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Full Length Research Paper

Comparative studies of anti-ulcerogenic activities of three Nigerian medicinal plants: A preliminary evaluation

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The root of *Ziziphus abyssinica,* stem barks of *Balanites aegyptiaca* and *Acacia nilotica* have been used singly and in combination as a folk medicine in Northwest Nigeria for the treatment of ulcer. The aim of this study was to evaluate and compare the antiulcer activities of each herb when used singly and in combination. Aqueous extracts of the three plants were obtained by Soxhlet extraction. The antiulcer activities of 300 mg/kg each of the extracts and the extracts combined in equal parts were evaluated by ethanol and indomethacin induced gastric lesions models in Wister rats. In ethanol induced ulcer model, *Z. abyssinica* gave the highest inhibition at 79.2%, while the *A. nilotica* 44.22% was the least. In the indomethacin induced ulcer model, the polyherb gave the highest inhibition at 50.43% while *A. nilotica* 10% was the least. Polyherb showed a significant decrease ($p < 0.05$) of the mean ulcer index in the indomethacin model when compared to the other extracts. The herbs when used in combination could exhibit a more potent gastroprotective effect against non-steroidal anti-inflammatory drug (indomethacin) induced gastric ulceration than when used singly. This justifies the traditional usage of these herbs as polyherbs for ulcer treatment.

Key words: *Ziziphus abyssinica*, *Balanites aegyptiaca*, *Acacia nilotica*, polyherbs, anti-ulcer, folk medicine.

INTRODUCTION

Peptic ulcer disease (PUD) is a benign lesion which occurs in the stomach or duodenum where the mucosal epithelium is exposed to acid and pepsin (Khazaei and Salehi, 2006; John, 2005; Tripathi, 2003). It develops when the delicate balance between some gastro-protective and aggressive factors is lost (Kent and Debas, 1994; Lima et al., 2006; Jainu et al., 2006).

Antacids, proton pump inhibitors, H_2 receptor blockers, prostaglandin analogues and others have been used in the treatment of ulcer. Despite the effectiveness of these drugs, many side effects have been reported. Therefore, screening of plant drugs for the development of safer, effective antisecretory and anti-ulcer drugs is very essential.

In Africa, up to about 80% of the population still rely on herbal medicine to treat diseases (WHO, 2002), because of their affordability and accessibility. In Northwest Nigeria, traditional healers have utilised three Nigerian plants, the root of *Ziziphus abyssinica* (ZA), stem barks of *Balanites aegyptiaca* (BA) and *Acacia nilotica* (AN), singly and at times in combination (polyherb) for the treatment of ulcer. The decoction of the individual plant or the polyherb is taken as a tea daily for the treatment of

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ulcer (Zailani and Ahmed, 2008). *Z. abyssinica* Del. Family Zygophyllaceae is a wild plant commonly known as desert plant and 'Aduwa' in Hausa. It grows in the dry land areas of Africa and South Asia (Hall and Walker, 1991).

In Northern Nigeria, the fruits have been soaked in water and drunk for the treatment of peptic ulcer or dyspepsia and other stomach ache (Zailani and Ahmed, 2008). Previous studies have revealed the anti-inflammatory, antifeedant, antidiabetic, molluscide, anthelminthes and contraceptive activities of the plant (Gaur, 2008; Liu and Nakanish, 1982; Iwu, 1991; Kamel et al., 1991; Ibrahim, 1992; Rao et al., 1997). *Balanites aegyptiaca* Hochst. A. Rich. Family Rhamnaceae commonly called catch thorn and 'Magaria' in Hausa, is a spiny shrub or tree up to 4 m high that grows in the Sahel and drier part of tropical Africa.

The herbalists in the northern community in Nigeria utilise the decoction of the root in the treatment of mental disorders and abdominal ulcer (Zailani and Ahmed, 2008). The antibacterial and antioxidant activities of this plant have been evaluated (Nyaberi et al., 2010). *Acacia nilotica* (L.) Willd. Family, Fabaceae, commonly called gum arabic tree and 'Bagaruwa' in Hausa, is a tree of 5 to 20 m high with a dense spherical crown, stem and branches.

It has been documented that the decoction from the stem bark of this plant is used for healing of all kinds of wounds (Inngjerdingen et al., 2004). Its anti-inflammatory, antioxidant (Daffallah and al-Mustafa, 1996), anti-malaria (Etkin, 1997), antitubercular (Oladosu et al., 2007) and antidiabetic (Dalziel, 1997) and gastroprotective effect of the young seedless pod extract (Basal and Goel, 2012) have been studied.

The purpose of the study therefore was to investigate the anti-ulcer properties of these plants and to compare them with when they are used together (polyherb).

MATERIALS AND METHODS

Collection and authentication of plant material

The root of *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A. nilotica* were obtained from the surroundings of Usmanu Danfodiyo University (UDUS) in December, 2008 and authenticated by the Taxonomist, Alh Umar Muh'd of Department of Botany, UDUS. Voucher specimens were deposited at their herbarium with voucher accession numbers 004, 005 and 006 for *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A.* nilotica, respectively.

Preparation of plant extracts

Each of the dried root or bark was pulverized by pounding using pestle and mortar. Then, 2 kg of the powdered materials were extracted in distilled water using Soxhlet apparatus. The filtrates were evaporated in the oven at 50°C. The yield (w/w) of each plant extract was recorded. The extracts were stored at -4°C from where they were used when required (Nwafor et al., 2000).

Standard drugs

Omeprazole and indomethacin were purchased from Swiss Pharma PVT Ltd India and Sishui Xierkang Pharmaceuticals Co. Ltd China respectively. The 95% ethanol was purchased from BDH Chemicals Ltd Poole England.

Animals

Wistar rats of either sex (180 to 250 g) were obtained from Veterinary Institute Vom, Jos and kept in the animal house of the Department of Pharmacology Usmanu Danfodiyo University Sokoto.

The animals were kept in well constructed cages under standard conditions (25 ± 2°C, 12 h light and dark cycle) that allowed freedom of movement for two weeks for acclimatisation to the laboratory conditions before commencement of study. Water and standard rat chow were provided *ad libitum* throughout the period of the study.

The study was approved by the Research Ethical Committee, Usmanu Danfodiyo University, Sokoto and was conducted in accordance with the Organization for Economic Development (OECD) guidelines (OECD, 2008).

Phytochemical testing

The qualitative analyses of the plants' constituents were carried out using the methods described by Trease and Evans (1983), El-Olemmy et al. (1994) and Harbone (1993). The presence of alkaloids, tannins, saponins, flavonoids, glycosides, anthraquinones, volatile oil and steroids were tested for.

Acute toxicity study

The Up and Down (Limit dose) method of acute toxicity studies was used (OECD, 2001). A limit dose of 3000 mg/kg of the extract and the polyherb were used for the study (n = 5). Each animal received oral dose of 3000 mg/kg body weight of the extract dissolved in distilled water as the vehicle. Each animal was observed after dosing for the first 5 min for signs of regurgitation and kept in a metallic cage.

Observation was done every 15 min in the first 4 h after dosing, every 30 min for 6 h and daily for 48 h for the short-term outcome according to the specifications of the OECD. The animals were monitored for a total of 14 days for the long-term possible lethal outcome which is death.

Evaluation of antiulcer activities

Ethanol (95%) induced gastric mucosal membrane lesions test

Lesions were induced according to the method of Mizui et al. (1987). The rats were randomly divided into 6 groups (n = 5). Food was withdrawn 24 h and water 2 h before the commencement of the investigation (Alphin and Ward, 1967). Groups 1 to 6 were pretreated orally with 10 ml/kg of distilled water, Omeprazole 20 mg/kg (positive control), and 300 mg/kg (10% of the dose for the acute toxicity) each of the extract of *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A. nilotica* and polyherb (consisting of equal weights of ZA, AN and BA), respectively. After 30 min, rats received 8 ml/kg of the 95% ethanol orally to induce gastric lesions. 2 h later, the animals were sacrificed by cervical dislocation and their stomach was removed and opened along the greater curvature. The ulcer indices were determined by the method of Arun and Asha (2008).

Table 1. Phytochemistry of the extracts.

Phytochemical constituents	AN	BA	ZA
Alkaloids	+	++	+++
Tannins	+++	++	+++
Flavonoids	-	++	-
Anthraquinones	++	-	+++
Saponins	++	+++	++
Carbohydrates	+	+	++
Steroids	+	++	+++
Glycosides	+	+	+++

+ (trace), ++ (moderate), +++ (high), - (absent)

Indomethacin induced gastric mucosal membrane lesions

Lesions were induced according to the method of Nwafor et al. (2000). The rats were randomly divided into 6 groups (n = 5). Food was withdrawn 24 h and water 2 h before the commencement of the investigation (Alphin and Ward, 1967). Groups 1 to 6 were pretreated orally with 10 ml/kg of distilled water, omeprazole 20 mg/kg (positive control), and 300 mg/kg each of the extract of ZA, AN, BA and polyherb respectively. After 1 h, gastric ulcer was induced with oral administration of 100 mg/kg of indomethacin. 4 h later, the animals were sacrificed by cervical dislocation and their stomach was removed and opened along the greater curvature. The ulcer indices were determined as described earlier.

Measurement of ulcer index

Immediately after the animals were sacrificed, their stomachs were dissected out, cut along the greater curvature and the mucosa were rinsed with cold normal saline to remove any blood contaminant present. The average of the length (mm) of all lesions for each stomach was used as the ulcer index (UI), and the inhibition percentage was calculated as follows according to Navarrete et al. (1998):

$$\% \text{ Inhibition of ulceration} = \frac{\text{Ulcer index control} - \text{Ulcer index test}}{\text{Ulcer index control}} \times 100$$

Statistical analyses

The results were expressed as mean ± standard deviation of mean (SD). Comparison of antiulcer activity in all the groups was made using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison tests. Significance level was $p < 0.05$.

RESULTS

Yield of plant extracts

Z. abyssinica, stem barks of *B. aegyptiaca* and *A. nilotica* had percentage yield of 11.6, 13.6 and 8.5% respectively after the extraction of 2 kg each of the pulverized plant materials.

Phytochemical screening

The result showed the presence of alkaloid, tannins, saponins, glycosides, carbohydrates and steroids in all the plants though in varying degrees (Table 1). Flavonoids were absent in AN and ZA while anthra-quinone was absent in BA.

Acute toxicity

At a limit dose of 3000 mg/kg, all the rats in the short and long terms observations survived. There was no mortality; however there were signs of drowsiness in the rats in all the groups for about 1 to 2 h.

Ethanol induced gastric lesions

All the treated groups showed a significant reduction of the mean UI ($p < 0.05$ for Omeprazole, BA, ZA and polyherb, while $p < 0.01$ for AN), when compared with the negative control (Table 2). The mean UI of ZA and BA were significantly ($p < 0.05$ and 0.01 respectively) lower than that of the polyherb. However, the mean UI of the polyherb was significantly ($p < 0.01$) lower than that of the AN. The mean UI of ZA was the lowest amongst the groups, lower than the positive control ($p < 0.001$).

Indomethacin induced gastric lesions

Treatment with Omeprazole, BA, ZA and polyherb reduced gastric lesion significantly ($p < 0.05$) when compared with the control. The polyherb showed the lowest mean UI (Table 3). It showed a significant reduction of the mean UI when compared to *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A. nilotica* ($p < 0.05$) and Omeprazole ($p < 0.001$). AN did not show a significant difference ($p < 0.05$) when compared with the negative control.

DISCUSSION

In this study, we evaluated the phytochemistry, the acute toxicity and the anti-ulcer properties of three Nigerian plants, *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A. nilotica*. The acute toxicity test result showed that all the rats in each of the plants' groups survived, indicating that the LD_{50} is greater than 3000 mg/kg (OECD 2001), and that the extracts may be relatively safe (Clarke and Clarke, 1977). In the phytochemical studies, these plants were shown to possess among others, tannins, flavonoids and saponins which are bioactive metabolites that have been documented to possess antiulcer activities (Borrelli and Izzo, 2000). The evaluation and

Table 2. Effects of plant extracts on ethanol induced gastric lesions.

Groups	Treatment	Dose (mg/kg)	Mean Ulcer Index	% inhibition
1	Control (DW)	10 ml/kg	18.00 ± 1.23	0.00
2	Omeprazole	20	4.72 ± 0.80*	73.74
3	ZA	300	3.37 ± 0.88*, a , c	79.27
4	AN	300	10.04 ± 1.46**	44.22
5	BA	300	5.05 ± 0.96*, b	71.92
6	Polyherb	300	7.60 ± 2.96*, d	57.77

Results expressed as mean ± SD, statistical analyses were performed using ANOVA followed by Dunnett's test. DW = Distilled water. *Ziziphus abyssinica* (ZA), *Balanites aegyptiaca* (BA), *Acacia nilotica* (AN). * $p < 0.05$, when compared with the control; **$p < 0.01$, when compared with the control; [a] $p < 0.05$, when compared with polyherb; [b] $p < 0.01$, when compared with polyherb; [c] $p < 0.001$, when compared with Omeprazole; [d] $p < 0.01$, when compared with AN.

Table 3. Effects of plant extracts on indomethacin induced gastric lesions.

Groups	Treatment	Dose (mg/kg)	Mean Ulcer Index	% inhibition
1	Control (DW)	10 ml/kg	2.45 ± 0.63	0.00
2	Omeprazole	20	1.37 ± 0.15*, b	44.06
3	ZA	300	1.82 ± 0.36*, a	25.90
4	AN	300	2.20 ± 0.42[a]	10.00
5	BA	300	1.69 ± 0.35*, a	31.00
6	Polyherb	300	1.21 ± 0.14*	50.43

Results expressed as mean ± SD, statistical analyses were performed using ANOVA followed by Dunnett's test. DW = Distilled water. *Ziziphus abyssinica* (ZA), *Balanites aegyptiaca* (BA), *Acacia nilotica* (AN). *$p < 0.05$, when compared with the control; [a] $p < 0.05$, when compared to polyherb; [b]$p < 0.001$, when compared to the polyherb.

comparison of the antiulcerogenic properties of extracts of *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A. nilotica* and polyherb which was done using the ethanol and indomethacin induced gastric lesion showed that the extracts possess varying degrees of antiulcer properties.

Ethanol induced gastric lesions are thought to arise as a result of direct damage of gastric mucosal cells, resulting in the development of free radicals and hyperoxidation of lipids (Terano et al., 1986) in the body system. Ethanol is noxious to the stomach. Oral administration of 95% ethanol antagonizes the cytoprotective mechanism in the body and produces lesions in the gastric mucosa by making the mucus membrane more susceptible to the attack of hydrochloric acid (HCl) (Marhuenda et al., 1993). All the extract groups were found to be effective at varying degrees in decreasing the mean ulcer indices. In this ulcer model, the polyherb did not show better protection than ZA or BA used singly.

Non-steroidal anti-inflammatory drugs (NSAID) like indomethacin act principally by non selectively inhibiting the activity of cyclooxygenase enzyme, leading to a decrease in the production of prostaglandins whose function is to increase production of bicarbonate and inhibit the secretion of HCl (Hiruma-Lima et al., 2006). This causes ulceration of the mucosal membrane. The polyherb showed the highest cytoprotective effect against NSAID induce ulcer. It is also interesting that its cyto-protective effect was better than that of the positive control, omeprazole. It has been proposed that mucosal protection induced by nonprostanoid compounds may be mediated through the mobilization of endogenous prostaglandins (Cho et al., 1983; Konturek et al., 1987). It is possible that one of the mechanisms of antiulcerogenic effects of the extracts may be due to their ability to mobilize prostaglandins in gastric mucosa by increasing its microcirculation.

Again, another possible mechanism of the antiul-cerogenic properties of the polyherb may be due to the combined effects of bioactive component from the different extracts. The phytochemical analysis of the extract revealed many bioactive substances including tannins, saponins and flavonoids which are substances known to affect the integrity of mucous membranes (Oliver, 1960). Tannins have vasoconstrictory effects and react with the proteins of the layers of tissues which they come in contact with (Aguwa and Nwako, 1988). Tannins being astrigent, can precipitate microproteins on the site of the ulcer thereby forming an impervious protective pellicle over the lining to prevent absorption of toxic substances and resist the attack of proteolytic enzymes (John and Onabanjo, 1990; Nwafor et al., 1996). A

number of mechanisms have been proposed to explain the gastroprotective effect of flavonoids; these are increase of mucosal prostaglandin content (Alcaraz and Hoult, 1985), decrease of histamine secretion from mast cells by inhibition of histidine decarboxylase (Bronner and Landry, 1985) and inhibition of *Helicobacter pylori* growth (Beil et al., 1995). In addition, flavonoids have been found to be free radical scavengers (Cavallini et al., 1978; Salvayre et al., 1982). A mixture of saponins (Aescin) has been shown to posses anti-ulcer activity in various ulcer models (cold restraint and pylorus-ligated) (Marhuenda et al., 1993), an effect which is, in part, due to inhibition of gastric acid and pepsinogen secretion. The polyherb may be acting through some or all of these ways.

Further studies however are needed to elucidate the exact mechanism(s) of action involved in the additive effect of the combined extracts (polyherb).

Conclusion

In conclusion, the oral administration of the plant extracts *Z. abyssinica,* stem barks of *B. aegyptiaca* and *A. nilotica* displayed significant antiulcerogenic activity without much apparent toxicological effects. The extracts when used in combination appear to be more effective than when used singly in the protection against NSAID induced ulcer. These findings, therefore validates their use in herbal medicine in North Western Nigeria for ulcer therapy.

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