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# Antiulcerogenic activity of *Solenostemon monostachyus*

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## Abstract

**Objective:** *Solenostemon monostachyus* P. Beauv (family Lamiaceae) used traditionally by the Ibibios of Southern Nigeria to treat stomach ulcer, malaria and other inflammatory diseases was evaluated for antiulcer activity. **Materials and Methods:** The effects of extract of *Solenostemon monostachyus* (75 - 225 mg/kg) and fractions (Aqueous and chloroform, 150 mg/kg) on experimentally induced ulcer were studied in rats using ethanol, indomethacin, reserpine and histamine –induced ulcer models. **Results:** The effect of ethanol extract of *S. monostachyus* (75 – 225 mg/kg) and fractions on experimentally induced ulcer were studied in rats. The extract (75 – 225 mg/kg) inhibited ethanol, indomethacin and histamine –induced ulcer models in a dose dependent fashion. The various degrees of inhibitions were statistically significant ($p<0.05$, 0.01, 0.001). The effect of the extract was comparable to that of the standard drugs used with the dichloromethane fraction having the highest activity. **Conclusion:** Thus, *S. monostachyus* extract demonstrated a good antiulcer activity which supports the use of this plant in the traditional medicine to treat ulcers.

**Keywords:** *Solenostemon monostachyus*, Gastric protective, Antiulcer.

## Introduction

Gastric ulceration is known to occur when there is an imbalance between aggressive factors (pepsin and hydrochloric acid) and mucosal defensive factors, such as blood flow, and mucus and bicarbonate secretion.[1] Although a number of antiulcer agents are in use, they have been shown to be associated with a wide array of deleterious and adverse effects as well as relapse, leading to their withdrawal in ulcer therapy.[2] Therefore, efforts are geared toward discovery of antiulcer active principles from natural sources as an alternative remedy for the treatment of gastric ulcer as plants have been shown to produce positive results in the treatment of gastric ulcers.

*Solenostemon monostachyus* P. Beauv (family Lamiaceae) is an important herb that is widespread in West and Central Africa. It occurs as an annual weed in anthropogenic habitats and rocky savannahs. It is slightly succulent, aromatic and grows up to 100 cm tall.[3] The aerial parts of the plant use in various decoctions traditionally by the Ibibios of the Niger Delta of Nigeria to treat stomach ulcer, fever/malaria[4,5], hemorrhoid and other inflammatory diseases. The decoction of the plant is also used to treat hypertension as well as a diuretic.[6] Phytochemical studies on *Solenostemon monostachyus* leaves have revealed the presence of water, proteins, lipids, glucids, calcium, phosphate[7], essential oil[8] and phytoconstituents such as diterpenoids[9], flavonoids, coumarin, polyphenol[10,11]. The leaf essential oil of S. monostachyus has been reported to contain; β-pinene, oct-1-en-3-ol, β-caryophyllene, octan-3-ol and (E,E)-α-farnesene.[8] The plant has been reported to possess antioxidant[10,11,12], antihypertensive[13] and antimicrobial activities.[14] We report the antiulcer activity of *Solenostemon monostachyus* to provide a scientific basis for its use in traditional medicine to treat ulcers.

## Materials and Methods

### Plant Collection

The plant material *Solenostemon monostachyus* (aerial parts) was collected in a farmland in Uruan area, Akwa Ibom State, Nigeria in August, 2014. The plant was identified and authenticated by Dr. Margaret Bassey of Department of Botany and Ecological Studies, University of Uyo, Uyo, Nigeria. Hebarium specimen (FPUU 573) was deposited at Department of Pharmacognosy and Natural Medicine Herbarium.

### Extraction

The plant aerial parts were washed and shade-dried for two weeks. The dried plant materials were reduced to powder using mortar and pestle. The powdered material was soaked in 50% ethanol.

The liquid filtrate was concentrated and evaporated to dryness in vacuo 40°C using a rotary evaporator. The extract (2 g) was partitioned with a 50:50 mixture of distilled water and chloroform. The aqueous fraction was evaporated to dryness in a water bath at 60°C and the chloroform fraction air-dried. The ethanol extract, the aqueous and chloroform fractions were stored at - 4°C until used in a refrigerator.[15]

**Phytochemical Screening**

Phytochemical screening of the crude extract was carried out employing standard procedures and tests [16,17], to reveal the presence of chemical constituents such as alkaloids, flavonoids, tannins, terpenes, saponins, anthraquinones, reducing sugars, cardiac glycosides among others.

**Animals**

Albino Swiss mice (17 – 25g, 5 – 8 weeks) and rats (97 – 130 g, 3- 6 months) of either sex were obtained from the University of Uyo animal house. They were maintained on standard animal pellets and water *ad libitum*. Permission and approval for animal studies were obtained from the College of Health Sciences Animal Sciences, Animal Ethics committee, University of Uyo (UU/CHS/AE/14/326).

**Determination of median lethal dose ($LD_{50}$)**

The median lethal dose ($LD_{50}$) of the extract was estimated using albino mice by intraperitoneal (i.p) route using the method of Lorke[18]. This involved intraperitoneal administration of different doses of the extract (100-1000 mg/kg) to groups of three mice each. The animals were observed for manifestation of physical signs of toxicity such as writhing, decreased motor activity, decreased body/limb tone, decreased respiration and death. The number of deaths in each group within 24 hours was recorded. The $LD_{50}$ was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$$LD_{50} = \sqrt{ab}$$

**Indomethacin induced ulcer**

Male adult albino rats were used for the experiment. They were randomized into five groups of six rats each. Food was withdrawn 24 hours and water 2h before the commencement of experiment [19]. Group 1(control) received only indomethacin (Sigma, 60 mg/kg p.o. dissolved in 5% $Na_2Co_3$); Groups 2- 4 were pretreated with *Solenostemon monostachyus* extract (75, 150 and 225 mg/kg p.o. respectively); Group 5 received an aqueous fraction (150 mg/kg); Group 6 received a chloroform fraction (150 mg/kg), and Group 7, cimetidine (100 mg/kg p.o. dissolved in 5% Tween 80). One hour later, groups 2 - 7 were administered with indomethacin. Four hours after indomethacin administration, animals were killed by cervical dislocation. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10% formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored [20]. Ulcer index (UI), preventive ratio (PR) and degree of ulceration (DU) of each of the groups pretreated with extract were calculated using standard methods [21,22].

**Ethanol induced gastric ulceration**

The procedure was similar to that used in indomethacin induced ulceration. The rats randomly assigned into were randomized into eight groups of six rats each. Food was withdrawn 24 hours and water 2 hours before the commencement of experiment [19]. Group 1(control) received only ethanol (2.5 ml/kg p.o), Groups 2- 4 were pretreated with *Solenostemon monostachyus* extract (75, 150 and 225 mg/kg p.o. respectively); Group 5 received an aqueous fraction (150 mg/kg); Group 6 received a chloroform fraction (150 mg/kg), and Group 7, received propranolol (40 mg/kg p.o. dissolved in distilled water). One hour later, groups 2 - 7 were administered with ethanol. Four hours after ethanol administration, animals were killed by cervical dislocation. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10% formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored [22].

**Histamine-induced gastric ulceration in rats**

The procedures were similar to that used in indomethacin-induced ulceration except that the negative control group (group 1) received only histamine acid phosphate (Sigma, 100 mg/kg i.p. dissolved in distilled water) [23] , Groups 2 - 4 were pretreated *Solenostemon monostachyus* extract (75, 150 and 225 mg/kg p.o. respectively); Group 5 received an aqueous fraction (150 mg/kg); Group 6 received a chloroform fraction (150 mg/kg), and Group 7, cimetidine (100 mg/kg p.o. dissolved in 5% Tween 80). One hour later, groups 2 - 7 were administered with histamine acid phosphate, 100 mg/kg i.p). Eighteen (18) hours after histamine administration, animals were killed by cervical dislocation. The stomachs were removed and opened along the greater curvature. The tissues were fixed with 10% formaldehyde in saline. Macroscopic examination was carried out with a hand lens and the presence of ulcer lesion was scored [20], stomach processing and examination as well as ulcer scoring were similar to that used in indomethacin-induced ulceration.

**Statistical analysis**

Data are reported as mean ± standard error of the mean(SEM) and were analyzed statistically using One way ANOVA followed by Tukey-kramer multiple comparison test and values of $p < 0.01$ were considered significant.

## Results

**Phytochemical screening**

The phytochemical screening of the ethanolic extract of the whole plant of *Solenostemon monostachyus* revealed the presence of alkaloids, cardiac glycosides, tannins, saponins, terpenes and flavonoids.

**Determination of median lethal dose ($LD_{50}$)**

The median lethal dose ($LD_{50}$) was calculated to be 748.331 mg/kg. The physical signs of toxicity included; excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which were followed by death.

**Indomethacin induced gastric ulceration**

The extract (p.o.) pretreatment of rats prior to indomethacin induced gastric ulceration exerted a dose dependent reduction in ulcer indices in pretreated groups relative to control. These reductions were statistically significant ($p<0.05$ - 0.001) when compared to control. The chloroform fraction exerted the highest antiulcerogenic effect (84.90%). The effects of the crude extract and fractions were incomparable to that of the standard drug, cimetidine (Table 1).

**Ethanol induced gastric ulceration**

The extract significantly protected rats from ethanol – induced ulcer (Table 2). There was a significant ($p<0.05$ - 0.001) dose-dependent reduction in the ulcer indices relative to control. The chloroform fraction exerted the highest effect (75.0%). The effects of the extract and fractions were less than that of the standard drug, propranolol.

**Histamine – induced ulceration**

Administration of the extract significantly ($p < 0.001$) reduced histamine-induced gastric ulceration in a dose dependent fashion compared to control (Table 3). The chloroform fraction exhibited a higher antiulcer potential than the aqueous fraction, but less than that of the standard drug cimetidine.

**Table 1:** Effect of *Solenostemon monostachyus* extract on indomethacin induced ulcer

| Treatment | Dose (mg/kg) | Ulcer Indices | Preventive Ratio (%) |
|---|---|---|---|
| Control (indomethacin) | 60 | 21.0 ± 0.32 | - |
| *Solenostemon monostachyus* extract p.o. | 75 | 15.61 ± 0.83[c] | 25.66 |
| | 150 | 5.66 ± 0.00[c] | 73.04 |
| | 225 | 4.10 ± 0.23[c] | 80.47 |
| Chloroform fraction | 150 | 3.17 ± 0.16[c] | 84.90 |
| Aqueous fraction | 150 | 10.65 ± 0.38[c] | 68.33 |
| Cimetidine | 100 | 2.00 ±0.27[c] | 90.47 |

Data were expressed as mean ± SEM. significant at cp< 0.001 when compared to control n = 6.

**Table 2:** Effect of *Solenostemon monostachyus* extract on ethanol induced ulcer

| Treatment | Dose (mg/kg) | Ulcer Indices | Preventive Ratio (%) |
|---|---|---|---|
| Control (ethanol) | 60 | 4.36 ± 0.31 | - |
| *Solenostemon monostachyus* extract p.o. | 75 | 3.56 ± 0.00 | 18.34 |
| | 150 | 2.32 ± 0.22[b] | 46.78 |
| | 225 | 2.14 ±0.27[b] | 50.91 |
| Chloroform fraction | 150 | 1.09±0.33[b] | 75.00 |
| Aqueous fraction | 150 | 3.23 ± 0.14[a] | 25.91 |
| Propranolol | 40 | 0.65 ± 0.25[b] | 85.09 |

Data were expressed as mean ± SEM. significant at ap < 0.05,bp<0.001 when compared to control n = 6.

**Table 3:** Effect of *Solenostemon monostachyus* extract on histamine - induced ulceration in rats

| Treatment | Dose (mg/kg) | Ulcer Indices | Preventive Ratio (%) |
|---|---|---|---|
| Control (Histamine) | 100 | 7.83 ± 0.90 | - |
| *Solenostemon monostachyus* extract p.o. | 75 | 5.36 ± 0.83 | 31.54 |
| | 150 | 4.50 ±0.76[a] | 42.52 |
| | 225 | 1.83 ± 0.66[c] | 76.62 |
| Chloroform fraction | 150 | 0.66 ±0.12[c] | 85.31 |
| Aqueous fraction | 150 | 3.25 ± 0.55[c] | 58.49 |
| Cimetidine | 100 | 0.90 ± 0.21[c] | 88.50 |

Data were expressed as mean ± SEM. significant at ap < 0.05, bp < 0.001 when compared to control n = 6.

## Discussion

The use of *Solenostemon monostachyus* to treat ulcer traditionally has been documented. Based on this, evaluation of the antiulcer activity of the plant extract was carried out using various experimental models such as indomethacin, ethanol, reserpine and histamine – induced ulcer models. Indomethacin, a known ulcerogen, especially in an empty stomach [24] causes ulcer mostly on the glandular (mucosal) part of the stomach[20,25] by inhibiting prostaglandin synthetase through the cycloxygenase pathway[26]. Prostaglandins function to protect the stomach from injury by stimulating the secretion of bicarbonate and mucus, maintaining mucosal blood flow and regulating mucosal turn over and repair[27,28]. Suppression of prostaglandin synthesis by indomethacin results in increased susceptibility of stomach to mucosal injury and gastroduodenal ulceration. The extract was observed to significantly reduce mucosal damage in the indomethacin – induced ulcer model, suggesting the possible extract mobilization and involvement of prostaglandin in the anti-ulcer effect of the extract. Administration of ethanol has been reported to cause disturbances in gastric secretion, damage to the mucosa, alterations in the permeability, gastric mucus depletion and free radical production[29]. This is attributed to the release of superoxide anion and hydroperoxy free radicals during metabolism of ethanol as oxygen derived free radicals has been found to be involved in the mechanism of acute and chronic ulceration in the gastric mucosa[30] . It was observed in this study that the extract reduced significantly ethanol- induced ulcer. This may be due to the cytoprotective effect of the extract via antioxidant effects. *S. monostachyus* has been reported to possess antioxidant [10,11,12].

The leaf essential oil of *S. monostachyus* has been reported to contain; β-pinene, oct-1-en-3-ol, β-caryophyllene, octan-3-ol and (*E,E*)-α-farnesene[8] in abundance and some of these compounds are sesquiterpenes. Several sesquiterpene lactones have been reported as the anti -ulcerogenic constituents of folk remedies; e.g dihydroleucodine, a guaianolide, from *Artemisia douglasiiang*[31] , parthenolide, a germacranolide from *Tainacetum parthenium* [32] , and 13-acetyl soltitialin A and soltitialin A from *Centaurea solstitialis*[33]. α, β-unsaturated carbonyl and α-methylene-χ-lactone moieties are suggested as specific requirements for antiulcerogenic activity in sesquiterpene lactones .[34] These moieties would serve as the Michael acceptors to induce a Michael addition reaction between the sulfhydryl containing peptides of the mucosa.

According to Begley *et al*. [35], the α-methylene-χ- butyrolactone moiety was shown to possess chemical reactivity toward biological nucleophiles, e.g thiol and amines. The antiulcerogenic activity of this extract may in part be due to the sesquiterpenes present in the extract. Moreso, since gastric damage induced by nonsteroidal antiinflammatory drugs (indomethacin) is due to a decrease in endogenous prostaglandin synthesis and an increase in acid secretion [36]. Sesquiterpene lactones bearing Michael acceptors offer cytoprotection also through stimulation of the endogenous synthesis of prostaglandins [34]. This has been suggested by Maria *et al*. [37], to be due to increased biosynthesis of glutathione which in turn leads to increased biosynthesis of $PGE_2$. The antiulcerogenic activity observed in this study with the root extract may in part be exerted through the above mechanism.

Ethanol is also reported to cause gastric mucosal damage by stimulating the formation of leukotriene C4 ($LTC_4$).[38] The gastroprotective effect of the extract may in part be due to the suppression, by the extract of lipoxygenase activity. [20] Histamine-induced ulceration is known to be mediated by enhanced gastric acid secretion as well as by vasospastic action of histamine.[39] The inhibition of ulcer due to histamine by the extract may be due to its suppression of histamine-induced vasospastic effect and gastric secretion. The mechanism of reserpine induced gastric damage is poorly understood, but it has been suggested by Salim [29] to be similar to that of ethanol as discussed above. Consequently, the reduction of reserpine induced ulcer by the extract in this study maybe link to its cytoprotective effect through antioxidant activity.

Some phytochemical constituents such as diterpenoids [9], flavonoids, coumarin, polyphenol [10,11] as well as β-pinene, oct-1-en-3-ol, β-caryophyllene, octan-3-ol and (*E,E*)-α-farnesene [8] had been reported to be present in the leaf extract of *Solenostemon monostachyus*. Flavonoids such as quercetin has been reported to prevent gastric mucosal lesions in various experimental models [40,41] by increasing the amount of neutral glycoproteins [40]. Flavonoids have been reported to protect the gastric mucosa from damage by increasing the mucosal prostaglandin content and by inhibiting histamine secretion from mast cells by inhibition of histidine decarboxylase. The free radical scavenging ability of flavonoids has been reported to protect the gastrointestinal tract from ulcerative and erosion lesion [42]. Saponins, especially triterpenes type have been implicated in antiulcer activity mediated by the formation of protective mucus on the gastric mucosa and also protect the mucosa from acid effects by selectively inhibiting PGF2α.[43, 44]

## Conclusion

In conclusion, the results of the present study show that stem extract and fractions of *Solenostemon monostachyus* display gastroprotective activity as demonstrated by significant inhibition of the formation of ulcers induced through three different ulcer models studied. The antiulcer activity of the extract may be due to the action of its phytochemical compounds present in the extract. The observation justifies the ethnomedical uses of the plants as antiulcer and antacid in addition to its nutritional values.

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### Conflict of interest

There is no conflict of interest

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