

Anti-ulcerogenic and Anti-inflammatory Activity of *Cissus multistriata* Extract in Experimental Animals

Omale James, Elejo Berikisu Ojogbane, Okpachi Christopher Abbah and
Moses Oluwatobi Tehinse

Department of Biochemistry, Faculty of Natural Sciences, Kogi State
University, P.M.B. 1008 Anyigba, Kogi State, Nigeria

Abstract: This present study was undertaken to evaluate the anti-ulcerogenic and anti-inflammatory properties of methanol extract from the leaves of *Cissus multistriata*. Gastric ulcer and inflammation were induced in experimental animals using ethanol and acetic acid respectively. Anti-ulcerogenic action of *C. multistriata* was evaluated in albino rats at doses of 30, 50 and 100 mg/kg body weight. *Cissus multistriata* showed gastro-protective action in the groups and the protection was dose dependent and comparable to the standard drug (Omeprazole) used. The mechanism involved in the gastro-protective effect of *C. multistriata* may be related to the mucosal protector factors, such as Nitric Oxide (NO) and Sulfhydryl (SH) compounds. Anti-inflammatory activity was also studied on the plant using the paw edema method on different groups of rats. The methanol extract of *C. multistriata* exhibited potent anti-inflammatory activity at 150 mg/kg b.w at 4 h after administration to group 4 when compared with reference standard drug (Indomethacin). Group 2 had 72% inhibition of edema as compared to 55% inhibition offered by the extract at 150 mg/kg, thus showing a great effect at higher doses. From this study, it is clear that *C. multistriata* leaf extract had significant anti-ulcer activity in animal model. It also demonstrated high anti-inflammatory potential at 150 mg/kg b.w. These observed pharmacological activities therefore, provide scientific support for the ethno-medicinal uses of this plant.

Keywords: Anti-inflammatory, anti-ulcerogenic, *Cissus multistriata*, experimental animals

INTRODUCTION

Gastric hyperacidity and ulcer are very common cause of human suffering today. It is an imbalance between damaging factors within the lumen and protective mechanisms within the gastro duodenal mucosa. Although prolonged anxiety, emotional stress, hemorrhagic surgical shock, burns and trauma are known to cause severe gastric irritation, the mechanism is still very poorly understood (Rao *et al.*, 2000).

Ulcer is defined as the erosion in the lining of the stomach or duodenum and is caused by the disruptions of the gastric mucosal defense and repair systems (Grossman, 1981). Ulcer in the stomach is called gastric ulcer and in the duodenum is called duodenal ulcer and together peptic ulcer.

In clinical practice, peptic ulcer is one of the most prevalent gastro intestinal disorders, commonly occurs in developed countries. Treatments available for ulcer is generally non-specific and is usually aimed at reducing the production of gastric acid and re-enforcing gastric mucosal protection such as regular food, adequate rest and avoidance of ulcerogenic agents such as coffee, alcohol and tobacco. The drugs used in the treatment of

ulcer are, receptor blockers, proton pump inhibitors, drugs affecting the mucosal barrier and act on the central nervous system (Manonmani *et al.*, 1995). Even though a range of drugs are available for the treatment of ulcers, many of these do not fulfill all the requirements and have side effects (Anoop and Jegadeesan, 2003; Dharmani *et al.*, 2005).

Inflammation is seen in condition such as Alzheimer's disease, cancer, irritable bowel syndrome and hepatic diseases. It is believed that controlling inflammation may help to alleviate these conditions or even prevent them (Mitchell and Cotran, 2000).

The classical description of inflammation accounts for the increases in the number of leucocytes and a variety of complex mediator molecule (Mautri and Witiak, 1994). Prostaglandins are ubiquitous substances that indicate and modulate cell and tissue responses involved in inflammation. Their biosynthesis has also been implicated in the pathophysiology of cardiovascular diseases, cancer, colonic adenomas and alzheimer's disease (Ialenti *et al.*, 1995). There are various components to an inflammatory reaction that can contribute to the associated symptoms and tissue injury. Oedema formation, leucocyte infiltration and

granuloma formation represents such components of inflammation (Mitchell and Cotran, 2000). Traditionally, the treatment for inflammation has been to use a Non-Steroidal Anti-Inflammatory Drug (NSAID), such as aspirin, for pain relief and to use corticosteroids or even disease-modifying drugs in an attempt to reduce other symptoms of the disease.

Recently, there has been much interest in natural medicines derived from the traditional knowledge of plant pharmacological properties. Large number of medicinal plants and dietary nutrients have been shown to poses gastro-protective activity (Borrelli and Izzo, 2000; Malairajan *et al.*, 2007; Kath and Gupta, 2006) and anti-inflammatory activity (Omonkhelin and Omogbai, 2007).

In Nigeria, *Cissus multistriata* is widely used in the management of diverse diseases such as kwashiorkor, marasmus, arthritis, infertility, stomach disturbances in children as well as remedy for cough (Omale *et al.*, 2010). Its application to fracture site have provided healing as claimed by herbal medicine practitioners. The various parts of the plant are put to use traditionally to remedy one ailment or the other including the fruit. The fruit also serves as attractant to fish and as such it is special hook bait in Ibaji, Kogi State, Nigeria. The medicinal properties or efficacy of this plant have been claimed extensively hence the need to assess it for anti-ulcer activity. It is relatively non-toxic (Omale *et al.*, 2010). It is rich in phytochemicals and posses anti-oxidant activity (Omale *et al.*, 2006; Omale and Okafor, 2008).

In spite of being one of the well known medicinal plants used in Nigerian traditional medicine, studies pertaining the pharmacological properties of *C. multistriata* are very rare. *Cissus multistriata* has so far not been screened for anti-ulcer activity. Hence we evaluate the anti-ulcer as well as anti-inflammatory effects of *C. multistriata* methanol leaf extract in the present investigation using animal models.

MATERIALS AND METHODS

Plant material: The leaves of *Cissus multistriata* were collected from Kogi State University Staff Quarters (#8 Dekina Avenue), Dekina Local Government Area, Kogi State, Nigeria during rainy season when the plant thrives well. Dirts were removed by rinsing the samples properly in clean water. The leaves were air-dried for 3 weeks and pulverized into fine powder using mortar and pestle.

Preparation of plant extract: A portion (300 g) of the powdered leaf sample was weighed out and soaked in a jar containing 1500 mL of methanol for 72 h. This was then filtered using vacuum pump. The filtrate was later concentrated by removing the solvent completely using a water bath at 40°C. The concentrate was a greenish residue which was kept in an air tight container until used.

Animal model: Albino rats (130-220 g) were obtained from Mr. Friday Titus Emmanuel who breeds them and housed in the departmental animal house during the experimental period in a standard environmental conditions. The rats were fed with rodent diet and given water *adlibitum*. Animals were handled following standard guidelines in using experimental animals.

Chemicals and reference drug: All chemicals used in this investigation were of analytical grade and were obtained from BDH.

Omeprazole (reference drug) was obtained from a pharmacy shop in Anyigba, Kogi State, Nigeria. The drug is an anti-ulcer drug which blocks the enzymes in the wall of the stomach from producing acid, the main culprit in peptic ulcer. By blocking the enzymes, the production of stomach acid is decreased, thus allowing the ulcer to heal (Zahra *et al.*, 2009).

Anti-ulcer activity study: The experiments were performed as described by Mizui and Doteuchi (1983) with minor modifications. Animals were divided into six groups of 4 rats each that had fasted for 24 h prior to receiving an oral dose of saline, (Omeprazole, 20 mg/kg) and extract of *C. multistriata* (30, 50 and 100 mg/kg). After 50 min, groups 2 to 6 were orally treated with 5 mL/kg of 100% ethanol for gastric-ulcer induction. Animals were killed 1 h after the administration of ethanol and the stomachs excised. The extents of lesions were measured in form of Ulcer Area (UA). The lengths of ulcer on the gastric mucosa were measured using a plane square ruler. The Ulcer Area (UA) was calculated. The percentage (%) of protection (P%) availed to the animals through the various treatments were calculated using the formula:

$$P\% = \frac{(\text{UA ulcer control} - \text{UA treatment})}{\text{UA ulcer control}} \times 100$$

Anti-inflammatory activity study: The anti-inflammatory property of the extract was evaluated in the right paw edema model. Paw edema was produced in rats by acetic acid injection following the method of Womter *et al.* (1962) with minor modifications. In this study, the experimental animals were divided into four groups of four animals each. The extract at the doses of 100 and 150 mg/kg body weight were administered orally an hour before the subcutaneous injection of 0.1ml of acetic acid in the right hind paw. The control group received distilled water while the reference drug indomethacin 10 mg/kg was also given to another group prior to induction of edema. Paw sizes were measured using a venier calipers (in millimeters) at 30 min, 1, 2, 3 and 4 h after acetic acid injection. Results obtained were compared with the control that received distilled water only. Percentages of inhibition were obtained from each group using the formula below:

Table 1: Effect of *C. multistriata* extract on ulcer induced by ethanol in rats

| Group/treatment | Dose mg/kg | Ulcer area (mm) | Protection (%) |
|-----------------------------|--------------|-----------------|----------------|
| 1 Control | - | 0.00±0.00 | - |
| 2 Ulcer control | 5 mL ethanol | 37.30±1.45* | 0.00 |
| 3 Drug control (Omeprazole) | 20 | 14.10±0.85** | 62.21 |
| 4 <i>C. multistriata</i> | 30 | 21.30±1.25* | 42.89 |
| 5 <i>C. multistriata</i> | 50 | 18.80±0.64** | 49.59 |
| 6 <i>C. multistriata</i> | 100 | 15.90±0.85** | 57.37 |

Values are expressed as mean±S.D. significant values; *: p<0.05; **: p<0.01

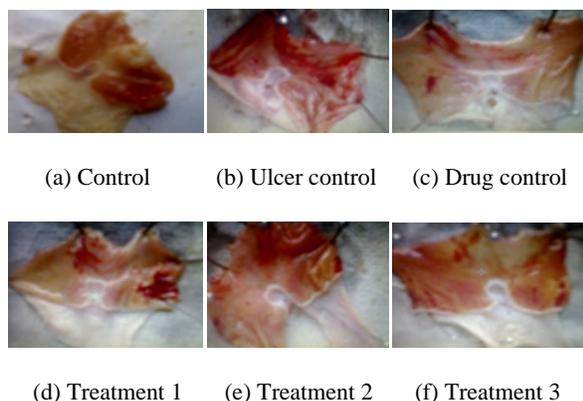


Fig. 1: Anti-ulcer activity of methanol extract of *Cissus multistriata* leaves (a) shows stomach normal control treated with only normal saline, (b) stomach of an ulcer control rat, (c) stomach of a drug control rat treated with 20 mg/kg of omeprazole, (d) stomach of treated group with 30 mg/kg of methanol extract of *C. multistriata*, (e) stomach of treated group with 50 mg/kg of methanol extract of *C. multistriata*, (f) stomach of treated group with 100 mg/kg of methanol extract of *C. multistriata*

$$\frac{[\text{Control (paw size)} - \text{treated (paw size)}]}{[\text{Control (paw size)}]} \times 100$$

Statistical analysis: All data were expressed as mean±standard deviation. Statistical comparisons were performed using ANOVA. The level of significance was from p<0.01, p<0.05.

RESULTS AND DISCUSSION

From Table 1, the effect of the extract in group 5 and 6 is significant when compared with group 3 that received the standard drug and this shows increased gastro-protective effect as the dose increases Fig. 1.

Table 1 shows the inhibitory effect of the extract and indomethacin, the highest percentage inhibition of edema was produced by the reference drug-indomethacin at the 4th h followed by the extract at 150 mg/kg in group 4, thus showing that at higher doses of the extract, the percentage inhibition would be higher than the drug.

The defense mechanism of the gastro-intestinal mucosa against aggressive factors such as HCl, bile acid and NSAIDS, mainly consists of functional, humoral and neuronal factors (Yoshikawa *et al.*, 1993). Peptic ulcers are common disorder of the entire gastro-intestinal tract that occurs mainly in the stomach and the proximal duodenum (Mota *et al.*, 2009). The various animal models for peptic ulcers have played a significant role in the elucidation of the peptic ulceration (Lee, 2000) since ulcer is a multi-factorial disease, its treatment faces great difficulties due to the limited effectiveness and severe side effects of the currently available drugs (Mota *et al.*, 2009) owing to the side effects of the available drugs, many plant-derived natural products have been evaluated as therapeutics for the treatment of a variety of diseases, including the peptic ulcer (Desousafakao *et al.*, 2008; Musthaba *et al.*, 2010). Ethanol is one of the ulcerogenic agents that induce intense damage in gastric mucosa by promoting disturbances in the mucosal microcirculation, ischemia and appearance of free radicals, endothelin release, degranulation of mast cells, inhibition of prostaglandins and decrease in gastric mucus production (Addel-Salam *et al.*, 2001).

As presented in Table 1, the methanol extract of the leaf of *Cissus multistriata* (30, 50 and 100 mg/kg) and Omeprazole (20 mg/kg, drug control) significantly inhibited ulcer formation in this model by 42.89, 49.59, 57.37 and 62.21%, respectively. The reduction of the lesions seen with the methanol extract of *C. multistriata* suggests that part of the protective mechanism could involve mucosal defensive factors. Gastric mucosal damage caused by ethanol and related non-steroidal anti-inflammatory drugs result from the inhibition of prostaglandins synthesis via the arachidonic pathway (Vane, 1971; Ferreira and Vane, 1974). Prostaglandins serve protective functions in the stomach by maintaining gastric microcirculation (Vane, 1971; Ferreira and Vane, 1974) and causing gastric secretion of bicarbonate (Garner *et al.*, 1979) and mucus (Menguy and Desbaillets, 1967). Thus, the effect of the extract in this model suggests it may possess cytoprotective action probably by enhancing prostaglandin synthesis. The extract significantly (p<0.05) protected gastric mucosa against ethanol challenge. Ethanol-induced gastric mucosal lesions, predominant in the glandular part of the stomach, are caused by the direct toxic action of ethanol, reduction of the secretion of bicarbonate and depletion of gastric wall mucus (Marhuend *et al.*, 1993).

Ethanol also reduces endogenous glutathione and prostaglandin levels, increases the release of histamine and influx of calcium ions (Galvin and Szabo, 1992) and stimulates the synthesis of leukotriene C₄ (LTC₄) (Cho *et al.*, 1987) and oxygen free radicals (Mizui and Doteuchi, 1986) thus causing increased lipid peroxidation which damages cells and cell membranes (Pihan *et al.*, 1987). Agents that enhance mucosal

Table 2: Inhibitory effects of *C. multistriata* extract and indomethacin on acetic acid induced paw edema in rats

| | Group/treatment | Dose mg/kg | Inhibition of edema (mm) | | | | |
|---|------------------------|------------|--------------------------|-----------|------------|-----------|------------|
| | | | 30 min | 1 h | 2 h | 3 h | 4 h |
| 1 | Control | - | 2.18±0.22 | 2.03±0.73 | 1.84±0.13 | 1.68±0.05 | 1.27±0.05 |
| 2 | Drug control | 10 | 1.53±0.11* | 1.42±0.09 | 1.02±0.05* | 0.67±0.02 | 0.35±0.05* |
| 3 | <i>C. multistriata</i> | 100 | 1.60±0.15* | 1.99±0.37 | 1.63±0.28 | 1.07±0.11 | 0.71±0.03 |
| 4 | <i>C. multistriata</i> | 150 | 1.74±0.15 | 1.57±0.20 | 1.53±0.08* | 1.89±0.11 | 0.57±0.03 |

Values are expressed as mean±S.D.; *: Significant values p<0.05

Table 3: Percentage (%) inhibition of edema

| | Group/treatment | Dose mg/kg | Inhibition of edema (mm) | | | | |
|---|------------------------|------------|--------------------------|-----|-----|-----|-----|
| | | | 30 min | 1 h | 2 h | 3 h | 4 h |
| 1 | Control | - | - | - | - | - | - |
| 2 | Drug control | 10 | 29 | 30 | 45 | 60 | 72 |
| 3 | <i>C. multistriata</i> | 100 | 26 | 28 | 11 | 35 | 44 |
| 4 | <i>C. multistriata</i> | 150 | 20 | 22 | 16 | 46 | 55 |

defensive factors inhibit ethanol-induced gastric mucosal lesions (Robert *et al.*, 1979). This is in conformity with our earlier suggestion that *C. multistriata* extract may owe its anti-ulcer effect to cytoprotection probably due to enhancement of prostaglandins synthesis. Although the precise mechanism of cytoprotection remains to be elucidated, the level of protection offered by the extract against ethanol induced ulcers directly suggests it may enhance prostaglandins synthesis.

Cissus multistriata contains many phytochemicals including flavonoids and other polyphenols (Omale *et al.*, 2006). The presence of polyphenols-flavonoids may be contributory to the anti-ulcerogenic property observed in this experiment. Polyphenols-flavonoids may prevent ulcer development due to their protein precipitating and vasoconstricting effects (Aguwa and Nwako, 1988). Their astringent action can help in precipitating micro proteins on the ulcer site, thereby forming an impervious layer over the lining that hinders gut secretions and protects the underlying mucosa from toxins and other irritants (Nwafor *et al.*, 1996, 2000; Al-Rehailey *et al.*, 2002).

This propensity to bind with proteins also explains the fact that polyphenols inhibit enzymes responsible for acid secretions in the stomach thus offered gastro protection observed.

As flavonoids have already been identified in this plant (Omale *et al.*, 2006), we believe strongly that the anti-ulcer activity of this extract is probably due to the antioxidant activity of the extract. Antioxidant activities of flavonoids have been well documented in the literature. Moreover, flavonoids have been reported for their anti-ulcerogenic activity and gastric protection already (Alarcon de la Lastra *et al.*, 1994; Parmar and Parmar, 1998).

The inhibitory activity on the induced rat hind paw edema, caused by the administration of *C. multistriata* extract at various assessment times after acetic acid injection are shown in Table 2. Induction of inflammation by inflammatory agents e.g., carrageenan or acetic acid involves three distinct phases of mediator release. The first phase involves the release of

histamine and serotonin and last between the first to the second hour, the second phase is the release of kinins lasting from the second hour to the third hour while the third phase involves the release of prostaglandins and lasts from the third to the fifth hour (Surrender and Mafumdar, 1995). Thus it can be inferred that the mechanism through which the extract elicits its effect is via the inhibition of the synthesis of kinins.

Since the extract was effective at these phases of mediator release. Indomethacin, a cyclooxygenase inhibitor, at the dose of 10 mg/kg b.w. exhibited significant (p<0.05) edema inhibition. *Cissus multistriata* extract's anti-inflammatory activity (Table 2) was dose dependent with 150 mg/kg b.w. giving highest percentage inhibition (55%) (Table 3).

At 100 and 150 mg/kg b.w. the extract caused significant (p<0.05) inhibition of the paw edema induced by acetic acid at 3 and 4 h. It is probable that the extract was capable of inhibiting the production of mediators involved in the inflammation produced by acetic acid.

CONCLUSION

This result therefore suggests that the plant extract contain anti-inflammatory agent that reduced the induced edema and provides a rationale for the use of this plant in the management of the diseases in folk medicine. Similarly, it is clear that *C. multistriata* leaf extract have significant anti-ulcer activity in animal model. It has muco-protective activity and gastric anti-secretory when compared with that of the reference drug Omeprazole. The anti-ulcer activity is probably due to the presence of flavonoids. Efforts are ongoing to characterize and explore the biological activity of the contributory compounds present in the extract.

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