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Antiulcer effect of epoxy-carvone

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Article

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Abstract: Epoxy-carvone is a monoterpene present in essential oils of various plants. It is a derivative of carvone, which has an epoxy group instead of the α- and β-unsaturated ketone group present in carvone. As recent studies have shown that several alcohol terpenes and compounds containing α, β-unsaturated ketone groups present antiulcer effect, the main of the present study was to evaluate the antiulcer effect of epoxy-carvone. The models of ulcers induced by ethanol and indomethacin were used in this study. Epoxy-carvone at the dose of 1 mg/kg did not present antiulcer effect against ulcer induced by ethanol, but at the doses of 10, 30 and 50 mg/kg it presented gastroprotective effect in both ulcer models. Epoxy-carvone also did not affect the gastric secretion in the pylorus ligation test. Moreover, pretreatment with indomethacin or L-nitroarginine methyl ester did not reverse the gastroprotection produced by this monoterpene. This study showed that epoxy-carvone presents antiulcer effect and suggests that this effect does not involve either antisecretory activity or increase of the nitric oxide and prostaglandin synthesis.

Introduction

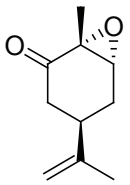
Ulcer is a disease that affects part of the world's population and is one of the most compromising disorders of the gastrointestinal tract. Gastric ulcers are usually caused by disturbances of the balance between aggressive (hydrochloric acid and pepsin) and defensive mucosal factors, such as blood flow, mucus, bicarbonate secretion, and epithelial layer (Wallace & Granger, 1996).

The most commonly treatment used for ulcers consists in the use of antisecretory agents, such as proton pump inhibitors and H_2 receptor antagonists of histamine. However, prolonged use of proton pump inhibitors appear to be associated with high incidence of hip fractures (Yang et al., 2006). Furthermore, access to health services is still limited in developing countries. On the other hand, the cultivation of medicinal plants in these countries is very intense. In Brazil, the medicinal plants are still very used by people of low income, especially in rural communities, a fact that provides information relevant to the study and discovery of new medicines from plants.

According to Falcão et al. (2008), several articles have been published about the gastroprotective action of medicinal plants, including aromatic herbs that are characterized by containing a high content of essential oils. Indeed, several studies have shown antiulcer effect of the essential oils extracted from several Brazilian plants, such as *Croton cajucara* Benth., Euphorbiaceae (Hiruma-Lima et al., 1999), *Hyptis mutabilis* Briq., Lamiaceae (Barbosa & Ramos, 1992) and *Casearia sylvestris* Sw., Salicaceae (Esteves et al., 2005). These effects usually are related to terpenes, which are the major constituents of essential oils. In this regard, antiulcer effect has been demonstrated in several alcohol terpenes isolated from essential oils, such as 1,8-cineole (Santos et al., 2004), isopulegol (Silva et al., 2009), 4-terpineol and elemol (Matsunaga et al., 2000). Antiulcer effect has also been detected in other substances containing oxygen groups, such as compounds containing α,β-unsaturated ketone groups (Maria et al., 2000).

Epoxy-carvone (**1**) is a monoterpene containing an epoxy group instead of the α,β-unsaturated ketone group present in carvone. It is present in essentials oils of *Catasetum maculatum* Kunth, Orchidaceae (Lindquist et al., 1985), *Carum carvi* L., Apiaceae (Iacobellis et al., 2005) and *Kaempferia galanga* L., Zingiberaceae (Jirovetz et al., 2001). Recents studies have shown that this monoterpene presents activity in the central nervous system (De Sousa et al., 2007) and antibacterial effect against *Staphylococcus aureus* and *Candida albicans* (Arruda et al., 2006). Since epoxy-carvone is an oxygenated terpene and previous studies have demonstrated the gastroprotective property of some oxygenated terpenes, the aim of present work was to

evaluate the possible gastroprotective activity of epoxy-carvone and, to further assess the possible mechanism involved.



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Material and Methods

Animals

Male Wistar rats (150-250 g) were provided by the Central Animal House of the Federal University of Sergipe, São Cristóvão-SE, Brazil. The animals were housed in plastic cages under standard laboratory conditions (light period 6.00 a.m. to 6.00 p.m., temperature 23±2 °C). The animals received standard rat pellet (Labina Animal Food Product, Brazil) and tap water *ad libitum,* but were deprived of food 16 h before the experiments. To prevent coprophagy, the rats were kept in cages with raised floors of wide-mesh. All experiments were initiated about 8:00 a.m. and were performed in accordance with current guidelines for the care of laboratory animals and ethical guidelines for investigations of experimental animals, approved by the Animal Use Ethical Committee of the Federal University of Sergipe (Protocol number 26/08).

Chemicals and drugs

Epoxy-carvone (**1**) was synthesized in the Chemistry Laboratory of Bioactive Synthetic and Natural Products of the Department of Physiology at the Federal University of Sergipe, according to procedure described previously (Santos et al., 1997). All others substances were obtained commercially: absolute ethanol (Impex); tween 80 (Vetec), ranitidine hydrochloride (Syrup, Ache), indomethacin (Sigma), N^G-nitro-L-arginine methyl ester (Sigma), sodium hydroxide (Labsynth), phenolphthalein (Sinth) and formaline (Impex). Epoxi-carvone was dissolved in 5% tween 80. Indomethacin was dissolved in 5% sodium bicarbonate and then neutralized with 0.2 M hydrochloric acid in a volume sufficient to obtain pH values between 7.4 and 7.8. N^G-nitro-L-arginine methyl ester (L-NAME) was dissolved in 0.9% saline solution.

Pharmacological assays

Ethanol-induced gastric ulcer

Seven groups containing ten rats each were used in this test. Two groups were treated with water or 5% tween 80 (10 mL/kg) and were used as control for ranitidine and epoxy-carvone, respectively. A third group was orally treated with ranitidine (50 mg/kg, positive control group). The other four groups received epoxy-carvone at the doses 1, 10, 30, and 50 mg/kg. All treatments above were performed by oral route at the volume of 10 mL/kg body weight. Sixty minutes after the treatments, alls rats were orally treated with absolute ethanol at the dose 0.4 mL/kg, as described by Robert et al. (1979), with small modifications. After 30 min, the rats were euthanized by guillotine decapitation. Afterwards, the stomachs were removed and incised along the greater curvature, washed with distilled water to remove gastric contents, and then fixed with 10% formalin for 15 min. The gastric surface was analyzed for the presence and severity of ulcerative lesions that were measured with a ruler and magnifying glass (10 x amplification) and expressed as ulcer index (UI) in millimeters (mm) and by ulcer inhibition percentage. The UI was obtained by the sum of the lesion lengths of each stomach. Superficial ulcers whose widths were smaller than 1 mm were multiplied by 1; superficial ulcers whose widths were between 1 and 2 mm were multiplied by 2; and those ulcers deeper and wider than 2 mm were multiplied by 3. In addition, each five petechial lesions were taken as equivalent to 1 mm of ulcer length (Alkofahi & Atta, 1999).

Indomethacin-induced gastric ulcer

Acute gastric lesions were induced in rats by oral administration of indomethacin (50 mg/kg). Six rats groups (n=10) were orally treated with distilled water (ranitidine vehicle, 10 mL/kg), 5% tween 80 (epoxy-carvone vehicle, 10 mL/kg), ranitidine (50 mg/kg), or epoxy-carvone (10, 30 or 50 mg/kg) 60 min before oral administration of indomethacin (50 mg/kg). Six hours after indomethacin administration, the animals were euthanized by decapitation and the lesions were measured and expressed as described above.

Evaluation of the prostaglandins participation on the gastroproctetive effect of epoxy-carvone in ethanol-induced ulcer

In order to investigate the involvement of endogenous prostaglandins in the gastroprotective activity of epoxy-carvone, indomethacin (10 mg/kg, *s.c.*) was injected 30 min before oral administration of epoxy-carvone (10 mg/kg), and vehicle. The indomethacin dose was used in accordance to previous reports (Murakami et al., 1996; Matsuda et al., 2003). In other two groups, indomethacin vehicle (5% $NaHCO_3$+0.2 M HCl, 1 mL/

kg, *s.c.*) was injected 30 min before oral administration of epoxy-carvone (10 mg/kg) or vehicle. One hour later, gastric damage was induced by intragastric administration of absolute ethanol (0.4 mL/100g). Thirty minutes after ethanol administration, lesions were measured and expressed as described above.

Evaluation of the nitric oxide role on the gastroproctetive effect of epoxy-carvone in ethanol-induced ulcer

In order to investigate the involvement of endogenous nitric oxide in the gastroprotective effect of epoxy-carvone, L-NAME (70 mg/kg) was intraperitoneally injected 30 min before oral administration of epoxy-carvone (10 mg/kg) or vehicle. The L-NAME dose was used in accordance to previous reports (Matsuda et al., 2003; Moraes et al., 2009). Two other groups were intraperitoneally treated with L-NAME vehicle (0.9% saline, 1 mL/kg) 30 min before oral administration of epoxy-carvone (10 mg/kg) or vehicle. Sixty minutes after these treatments, the gastric mucosal lesions were induced by intragastric administration of absolute ethanol (0.4 mL/100g). Thirty minutes after ethanol administration, the lesions were measured and expressed as described above.

Evaluation of epoxy-carvone effect in gastric secretion in the pylorus-ligation test

Pyloric ligation was carried out according to the method described by Shay et al. (1945) with small modifications. Six groups of rats (n=10 each), fasted for a 16 h period, were anaesthetized with ether. Then, the stomach was incised and the pylorus ligated. Distilled water (10 mL/kg), ranitidine (50 mg/kg), 5% tween 80 (10 mL/kg), or epoxy-carvone (10, 30, and 50 mg/kg) were administered intraduodenally immediately after the pylorus ligation. Four hours later, the rats were euthanized with an ether overdose, and the cardia sphincter was ligated. The stomachs were removed, and the gastric contents were collected and centrifuged at 3500 x *g* for 30 min. The resulting supernatant was transferred to a test tube for the determination of gastric volume (mL), pH, and hydrogen ion concentration. The pH was measured with the aid of a digital pH meter, and the total acidity was determined by titration with 0.1 M NaOH using 2% phenolphthalein as indicator and expressed in mEq/mL/4h.

Statistical analysis

Values were expressed as means±SEM. For statistical analysis, one-way analysis of variance followed by Tukey's test was used. *p* values less than 0.05 were considered significant.

Results and Discussion

This present study evaluated the antiulcer effect of monoterpe epoxy-carvone (**1**). This compound is a derivative of carvone, which has an epoxy group in substitution to α,β-unsaturation presents in carvone. Recent studies have shown that several alcohol terpenes and compounds containing α,β-unsaturated ketone groups exhibit antiulcer effect (María et al., 2000). Therefore, it is reasonable to investigate whether the epoxy-carvone also presents this activity.

Ethanol-induced ulcer model in rats has been widely used to evaluate gastroprotective activity of various substances, since it is a simple and reliable test for evaluation of antiulcer agents, especially with regards to cytoprotective activity (Robert et al., 1979). In our experiments, oral treatment with absolute ethanol produced gastric lesions whose magnitudes were not significantly different between rats orally treated with water and 5% tween 80. The ulcers index (UI) obtained in the control groups treated with water and tween 80 were 175.7±27.6 and 120.3±19.2 mm, respectively (Figure 1). Oral administration of epoxy-carvone at the dose of 1 mg/kg did not show gastroprotection against ethanol-induced ulcer. However, epoxy-carvone at the doses of 10, 30, and 50 mg/kg reduced the formation of gastric ulcers induced by ethanol, which indicates that the epoxy-carvone is a monoterpene with potent antiulcer activity. The inhibition percentages obtained were 77.7, 69.2 and 61.4%, respectively (Figure 1).

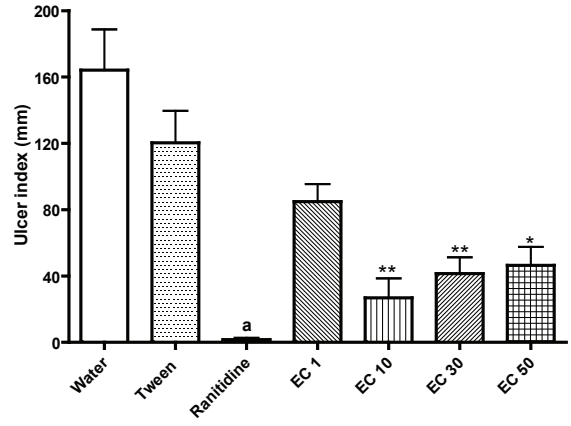

Figure 1. Effect of oral administration of epoxy-carvone and ranitidine (50 mg/kg) on ethanol-induced gastric ulcers. Results are expressed as ulcer index. Bars represent the means±SEM (n=10). **p*<0.05; ***p*<0.01 compared to the control group treated with 5% tween 80; [a]*p*<0.001, compared to the control group treated with water. One way anova with Tukey's post-test. F value = 15.75. EC 1, EC 10, EC 30, and EC 50 = epoxy-carvone at the doses of 1, 10, 30, and 50 mg/kg, respectively.

Epoxy-carvone also presented gastroprotective activity in indomethacin-induced ulcers. The UI obtained in the tween-treated control animals (16.9±3.1 mm) was reduced to 6.7±1.2, 8.8±1.8 and, 6.3±1.5 mm in animals treated with epoxy-carvone at the doses of 10, 30, and 50 mg/kg, respectively (Figure 2). Indomethacin acts by inhibiting the synthesis of prostaglandins, mediators known to exhibit protective effects of gastric mucosa, such as inhibition of the gastric acid production, stimulation of the production of mucus and bicarbonate, and mucosal blood flow increase (Wallace & Granger, 1996). Consequently, the gastroprotective effect observed against indomethacin-induced ulcer, suggests that epoxy-carvone produces gastroprotection by increasing the synthesis of endogenous prostaglandins.

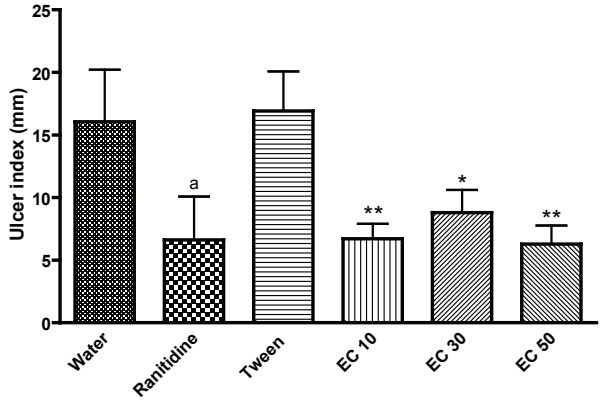

Figure 2. Effect of oral administration of epoxy-carvone and ranitidine (50 mg/kg) on indomethacin-induced gastric ulcers. Results are expressed as ulcer index. Bars represent the means±SEM (n=10). **p*<0.05; ***p*<0.01, compared to the control group treated with 5% tween 80; [a]*p*<0.05, compared to the control group treated with water. One way anova with Tukey's post-test. F value: 3.1; EC 10, EC 30, and EC 50 epoxy-carvone at the doses of 10, 30, and 50 mg/kg, respectively.

In order to investigate the role of prostaglandins in the gastroprotection produced by epoxy-carvone, two groups of rats were pretreated with indomethacin (10 mg/kg, *s.c.*) 30 min before oral administration of epoxy-carvone (10 mg/kg) or vehicle (5% tween 80). Two other groups were orally pretreated with indomethacin vehicule. At the dose of 10 mg/kg by subcutaneous rout, indomethacin inhibits the synthesis of prostaglandins, but does not produce ulcers (Matsuda et al., 2003). In our experiments, subcutaneous administration of indomethacin at the dose of 10 mg/kg did not produce gastric ulcers in rats evaluated up to six hours after its administration (data not shown). Moreover, pretreatment with indomethacin did not reverse the antiulcer effect produced by epoxy-carvone 10 mg/kg (Figure 3). The UI obtained were 36.7±10.3 and 53.9±10.6 in groups untreated and treated with indomethacin, respectively. Pretreatment with indomethacin also did not produce significant change in the gastric lesions in the control animals (Figure 3). These results suggest that the antiulcer effect of epoxy-carvone does not involve increase of the prostaglandin synthesis. Therefore, antiulcer effect of epoxy-carvone probably involves cytoproective mechanisms.

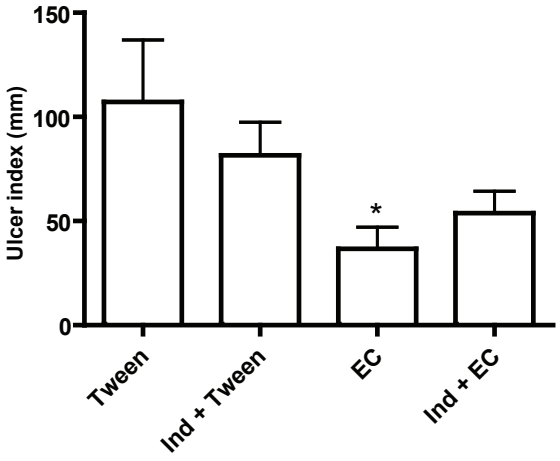

Figure 3. Effect of epoxy-carvone on ethanol-induced gastric ulcers in rats with and without indomethacin pre-treatment. Indomethacin (10 mg/kg) was administered by subcutaneous route 30 min before oral administration of epoxy-carvone and tween. Ethanol was administered 1 h after administration of epoxy-carvone and tween. Bars represent the means±SEM (n=10). **p*<0.05 compared to control group treated with 5% tween without indomethacin pre-treatment. One way anova with Tukey's post-test. F value: 3.0; Ind: indomethacin; EC: 10 mg/kg epoxy-carvone.

Another important mediator of the gastric mucosal defense is nitric oxide. This gas participates in the defense mechanism by increasing gastric mucosal blood flow, mucus secretion, and prostaglandin synthesis (Wallace & Granger, 1996). In the present study, we evaluated if the gastroprotective effect of epoxy-carvone involves nitric oxide synthesis increase. To evaluate this possibility, L-NAME (70 mg/kg, *i.p.*) was administered 30 min before oral administration of epoxy-carvone (10 mg/kg). L-NAME is an analogue of L-arginine and acts by inhibiting of nitric oxide synthase, an enzyme responsible by biosynthesis of nitric oxide (Rees et al., 1990). Pre-treatment with L-NAME did not reverse the gastroprotective effect produced by epoxy-carvone. The UI values obtained were 28.8±6.2 and 44.1±8.2 mm in groups untreated and treated with L-NAME, respectively (Figure 4). This result indicates that the antiulcer action of epoxy-carvone also does not involve increase of the nitric oxide synthesis, and it is according to some studies which have shown the non-involvement of nitric oxide in the gastroprotective effect of some terpenes, such as

isopulegol (Silva et al., 2009) and eugenol (Santin et al., 2011).

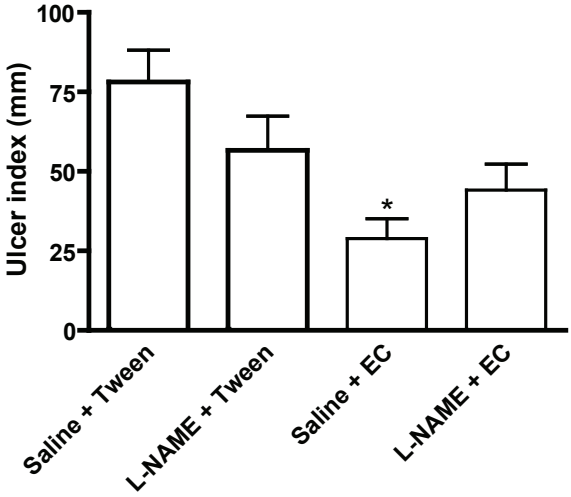

Figure 4. Effect of epoxy-carvone on ethanol-induced gastric ulcers in rats with and without L-NAME pre-treatment. L-NAME (70 mg/kg) was administered by intraperitoneal route 30 min before oral administration of epoxy-carvone and tween. Ethanol was administered 1 h after administration of epoxy-carvone and tween. Bars represent the means±SEM (n=10). *p<0.05, compared to the control group treated with 5% tween without L-NAME pre-treatment. One way anova with Tukey's post-test. F value: 5.9; Ind: indomethacin; EC: 10 mg/kg epoxy-carvone.

The main drugs used today to treat ulcers act by inhibiting the secretion of gastric acid, such as antagonists of histamine H_2 receptor and proton pump inhibitors. In our experiments, we also evaluated if epoxy-carvone exerts antiulcer effect by inhibiting gastric acid secretion. This mechanism was evaluated in pylorus-ligated rats (Shay et al., 1945). The volume of gastric contents in animals treated with epoxy-carvone at the doses of 10, 30, and 50 mg/kg did not differ significantly from control animals (Table 1). On the other hand, the antisecretory drug ranitidine decreased the gastric volume value of 5.1±0.4 to 2.2±0.3 mL observed in control animals treated with water. The pH and proton concentration values of gastric content were not modified by epoxy-carvone, indicating that the antiulcer effect of this monoterpene does not involve antisecretory action.

Agents that present gastroprotection against ethanol-induced gastric lesions act mainly by stimulation of defense mechanisms (cytoprotective effect) in preference to inhibition of the aggressive factors production or release (antisecretoy effect). However, our experiments showed that the antiulcer effect of epoxy-carvone does not involve increase of nitric oxide synthesis. Another cytoptotective mediator involved in the gastric mucosal defense is the glutathione (GSH). Ethanol-induced damage is associated with a significant decrease in the mucosal GSH level, and it has been reported that the cytoprotective action of certain drugs was attenuated by SH blockers, such as *N*-acethylmaleimide (Szabo & Brown, 1987; Szabo et al., 1981). Therefore, it is possible that epoxy-carvone acts by increasing GSH level. Nevertheless, this mechanism was not evaluated in our study.

The present results showed for the first time that epoxy-carvone presents antiulcer activity and extends the number of terpenes presenting such activity. Moreover, we were able to conclude that the antiulcer activity of epoxy-carvone does not involve either inhibition of gastric acid secretion or increased synthesis of prostaglandins and nitric oxide.

Table 1. Effects of epoxy-carvone and ranitidine on gastric secretion in pylorus-ligated rats.

Treatment	Dose	n	Gastric volume (mL)	Proton concentration (mEq/mL/4h)	pH
Water	10 mL/kg	10	5.05±0.36	21.18±1.49	1.61±0.16
Tween	10 mL/kg	10	5.42±0.61	22.04±0.95	1.37±0.06
Ranitidine	50 mg/kg	10	2.22±0.30*	13.32±1.23*	3.98±0.58*
EC	10 mg/kg	10	5.44±0.65	17.31±2.59	1.46±0.17
EC	30 mg/kg	10	4.46±0.47	21.34±2.05	1.73±0.39
EC	50 mg/kg	10	4.17±0.41	19.25±2.06	1.77±0.31

The pylorus was ligated under ether anesthesia; then, epoxy-carvone, ranitidine, and vehicles were intraduodenally administered. Four hours later, the animals were sacrificed, and the volume, proton concentration, and pH of the gastric juice were measured. Values represent the means±SEM. EC: epoxy-carvone. *p<0.05, compared to the control group treated with water (one-way ANOVA with Tukey's post-test).

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