American Journal of Biomedical Research, 2016, Vol. 4, No. 1, 13-17
Available online at http://pubs.sciepub.com/ajbr/4/1/3

DOI:10.12691/ajbr-4-1-3

Assessment of Anti-ulcer Efficacy of Stem Bark Extract of *Nauclea latifolia* (African Peach) in Rats

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Abstract **Aims:** *Nauclea latifolia* Sm. (Rubiaceae) is known for its therapeutic uses, especially in alternative medicine. Its leaves, roots and bark have been used traditionally in Nigeria to treat various diseases including ulcer-related diseases. **Methods:** The aqueous stem bark extract of *Nauclea latifolia* was investigated for anti-ulcerogenic effects using ethanol/HCI and indomethacin as the ulcerogens. The effect of the extract on gastric mucous secretion was also investigated. The extract was administered orally at the doses of 100 and 200 mg/kg b. wt. for the experimental groups while the control and reference groups received distilled water (2 ml/kg, p.o) and omeprazole (20 mg/kg, p.o) respectively. **Results:** Phytochemical studies revealed the presence of saponins, tannins, alkaloids, terpenes and glycosides. The results show that the extract significantly ($p < 0.05$) reduced the ulcer index from 4.55 ± 1.45 to 1.20 ± 0.19 and from 4.20 ± 0.72 to 0.94 ± 2.51 in the ethanol/HCI and indomethacin induced ulceration respectively. The extract also significantly ($p < 0.05$) increased the gastric mucous secretion in a dose-dependent manner. **Conclusions:** The results suggest that the *N. latifolia* stem bark extract possesses significant anti-ulcer effects which might be due to its ability to increase gastric mucous secretion.

Keywords: *Nauclea latifolia, anti-ulcerogenic, indomethacin, phytochemical screening, gastric mucous, rats*

Cite This Article: Morufu Eyitayo Balogun, Daniel Chukwu Nwachukwu, Shakiru Ademola Salami, Elizabeth Enohnyaket Besong, Dorathy Chinwe Obu, and Serges Fankou Athanase Djobissie, "Assessment of Anti-ulcer Efficacy of Stem Bark Extract of *Nauclea latifolia* (African Peach) in Rats." *American Journal of Biomedical Research*, vol. 4, no. 1 (2016): 13-17. doi: 10.12691/ajbr-4-1-3.

1. Introduction

Peptic ulcer is the most common gastrointestinal abnormality [1] and is produced when there is an imbalance between the amount of acid secreted and the mucous defense barrier, allowing the acids to damage the stomach mucosal epithelium [2,3,4]. This imbalance may be caused by increased acid-pepsin secretion, impaired bicarbonate neutralization, impaired mucous secretion, infection with helicobacter pylori and lifestyle such as alcohol consumption, cigarette smoking and excessive intake of non steroidal anti-inflammatory drugs [5,6]. Although many antiulcer drugs such as histamine (H_2) receptor antagonists, proton pump inhibitors and cytoprotectants are used for ulceration, there have been reports of harmful effects and limitations [7,8].

Medicinal plant research has been on the increase worldwide providing numerous evidences to show great potentials of medicinal plants used in various traditional system of medicine [9]. In addition, over 80% of people in developing countries such as Nigeria use herbal medicines as first line of choice in the treatment of diseases [10]. This has been attributed to the cheapness, availability and accessibility of these natural drugs. Furthermore, the cost of orthodox medicines has put them beyond the reach of many people, particularly, in resource poor countries [11,12]. Several medicinal plants have been reported to possess antiulcer properties that enhance gastric mucosal defense factors (mucous and bicarbonate) [13]. Moreover, these medicinal plants are able to reduce aggressive factors (acid and pepsin) secretions and have proven to be safe, effective and show better patient tolerance. They are also less expensive and therefore globally competitive.

Nauclea latifolia (*N. latifolia*) belongs to the family Rubiaceae. It is a pin cushion tree being a straggling shrub or small tree; native to the tropical Africa and Asia [14]. It bears an interesting flower, large red ball fruit with long projecting stamens. It grows up to an altitude of 200 meters. It is widespread in the humid tropical rainforest zones or in the savannah woodland of West and Central Africa [15]. In Nigeria, different tribal groups have their indigenous names as "Ubulu inu" among the Igbo in the Eastern part of Nigeria; as "Tafashiya" among the Hausas in the Northern part of Nigeria; as "Egbesi" among the Yoruba in the Western part of Nigeria and as "Itu" among the Itsekiri [16]. In West and South Africa, infusions and decoctions of the stem bark and leaves of *N. latifolia* are used for treatment of stomach pain, fever, diarrhea and constipation [17]. The sticks are used as chewing sticks

and a remedy against tuberculosis [18]. Previous studies have reported hypolipidemic and hypoglycemic effects of the plant extracts [19, 17]. The phytochemical constituents like flavonoids, saponins, tannins, terpenes, and alkaloids have been reported in several anti-ulcer literatures as possible gastro protective agents. Flavonoids, tannins and triterpenes are among the cytoprotective active materials for which anti ulcerogenic efficacy has been confirmed [20,21,22]. We had previously reported on the anti-ulcer and gastro protective activities of the leaf extract of *N. latifolia* [23,24], however, there is paucity of information on the use of the stem bark extract for the management of gastric ulcers. Thus, the present study was undertaken to investigate the anti-ulcerogenic potentials of the aqueous stem bark extract of the plant using ethanol/HCI and indomethacin as the ulcerogenic agents. This is with a view to providing a pharmacological justification (or, otherwise) for the ethnomedical uses of the stem bark in the management, control and treatment of gastric ulcers.

Figure 1. Plant of *Nauclea latifolia* (smith).

Figure 2. Plant of *N. latifolia* Herbarium specimen (FHI. 110284)

2. Methodology

2.1. Drugs, Chemicals and Reagents

All chemicals, drugs and reagents used in this investigation were of analytical grade. All chemicals and reagents were purchased from Sigma Chemical Company (St. Louis, U.S.A.). All test drugs and reagents were freshly prepared before use. Omeprazole (proton pump inhibitor) was used as the reference anti-ulcer drug.

2.2. Preparation of Drugs

Omeprazole: Omeprazole (Globela Pharma PVT. Ltd, India) was purchased from Godal Pharmacy in Abakaliki. The dose administered was 20mg/kg b. wt. suspended in distilled water (2ml/kg) orally before ulcer induction [25].

Indomethacin: Indomethacin (Embassy Pharmaceutical and Chemical Ltd) was purchased from Godal Pharmacy, Abakaliki, Nigeria. The dose used for ulcer induction was 10mg/kg b. wt. administered orally [26].

2.3. Experimental Animals

Male albino rats of Wistar strain weighing between (180 to 220 g) obtained from the Animal Unit, Faculty of Medicine, Ebonyi State University, Abakaliki, Nigeria were used for the experimental studies. They were maintained under standard laboratory conditions and were fed with commercially formulated rat's pellets (Pfizer Livestock Feeds PLC, Abakaliki, Nigeria) and tap water ad libitum. Excess feeds and water were removed and replaced daily. The experimental procedures and techniques used in the study were in accordance with accepted principles for laboratory animal use and care by the National Institute of Health [27]; all protocols and procedure were approved by Institution Animal Ethics Committee (IAEC) of the University with reference number (EBSU/REC/BM14/032).

2.4. Collection of Plant Materials

The fresh stem bark of *N. latifolia* Sm. was collected from their natural habitat in Iseyin town, Oyo State, Nigeria in the month of June, 2014. The plant specimen was identified and authenticated by Mr. K. A. Adeniji in the herbarium of the Forestry Research Institute of Nigeria (FRIN) Ibadan. A voucher specimen (FHI. 110284) was also deposited in the Herbarium of the institute.

2.5. Preparation of the Plant Extract

The stem bark was air dried and milled to fine powder. 250 g of the powdered bark was evaporated by cold maceration using 1 L of distilled water. The mixture was evaporated in a carefully regulated water bath (maintained at 65°C to yield 23.8 g of a dark solid extract. The extract was stored in a refrigerator at 4°C through the period of the study to preserve the prepared extract. The resulting residue was reconstituted in sterile distilled water to give the required doses of 100 and 200 mg/kg/2 ml body weight, respectively [28]. The dosages were prepared fresh on the day of experiments prior to the administration.

2.6. Preliminary Phytochemical Screening

The aqueous stem bark extract was subjected to various qualitative phytochemical tests, to identify the secondary metabolites; saponins, tannins, terpenes, steroids, alkaloids, flavonoids, glycosides and anthraquinones present in the stem bark using standard phytochemical procedures and tests [29].

2.7. Acute Toxicity Studies

Acute toxicity study was carried out to determine the median lethal dose (LD_{50}) using the modified method of Miller and Tainter as described by Jigam *et al*. [30].

2.8. Experimental Design

Sixty-four animals in total were used for the experiment. The animals were divided into two groups of 32 animals each following two experimental models (ethanol/HCI and Indomethacin-induced ulcer models). In each experimental model, animals were further subdivided into four groups of four animals each for study on ulcerogenesis and gastric mucous secretion. Group 1 and 2 received distilled water (2 ml/kg, negative control) and omeprazole (20 mg/kg, positive control) respectively. Groups 3 and 4 were given 100 and 200 mg/kg b. wt. of *N. latifolia* respectively and administration was orally for all groups.

2.9. Ethanol/HCl-induced Ulcer

Gastric ulcer was induced according to the method described by Mizui and Douteuchi [31]. Ulceration was induced in 24 h fasted rats by the oral administration of 1mL of ethanol/hydrochloric acid (0.3m HCl in 60% ethanol) 30 minutes after the extract of *N. latifolia* (100 and 200mg/kg), omeprazole (20 mg/kg) and distilled water (2 ml/kg) were administered. The animals were sacrificed 1 h after the ethanol-acid administration. The abdominal cavities and subsequently the stomachs of the animals were dissected out and examined for gastric ulcers. The ulcer score was calculated for each animal according to the scale used by Singh *et al*. [32], where 0 = no lesion, 1 = hyperemia, 2 = one or two slight lesions, 3 = very severe lesions, 4 = mucosal full of lesions. Ulcer index was calculated as mean ulcer scores [33].

2.10. Indomethacin-induced Ulcer

Indomethacin-induced ulcer was carried according to the method described by Parmar and Desai [26]. Food was withdrawn 24 hours and water one hour before drug treatment. Indomethacin 10 mg/kg (dissolved in 5% sodium bicarbonate solution) was administered (orally) 30 min after the extract of *N. latifolia* (100 and 200 mg/kg), omeprazole (20 mg/kg) and distilled water (2 ml/kg) administration. Administration of indomethacin was repeated after 15 h. All the rats were sacrificed 1 h after the last dose of indomethacin and the stomachs were dissected in order to evaluate the level of mucosal damage. The ulcer index was determined as described earlier in ethanol-acid induced ulcers.

2.11. Determination of Gastric Mucous Contents

Gastric wall mucus content was determined by the method described by Corne, *et al.* [34] with slight modifications. The glandular portions of stomachs from all the animals of untreated control and treated groups were collected and weighed. The segments were immediately transferred to the 1% alcian blue solution in 10% sucrose. Thus, glandular mucous was allowed to complex with alcian blue for 10min. The excess dye of each segment was removed by rinsing with sucrose solution and complexed dye was extracted for 15min in 5ml of 5% magnesium chloride solution, which was then shaken with equal volume of diethyl ether. The resulting emulsions were centrifuged at 4000rpm for 15min and the absorbencies of the aqueous layers were measured at 580nm using a Spectrophotometer. The quantity of alcian blue extract per gram wet stomach was then calculated from a standard curve.

2.12. Statistical Analysis

The data were statistically evaluated by one way ANOVA. Comparison between treatment and control group were made by Student's t- test then followed with Fisher's exact. Differences between groups were considered significant at $P<0.05$ using Graph pad Instat 3.10.

3. Results

3.1. Phytochemical Screening

The results of preliminary phytochemical studies indicate that the extract contains saponins, tannins, alkaloids, terpenes and glycosides (Table 1).

Table 1. Secondary plant metabolites found in stem bark extract of *N. latifolia*

Secondary Metabolites	Stem bark (AE)
Glycosides	++
Anthraquinones	-
Flavonoids	-
Alkaloids	++
Terpenes	++
Saponins	++
Steroids	-
Tannins	++

AE = Aqueous extract; **++** = presence of the compound; **-** = compound not detected; **+** = trace amount of compound

3.2. Acute Toxicity Studies

The median lethal dose (LD_{50}) was determined to be 1,789 ± 0.02 mg/kg.

Table 2. Effects of *N. latifolia* extract on ulcer induced by ethanol/HCl in rats

Group	Treatment	Dosage (p.o.)	Mean Ulcer Index ± SEM	Percentage protection (%)
1	Distilled water	2 ml/kg	4.55 ± 1.45	0.00
2	Omeprazole	20 mg/kg	1.24 ± 0.10*	72.75
3	Extract	100 mg/kg	1.52 ± 0.25*	66.59
4	Extract	200 mg/kg	1.20 ± 0.19*	73.63

*Significant. All values are expressed as mean ± S.E.M; n = 4 in each group. *$P < 0.05$ as compared with the negative control animals.

Percentage inhibition to ulcer formation in rats by the extract was calculated as follows:

$$\% \text{ Inhibition of Ulceration} = \frac{(\text{Ulcer Index Control} - \text{Ulcer Index Test})}{\text{Ulcer Index Control}} \text{x}100\%.$$

3.3. Anti-ulcer Activity

The results of the anti-ulcer studies are shown in Table 2 and Table 3. Table 2 shows that the extract of *N. latifolia* significantly ($p<0.05$) reduced the ulcer index from 4.55 ± 1.45 (control) to 1.20 ± 0.19 (200mg/kg) in the ethanol/HCl induced ulceration group. Similarly as shown in Table 3, the extract significantly ($p<0.05$) reduced the ulcer index from 4.20 ± 0.72 (control) to 0.94 ± 2.51 (200mg/kg) in the indomethacin-induced ulceration group. Pre-treatment with omeprazole and the extract significantly

($p<0.05$) reduced the severity of ethanol/HCl and indomethacin-induced ulcers. The protective effects of the extract as shown in Table 2 and Table 3 were dose-dependent.

Table 3. Effects of *N. latifolia* extract on ulcer induced by indomethacin in rats

Group	Treatment	Dosage (p.o.)	Mean Ulcer Index ± SEM	Percentage protection (%)
1	Distilled water	2 ml/kg	4.20 ± 0.72	0.00
2	Omeprazole	20 mg/kg	0.99 ± 0.14*	76.43
3	Extract	100 mg/kg	1.12 ± 0.02*	73.33
4	Extract	200 mg/kg	0.94 ± 2.51*	77.62

*Significant. All values are expressed as mean ± S.E.M; n = 4 in each group. $^{*}P < 0.05$ as compared with the negative control animals.
Percentage inhibition to ulcer formation in rats by the extract was calculated as follows:

$$\% \text{ Inhibition of Ulceration} = \frac{(\text{Ulcer Index Control} - \text{Ulcer Index Test})}{\text{Ulcer Index Control}} \text{x}100\%.$$

3.4. Gastric Mucous Studies

N. latifolia stem bark extract produced a significant ($p<0.05$) and dose dependent increase in gastric mucous production in the ethanol-acid and indomethacin induced gastric ulcers groups as compared to control (Table 4 and Table 5). The effect of the aqueous extract on gastric mucous secretion was more pronounced in indomethacin induced gastric ulcers groups (Table 5).

Table 4. Effects of *N. latifolia* extract on gastric mucous secretion in ethanol/HCl induced gastric ulceration in rats

Group	Treatment	Dosage (p.o.)	Mucous content (µg Alcian blue/g wet stomach)
1	Distilled water	2 ml/kg	0.26 ± 2.51
2	Omeprazole	20 mg/kg	0.78 ± 0.25*
3	Extract	100 mg/kg	0.60 ± 1.52*
4	Extract	200 mg/kg	0.72 ± 0.04*

*Significant. All values are expressed as mean ± S.E.M; n = 4 in each group. $^{*}P < 0.05$ as compared with the negative control animals.

Table 5. Effects of *N. latifolia* extract on gastric mucous secretion in indomethacin-induced gastric ulceration in rats

Group	Treatment	Dosage (p.o.)	Mucous content (µg Alcian blue/g wet stomach)
1	Distilled water	2 ml/kg	0.21 ± 1.25
2	Omeprazole	20 mg/kg	0.84 ± 0.07*
3	Extract	100 mg/kg	0.68 ± 0.10*
4	Extract	200 mg/kg	0.79 ± 0.22*

*Significant. All values are expressed as mean ± S.E.M; n = 4 in each group. $^{*}P < 0.05$ as compared with the negative control animals.

4. Discussion and Conclusion

In this study, the anti-ulcer effects of the aqueous stem bark extract of *N. latifolia* was investigated using two experimental models (ethanol-acid and indomethacin induced gastric ulcer) in albino rats. The results of the toxicity study suggest that the extract has a wide margin of protection and thus administration as done in folk medicine may not have any immediate adverse effects. The findings of the present study demonstrated that aqueous extract of *N. latifolia* significantly protected against mucosal damage induced by ethanol-acid and indomethacin. The curative ratios of plant extracts at 100 and 200mg/kg were 66.59% and 73.63% respectively in ethanol-acid induced gastric ulceration. In the indomethacin-induced ulceration the protective ratios of the extracts at 100 and 200mg/kg were 73.33% and 77.62% respectively. It is remarkable that the stem bark extract at 200mg/kg dose produced a greater protection than omeprazole (20 mg/kg) against the ethanol-acid and indomethacin. The effect of the extract compared favorably to omeprazole 20 mg/kg (positive control). However, the mechanisms by which the stem bark extract of *N. latifolia* produced its gastro protective effects in rats are not fully clear. It has been shown that ethanol-acid induced ulcer model represents a form of gastric irritation resulting from the inhibition of prostaglandins synthesis. Indomethacin is a non-steroidal anti-inflammatory drugs which produces their effects by inhibiting prostaglandins synthesis [35,36]. Increase in prostaglandins particularly PGE_2 and PGI_2 has been associated with cytoprotection [37,38]. Therefore, agents that inhibit the effects of non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin will exhibit cytoprotection. The results obtained from using the indomethacin ulcer model showed that the extract may significantly inhibit the aforementioned gastric effect of indomethacin and thereby enhance cytoprotection. Generally, the activities of the extract may not be unconnected with its secretory ability since gastric mucous production was significantly increased by the extract. Usually some substances like the NSAIDS produce gastric mucosal irritation in addition to various degrees of analgesic, anti-inflammatory and antipyretic effects [36,37]. Stem bark extract of *N. latifolia* has been shown to contain phytochemical constituents like saponins, tannins, alkaloids and terpenes which are capable of promoting gastric mucosal formation; reduce gastric acid secretion and inhibit pepsinogen production thereby reducing gastric lesions and ulcers [20,21]. Flavonoids, tannins and triterpenes are among the cytoprotective materials for which antiulcerogenic efficacy has been extensively confirmed [22,39]. It has been suggested that these compounds will be able to stimulate mucous, bicarbonate and the prostaglandin secretion. Furthermore, they have been reported to counteract the deleterious effects of reactive oxidants in gastrointestinal lumen [40,41]. Saponins, especially triterpenes type have been implicated in antiulcer activity mediated by formation of protective mucous on the gastric mucosa and also protect the mucosa from gastric acid effects by selectively inhibiting prostaglandin F 2α (PGF2α) [42,43]. It is very possible that the decrease in gastric ulceration, with concomitant increase in the gastric mucous secretion produced by the extract in this study could be due to the presence of these components or some other mechanisms yet unidentified. Hence, further studies are needed to elucidate the gastro protective mechanism(s) of *N. latifolia* plant. In conclusion, the overall findings of this study show that the stem bark extract of *N. latifolia* possesses anti-ulcer activity mediated possibly via increase in gastric mucous secretion. This provides a novel scientific basis for its use as an anti-ulcerogenic agent in traditional medicine.

Acknowledgements

We acknowledge the technical assistance of Messrs Paul Okike and Moshood A. Folawiyo of the Department

of Physiology, Faculty of Medicine, Ebonyi State University, Abakaliki.

Authors' Contributions

This work was carried out in collaboration between all authors. Author MEB, DCN and SAS designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript and managed literature searches. Authors EEB, DCO and SFAD managed the analyses of the study and literature searches. All authors read and approved the final manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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