and gastrointestinal motility disorders are common ailment with negative impact on human health and quality of life [1]. Pharmacological approaches to ameliorating these intestinal discomforts sometimes come with some reported side effects such as indigestion and flatulence [2]. There is growing interest in traditional interventions using herbal medicines to treat these disorders [3].*Ficus carica* L. is a plant belonging to the family Moraceae [4, 5], popularly known as Opoto in Southwest Nigeria. Previous reports have identified some beneficial effects of *Ficus carica* L. plant species which includes its anti-microbial [6], hepato-protective [7], anti-oxidant, anti-inflammatory, anti-cancer effects [8], anti-diabetic and antiobesogenic effects in vitro [9]. Its anti-inflammatory and antiproliferative activities against diverse human cancer cell lines in vitro have been reported [10]. Ou and colleagues [11] reported that *Ficus carica* L. fruit extract inhibited tumor growth associated with pancreatic cancer.

Ficus carica L. is also rich in calcium, flavonoids and polyphenols with antioxidant properties [12], the seed oil reduced serum level of reduced-glutathione [13], the aqueous leaf extract reduced red cell membrane fragility, while increasing the red cell and platelets count in Plasmodium Berghei infected mice [14]. There are also report of the hepatoprotective activities of the ethanol extract of the leaf on liver damaged induced by carbon tetrachloride [15]. In a clinical trial on the effect of the decoction of the *Ficus carica* leaf administered orally to type -1 diabetes patients as a supplement to breakfast, it was reported to reduce the postprandial glycaemia showing its hypoglycaemic activities [16]. However, there is paucity of scientifically proven information on the beneficial effects of *Ficus carica* L. on gastrointestinal functions. Therefore, our present study was designed to evaluate the effects of aqueous leaf extract of *Ficus carica* L. on gastric acid secretion and intestinal motility in Spraque Dawley rats.

MATERIALS AND METHODS

Preparation of aqueous leaf extract of *Ficus carica*

Fresh leaves of *Ficus carica* were purchased from Ojuwoye market, Mushin Lagos and oven dried in the laboratory. Identification was carried out By Mr. Adeleke at the herbarium of the department of Pharmacognosy, Faculty of Pharmacy, University of Lagos, Nigeria. Aqueous extraction was carried out using Soxhlet extractor and the LD50 value was adapted from our previous report [17]. The aqueous leaf extract was vacuum dried with rotary evaporator and stored at 5 °C in an airtight amber sample bottle until used.

Animals grouping and treatment

The study was divided into two phases. The first phase was designed to assess the effect of the aqueous leaf extract of *Ficus carica* L. on gastric acid secretion while the second was designed to determine the effect of the extract on intestinal motility. A total of forty-two male

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Sprague Dawley rats used for this study were purchased from animal house of the College of Medicine, University of Lagos and they were housed in plastic cages with animal beddings at a population of five rats per cage and in a clean animal room. Sample size was determined using GPower 3.1 sample size determination software. The animals were acclimatized to the laboratory environment for two weeks before the commencement of the experiment. The animals were divided into two groups each for gastric acid secretion and motility studies while each group was further divided into control and extract treated sub groups and were supplied with rat chow and clean tap water ad libitum. Distilled water was used all through the experiment except when clean tap water was provided for drinking by the animals ad libitum. The extract treated groups were orally gavaged 2.0 g/kg body of the aqueous leaf extract of *Ficus carica* L. (AqLexFC) with the aid of oral dosing needle for three weeks while the control received equal volume of distilled water the vehicle. The LD50 value for *Ficus carica* L. leave extract was 4.00 ± 0.04 g/kg body weight as reported in our previous work [17], and the dose used in the present study was arrived at after double diluting down the LD50 value. All procedures employed in this study were approved by the Institutional experimentation and ethics Committee (CM/HREC/010/16/064) of College of Medicine, University of Lagos and were carried out in accordance with guidelines laid out for the care and use of laboratory animals in experimentation and are in conformity with Helsinki declaration ethical conduct of research in health and biomedical field using laboratory animals [18].

Assessment of effect of *Ficus carica* L. on gastric acid secretion

Rats used for gastric acid secretion were divided into two groups; AqLexFC treated and control groups each containing four rats each. The treated rats were pre-treated orally with the aqueous leaf extract of *Ficus carica* for three weeks. The animals were fasted for twenty-four hours prior to the day of the gastric secretion test to ensure that their stomachs are completely empty. On the day of the test, the rats were anaesthetized with a mixture of urethane (25 %) and chloralose (1 %) given intraperitoneally (i.p) at 1.0 ml/kg body weight. The animals were allowed to be under full anaesthesia with complete loss of response to cutaneous stimulation. The rat was positioned supine on the dissecting slab and restrained with a limb clip carefully to the four corners of the dissecting slab. The fur was cleaned with 70 % alcohol and an incision made on the trachea and a trachea tube PE250 was inserted to allow for air passage. An incision was also made along the upper right quadrant of the abdomen, the stomach was carefully exposed under aseptic condition and the pylorus cannulated with a small rubber catheter. A sterile rubber cannula was also passed through the oesophagus into the stomach and the stomach was flushed with warm saline (0.9 % NaCl) from suspended mariolite bottle while effluent was collected via the cannulated pylorus. Perfusion rate for the saline was set

at 2.0 ml per three minute and collection of the effluent was at fifteen-minute intervals for 60 minute. The entire set up was allowed to rest for thirty minute before the commencement of effluent collection. The effluent was titrated against freshly prepared 0.025 N NaOH using phenolphthalein as endpoint indicator to determine the acidity. Acidity was determined using the formula, Ma=MbVb/Va, where Ma is the gastric acid concentration in the gastric effluent, Mb is the concentration of the base, Vb is the volume of the base used in reaching the end point and Va is the volume of the gastric effluent used in the titration process. Gastric acid secretion response against histamine (1.0 mg/kg b.w, sc.) and cimetidine; a histamine receptor antagonist (1.0 mg/kg b.w, sc) was also recorded.

Assessment of effect of *Ficus carica* L. on intestinal motility

A total thirty-two rats were used for this study. The rats were divided into control and AqLexFC groups with sixteen rats each. The treated rats were administered orally 2 mg/kg body weight of AqLexFC for three weeks while the control rats received equal volume of distilled water the vehicle. The animals were fasted for 24 hours and overnight before the day of the motility study. On the day of the test, the animals were fed with feed mixed with activated charcoal (1 portion of rat feed to 5 portion of activated charcoal) [11]. Four rats each from the two groups were sacrificed by CO2 asphyxiation followed by cervical dislocation every fifteen minute for sixty minute. The animals were thereafter placed supine on the dissecting slab and the abdomen carefully dissected opened. The intestine was carefully dissected out and placed on a white clean paper beside a meter rule. The length of the intestine and the distance travelled by the charcoal missed rat feed was measured and recorded for 15, 30, 45 and 60 minutes respectively in both control and AqLexFC groups. Peristaltic index (%) was calculated i.e. (length travelled/length of intestine) x 100.

Statistical Analysis

The results obtained was presented in tables and expressed as mean ± SEM after been analysed using student t-test for the motility study and One-way ANOVA for the gastric acid secretion results. Differences between groups were considered significant at $p < 0.05$. The results are also displayed in a table and with the aid of figures.

RESULTS

Timed gastric acidity of gastric effluent form rats gavaged with 2 mg/kg aqueous leaf extract of *Ficus carica* L. along results obtained after histamine and cimetidine intervention (Table 1).

The basal gastric acidity of effluent collected after 15 minutes interval from rats treated with aqueous leaf extract of *Ficus carica* was found to be significantly lower ($p < 0.05$) compared to the basal level in the control group. Histamine administration failed to significantly increase gastric acidity in the extract

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treated group within the collection period (Table 1). The gastric acidity results in the rats treated with the extract and cimetidine was significantly ($p < 0.05$) lower compared with the results obtained from either cimetidine or the extract alone all through the collection period.

Timed intestinal motility and the peristaltic index in rats administered 2 mg/kg body weight of aqueous leaf extract of *Ficus carica* L. orally for three weeks (Figure 1 and Figure 2)

The charcoal loaded feed travelled faster covering a significantly longer distance in extract treated rats intestine compared with the control rat's intestine. Over 50 % of the length was covered within the first 30 minute in treated rats (Figure 1). The peristaltic index increased significantly in rat gavaged the aqueous leaf extract of *Ficus carica* L. treatment in the first and second intervals of 15 minute each (Figure 2). This gap in peristaltic index was closed up after the interval of 30 minute.

DISCUSSION

Gastric ulcer is a common and recurrent gastrointestinal disease affecting millions of people yearly [19] and it ranks top of gastrointestinal disorders worldwide [20]. Increased gastric acid secretion is a known cause of gastric ulceration in the peptic or duodenal region of the stomach. Synthetic pharmacological medications in the form of anti-inflammatory drugs, proton pump inhibitors, etc have also contributed to the development of the disease. Therefore, considering that some of these synthetic drugs which are routinely prescribed and used may promote the development of this disease, there is the need to consider alternative therapy from medicinal plants and herbs that can easily be part of our meals [20]. The present animal study showed that oral prophylactic use of aqueous leaf extract of *Ficus carica* L. at a dose of 2 mg/kg body weight for a period of three weeks significantly reduced the gastric acidity especially after fifteen and sixty minutes. The gastric acid secretagogue effect of histamine was also blunted by the administration of this extract with a significant reduction in gastric acidity compared with the control. Histamine secreted by the enterochromaffin-like cells of the gastric glands binds to the histamine receptors on the parietal cells to stimulate increase gastric acidity via the activities of the H+K+ ATPase proton pump [21, 22]. In contrast, proton pump inhibitors act directly on H+K+ ATPase proton pump which is the final step in acid secretion and therefore control acid secretion independent of the stimuli acting on the parietal cells [23, 24]. In the present result, there is the possibility that the extract of *Ficus carica* L. contains histamine receptor blockers or a proton pump inhibitor which may explain the reduction in the histamine stimulatory effect on gastric acidity. There are reports that plant extracts rich in flavonoids expressed H+-K+-ATPase proton pump inhibitory activities or increased PGE2 and mucus release from the gastric glands which could explain their anti-ulcerogenic action [25, 26]. We have previously reported the rich flavonoid presence in the

leaf extract of *Ficus carica* leaves as well as its anti-red cell membrane fragility activities in Plasmodium Berghei infected mice [14, 16]. The administration of cimetidine which is a histamine receptor blocker after pre-treatment with the extract produced a stronger and synergistic effect that further reduced significantly the gastric acidity below what was recorded in either of the extract or the cimetidine alone. Other authors have also reported the anti-ulcer activities of ethanol leaf extract *Ficus carica* L. against histamine induced peptic ulcer [27].

The aqueous leaf extract of *Ficus carica* L. also significantly shortened the transit time of food particles through the gastrointestinal conduit [Table 1]. This is in agreement with findings of Rtibi and colleagues [28] that *Ficus carica* increased gastrointestinal transit ratio. *Ficus carica* was reported to contain large quantity of calcium ions [29] which may have stimulated the increased segmentation contractions in the intestine [30, 31]. The increased intestinal motility was further confirmed by the significant increase in the peristaltic index observed in the extract treated group. The present findings may have justified the use of leaf extract as a laxative in traditional medicine and as previously reported [28]. Findings suggest that there is a significant delay in gastric motility in both the active and healed stages in patients with recurrent gastric ulcers [32] and ulcerative colitis [28]. Thus the increased intestinal motility as recorded in the AqLexFC treated rats in this study will also contribute to the reduction recorded in gastric acidity which becomes beneficial to preventing ulceration of the mucosa wall of the gastrointestinal system especially the stomach.

CONCLUSION

It can be concluded from the study that aqueous leaf extract of *Ficus carica* L. inhibits gastric acidity while promoting gastrointestinal motility in experimental rats.

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Table 1: Intestinal motility in rats treated with aqueous leaf extract of *Ficus carica L.* for three weeks and the control group that received equal volume of distil water

Time (min)	Control			AqLexFC		
	Intestine length (cm)	Intestinal length moved (cm)	% length moved	Intestine length (cm)	Intestinal length moved (cm)	% length moved
15	91.6 ± 0.80	0.50 ± 0.50	0.55 ± 0.55	85.61 ± 2.59	52.50 ± 0.50	61.40 ± 2.45*
30	93.40 ± 0.60	54.00 ± 1.00	48.19 ± 1.38	96.43 ± 0.87	61.40 ± 1.60	63.66 ± 1.08*
45	98.50 ± 0.50	90.00 ± 1.00	91.38 ± 1.48	98.50 ± 0.50	98.00 ± 0.00	99.49 ± 0.51*
60	105.50 ± 3.50	98.22 ± 0.18	93.21 ± 3.26	85.55 ± 0.54	85.45 ± 0.45	99.48 ± 0.41*

***** Significantly different compare to control at $p < 0.05$

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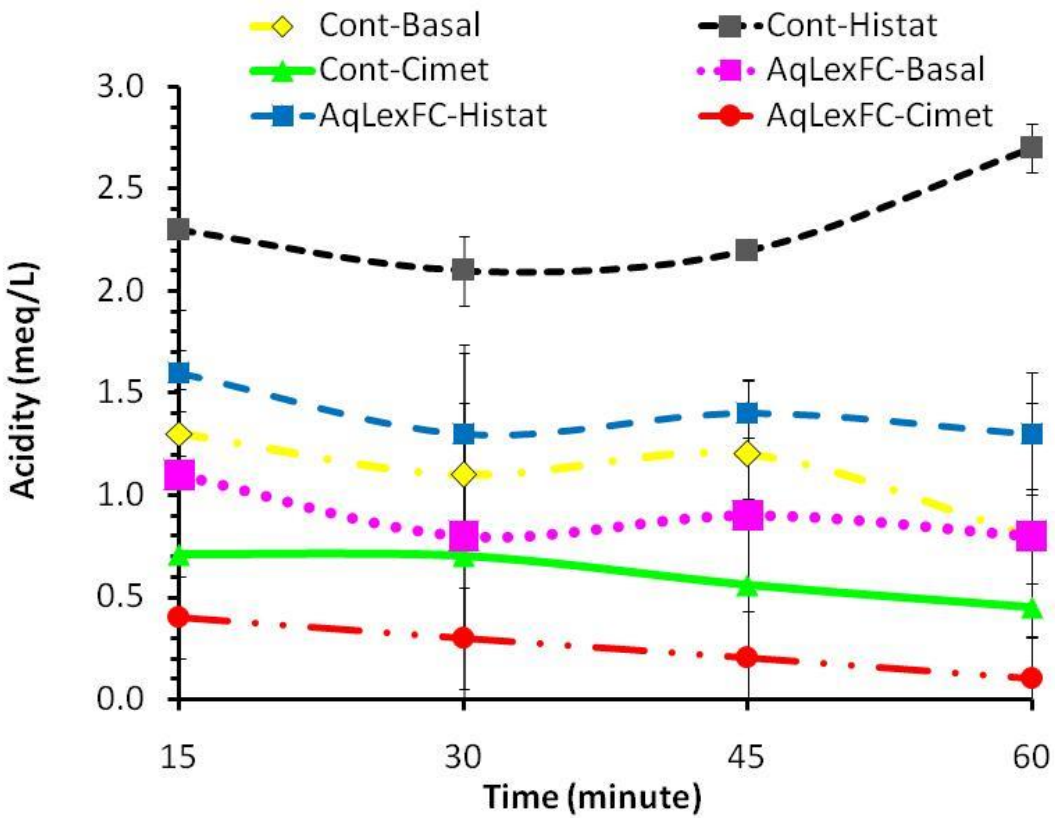

Figure 1: Acidity of gastric effluent collected from rats treated with aqueous leaf extract of *Ficus carica L. at* 2 mg/kg body weight for three weeks and the control group that received equal volume of distilled water before and after being challenged separately with histamine and cimetidine. . Results presented as mean ± SEM, $p < 0.005$

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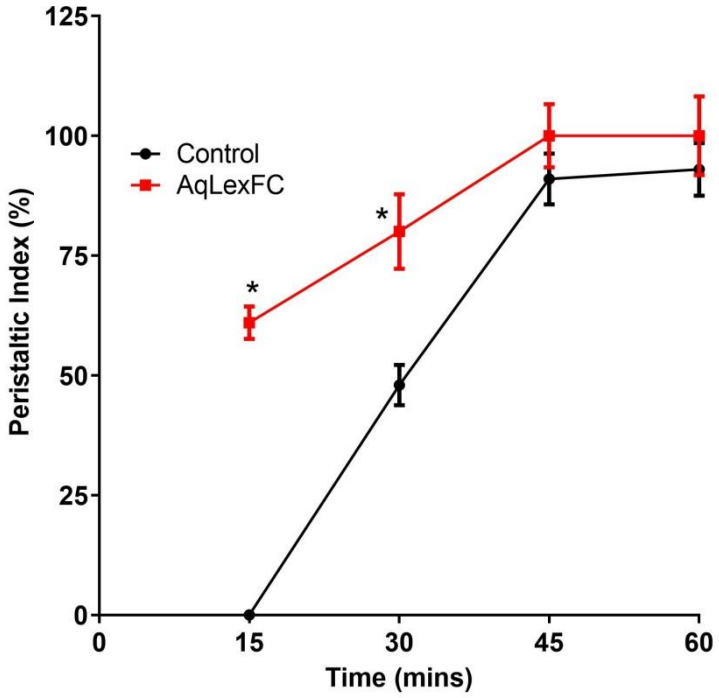

Figure 2: Peristaltic index in rats pre-treated orally with aqueous leaf extract of *Ficus Carica L.* for three weeks. * $p < 0.05$