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Inhibition of gastric acid secretion is a probable mechanism underlying the anti-ulcer activity of *Alchornea cordifolia* (Schumach. & Thonn.) Mull. Arg.

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Keywords

Gastric acid,
Alchornea cordifolia,
Anti-ulcer,
Inhibition

Abstract

This study was undertaken to investigate the possible mechanism of anti-ulcer action of the aqueous leaf extract of *Alchornea cordifolia* (ACAE) in male albino rats. Preliminary phytochemical analysis and acute toxicity study were carried out on the extract using standard methods. A total of thirty (30) rats were assessed for both basal and maximal (histamine-induced) gastric acid secretion and the effect of ACAE (200 mg/kg) on the acid secretion. Gastric acid output was measured by the continuous perfusion of rat's stomach under anesthesia with normal saline at the rate of 1 ml/min. Preliminary phytochemical analysis revealed the presence of phenols, flavonoids, glycosides, alkaloids, steroids, saponins, terpenes and tannins. Acute toxicity studies showed there were no deaths within 24 h after the administration of the extract up to a dose of 5000 mg/kg B.W (p.o). A significant ($P<0.05$) decrease in basal and histamine- induced gastric acid secretion was produced by the extract. It was concluded that inhibition of gastric acid secretion therefore, might be a probable mechanism of anti-ulcer action of the extract.

Introduction

The central role of gastric acid hypersecretion in the etiology of gastro-duodenal ulcers, gastro-oesophageal reflux disease and gastric cancer is well known. Thus, while ulcers are almost always present in patients with Zollinger-Ellison syndrome, which is characterised by excessively high gastric acid secretion, they are absent in achlorhydric patients. The gastric acid hypersecretion can be of stress or genetic origin but can as well result from the interaction between genetic components with environmental factors (Grossman, 1985; Edward, *et al.*, 1995). Outstanding findings in the understanding of peptic ulcer etiology include the discovery histamine H_2-receptors, the H^+K^+-ATPase-driven parietal cell pump by the end of the 1970s, and the more recent discovery of the role of *Helicobacter pylori* in the development of duodenal ulcer by Marshall and Warren, (1984). Corresponding breakthroughs in the treatment of acid-peptic disorders include the discovery of the prototypical H_2 antagonist, cimetidine in the mid to- late 1960s (Black, 1972), the development of proton pump inhibitors (Fellenius, 1981, and the development of the *H. pylori* triple therapy eradication regimens (Dixon *et al.*, 1996; McColl, 1998).

These drugs are quite effective but they are not without side effects. Dizziness, headache, vomiting, diarrhea have been associated with multiple therapy. Considering these challenges, there is a need for the development of safer compounds that could be used as a single therapy for inhibiting/ reducing gastric acid secretion. Aside from the issue of these side effects, the global upsurge in the use of herbs and herbal products is also largely due to the wide acceptability, accessibility and affordability of these herbs/ herbal products (Idakwoji and Uzuazokaro, 2018). In Nigeria, a number of medicinal plants have been reported but there is dearth of information as regards their mechanism of anti-ulcer action. Since acid secretory function of the stomach is critical to the pathogenesis of gastric ulcer, there is need to evaluate the acid secretory function of the stomach in response to oral administration of these plants (as a probable mechanism of action). This study was aimed at evaluating the gastric anti-secretory effect of the aqueous leaf extract of *Alchornea cordifolia* which is one of the plants with reported anti-ulcer effects.

A. cordifolia (Schumach. & Thonn.) Mull. Arg. belongs to the family Euphorbiaceae and is distributed in secondary forests usually near water, moist or marshy places. It grows to a considerable height but is always of a shrubby or scrambling habit. It has long stalked cordate leaves and flowers in hanging racemes about one foot long (Dalziel, 1956). The antimicrobial properties of crude extracts prepared from plants have been reported (Kubmarawa *et al.*, 2007). *A. cordifolia* leaf extracts have been reportedly used in various African countries such as Senegal in the treatment of venereal diseases, conjunctivitis, dermatoses, stomach ulcers, bronchitis, cough, toothache (Le Grand and Wondergem, 1987; Le Grand, 1989). In Nigeria for gonorrhoea, yaws, rheumatic pain and cough (Gbile and Adeshina, 1986; Ogungbamila and Samuelson, 1990). Extracts from leaves of *A. cordifolia* have been reported to inhibit the growth of bacteria such as *Staphylococcus aureus, S. albus, Escherichia coli, Bacillus sp* and *Pseudomonas aeruginosa* (Ebi, 2001). Anti-inflammatory activities of *A. cordifolia* have also been reported (Osadebe and Okoye, 2003; Manga *et al.*, 2004).

Materials and Methods

Materials

Chemicals and drugs

All chemicals and drugs used in this study were of analytical grade and were purchased from Sigma Chemical Co. Ltd (USA) through a local vendor. Cimetidine (H_2- receptor antagonist) was purchased from a local pharmacy shop.

Animals

Male adult wistar rats weighing 180–220g were used for this study. They were kept in stainless steel cages under standard laboratory conditions. They were maintained on clean water and standard rodent feed.

Methods

Plant Collection and Identification

The leaves of *Alchornea cordifolia* were collected from a natural habitat in Agbeji Area of Kogi State, Nigeria. The plants were identified at the herbarium unit of Biological Sciences Department, Federal University, Lokoja and voucher specimens were deposited for future references.

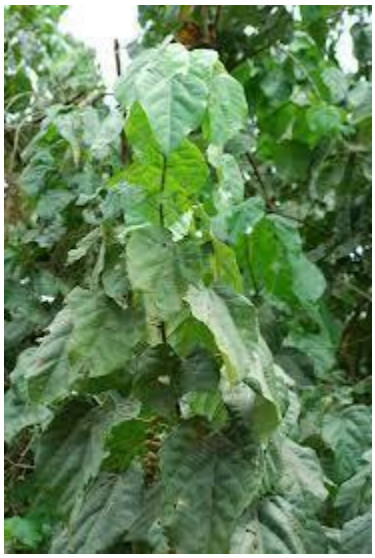

Figure 1: *Alchornea cordifolia*

Preparation of Extract

The leaves of the plant were shade- dried for seven (7) days and pulverized using an electric blender. One thousand and five hundred (1500) gram of the pulverized leaves was soaked in distilled water for 48h. The resulting mixture was filtered using Whatmann filter paper (Size No1) and the extract was concentrated using a free- dryer. The resulting extract was labelled 'ACAE' and preserved in the refrigerator till when required for experiment.

Phytochemical analysis of Extract

The extract was subjected to phytochemical screening adopting the standard methods described by Sofowora (1993).

Acute Toxicity Study

The oral median lethal dose (LD50) of the extract was determined in rats according to the method of Lorke (1983).

Experimental Design

A total of thirty (30) rats were assessed for both basal and maximal (histamine-induced) gastric acid secretion.

Gastric acid secretion in situ

The effects of ACAE (200 mg/kg) on basal and histamine-induced gastric acid secretion in albino rats were studied as described by Ghosh and Schild, (1958), modified by Amure and Ginsburg, (1964). This was used together with the titration method described by Olowokorun, (1975). Thirty (30) male albino rats were randomly divided into 6 groups (n=5) rats each. Adult male rats (180–250 g) fasted for 24h were anesthetized with an i.p injection of 0.6 ml/100 g of 25% urethane (ethyl carbamate). The femoral vein, esophagus and pyloro-duodenal junction were cannulated. The stomach was perfused with normal saline (37°C) and gastric effluent was collected at a constant rate of 10 ml/10 min. The effluent was titrated against M/400 (NaOH) solution with phenolphthalein as indicator. The effects of ACAE (200 mg/kg) alone and in combination with histamine and/or cimetidine, on gastric acid secretion were studied. Titrable acidity was expressed in μEq/L/10mins. The histamine-induced gastric acid was collected 30 minutes post-surgery at which time a steady (basal) acid secretion had been obtained.

Statistical analysis

Results were expressed as mean ± S.E.M. The data were statistically evaluated by one way ANOVA. Comparison between treatment and control group were made by Student's t- test, then followed by Fisher's exact. Significance of difference was accepted at $P < 0.05$ using Graph-Pad Prism version 5.00 for Windows (Graph Pad Software, San Diego, California, USA).

Results

Results showed the presence of phenols, flavonoids, alkaloids, steroids, glycosides, terpenes tannins and saponins but in different proportions (Table 1).

Table 1: Qualitative Phytochemical Composition of the Aqueous Extract of *Alchornea cordifolia* Leaves (ACAE)

Phytochemicals	ACAE
Phenols	+++
Flavonoids	++
Alkaloids	+++
Steroids	+++
Glycosides	+
Terpenes	++
Tannins	+++
Saponins	+++

Key: + Slightly present, ++ moderately present, +++ highly present

Acute Toxicity

The results of acute toxicity studies showed no sign of toxicity or mortality up to a dose of 5000 mg/kg of ACAE (Table 2). The oral LD_{50} was then taken to be > 5000 mg/kg for the extract.

Table 2: Observed Effects of the Aqueous Extract of *Alchornea cordifolia* Leaves (ACAE) on Rats

Phase	Group	Treatment (mg/kg)	D/T	Observed Sign of Toxicity
I	1	ACAE (10)	0/3	-
	2	ACAE (100)	0/3	-
	3	ACAE (1000)	0/3	-
II	1	ACAE (1600)	0/1	-
	2	ACAE (2900)	0/1	-
	3	ACAE (5000)	0/1	-

Key: D= Number of deaths, T= Number of treated animals

Gastric Acid Secretion in Rats

As shown in Table 3, ACAE produced a significant ($P<0.05$) decrease in basal and histamine- induced gastric acid secretion in rats. The effect of the extract was comparable to that of the standard drug-cimetidine. Moreover, the co-administeration of the extract and cimetidine also produced a significant ($P<0.05$) inhibition of gastric acid secretion in a manner suggestive of additive interaction.

Table 3: Effects of the Aqueous Extract of *Alchornea cordifolia* Leaves (ACAE) on Gastric Acid Secretion in Rats

Groups	Pre-treatment	Basal acid output (µEq/L/10mins)	Gastric acid secretion (µEq/L/10mins)
1	Normal saline (5 ml/kg)	1.55±0.09	1.58±0.09
2	Extract (200 mg/kg)	1.48±0.10	1.05±0.02*
3	Histamine (100 mg/kg)	1.50±0.08	6.22±0.43*
4	Histamine + Extract	1.53±0.11	3.04±0.17*
5	Cimetidine (32 mg/kg)	1.55±0.14	1.04±0.29*
6	Cimetidine + Extract	1.46±0.07	0.77±0.05*

* Significant. Values are expressed as mean ± SEM, n=5.*P<0.05 compared with the negative control.

Discussion

This research work was designed to investigate the gastric acid anti-secretory effects of aqueous leaf extract of *A. cordifolia* in Wistar rats. Preliminary phytochemical analysis of the extract identified phenols, flavonoids, glycosides, saponins, tannins and terpenes as the major components. Flavonoids are reported to be responsible for the anti-ulcerogenic efficacy of many plants as they are regarded as cytoprotective materials (Di Carlo, 1999; Borelli & Izzo, 1999; Galati *et al.,* 2001). It is suggested that, these active compounds stimulate mucous, bicarbonate, and the prostaglandin secretion and counteract with the deteriorating effects of reactive oxidants in gastrointestinal lumen (Salvayre *et al.,* 1982; Asuzu & Onu, 1990; Suja & Anuradha, 2002). Tannins are also known to affect the integrity of mucosa membrane. Tannins being astringent may precipitate micro-proteins in the site of ulcer thus preventing absorption of toxic substances by forming a protective layer and resisting the mucous layer against the attack of proteolytic enzymes (Bigoniya *et al.,* 2006). Saponins protect stomach mucosa from acid by selectively inhibiting prostaglandin F2 (PGF2), which causes vasoconstriction of mucosal blood vessels (Aguwa and Okunji, 1986). Presence of these phytochemical components might be responsible for the reported anti-ulcer effect of the extract.

In this study, we carried out an acute toxicity study on *A. cordifolia* to establish its safety. Results revealed that up to a dose of 5000 mg/kg, the extract did not produce mortality or any sign of toxicity. That is to say the extract has a wide margin of safety and thus administration as done in folk medicine may not have any immediate deleterious effects. This observation is an edge over the orthodox anti-ulcer drugs which usually come with side effects especially when administered at high doses. Further studies are however recommended to ascertain the safety of the extract when used for a longer period of time.

Gastrin acts on parietal cells directly and indirectly too, by stimulating the release of histamine. Histamine induces gastric acid secretion by binding directly to H_2-receptors on parietal cell. When stimulated, adenylate cyclase increases the cAMP which in turn activates protein kinase A. The activation of this pathway stimulates the proton pump in the parietal cell, and results in acid secretion (Jain *et al.,* 2007). The release of histamine is the most important positive regulation mechanism of the secretion of gastric acid in the stomach. Its release is stimulated by gastrin and acetylcholine and inhibited by somatostatin. The significant reduction in total gastric acidity observed in this study strongly suggests that *A. cordifolia* may act by inhibiting gastric acid secretion. Moreover, this extract inhibited basal and histamine-induced acid secretion and seems to augment the inhibitory action of cimetidine (an H_2-receptor blocker) on gastric acid secretion. These findings indicate that the extract probably acts by inhibiting H_2-receptor leading to blockade of histamine release whose stimulatory action on gastric acid secretion via H_2-receptor, has been well reported (Berglindh, 1977; Dial *et al.,* 1981; Bottcher *et al.,* 1989). There is, however, the possibility of the involvement of other receptors, which are yet to be investigated.

Conclusion

This study further confirmed the anti-ulcer potentials of the aqueous leaf extract of *A. cordifolia* by revealing its inhibitory effect on gastric acid secretion. Inhibition of gastric acid secretion therefore, might be a probable mechanism of anti-ulcer action of the extract.

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