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Medicinal Plants Used in the Traditional Treatment of Peptic Ulcer Diseases: A Case Study of *Napoleona vogelii* Hook and Planch (Lecythidaceae)

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Abstract: The methanol and the n-hexane leaf extracts of *Napoleona vogelli* (Lecythidaceae) were investigated for antiulcer properties using 3 experimental ulcer models induced by ethanol, indomethacin and hypothermic- restraint stress in rats. Anti-ulcer related properties of the extract such as gastrointestinal transit, the activity on isolated gut tissue preparations and the antimicrobial activities were also determined. Ethanol-induced ulcer was significantly ($p<0.05$) protected by HE (200 and 400 mg kg^{-1}) and by ME (800 mg kg^{-1}).The extracts ME (400 and 800 mg kg^{-1}) and HE (200 and 400 mg kg^{-1}) showed significant and dose-related ($p<0.05$) protection of the rats against indomethacin-induced ulcers. The stress ulcer was not protected by the administration of ME (200, 400 and 800 mg kg^{-1}), but was significantly ($p<0.05$) protected by HE at 400 mg kg^{-1}. The extracts appear to exhibit better protection against indomethacin and ethanol-induced ulcers than against the stress ulcer. Gastrointestinal propulsion in mice was significantly ($p<0.05$) reduced, in a dose-dependent manner by the methanol extract an n-hexane fraction of *N. vogelii*. On the rabbit jejunum, ME and HE showed a concentration-dependent antispasmolytic effect and inhibited ACh-evoked contractile response with IC_{50} of 389.05 and 372.73 μg mL^{-1}, respectively. The extracts inhibited the growth of the bacteria used in the study but had no activity against the fungi tested. The ME showed better antibacterial activity than the HE. The methanol leaf extract administered orally up to 5000 mg kg^{-1} did not produce lethality or signs of acute toxicity in mice after 24 h. Flavonoids, tannins, saponins, carbohydrate, terpenes, resins, steroids and alkaloids were found present in the extracts of *N. vogelii*. Gastro-protection and antispasmodic mechanisms could be responsible for the anti-ulcer properties of this plant.

Key words: *Napoleona vogelii*, anti-ulcer activity, gastro-protection, ulcers, antispasmodic activity

INTRODUCTION

Medicinal plants are reservoirs for drugs and lead compounds for many therapeutic agents (Farnsworth, 1989; Harvey, 1999). There are avalanche of scientific support on the efficacy of medicinal plants in the treatment of gastrointestinal disorders and in the management of ulcers of different aetiologies (Al-Harbi *et al*., 1997; Antonio and Brito-Souza, 1998; Anandan *et al*., 1999; David *et al*., 1999; Akah *et al*., 2001; Austin and Jegadeesan, 2002; Nwafor and Akah, 2003; Nwafor and Okoye, 2005).

Napoleona vogelii Hook and Planch (Lecythidaceae) is known locally as Akpuruke, Mkpodu, or Odure by the Ibos of South-eastern Nigeria. The plant is found mostly in rain forest and along the sea shores, extending from Sierra Leone to Nigeria (Keay *et al*., 1964). *Napoleona vogelii* tree grows up to 15 m high with few branches. The leaves, usually 7.5-15 cm long and 3.25-7.5 cm wide, are broadly elliptic, abruptly acuminate, shallowly toothed, thinly leathery and glossy looking (Keay *et al*., 1964). The plant is used in making wooden poles, warps, chewing stick and mats. Although, the plant is widely used in South-eastern Nigeria for the treatment of stomach aches and diarrhoea, there has not been any scientific investigation into the gastrointestinal properties of the plant. The medicinal values of another species *N. imperialis* (which is distinguished from *N. vogelii* by its smaller leaves) used in cough and asthma, as a tonic and as an analgesic has been reported (Iwu, 1993). The high cure rates claimed in the folk use of *N. vogelii* stimulated interest in investigating the gastro-protective and anti-ulcer related properties of the leaf extracts of the plant in experimental ulcer models.

MATERIALS AND METHODS

Animals: Adult Wistar rats (110-180 g), adult Swiss albino mice (20-25 g) of both sexes and New Zealand rabbits (1.8-2.5 kg) obtained from the animal house of the

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Department of Pharmacology and Toxicology, University of Nigeria, Nsukka, Enugu State, Nigeria, were used for the study. The animals were housed under standard conditions of temperature (25±2°C) and 12 h light/dark cycle. The rats and mice were fed with standard livestock feeds while the rabbit were fed with a local grass, *Panicum maxima* L. All the animals were allowed free access to clean drinking water.

Plant material: Fresh leaves of *N. vogelii* were collected from Adani, a community in Enugu State, Nigeria in the month of June. The plant material was authenticated by Mr. J.M.C. Ekekwe, a plant taxonomist formerly of the Department of Botany, University of Nigeria, Nsukka.

Extraction and activity-guided solvent fractionation: The fresh leaves were cleaned, shade-dried and crushed into coarse powder using Thomas-Wiley Laboratory Mill. The leaf powder (250 g) was extracted with 1.5 L of methanol in soxhlet extractor and concentrated *in vacuo* at 40°C using a rotary evaporator to give 40.59 g of a solid residue (ME). Another 500 g portion of the leaf powder was also successively extracted with 1.5 L each of n-hexane, chloroform, ethyl acetate and methanol in a soxhlet extractor and upon concentration *in vacuo* yielded HE (40.44 g), CE (20.45 g), EE (6.95 g) and ME (6.40 g), respectively. In a preliminary screening of these extracts, only the ME and the HE showed significant antiulcer properties and were therefore studied further for antiulcer and other gastroprotective properties.

The extracts were subjected to phytochemical screening according to the methods of Harbourne (1998) and Evans (2004). The acute toxicity of ME was also estimated in mice by the oral route using the method described by Lorke (1983).

Anti-ulcer tests: The extracts, ME and HE were suspended in 3% Tween 85 and tested orally for anti-ulcer activities using 3 models of experimental gastric ulcers. The methanol extract of *N. vogelii* was tested for antiulcer properties at 200, 400 and 800 mg kg^{-1} while the n-hexane extract was tested at 200 and 400 mg kg^{-1}. All the rats employed were fasted 18 h prior to the tests but were allowed free access to water. Cimetidine (100 mg kg^{-1}) and 3% Tween 85 (5 mL kg^{-1}) were used as reference antiulcer drug and negative control treatments, respectively.

Ethanol-induced ulcer model: Ethanol (1 mL of 96 %, v/v) was administered orally to 7 groups (n = 5) of adult Wistar rats 1 h after treatments with ME (200, 400 and 800 mg kg^{-1}), HE (200 and 400 mg kg^{-1}), cimetidine (100 mg kg^{-1}) and vehicle (5 mL kg^{-1}).The animals were sacrificed 1 h later (Morimoto *et al*., 1991).

Indomethacin-induced ulcer model: In this model, indomethacin (100 mg kg^{-1}) was administered orally to seven groups of rats (n = 5) 1 h after the various treatments with ME (200, 400 and 800 mg kg^{-1}), HE (200 and 400 mg kg^{-1}), cimetidine (100 mg kg^{-1}) and vehicle (5 mL kg^{-1}).The animals were sacrificed 8 h later (Urishidani *et al*., 1979).

Hypothermic restraint-stress ulcer model: The rats were placed into groups (n = 5) and pretreated as in ethanol- and indomethacin-induced ulcers. One hour later, they were immobilized individually in restraining cages containing cold water (15-20°C) and were made to swim for 18 h. The rats were then sacrificed thereafter (Akah and Nwafor, 1999).

For each model, the stomach of the animals were removed and opened along the greater curvature. They were rinsed under a stream of tap water, pinned flat on a corkboard and observed with a hand lens (x 10). Erosions formed on the glandular portions of the stomach were counted and each given a severity rating on a 0-3 scale based on the diameter of ulcer (i.e., 0, no ulceration; 1, ulcers = 1 mm; 2, ulcers > 1 mm = 2 mm; 3, ulcers > 3 mm) (Main and Whittle, 1975; Nwafor and Okoye, 2005). The total ulcer score for each stomach divided by a factor of 5 was calculated for each group and expressed as the Ulcer Index (U.I.).The degree of ulcer protection was calculated as a percentage of the negative control (Suziki *et al*., 1976).

Effect of extract on gastrointestinal transit: Swiss albino mice (of either sex) were fasted for 24 h prior to the experiment, but were allowed unrestricted access to clean water. They were randomized into six groups (n = 5). One group received Tween 85 (20 mL kg^{-1}, p. o.) and a second group received atropine (10 mg kg^{-1}, p. o.). The methanol extract (400, 800 mg kg^{-1}, p.o.) and n-hexane extract (400 and 800 mg kg^{-1}, p. o.) were administered to the remaining four groups respectively. After 1 h of treatment, each mouse received 0.5 mL of charcoal meal (5% charcoal in 10% tragacanth mucilage) orally. The mice were killed with chloroform, 30 min later and the intestine carefully removed and displayed. The intestinal distance moved by the charcoal meal from the pylorus was measured and expressed as a percentage of the distance from the pylorus to the ileocaecal junction for each animal (Nwafor *et al*., 2000).

Studies on isolated gut preparations: The effects of ME and HE on isolated guinea pig ileum and isolated rabbit jejunum preparations were studied. Segments of the tissues, 2-3 cm long, were suspended in 20 mL organ bath

filled with Tyrode solution of composition (mM/L): NaCl-136.7, KCl-2.7, $CaCl_2$-1.8, $NaHCO_3$-11.9, $MgCl_2$-1.0, Na_2HPO_4-0.4 and glucose-5.5 maintained at 37±1 °C and aerated with air. The preparations were set up under a resting tension of 0.5 g and allowed to equilibrate for 60 min during which the bathing fluid was changed every 10 min. At the end of equilibration, the effects of extracts ME and HE (100-1600 μg mL^{-1}) on the guinea pig ileum preparation and on the rhythmic movement of the rabbit jejunum preparations were studied. The effect of the extracts on ACh-evoked contractile responses of rabbit jejunum was determined. The IC_{50} of each treatment sample was determined. The contact time for the activity of each treatment is 30 sec with a tissue recovery period of 1 min. Responses were determined in triplicate and recorded on Ugo Basile Unirecorder (7050) through an isometric transducer (7004).

Antimicrobial screening: Seven microorganisms were used in the study. These include *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Salmonella paratyphi*, *Candida albican* and *Aspergillus niger*. They were hospital strains maintained on nutrient broth agar at 4°C. Prior to use, they were subcultured in nutrient broth agar plates at 37°C for 24 h. The agar disc diffusion method was employed (Lovian, 1980). The doses of the extracts were applied to appropriately labelled wells made in gelled agar containing 1.0×10^6 organisms mL^{-1}. The plates were incubated at 37°C for 24 h for bacteria and 72 h for fungi. The effects of the extract on the growth of the microorganisms were studied by observing the zones of inhibitions. The experiments were carried out in triplicates and the average clear diameter of zone of inhibition was recorded in each case.

Statistical analysis: The results were analysed by one-way ANOVA, subjected to LSD post Hoc tests and expressed as mean±standard error of mean. Significant differences between mean were accepted when p = 0.05.

RESULTS

The *N. vogelii* extracts showed positive reactions for saponins, tannins, glycosides, flavonoids, terpenoids, steroids, alkaloids, carbohydrates, fats and oil. The Methanol leaf Extract (ME) administered orally up to 5000 mg kg^{-1} did not produce lethality or signs of acute toxicity in mice after 24 h. Ethanol-induced ulcer was significantly ($p<0.05$) protected by HE (200 and 400 mg kg^{-1}) and by ME (800 mg kg^{-1}). The extracts of *N. vogelii* ME (400 and 800 mg kg^{-1}) and HE (200 and 400 mg kg^{-1}) showed significant and dose-related ($p<0.05$) protection of the rats against indomethacin-induced ulcers. The stress ulcer was not protected by the administration of ME (200, 400 and 800 mg kg^{-1}), but was significantly ($p<0.05$) protected by HE at 400 mg kg^{-1} (Table 1).

All other extracts (CE, EE and ME) of *N. vogelii* studied did not exhibit significant ($p>0.05$) anti-ulcer properties (data not shown) and was, therefore, not investigated further for other antiulcer-related properties. Gastrointestinal propulsion in mice was significantly ($p<0.05$) reduced, in a dose- dependent manner by ME and HE. In the control group, the charcoal meal head traversed 70.18% of the total length of the small intestine. The methanol extract, 400 and 800 mg kg^{-1}, inhibited intestinal propulsion by 20.78 and 35.31%, respectively while HE produced similar intestinal propulsion inhibition when compared to the control (Table 2).

Table 1: Effect of *N. vogelii* extracts on ulcers induced by different ulcerogens

		Ulcer index for different ulcerogens		
		Ethanol-ulcer (1 mL of 96 %, p. o)	Indomethacin-ulcer (30 mg kg^{-1}, p. o)	Stress-ulcer (hypothermic-restraint)
Tween 85	5 (mL kg^{-1})	5.24±2.4	5.68±0.64	12.48±3.02
ME	200 (mg kg^{-1})	3.20±0.84 (32.37)	4.88±0.52 (14.08 %)	10.08±2.64 (19.23 %)
	400 (mg kg^{-1})	3.05±1.40 (41.80 %)	3.10±0.61 (45.42 %)*	8.96±1.80 (28.21 %)
	800 (mg kg^{-1})	2.80±0.33 (46.56 %)*	2.30±0.86 (59.51 %)*	7.88±2.30 (36.86 %)
HE	200 (mg kg^{-1})	2.65±0.56 (50.93 %)*	2.46±0.76 (56.69 %)*	8.85±1.14 (29.09 %)
	400 (mg kg^{-1})	2.40±0.97 (54.20 %)*	1.88±0.57 (66.90 %)*	3.96±0.67 (68.27 %)*
Cimetidine	100 (mg kg^{-1})	0.00±0.00 (100.00 %)*	2.40±0.64 (57.75 %)*	3.08±1.50 (75.32 %)*

n = 5; *p<0.05; Percentage ulcer protection are in parenthesis

Table 2: The effect of *N. vogelii* extracts on gastrointestinal motility

Treatment	Dose (mg kg^{-1})	Intestinal Distance traveled (%)	Inhibition (%)
ME	400	55.60±09.03	20.78*
	800	45.40±04.28	35.31*
HF	400	52.00±09.72	25.90*
	800	45.60±08.61	35.02*
Atropine	10	39.83±02.34	43.25*
Control	-	70.18±14.48	-

n = 5, *: p<0.05

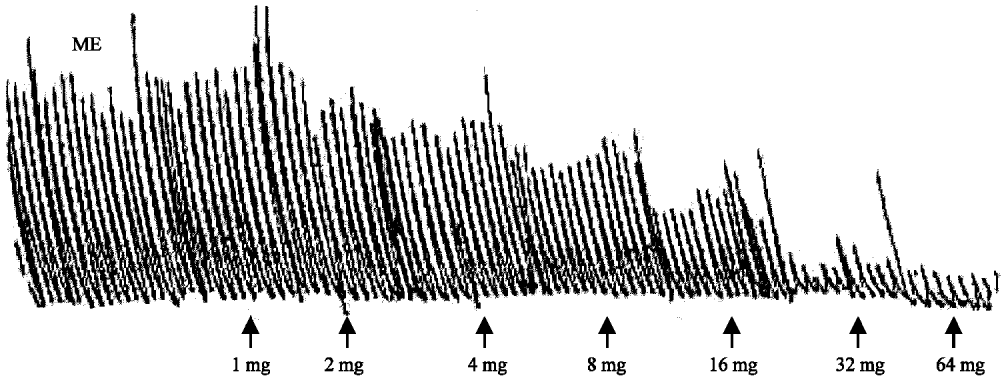

Fig. 1: The effect of methanol extract of *N. vogelii* on rhythmic movement of rabbit jejunum preparation

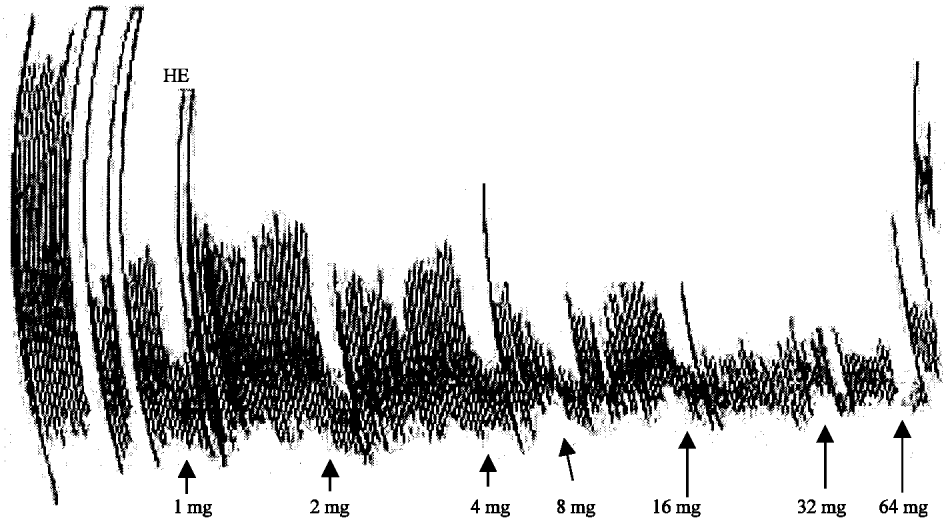

Fig. 2: The effect of n-hexane extract of *N. vogelii* on rhythmic movement of rabbit jejunum preparation

Table 3: The effect of *N. vogelii* extracts on ACh-evoked contraction of rabbit jejunum preparation

Extract	Concentration (μg mL^{-1})	Maximal (%) contraction	Concentration-response equation (R^2 value in parenthesis)	IC_{50} (μg mL^{-1})
ME	100	84.62±4.5		
	200	69.23±4.1		
	400	53.85±3.9	y = -63.883x + 215.46 (0.989)	389.05
	800	30.77±3.4		
	1600	7.69±2.7		
HE	100	91.67±3.3		
	200	75.00±3.8		
	400	33.33±1.5	y = -67.823x + 224.4 (0.927)	372.73
	800	25.00±0.8		
	1600	14.58±0.4		

Maximal contraction was produced by ACh (1 μg mL^{-1}); y = Maximal response (%); x = $\log_{10}$ (conc. of extract); IC_{50} = 50 % inhibitory concentration, n = 3

On the isolated rabbit jejunum, ME and HE showed a concentration-dependent antispasmolytic effect (Fig. 1 and 2) and inhibited ACh-evoked contractile response with IC_{50} of 389.05 and 372.73 μg mL^{-1}, respectively (Table 3). The extracts had no effect on guinea pig ileum preparation.

Both ME and HE inhibited the growth of the bacteria used in the study; however, they had no activity against the fungi tested. The n-hexane extract appeared to possess better antibacterial activity when compared to ME (Table 4).

Table 4: Sensitivity test on some microorganisms to 100 mg mL^{-1} of *N. vogelii* methanol and n-hexane extracts

	Inhibition zone diameter (mm)±SEM	
Micoorganism	Methanol extract (ME)	n-Hexane extract (HE)
E. coli	38.7±6.300	6.00±0.00
S. paratyphi	16.0±8.300	4.70±2.40
Ps. aeruginosa	11.0±0.600	5.30±0.80
K. pneumonia	10.3±0.300	0.00±0.00
S. aureus	03.3±1.300	1.30±0.30
C. albicans	00.00±0.00	0.00±0.00
A. niger	00.00±0.00	0.00±0.00

n = 3

DISCUSSION

Although in many cases the aetiology of peptic ulcer is not known, however, investigations into the pathogenesis have revealed that whenever there is a shift in the balance between the aggressive action of acid-peptic secretion and the maintenance of the mucosal integrity through the endogenous defense mechanisms ulcer develops (Venkataranganna *et al*., 1998). The goals of therapy for ulcers are to relief from pain, to promote complete healing, to prevent reoccurrence and to prevent the development of complications (Afifi *et al*., 1997). The therapeutic strategies are aimed at balancing the aggressive factors against defensive factors. To regain this balance, different therapeutic agents are used to either inhibit the gastric secretion or to boost the mucosal defense mechanisms (Greenberger, 1982; Afifi *et al*., 1997; Dhuley and Naik, 1998). No one anti-ulcer agent appears to have all these qualities. The search for a safe anti-ulcer drug that optimizes these properties is continuing and part of the search is the evaluation of medicinal plants for gastro-protective properties (Afifi *et al*., 1997; Akah *et al*., 1998a; Asuzu and Onu, 1990; Akah and Nwafor, 1999; Akah *et al*., 2001; Nwafor and Akah, 2003; Nwafor and Okoye, 2005).

Because *N. vogelii* is widely used in folk medicine for the treatment of PUDs, we investigated the anti-ulcer properties of the leaf extracts of the plant using three experimental ulcer models. Various mechanisms may be associated with the formation of gastric mucosal lesions in these experimental models (Parmar and Ghosh, 1981). It has been postulated that ethanol-induced gastric mucosal lesions are caused by the direct toxic action of ethanol, reduction in bicarbonate secretion and depletion of gastric wall mucous (Koo *et al*., 1986; Marhuenda *et al*., 1993). The *N. vogelii* extract, especially the hexane extract protected the rats from ethanol-induced gastric erosion. It has been observed that gastric acid is virtually not involved in the formation of such lesions (Antonio and Souza-Brito, 1998), but endogenous glutathione and Prostaglandin (PG) levels are reduced while the release of histamine, influx of calcium ions and generation of free radicals are increased (Galvin and Szabo, 1992). Indomethacin, a non-steroidal anti-inflammatory agent, causes ulceration mostly at the glandular part of the stomach (Nwafor *et al*., 1996). This ulceration is related to inhibition of endogenous prostaglandin synthesis (Rainford, 1978). Prostaglandins has been demonstrated to serve useful gastro-protective functions by maintaining gastric microcirculation (Vane, 1971), stimulation of mucous and bicarbonate secretions and inhibition of gastric acid secretions (Konturek *et al*., 1988). Conversely, prostaglandin inhibition leads to over production of leukotrienes which can induce mucosal vaso-constriction thereby reducing local blood flow (Hawkey, 1989; Dajani and Agrawal, 1995). Although, the methanol and the hexane extracts decreased ulcer indices in all the three models, better protection appears to be shown against the indomethacin-induced ulcer suggesting cytoprotective mechanism of action. Hypothermic restraint ulcer model is associated with increase in gastric acid secretion and a decrease in pH (Murakami *et al*., 1985). Previous studies has suggested a role of Leukotriene-C4 (LTC4), a lipoxygenase derived metabolite of arachidonic acid in stress-induced ulcer. This tissue derived mediator acts on gastric microvasculature constricting sub-mucosal venules with subsequent stasis of blood flow and plasma leakage from vascular bed causing the wide spread mucosal injury in these model (Hua *et al*., 1985). Other studies have shown that histamine has an essential role in the pathogenesis of stress ulcer since it is a potent stimulator of gastric acid secretion (Ibu *et al*., 1985; Al-Mashhadani *et al*., 1991). The methanol extract did not show significant protection ($p>0.05$) against stress ulcer while the hexane extract protected the rats significantly ($p<0.05$) only at 400 mg kg^{-1}.

In addition to other phyto-constituents, flavonoids and saponins were found present in abundance in the both the methanol and n-hexane extracts. These constituents are known to offer protection against ulcers. In different studies, flavonoids have shown anti-secretory and cytoprotective properties (Hashizume *et al*., 1978; Guaraldo *et al*., 2001). Saponins, especially those of the triterpene type (like glycyrrhetinic acid and carbenoxolone) found in the licorice root have been shown to posses anti-ulcer properties through the formation of protective mucous on the gastric mucosa and by selectively inhibiting PGF2α (Aguwa and Okunji, 1986; Lewis and Hanson, 1991).

The extracts of *N. vogelli* also showed a dose-dependent reduction in gastrointestinal motility. In ulcer patients, reduction in gut motility helps to ameliorate the ulcer pain and hasten the healing of ulcer wounds (Mersereau and Hinchey, 1988). In the *in vitro* studies, the extract produced no contraction of guinea pig ileum preparation, but inhibited the rhythmic contractions of isolated rabbit jejunum preparations. The inhibitions of the spontaneous pendular movements of the jejunum by the extracts corroborated the reduction in peristalsis recorded in the *in vivo* studies and are desirable and could be found useful in the management of peptic ulcers (Offiah *et al*., 1996; Brunton, 1996). The extract inhibited ACh-evoked contraction of rabbit jejunum preparation, but had no effect on the contractions evoked by histamine. We have not been able to associate these mediators and their receptors with definite roles in the gastro-protective properties of *N. vogelii*.

Microbial colonization of the gastrointestinal system has been associated with a variety of peptic ulcer diseases (Tally and Ormand, 1989; Rauws and Hulst, 1995). *Helicobacter pylorus has* been implicated as the microorganism involved in the pathogenesis of ulcer and has made antibiotics an essential component in the management of the PUDs. This stimulated our interest in screening the extracts of *N. vogelii* for antimicrobial activity. Eradication of *H. pylori* infection with antibiotics provides a more permanent cure than the conventional method of symptoms alleviation and temporary ulcer healing therapies (NIH Consensus, 1994; Harris *et al*., 1995). Although we could not culture *H. pylori* for use in the antimicrobial studies, the effects of the extracts against other Gram negative enteric pathogens, which belong to the same class as *H. pylori*, were tested and could be relevant to the anti-ulcer activity of these plant extracts.

CONCLUSION

The methanol as well as the n-hexane extracts of *N. vogelii* protected rats against ulcers induced by different ulcerogens. The traditional use of *N. vogelii* leaf decoctions in the treatment of peptic ulcer diseases, heart burn and other stomach disturbances could be justified by the results of this study.

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