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Antisecretagogue, Antiulcer and Cytoprotective Effects of 'Peppermint' *Mentha piperita* L. In Laboratory Animals

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'Peppermint,' *Mentha piperita* is known to possess various therapeutic properties. We evaluated the anti-ulcerogenic property of an aqueous suspension of peppermint in different ulcer models in wistar albino rats. The suspension at 250 and 500 mg kg^{-1} body weight, orally (i.p. in Shay rat model) has significant effect in pyloric ligation induced basal gastric secretion, indomethacin and noxious chemical (80% ethanol, 0.2 M NaOH and 25% NaCl) induced gastric ulceration; showed significant protection in all models used. These findings were supported by histopathological assessment of gastric tissue and by the determination of non-protein sulfhydryl (NP-SH) contents of the stomach, as these parameters showed protection of various indices and replenishing the depleted NP-SH level by the suspension treatment, respectively. Conclusively, the ulcer protective effect of peppermint suspension may possibly be due to its anti-secretory along with antioxidative and cytoprotective through prostaglandins mediated mechanism.

Key words: Peppermint, *Mentha piperita*, gastric secretion, antiulcer

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INTRODUCTION

Gastric hyperacidity and ulcer is a very common global problem today. It is now generally agreed that gastric lesions develop when delicate balance between some gastroprotective and aggressive factors is lost. Major aggressive factors are acid, pepsin, *Helicobacter pylori* and bile salts. Defensive factors mainly involve mucus-bicarbonate secretion, prostaglandins (Hoogerwerf and Pasricha, 2001) and antioxidative agents (Madsen and Bertelsen, 1995). Hypersecretion of gastric acid is a pathological condition, which occurs due to uncontrolled secretion of hydrochloric acid from the parietal cells of the gastric mucosa through the proton pumping H^+K^+ATPase (Sachs *et al*., 1995). Even the normal rate of acid secretion may cause ulceration in breached mucosa when some gastroprotective factors are lost. The conventional approach to control gastric ulceration is to inhibit gastric acid secretion, to promote gastroprotection to block apoptosis and to stimulate epithelial cell proliferation for effective healing (Bandhopadhyay *et al*., 2002). Most of the antisecretory drugs such as proton pump inhibitors and histamine H_2-receptor blocker are extensively used to control increased acid secretion and acid related disorders caused by stress, NSAID's and *H. pylori*, but there are reports of adverse effects and relapse in the long run (Martelli *et al*., 1998; Wolfe and Sachs, 2000). On the contrary most of the herbal drugs reduces the offensive factors and proved to be safe, clinically effective and better patient tolerance (Goel and Sairam, 2002; Al-Yahya *et al*., 1990). The ethnopharmacological approach provides the way for developing new plant derived drugs. Herbs and spices, however, are some of the most attractive sources of new drugs and have been shown to produce promising results in the treatment of gastric ulcers (Rafatullah *et al*., 1990; Al-Mofleh *et al*., 2005a).

Peppermint 'Naa'naa', *Mentha piperita* L. (Lamiaceae family) is an ancient spice known to Chinese, Greek and Arab physicians. In Saudi Arabia and other Middle Eastern countries, peppermint tea is customarily used as a substitute for black tea refreshing drink. Apart from its use as condiment and as a flavoring agent, various medicinal properties are attributed to this tiny spicy herb, which range from dyspepsia, flatulence, indigestion, biliousness and to check morning sickness, nausea and summer diarrhea. The oil of peppermint is also indicated for both external and internal use. The food and drug administration (FDA) granted the oil of peppermint a "Generally Regarded As Safe" (GRAS) status (Food and Drugs, 1998). Recently, sixteen clinical trials (randomized double blind crossover) have been undertaken on peppermint oil in Irritable Bowel Syndrome (IBS) or recurrent abdominal pain in children and found to be efficacious (Grigoleit and Grigoleit, 2005a). In an another study, the oil exerted as spasmolytic and antispasmodic effect on the smooth vasculature of the intestinal tract (Grigoleit and Grigoleit, 2005b, c). A multiherbal formulation, in which *Mentha piperita* is one of the ingredients has shown antiulcerogenic property. Whereas, recently peppermint has exhibited pronounced antioxidative activity (Capecka *et al*., 2005; Mi-Hyun *et al*., 2005). There is a great controversy regarding the consumption of spices. It is said that the use of spices leads to gastric derangement and even ulceration; on the other hand, when such situations occur people use certain spices or plants in order to relieve their discomfort.

The present study was carried out to investigate the antisecretory, antiulcer and cytoprotective properties of an aqueous suspension of Peppermint, a popular spice, in laboratory animals to substantiate the claims and its use in Unani and Arabian traditional medicine.

MATERIALS AND METHODS

Plant material: The fresh peppermint was purchased from local vegetable market of Riyadh and identified. The leaves were shade dried, finely powdered, sieved and suspended in distilled water before administration to the animals.

Animal stock: Wistar albino rats of either sex (home bred) aged 7-8 weeks and weighing 150-200 g, were obtained from the Experimental Animal Care Centre, King Saud University, Riyadh, Saudi Arabia. The animals were fed on Purina chow diet and water ad libitum and were maintained under standard conditions of humidity (55±5%), temperature (22±2°C) and light (12 h light/12 h dark cycle). The rats were randomly assigned to different control and treatment groups. The conduct of experiments and the procedure of sacrifice (using ether) were approved by the Ethics Committee of the Experimental Animal Care Society, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.

Chemicals: Ethanol (BDH, England), indomethacin (Sigma), sodium hydroxide and sodium chloride (Merck) were used.

Antisecretory studies

Pylorus ligated (Shay) rats: The animals were fasted for 36 h with access to water ad libitum before the pylorus was ligated under ether anesthesia, care being taken

not to cause bleeding or to occlude blood vessels (Shay *et al*., 1945). Peppermint suspension (250 and 500 mg kg^{-1} body weight) was administered immediately after pylorus ligation by intraperitoneal injection. The animals were sacrificed 6 h after the pylorus ligation, stomachs were removed and contents were collected, measured, centrifuged and subjected to analysis for titratable acidity against 0.01 N NaOH to pH 7. Each stomach was examined for lesions as described earlier.

Indomethacin-induced gastric ulcer: Indomethacin was suspended in 1% carboxymethylcellulose in water (6 mg mL^{-1}) and administered to the fasted rats in a dose of 30 mg kg^{-1} (0.5 mL 100 g). Rats were treated with peppermint suspension (250 and 500 mg kg^{-1}, orally) 30 min before indomathacin. Control rats were treated similarly with an equivalent amount of vehicle (Bhargava *et al*., 1973). The stomachs of the animals were removed, rinsed with normal saline and studied according to the standard procedure (Szabo *et al*., 1985).

Gastric lesions induced by necrotizing agents: The animals in the test groups were given 1 mL of necrotic agents, either 80% ethanol, 0.2 M NaOH or 25% NaCl, which are known to produce gastric lesions (Robert *et al*., 1979). Hypertonic saline and NaOH (0.2 M) were used only in cytoprotection studies. Peppermint suspension was given 30 min before the necrotizing agents. The animals were killed under anesthesia, using diethyl ether 1 h after treatment with the necrotic agents. The stomach of each of the animals was excised and opened along the greater curvature. After washing with normal saline the gastric lesions were quantified using a binocular magnifier. The ulcers were scored according to the method of Valcavi *et al*. (1982). Control animals were treated with vehicle only.

Estimation of nonprotein sulfhydryl groups (NP-SH): Gastric mucosal NP-SH was measured according to the method reported earlier (Sedlak and Lindsay, 1968). The glandular stomachs of control and treated rats were removed and homogenized in ice-cold 0.02 M ethylenediaminetetraacetic acid. The homogenate was mixed with distilled water and 50% TCA and centrifuged; the supernatants were mixed with Tris buffer, 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB) was added and the sample was shaken. The absorbance was measured, within 5 min of addition of DTNB, at 412 nm, against a reagent blank with no homogenate.

Statistical analysis: The differences between control and treated groups were compared using the ANOVA and Student's t-test as appropriate and were considered significant if p was <0.05.

Histopathological studies: The gastric tissue was fixed in 10% ethanol buffer for malin and processed though graded ethanol, xylene and impregnated with paraffin wax; sections were made by microtome. After staining with haemotoxylin and eosin stain (Culling, 1974), the sections were examined under a research microscope by a person who was not aware of experimental protocols. The different histopathological indices screened were: congestion, hemorrhage, edema, necrosis, inflammatory and dysplastic changes erosions and ulcerations.

RESULTS

Effect of anti-secretory activity: Treatment with aqueous suspension of peppermint immediately after pylorus ligation of rats resulted in a significant decrease of basal gastric secretory volume, acidity and ulceration. However, the reduction in titratable acidity was not found to be statistically significant in low dose (250 mg kg^{-1}) group (Table 1).

Effect on indomethacin-induced gastric ulcers: Pretreatment of fasted rats with aqueous suspension of peppermint in both doses, significantly protected gastric mucosal damage induced by indomethacin (Table 2).

Table 1: Effect of an aqueous suspension of peppermint on the volume of gastric secretion, titratable acidity and the degree of ulceration in 6 h pylorus ligated (Shay) rats

		Mean±SE		
Treatment	Dose (mg kg^{-1}, i.p)	Volume of gastric content (mL)	Titratable acid (mEq L^{-1})	Ulcer index
Control	-	5.75±0.72	133.88±2.34	0.66±0.33
Peppermint suspension	250	0.5±0.22***	00.0***	0.0***
Peppermint suspension	500	0.83±0.54***	28.33±18.05***	0.0***

Six animals were used in each group. ***p<0.001. Student's t-test

Table 2: Effect of an aqueous suspension of peppermint on the gastric mucosal damage induced by indomethacin in rats

Treatment	No. of animals	Dose (mg kg^{-1}, p.o.)	Ulcer index (Mean±SE)
Control	6	-	41.50±4.68
Peppermint suspension	6	250	15.66±5.1**
Peppermint suspension	6	500	13.83±3.88***

**p<0.01; ***p<0.001. Student's t-test

Table 3: Effect of an aqueous suspension of peppermint on the gastric lesions induced by various necrotizing agents in rats

		Mean±SE		
Treatment (n=6)	Dose (mg kg^{-1}, p.o.)	Ulcer index 80% EtOH	0.2M NaOH	25% NaCl
Control	-	7.16±0.47	7.66±0.33	7.66±0.33
Peppermint suspension	250	5.00±0.81*	5.66±0.84*	2.50±0.42***
Peppermint suspension	500	4.00±0.68***	3.33±0.42***	2.50±1.00***

*p<0.05. ***p<0.001. Student's t-test

Table 4: Effect of an aqueous suspension of peppermint on glutathione (NP-SH) concentration in gastric tissue of rats

S. No.	Treatment and dose (mg kg^{-1}, body weight)	NP-SH concentration (μmol 100 mg wet tissue) Mean±SE
1	Control (distilled water, 1 mL/rat)	8.59±0.33
2	Control (80% ethanol, 1 mL/rat)	5.89±0.16^{a}**
3	Peppermint suspension (250)+ 80% ethanol (1 mL/rat)	6.64±0.12^{b}*
4	Peppermint suspension (500)+ 80% ethanol (1 mL/rat)	7.58±0.38^{b}*

Six rats were used in each group. ^{a} = as compared to control (distilled water) group. ^{b} = as compared to control (80% ethanol) treated group.
*p<0.001; **p<0.001 (Student's t-test)

Table 5: Effect of an aqueous suspension of peppermint on ethanol-induced histopathological lesions in gastric mucosa of rats

	Treatment	Histopathological Lesions Induced							
Group No.	and dose (mg kg^{-1}, body weight)	Congestion	Haemorrhage	Edema	Necrosis	Inflammatory changes	Dysplastic changes	Erosions	Ulceration
1	Control. (distilled water) (1 mL/rat)	-	-	-	-	-	-	-	-
2	Ethanol, 80% (1 mL/rat).	+++	++	++	+	+	+	++	++
3	Peppermint (250)+ethanol, 80% (1 mL/rat).	++	+	++	+	+	-	+	+
4	Peppermint suspension (500)+ ethanol, 80% (1 mL/rat)	+	+	-	-	-	-	+	+

- = Normal; + = Moderate effect; ++ = Severe effect; +++ = Intensely severe effect

Effect on necrotizing agents-induced gastric lesions: Aqueous suspension of peppermint showed the ability to reduce significantly the severity of ulceration of stomachs induced by ethanol and strong alkalies at both doses (Table 3).

Estimation of NP-SH in gastric tissue: Ethanol 80% induced a significant decrease in gastric mucosal NP-SH level. Prior treatment of animals with aqueous suspension of peppermint significantly increased the depleted gastric NP-SH contents in both dose groups (Table 4).

Effect on histopathological gastric lesion: Pretreatment with peppermint was found to induce moderate protection of the different histopathological lesions such as congestion, haemorrhage, erosions and ulceration-induced by ethanol in the gastric mucosa of rats. The lesions such as edema, necrosis and inflammatory changes were inhibited at the higher doses, whereas the dysplastic changes were absolutely inhibited at both the doses (Table 5).

DISCUSSION

In the present study the antisecretagogue, antiulcer and cytoprotective activities of the aqueous suspension of peppermint are evident following pylorus ligation, indomethacin and noxious chemicals induced gastric mucosal damage in rats. The antisecretory action of peppermint suspension may account for its antiulcer activity in various experimental models in which increased gastric acidity is involved in the pathogenesis of gastric and duodenal lesions (Rafatullah *et al.*, 1995). In addition, the ulcer disease has also been ascribed to acid or the consequences of hyperacidity (Modlin, 1995). Acid hypersecretion is an important pathophysiologic factor in the genesis of peptic ulcer; and potent antisecretory agents may benefit the healing through their acid secretion inhibitory properties (Arakawa *et al.*, 1992). How far this antisecretory effect may contribute to its antiulcer activity is not clear; however, some of the compounds, such as carbenoxolone and sucralfate, even with a low antisecretory profile, have been shown to possesses

antiulcer properties (Borella *et al*., 1979; Chiu *et al*., 1984). Present studies, on indomethacin-induced gastric damage showed inhibition of gastric lesions by peppermint suspension. The mechanisms of indomethacin-induced stomach ulcers have been well documented (Fitzpatrick and Wynalda, 1976). These include inhibition of prostaglandin biosynthesis (Tariq *et al*., 1985), a reduction in the local blood flow, topical irritation and an interference with restitution and tissue repair (Ito and Lacy, 1985; Taha *et al*., 1995). The results of this study suggested that the ability of peppermint suspension to prevent ulceration, at least in part by prostaglandin biosynthesis mechanism (Kiuchi, 1982). On the other hand, the aqueous suspension of peppermint also exhibited a significant inhibition of gastric lesions induced by various necrotizing agents, suggesting an increased mucosal resistance or potentiation of defensive factors against noxious chemical (Ligumsky *et al*., 1995). The chemical constituents of peppermint responsible for its antiulcer activity are not known. However, peppermint contains caryophellene, menthol, flavonoids, carotenoids, tocopherols, tannin, volatile oils, flavones, monoterpenes (Voirin and Bayet, 1992; Voirin *et al*., 1994; Zakharova *et al*., 1987).

Previously, Ruiz *et al*. (1996) have reported antigastric ulcer potential of flavonoids similarly, flavonoids, have also been shown their protective effect on human gastric cancer cells (Matsukawa *et al*., 1990). Akhtar *et al*. (1992) have demonstrated an antiulcerogenic effect of volatile oil and flavonoids of a plant belongs to peppermint family. Nonprotein sulfhydryls (NP-SH) are thought to be involved in protecting gastric mucosa against various chemicals (Szabo *et al*., 1981; Rogers *et al*., 1988). Decreased levels of endogenous sulfhydryls have been associated with tissue damage by various chemical agents (Miller and Lid, 1985; Parmar *et al*., 1988). Our observation showed a significant reduction in NP-SH content of the gastric mucosa after 80% ethanol administration. Pretreatment of rats with peppermint suspension significantly prevented NP-SH depletion. On the other hand, peppermint suspension exerted an antispasmodic activity on acetylcholine induced contraction of guinea pig ileum, which again suggests an anticholinergic mechanism may involved in preventing gastric lesions in rats (Orisakwe *et al*., 1996).

The results on histopathological investigation on the gastric mucosa of rats revealed the pretreatment with peppermint suspension partly inhibited the ethanol-induced congestion, hemorrhage, erosions and ulcerations and absolutely inhibited the edema, necrosis, inflammatory and dysplastic changes. Present results are in corroboration with the anti-gastric ulcer activity of the extract observed under the studies on pharmacological and biochemical evaluation.

In conclusion, it appears that peppermint possesses antiulcerogenic principles which protect against gastric mucosal damage induced by indomethacin and noxious chemicals, through inhibition of basal gastric acid secretion (attenuation of aggressive factors) and stimulation of mucus secretion (potentiation of defensive factors). Probably the antiulcer effect is due partly at least, to the presence of menthol, although the involvement of other chemical compounds in the plant cannot be ruled out. The data so far obtained do not indicate, however, which specific mechanism(s) is (are) responsible for the antisecretory, antiulcer and cytoprotective activities. Further studies are required to isolate the antiulcer compounds and to elucidate their mechanism of action and to substantitate its use in Unani and Arabian traditional medicine for various gastric ailments.

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