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Effect of *Carum carvi* on Experimentally Induced Gastric Mucosal Damage in Wistar Albino Rats

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Abstract: The effect of *Carum carvi* L. pretreatment on gastric mucosal injuries caused by NaCl, NaOH, ethanol and pylorus ligation accumulated gastric acid secretions was investigated in rats. Pretreatment at oral doses of 250 and 500 mg kg⁻¹, body weight was found to provide a dose-dependent protection against the (i) ulcerogenic effects of different necrotizing agents (ii) ethanol-induced histopathological lesions, depletion of stomach wall mucus and Nonprotein Sulfhydryl groups (NP-SH) and (iii) pylorus ligated accumulation of gastric acid secretions. The protective effect of *Carum carvi* against ethanol-induced damage of the gastric tissue appears to be related with the free-radical scavenging property of its constituents. The exact mechanism of action of the gastroprotective activity is not known. However, it might be due to flavonoid related suppression of cytochrome P450 1A1 (CYP1A1) which are known to convert xenobiotics and endogenous compounds to toxic metabolites.

Key words: *Carum carvi* L., protection, gastric ulceration, secretions, gastric mucus, glutathione

INTRODUCTION

Since times immemorial, herbs including spices have been used in traditional medicine to treat a wide range of ailments, including gastrointestinal disorders such as dyspepsia, gastritis and Peptic Ulcer Disease (PUD). As part of our ongoing screening program of spices, the present study assessed the anti-gastric ulcer activity of *Carum carvi*, which belongs to the family Umbelliferae. *Carum carvi* is a biennial herb, widely cultivated in West Asia, Europe and North America. The part used is the dried ripe fruit (Leung, 1980). The fruit of (caraway fruit) is usually referred to as a seed and has an aromatic fresh taste and smell caused by an essential oil contained in ducts of the pericarp (Toxopeus and Bouwmeester, 1992). In folk medicine, it is used as an antispasmodic, carminative, expectorant and stomachic, in addition to relieve menstrual discomforts, promoting milk secretion (Leung, 1980). In combination with *Rhamnus frangula* and *Citrus aurantium*, *Carum carvi* was found to be effective against obstipation syndrome (extreme constipation) (Matey *et al.*, 1981). Carvone, the main constituent of *Carum carvi* has a sweet spearmint odor. It has several applications as fragrance and flavor, potato sprouting inhibitor, antimicrobial agent, building block and biochemical environmental indicator, along with its relevancy in the medical field (Carla *et al.*, 2005).

Reactive oxygen species are well known to play a major role in the etiology and pathophysiology of human diseases, in general and digestive system disorders in particular (Repetto and Llesuy, 2002). A number of experimental studies have demonstrated that oxygen-generated free radicals and lipid peroxidation play an important role in the pathogenesis of acute gastric lesions (Salim, 1990; Zimmerman and Granger, 1994; Rastogi *et al.*, 1998). Dietary antioxidants might play a positive role to combat tissue injury (Barry, 1991). Hence, there is a world-wide search of useful antioxidants to combat the diseases of the stomach.

Studies on *Carum carvi* against the pathogenesis of gastric lesions became important with the discovery of its antioxidant activity. In one of the earlier reports, it is found to inhibit superoxide radicals, lipid peroxides and hydroxyl radicals (Satyanarayana *et al.*, 2004). Furthermore, some constituents of *Carum carvi* have been reported to possess antioxidant and gastro-protective activity. Terpenes including carvones and limonene are known to induce the detoxifying enzyme glutathione S-transferase in several mouse target tissues (Zheng *et al.*, 1992). Flavonoids, including quercetin and kaempferol have been reported to possess antioxidant and antiulcer activities (Hirschmann and Yesilada, 2005; Sannomiya *et al.*, 2005).

The present study on the inhibition of gastric mucosal damage was undertaken in view of (i) the known antioxidant potentials of *Carum carvi* and its

constituents (ii) its use in folk medicine as an aromatic carminative, stomachic, antispasmodic and against gastrointestinal discomforts such as dyspepsia and flatulence and (iii) the economic importance of its principal constituent (carvone).

MATERIALS AND METHODS

The present study on effect of *Carum carvi* on experimentally induced gastric mucosal damage in Wistar albino rats was conducted in the Department of Pharmacology, College of Pharmacy, King Saud University. The experimental part was undertaken during the period July to October 05.

Plant material and preparation of aqueous suspension: Seeds of *Carum carvi* (family, Umbelliferae) were collected from local market in Riyadh, identified under expert guidance and preserved for future reference. The seeds were ground to a very fine powder and used as an aqueous suspension for treatment in different experiments.

Animals: Male Wistar albino rats (home bred), aged 8-10 weeks, weighing about 150-200 g were obtained from the Experimental Animal Care Center, King Saud University, Saudi Arabia. The animals were maintained under standard conditions of temperature, humidity and light (12 h dark, 12 h light). They were provided with *Purina chow* and free access to water. Before testing, the animals were fasted for 36 h with access to water *ad libitum*. 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.

Dose selection and route of administration: The doses (250 and 500 mg kg⁻¹, body weight) selected for the conduct of the experiments were based on the MTD value (30 g kg⁻¹, body weight) and the preliminary experiments conducted on the pharmacological activity of *Carum carvi* (Chan *et al.*, 1986). The route of administration of the aqueous suspension was oral (gastric intubation) in all the experiments.

Gastric lesions induced by necrotizing agents: The animals in the test groups were given 1 mL per rat of different necrotizing agents (80% ethanol, 0.2 M NaOH and 25% NaCl) which are known to produce gastric lesions (Al-Bekairi *et al.*, 1992). NaCl (25%) and NaOH (0.2 M) were used only in cytoprotection studies. Based on the gastric emptying in fasted rats, *Carum carvi* was

given 30 min before the necrotizing agents. Animals were killed under ether anesthesia 1 h after treatment with ulcerogenic agents. The stomach 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) and assessed on the basis of their dimensions: Deep circular ulcers more than 8 mm = 10; 7-8 mm = 8; 6-7 mm = 7; 5-6 mm = 6; 4-5 mm = 5; 3-4 mm = 4; 2-3 mm = 3; 1-2 mm = 2 and 0-1 mm = 1. The deep linear ulcer more than 10 mm in length = 6 and linear ulcer less than 10 mm in length = 3. The scores for each single lesion were then summed up for the determination of ulcer index.

Gastric wall mucus determination: The modified procedure of Corne *et al.* (1974) was used to determine gastric-wall mucus. The glandular segments from the stomachs were removed and weighed. Each segment was transferred immediately to 1% Alcian blue solution (in sucrose solution, buffered with sodium acetate pH 5) and the excess dye was removed by rinsing with sucrose solution. The dye complexed with the gastric wall mucus was extracted with magnesium chloride solution. A 4 mL aliquot of blue extract was then shaken with an equal volume of diethyl ether. The resulting emulsion was centrifuged and the absorbance of the aqueous layer was recorded at 580 nm. The quantity of Alcian blue extracted/g (net) of glandular tissue was then calculated.

Estimation of nonprotein sulfhydryl groups: Gastric mucosal (NP-SH) was measured according to the method of Sedlak and Lindsay (1968) to analyze the oxidant/antioxidant balance. The glandular stomach was removed and homogenized in ice-cold 0.02 M ethylenediaminetetraacetic acid. The homogenate was mixed with distilled water and 50% (w/v) aqueous TCA and centrifuged; the supernatants were mixed with phosphate buffer (pH 8), 5, 5'-dithiobis (2-nitrobenzoic acid) (DTNB) was added and the sample was shaken. The absorbance was read within 5 min of addition of DTNB, at 412 nm, against a reagent blank with no homogenates.

Histopathology of gastric tissue: The gastric tissue samples were fixed in neutral buffered formalin for 24 h. After fixation each sample was dehydrated, cleared and embedded in paraffin wax. Sections of tissues from stomachs were histopathologically examined to study the anti-ulcerogenic and/or ulcerogenic activity of the test spice. The tissues were fixed in 10% buffered formalin and using a VIP tissue processor did the processing. The

processed tissues were embedded in paraffin blocks and sections of thickness about 5 µm thickness were cut by employing an American optical rotary microtome. These sections were stained with haematoxylin and eosin using routine procedures. The slides were then examined under a microscope for pathomorphological changes as congestion, hemorrhage, edema and erosions using an arbitrary scale for the assessment of severity of these changes (Al-Harbi *et al.*, 1995).

Determination of anti-secretory activity: The method of Shay *et al.* (1945) was used to determine the anti-secretory activity. The animals were fasted for 36 h with free access to water. Ligation of the pylorus was done under light ether anaesthesia. Care was taken not to bleed or occlude the blood vessels. Aqueous suspension of *Carum carvi* was administered intraduodenally, immediately after pylorus ligation. The animals were sacrificed, 6 h after the pylorus ligation. The stomachs were removed, contents collected, measured, centrifuged and subjected to analysis for titratable acidity against 0.01 N NaOH to pH and total acid output was calculated.

Gastric lesions induced by indomethacin: Indomethacin was suspended in 1.0% carboxy-methylcellulose in water (6 mg mL⁻¹) and administered orally to the fasted rats at a dose of 30 mg kg⁻¹, body weight (0.5 mL/100 g). Control rats were treated similarly with an equivalent amount of the vehicle. The animals were sacrificed 5 h after the treatment (Valcavi *et al.*, 1982). The stomachs of the

animals were excised off the body, rinsed with normal saline and studied according to the procedure of Szabo *et al.* (1985).

Statistical analysis: The readings shown are mean±standard error of means. The mean determination of treatment groups was compared statistically with that of control by using Student's t-test.

RESULTS

Aqueous suspension of *Carum carvi* was found to significantly reduce the gastric ulcers induced by ethanol, NaOH and NaCl at 500 (p<0.001) and 250 (p<0.05) mg kg⁻¹, body weight as compared to the values obtained in the control (Table 1). The treatment with ethanol (80%) caused a significant (p<0.01) decrease in the mucus content of gastric wall in the untreated animals. The depletion was found to be significantly (p<0.05) replenished after pretreatment with *Carum carvi* at both the doses (250 and 500 mg kg⁻¹, body weight) (Table 2).

Ethanol (80%) induced a significant (p<0.001) decrease in concentrations of NP-SH in the gastric tissue. A significant (p<0.05) increase of these levels was observed after the pretreatment with *Carum carvi* at the high dose (500 mg kg⁻¹, body weight) (Table 3).

Pretreatment with *Carum carvi* (500 mg kg⁻¹, body weight) was found to completely protect the different histopathological changes (hemorrhage, inflammatory, erosions and ulceration) caused in the

Table 1: Effect of *Carum carvi* on the gastric lesions-induced by various necrotizing agents

Groups	Treatment	Dose (mg kg ⁻¹ , p.o.)	Ulcer index (Mean±SE)		
			80% EtOH	0.2M NaOH	25% NaCl
1	Control	-	6.83±0.40	7.83±0.16	6.83±0.40
2	<i>Carum carvi</i>	250	3.33±0.80**	7.00±0.51*	5.80±0.44*
3	<i>Carum carvi</i>	500	3.00±0.51***	3.16±0.65***	2.83±0.70***

Six rats were used in each group, *p<0.05, **p<0.01, ***p<0.001 (Student's t-test)

Table 2: Effect of *Carum carvi* on ethanol-induced gastric wall mucus changes in rats

Groups	Treatment	Dosage (mg kg ⁻¹ , p.o.)	Gastric wall mucus µg Alician blue of wet glandular tissue (Mean±SE)
1	Control	-	405.39±24.14
2	80% Ethanol only	-	260.51±15.64**
3	<i>Carum carvi</i> + 80% ethanol	250	318.01±15.13*
4	<i>Carum carvi</i> + 80% ethanol	500	324.79±18.11*

Six rats were used in each group, Group 2 was statistically compared to group 1 and groups 3 and 4 were statistically compared to group 2, *p<0.05, **p<0.01 (Student's t-test)

Table 3: Effect of *Carum carvi* on glutathion (NP-SH) concentration in gastric tissue of rats

Groups	Treatment and dose (mg kg ⁻¹ , body weight)	No. of animals	NP-SH concentration (µmol/100 mg wet tissue) Mean±SE
1	Control (tap water, 1 mL/rat)	6	12.35±0.79
2	Control (80% ethanol (1 mL/rat)	6	5.84±0.16**
3	<i>Carum carvi</i> (250) + 80% ethanol (1 mL/rat)	6	5.86±0.30
4	<i>Carum carvi</i> (500) + 80% ethanol (1 mL/rat)	6	6.14±0.28*

Six rats were used in each group, Group 2 was statistically compared with group 1 and groups 3 and 4 were statistically compared with group 2, *p<0.05, **p<0.001 (Student's t-test)

Table 4: Effect of *Carum carvi* on ethanol-induced histopathological lesions in gastric mucosa of rats

Groups	Treatment and dose- (mg kg ⁻¹ , body weight/day)	Histopathological lesions induced							
		Congestion	Haemorrhage	Edema	Necrosis	Inflammatory	Dysplastic changes	Erosions	Ulcerations
1	Control (distilled water) (1 mL/rat).	-	-	-	-	-	-	-	-
2	Ethanol, 80% (1 mL/rat).	++	++	+	-	+	-	++	++
3	<i>Carum carvi</i> (250) + ethanol, 80% (1 mL/rat).	+	+	+	-	-	-	+	-
4	<i>Carum carvi</i> (500) + ethanol, 80% (1 mL/rat).	+	-	+	-	-	-	-	-

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

Table 5: Effect of *Carum carvi* on the volume of gastric secretion, titrable acidity and the degree of ulceration in 6 h pylorus-ligated (Shay) rats

Groups	Treatment	Dose (mg kg ⁻¹ , p.o.)	(Mean±SE)		
			Volume of gastric content (mL)	Titrable acid (mEq L ⁻¹)	Ulcer index
1	Control	-	9.17±1.23	130.55±2.64	0.83±0.31
2	<i>Carum carvi</i>	250	3.58±0.79**	55.00±24.64*	0.0***
3	<i>Carum carvi</i>	500	3.33±1.21**	48.33±21.73**	0.0***

Six rats were used in each group, *p<0.05, **p<0.01, ***p<0.001

Table 6: Effect of *Carum carvi* L. on the gastric mucosal damage induced by indomethacin in rats

Groups	Treatments	No. of animals	Dose (mg kg ⁻¹ , p.o.)	Ulcer index (Mean±SE)
1	Control	6	-	30.83±4.58
2	<i>Carum carvi</i>	6	250	29.17±3.01
3	<i>Carum carvi</i>	6	500	21.33±4.43

Six rats were used in each group, p>0.05 (Student's t-test)

gastric mucosa of ethanol treated rats. However, the lower dose of *Carum carvi* was found to partially (congestion, hemorrhage and erosions) and completely protect the inflammatory changes and ulcerations (Table 4).

Treatment with *Carum carvi* after pylorus ligation resulted in a significant decrease in the volume of the gastric contents (p<0.01) and ulcer index (p<0.001) at both the doses. The titrable acid was also significantly reduced at 250 (p<0.05) and 500 (p<0.01) mg kg⁻¹, body weight as compared to the values obtained in the control (Table 5). Pretreatment of with *Carum carvi* showed a decreasing trend in the ulcers caused by indomethacin (Table 6).

DISCUSSION

Results of present study clearly demonstrate that *Carum carvi* confers a dose-dependent protection against the gross damaging action of ethanol and other necrotizing agents on gastric mucosa of rats. Present results on histopathological assessment revealed that the pretreatment with *Carum carvi* prevented the congestion, hemorrhage, inflammatory changes, erosions and ulcerations caused by the destructive stimuli in the gastric tissue. These data are supported by our observation on the effect of *Carum carvi* to inhibit the pylorus ligation-accumulated secretions and the related ulcers and protection against the ethanol-induced depletion of mucus. Present results confirm gastric acid output to be

the root cause of gastric ulcers, the cytoprotection observed may be related to the imbalance between mucus and erosive action of acid and gastric mucosal resistance (Salim, 1990). Present data on indomethacin-induced ulcers showed a mild effect of *Carum carvi* to reduce the ulcers. However, a significant activity was absent. Thus, it is not likely that prostaglandin may have any role in the observed cytoprotective and antisecretory activity of *Carum carvi*. Nevertheless, *Carum carvi* suspension is found to decrease the basal gastric secretion and gastric ulcers and increase the mucosal defense in the stomach by a direct mechanism (Manonmani *et al.*, 1994).

The exact mechanism of action of the cytoprotective effect of *Carum carvi* is not clear. However, there appears to be a possible relation between mucosal injury, inhibition of acid secretion and the observed antioxidant activity of *Carum carvi*. One aspect of the cytoprotective activity of *Carum carvi* may be the relation of gastric lesions with the cholinergic activity of ulcerogens. Literature reports also confirmed the relation of antagastric ulcer and antisecretory activities to be the anticholinergic property of gastroprotective agents (Blandizzi *et al.*, 1993; Orisakwe *et al.*, 1996). There has been convincing experimental evidence of the anticholinergic activity of *Carum carvi* (Al-Mofleh *et al.*, 1998). Recent studies also ascribed *Carum* species (*Carum copticum*) to possess anticholinergic activity (Boskabady *et al.*, 2003).

The other possibility of the cytoprotective activity of *Carum carvi* is attributed to a possible reduction of gastric oxidative injury, resulting in an increased bioavailability of mucosal sulfhydryl compounds. There is considerable evidence concerning the participation of reactive oxygen species in the etiology and pathophysiology of the gastric ulcer disease (Repetto and Llesuy, 2002; Khosla *et al.*, 2004). The genesis of lipid peroxides is also associated with the pathogenesis of gastric lesions, irrespective of whether they are induced by (i) pylorus ligation (ii) ethanol, (iii) ischemia-reperfusion (iv) activation of polymorphonuclear leukocytes (v) inhibition of prostaglandins (vi) depletion of mucus (vii) drugs or (viii) necrotizing agents (Salim, 1990; Zimmerman and Granger, 1994; Rastogi *et al.*, 1998).

Satyanarayana *et al.* (2004) reported *Carum carvi* to show strong antioxidant activity that was superior to the known antioxidant, ascorbic acid. Studies on phytochemical analysis of *Carum carvi* revealed several antioxidant constituents, such as; monoterpenes (carvone, limonene) germacrene D and trans-dihydrocarvone, glucoside, glucide, quercetin, kaempferol (Kunzemann and Herrmann, 1977; Matsumura *et al.*, 2002; Iacobellis *et al.*, 2005). Carvones and limonene are known to induce the detoxifying enzyme glutathione S-transferase in several mouse target tissues (Zheng *et al.*, 1992). Flavonoids are reported to prevent gastric mucosal lesions induced by different necrotic agents. They are shown to increase the mucus in gastric mucosa showing cytoprotective effects (Martin *et al.*, 1994; Motilva *et al.*, 1994; Sannomiya *et al.*, 2005). Martin *et al.* (1993) and Vela *et al.* (1997) have demonstrated the flavonoids to directly act against the gastric ulcer activity.

The results of present study establish the antigastric ulcer and antisecretory activity of *Carum carvi* and confirm its traditional use against gastric disorders (Leung, 1980; Matey *et al.*, 1981). Notwithstanding the possible role of a combined effect of different constituents, the literature reports suggest a strong correlation of flavonoids and terpenes in the antigastric ulcer activity of *Carum carvi*. The exact mechanism of action of the gastroprotective activity of *Carum carvi* is not known. However, it might be due to flavonoid related suppression of cytochrome P450 1A1 (CYP1A1) which are known to convert xenobiotics and endogenous compounds to toxic metabolites. In one of the recent reports, Naderi-Kalali *et al.* (2005) have found flavonoids and steroid-like compounds to suppress CYP1A1.

CONCLUSIONS

The protective effect of *Carum carvi* against induced damage of the gastric tissue appears to be related with the free-radical scavenging property of its constituents.

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