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Ulcer protective effect of *Byrsocarpus coccineus* leaf extract in different experimental animal models

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ABSTRACT

Objective: To evaluate the antiulcer activity of ethanolic leaf extract of *Byrsocarpus coccineus*, a plant used in herbal medicine for the management of various diseases in Nigeria.
Methods: Ethanol-, acetylsalicylic acid-, histamine- and water immersion stress-induced gastric ulcers in rats were used to investigate the antiulcer activity of the leaf extract. Acute toxicity studies were also carried out.
Results: The ethanolic leaf extract significantly ($P < 0.05$) reduced the ulcer index in all assays used with the maximal antiulcer activity recorded at 400 mg/kg. The LD_{50} values obtained were greater than 5 000 mg/kg in rats.
Conclusions: The implication of this finding is that *Byrsocarpus coccineus* ethanolic leaf extract possesses potent antiulcer activity and the leaf of this plant can serve as a potential source of safe and affordable antiulcer agents.

1. Introduction

The epithelium of gastric mucosa is constantly exposed to potentially harmful agents including gastric acid, bile acid, bacterial products and certain drugs. This exposure can result in gastric ulcer, which is the most prevalent intestinal disorder[1,2]. Different factors such as the infection of stomach by *Helicobacter pylori*, alcohol, cigarette smoking and frequent use of non-steroidal anti-inflammatory drugs can lead to the formation of gastric ulcers[3,4]. Anxiety, emotional stress and trauma can also result in gastric irritation[5]. The roles of oxidative stress and free radicals have been implicated in aetiology of gastrointestinal disorders[6]. Peptic ulcer disease can be prevented by enhancing the defensive mechanisms of gastric mucosa rather than targeting factors of aggression causing ulceration. Although the commercially available antiulcer drugs are effective in the treatment of gastric ulcer, they are associated with various side effects. There are attempts to search for more effective antiulcer agents from plants and animal products. Studies have shown that various bioactive substances from plants not only afford gastroprotection but also improve ulcer healing[7]. The plant *Byrsocarpus coccineus* (*B. coccineus*) is a scadent shrub widely distributed in many African countries. It is widely used in ethnomedicine for the treatment of diverse diseases such as skin diseases, tumors, rheumatic pains, jaundice and dysentery[8]. The plant possesses oxytocic, antioxidant, antidiarrhoeal, antimicrobial, analgesic, anti-inflammatory and antipyretic properties[9-12]. The aim of the present study is to evaluate the activity of ethanolic leaf extract of *B. coccineus* on gastric mucosal damage by using models of different types of ulcers.

2. Materials and methods

2.1. Plant collection

The fresh leaves of *B. coccineus* identified by a taxonomist were

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collected in July 2010 in north and central Nigeria. Specimen number NIPRD/H/6406 was maintained in the Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and Development, Abuja, Nigeria. The international plant number index is Connaraceae *B. coccineus* Schem. and Thonn. Beskr. Guin. Pl. 226. 1827(IK). The collected leaves were later cut into pieces, air-dried at room temperature and ground to dry powder by using a mortar and pestle.

2.2. Extraction

A total of 330 g of the leaf powder was macerated in ethanol for 24 h. The resultant filtrate was dried on a water bath at reduced temperature to obtain 35.44 g extract (10.74% w/w). The extract was stored in an airtight container till used for the experiment.

2.3. Phytochemical analysis

Phytochemical screening was carried out by using standard methods for detecting the presence of secondary metabolites like alkaloids, steroids, flavonoides, terpenoids, tannins and saponins[13,14].

2.4. Acute toxicity studies

The acute toxicity studies of ethanolic leaf extract of *B. coccineus* were conducted according to the guidelines set by Organization for Economic Cooperation and Development[15]. The studies were done in two phases. In the first phase, nine rats were randomized and divided into three groups. The rats in each group were orally administered with 100, 600 and 1 000 mg/kg of the leaf extract, respectively. The animals were observed in the first 4 h and 24 h for the signs of toxicity and mortality. This was followed by the second phase in which 2 000, 3 000 and 5 000 mg/kg of the extract was administered to the other three groups with three rats per cage. The signs of toxicity and mortality were observed for 24 h, 48 h and 72 h respectively.

2.5. Animals

Ninety adult Albino rats (200–250 g) of both sexes acclimatized in animal house of Department of Pharmacology and Therapeutic, Ebonyi State University, Abakaliki, Nigeria were used in the study. Animals were grouped and housed in cages with no more than six rats per cage and allowed access to standard pellets and water. The National Institutes of Health Guide for Laboratory Animal Care and Use approved by the Institutional Ethical Committee was adopted for the study[16].

2.6. Ethanol-induced ulcers

The method of Akuodor *et al*. was used to induce gastric ulcers in rats by ethanol[17]. Adult albino rats (200–250 g) fasted for 24 h and were divided into 5 groups with 6 rats per cage. Group 1 (control) was treated with 20 mL/kg of normal saline. The ethanolic leaf extract of *B. coccineus* (100, 200 and 400 mg/kg) were administered to Groups 2, 3 and 4 respectively, while Group 5 was administered with the standard drug ranitidine (20 mg/kg). All were administered by oral route. After 60 min, gastric ulcers were induced by 1 mL of 90% ethanol orally (via cannula). One hour later, animals were all sacrificed by ether anaesthesia and their stomaches were removed and examined for ulcers.

2.7. Aspirin-induced ulcers

The procedure of aspirin-induced ulcers as described by Kannappan *et al*. was adopted[18]. Animals were kept fasting for 48 h and had an access to water before the experiment. Rats for the study were later divided into 5 groups with 6 per cage. Group 1 (control) was treated with 20 mL/kg normal saline, while the extract of *B. coccineus* at the concentrations of 100, 200 and 400 mg/kg was administered to Groups 2, 3 and 4 respectively. Ranitidine (20 mg/kg) which served as standard drug was administered to Group 5. All were administered orally. One hour later, gastric lesions were induced with aspirin. Each rat was anaesthetized after 5 h with diethyl ether and sacrificed for ulcerative index determination[19].

2.8. Water immersion stress-induced ulcers

The procedure of water immersion stress-induced ulcers according to Akuodor *et al*. was used[17]. The animals selected for this study fasted for 48 h and were grouped in 5 cages ($n = 6$) with an access to water. Group 1 was treated with 20 mL/kg normal saline. The leaf extract (100, 200 and 400 mg/kg) was administered to Groups 2, 3 and 4 respectively. The standard drug ranitidine (20 mg/kg) was administered to Group 5. The drugs were all administered by oral route. After 1 h of drug administration, animals were subjected to swim in a cylinder and gastric ulcers were evaluated as described in our previous study[7].

2.9. Histamine-induced ulcers

The method of Amazu *et al*. with slight modification was employed to induce gastric ulcers by histamine[20]. Prior to the experiment, animals fasted for 48 h. After the fasting period, the rats were divided into 5 groups (6 rats per cage). Normal saline (20 mL/kg) was administered to Group 1 (control) while Groups 2, 3 and 4 were treated with ethanolic leaf extract of *B. coccineus* at a dose of 100, 200 and 400 mg/kg, respectively. Group 5 received 20 mg/kg of standard drug ranitidine. An hour later, gastric lesions were induced by subcutaneous administration of 100 mg/kg of histamine. Following the administration of diethyl ether, the animals were sacrificed 4 h later and their ulcerative index was observed.

2.10. Evaluation of ulcer index

The ulcerative lesions were assessed as described by Malairajan *et al*.[21]. Ulcer index of the experimental rats were calculated by adding the values, and their mean values were determined as follows: (i) 0 = no ulcer, (ii) 1 = hemorrhagic and slightly dispersed ulcers less than 2 mm length, (iii) 2 = 1 ulcer, hemorrhagic and up to 5 mm length, (iv) 3 = more than 1 ulcer, each up to 5 mm length, (v) 4 = 1 ulcer above 5 mm in length, (vi) 5 = more than 1 ulcer above 5 mm in length[8]. Percentage of ulcer protection index was calculated by adopting the following formula:

% Protection = (Uc - Ut/Uc) × 100

Where, Uc was the ulcer index in control group, and Ut was the ulcer index in treated groups.

2.11. Statistical analysis

Data were analyzed by using One-way ANOVA. Results were expressed as mean ± SEM. Results with $P < 0.05$ were considered statistically significant.

3. Results

3.1. Phytochemical analysis

The phytochemical test of the leaf extract showed the presence of alkaloids, tannins, saponons, terpenoids, steroids and flavonoids. These classes of compounds were reported to show important biological activities[22,23].

3.2. Acute toxicity test

There was no mortality observed in the rats after the oral administration of the extract. It suggestted that the extract used were within safety margin of doses.

3.3. Effect of B. coccineus leaf extract on ethanol-induced gastric ulcers

The extract significantly protected rats against gastric mucosal damage. The percent of ulcer protection index at the dose of 100, 200 and 400 mg/kg was observed to be 59%, 73% and 82%, respectively. The standard drug ranitidine showed a 91% protection index. The results were shown in Table 1.

Table 1
Effect of ethanolic leaf extract of *B. coccineus* on ethanol-induced ulcers.

Group	Dose	Ulcer index	% of ulcer protection index
Normal saline	0.2 mL/kg	4.23 ± 0.34	-
B. coccineus	100 mg/kg	1.75 ± 0.33	59*
	200 mg/kg	1.13 ± 0.24	73*
	400 mg/kg	0.77 ± 0.18	82*
Ranitidine	20 mg/kg	0.37 ± 0.23	91*

*: Significantly different from control group at $P < 0.05$; $n = 6$.

3.4. Effect of B. coccineus leaf extract on aspirin-induced gastric ulcers

Pretreatment with ethanol extract of *B. coccineus* leaf at doses of 100, 200 and 400 mg/kg exhibited significant ($P < 0.05$) ulcer protection index of 69%, 75% and 83% respectively, while ranitidine (20 mg/kg) showed 89% of ulcer protection index, as shown in Table 2.

Table 2
Effect of ethanolic leaf extract of *B. coccineus* on aspirin-induced ulcers.

Group	Dose	Ulcer index	% of ulcer protection index
Normal saline	0.2 mL/kg	4.08 ± 0.37	-
B. coccineus	100 mg/kg	1.65 ± 0.33	69*
	200 mg/kg	1.03 ± 0.28	75*
	400 mg/kg	0.70 ± 0.31	83*
Ranitidine	20 mg/kg	0.43 ± 0.28	89*

*: Significantly different from control group at $P < 0.05$; $n = 6$.

3.5. Effect of B. coccineus leaf extract on water immersion stress-induced gastric ulcers

B. coccineus 1 h before stress induced ulcers, showed remarkable ulcer protection in rats

Table 3 reveals that the extract at the doses of 100, 200 and 400 mg/kg exerted the marked ulcer protection activity of 59%, 75% and 80% while the standard drug ranitidine (20 mg/kg) showed 88% protection index.

Table 3
Effect of ethanolic leaf extract of *B. coccineus* on water immersion stress-induced ulcers.

Group	Dose	Ulcer index	% of ulcer protection index
Normal saline	0.2 mL/kg	4.32 ± 29.00	-
B. coccineus	100 mg/kg	1.78 ± 31.00	59*
	200 mg/kg	1.07 ± 0.22	75*
	400 mg/kg	0.85 ± 0.22	80*
Ranitidine	20 mg/kg	0.52 ± 0.33	88*

*: Significantly different from control group at $P < 0.05$; $n = 6$.

3.6. Effect of ethanolic leaf of B. coccineus on histamine-induced gastric ulcers

Administration of *B. coccineus* leaf extract significantly ($P < 0.05$) protected the animals against gastric mucosal damage. At different doses of the extract (100, 200 and 400 mg/kg), the plant exhibited 50%, 70% and 78% protection index, while ranitidine (20 mg/kg) showed 89% protection index against histamine-induced gastric ulcers (Table 4).

Table 4
Effect of ethanolic leaf extract of *Byrsocarpus coccineus* on histamine-induced ulcers.

Group	Dose	Ulcer index	% of ulcer protection index
Normal saline	0.2 mL/kg	4.10 ± 0.29	-
B. coccineus	100 mg/kg	2.05 ± 0.43	50*
	200 mg/kg	1.22 ± 0.25	70*
	400 mg/kg	0.92 ± 0.28	78*
Ranitidine	20 mg/kg	0.45 ± 0.23	89*

*: Significantly different from control group at $P < 0.05$; $n = 6$.

4. Discussion

Peptic ulcers are caused by an increase in gastric acid secretion and a reduction in mucosal protection factors[24]. Potential ulcer healing agents including plant extracts decrease the gastric acid secretion and enhance the mucosal defence mechanisms[25].

The study was carried out to investigate the anti-ulcerogenic activity of the leaf extract of *B. coccineus* in four different ulcer models including ethanol-, aspirin-, histamine- and water immersion stress-induced ulcers.

Ethanol-induced ulcers are direct damage of gastric mucosal cells leading to the development of free radicals and hyperoxidation of lipid[26]. Endogenous glutathione and prostaglandin levels are also lowered by ethanol, whereas the release of histamine, influx of calcium ions and production of leukotrienes are all elevated. *B. coccineus* leaf extract might have exerted its antiulcer activity through an increase in mucus production and a possible leukotriene antagonism.

Furthermore, the significantly analgesic, anti-inflammatory and antipyretic effects of the leaf extract support the fact that the inhibition of prostaglandins might also be a possible mechanism for its ulcer protective activity[9,12]. Moreover, an agent which is highly effective in preventing ethanol-induced gastric lesions may possess cytoprotective effect.

Hence, this could partially be one of the possible mechanisms by which *B. coccineus* significantly inhibited ethanol-induced gastric lesions. The gastroprotective activity of the leaf extract could be attributed to the suppression of lipoxygenase activity[27].

Aspirin causes ulcer as a result of its activity on cyclo-oxygenase enzyme, leading to a reduction in prostaglandin synthesis and an increase in acid secretion. The mucosal protective effect of *B. coccineus* might partly be due to the stimulation of prostaglandin synthesis since endogenous prostaglandins play a crucial role in gastroprotective activity[28]. Aspirin-induced ulcers are mediated through cell membrane damaging free radicals which are produced from the conversion of hydroperoxyl to hydroxy fatty acids leading to cell destruction[29].

The ethanol extract of the leaf at the doses used in the anti-ulcer evaluation, showed a significant ($P < 0.05$) and dose-dependent decrease in ulcer index. The observed activity further supports its cytoprotective potential which is likely to be mediated by prostaglandins.

Inflammation and neutrophil infiltration are known to play an important role in non-steroidal anti-inflammatory drugs-induced gastric mucosa damage[30]. Aspirin-induced gastric mucosa inflammation is accompanied by increased tumor necrosis factor-α production and this augments neutrophil-derived superoxide generation which stimulates interleukin-1β production leading to neutrophil accumulation[31,32]. Suppression of neutrophil infiltration during inflammation enhances gastric ulcer healing.

Stress-induced ulcers are due to accumulation of hydrochloric acid and also generation of free radicals[33].

However, the ulcers produced are due to the presence of histamine leading to an increase in acid secretion, a reduction in mucus production, pancreatic juice reflux as well as poor flow of gastric blood[34].

In addition, stress causes an increase in gastrointestinal tract motility resulting in stomach folds which are more susceptible to damage when they come in contact with acid[35]. The ethanol extract of *B. coccineus* leaf showed a dose-dependent activity in stress-induced gastric ulcers. The activity of the leaf extract was comparable to the standard drug, ranitidine. Therefore, it is possible that the ethanol extract of *B. coccineus* leaf may follow inhibitory mechanism of ranitidine.

Histamine-induced gastric ulcers has long been recognized and mediated through stimulation of H2 receptors which results in enhanced gastric acid secretion and vasodilatation[36]. Histamine not only enhances gastric acid secretion, but also causes disturbances of the gastric mucosa, microcirculation, abnormal motility and reduction in mucus production. The ethanol extract of *B. coccineus* significantly reduced the ulcers induced by histamine probably by blocking H2 receptors, thus inhibiting gastric acid secretion.

The gastric mucosal protective effect of the extract could be due to the presence of flavonoids and tannins (shown to be present in the ethanolic extract). Thus, the result of this study has shown that *B. coccineus* leaf extract may inhibit the aggressive factors such as acid and pepsin which play an important part in the pathogenesis of gastric ulcer.

In conclusion, this study has shown that ethanolic leaf extract from *B. coccineus* possesses ulcer healing property which confirms the folkloric claims of the benefit of this plant in ulcer treatment.

Conflict of interest statement

We declare that we have no conflict of interest.

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