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Baccharis dracunculifolia, the main botanical source of Brazilian green propolis, displays antiulcer activity

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Abstract

Baccharis dracunculifolia is the most important botanical source of Southeastern Brazilian propolis, known as green propolis for its colour. In a previous study, we described the gastric protective effect of the hydroalcoholic extract of Brazilian green propolis. We therefore wanted to investigate the possibility of using *B. dracunculifolia* extract for antiulcer treatment. This study was undertaken to evaluate the anti-ulcerogenic property of hydroalcoholic extract of *B. dracunculifolia* aerial parts. The HPLC analysis of the chemical composition of *B. dracunculifolia* extract used in this study revealed the presence mainly of cinnamic acid derivates and flavonoids. Doses of 50, 250 and 500 mg/kg of *B. dracunculifolia* crude extract and positive controls (omeprazole or cimetidine) significantly diminished the lesion index, the total lesion area and the percentage of lesion compared with negative control groups. The percentage of ulcer inhibition was significantly higher in groups treated with *B. dracunculifolia*, cimetidine or omeprazole, with all protocols used, compared with negative control groups. Regarding the model of gastric secretion, reductions in the volume of gastric juice and total acidity were observed, as well as an increase in the gastric pH. These results were similar to results from studies carried out with green propolis extract. Although more investigations are required, our results suggest that *B. dracunculifolia* has potential to be used as a phytotherapic preparation for the treatment of gastric ulcer.

Introduction

Gastric and duodenal ulcers affect a considerable number of people in the world and are induced by several factors, such as: stress, smoking, nutritional deficiencies and ingestion of non-steroidal-anti-inflammatory drugs (NSAIDs) (Nash et al 1994). The current medicinal treatment of peptic ulcer is generally based on the inhibition of gastric acid secretion by histamine H2 antagonists, proton-pump inhibitors and antimuscarinics, as well as on acid-independent therapies provided by sucralfate and bismuth cholinergics (Bighetti et al 2005). However, the majority of these drugs produce adverse reactions, such as hypersensitivity, arrhythmia, impotence, gynaecomastia and haematopoietic changes (Chan and Leung 2002). Thus, it is necessary to develop more effective and less toxic antiulcer agents.

An extensive variety of chemical compounds isolated from medicinal plants display anti-ulcer activity (Borrelli and Izzo 2000), and several plants are used in folk medicine for their anti-ulcer properties.

The *Baccharis* genus includes more than 500 species, distributed mainly in the tropical areas of South America. Many of these are used extensively in folk medicine, for the treatment and prevention of anaemia, inflammation, diabetes and stomach, liver and prostate diseases (Verdi et al 2005).

B. dracunculifolia DC (Asteraceae), a native plant from Brazil, commonly known as 'Alecrim-do-campo' and 'Vassoura', is widely used in folk medicine for the treatment of inflammation, hepatic disorders and stomach ulcers (Menezes 2005). Phytochemical studies carried out with *B. dracunculifolia* have demonstrated the presence of many classes of constituents, including flavonoids (isosakuranetin, aromadendrin-4′-methyl ether) terpenes (baccharin), phenolic acids (artepelin C, caffeic acid, *p*-coumaric acid, ferulic acid)

(Bohlmann et al 1981; Banskota et al 1998, Akao et al 2003, Silva Filho et al 2004, Mendez 2005, Loots et al 2006). *B. dracunculifolia* is the most important botanical source of Southeastern Brazilian propolis, known as green propolis for its colour (Marcucci et al 1998; Park et al 2002). Corroborating with this, it was observed that many compounds present in *B. dracunculifolia* are also present in green propolis, such as prenylated *p*-coumaric acid derivates and flavonoids (Labbe et al 1986; Marcucci et al 1998; Kumazawa et al 2003).

In a previous study we described the gastric protective effect of the hydroalcoholic extract of Brazilian green propolis (Barros et al 2006). Thus, we decided to evaluate the possibility of using *B. dracunculifolia* extract for antiulcer treatment. This study was undertaken to evaluate the antiulcerogenic properties of the hydroalcoholic extract of *B. dracunculifolia* aerial parts.

Materials and Methods

Plant material and preparation of extract

The aerial parts of *B. dracunculifolia* De Candole (Asteraceae) were collected in Franca, São Paulo State, Brazil, in February 2005. The plant material was authenticated by Nelson Ivo Matzenbacher, and a voucher specimen was deposited in the herbarium of the Centro Pluridisciplinar de Pesquisas Químicas, Biológicas e Agronômicas (CPQBA) of Universidade Estadual de Campinas (UNICAMP), Campinas, São Paulo State, Brazil.

The leaves of *B. dracunculifolia* were dried under air circulation (40°C). The dried leaves (350 g) were ground in a knife mill, and macerated with aqueous ethanol 70% (v/v) at room temperature for 7 days. The macerated material was filtered and concentrated under reduced pressure, yielding 50.2 g crude hydroalcoholic extract (14.3% yield).

Drugs, reagents and solvents

Indometacin, cimetidine and omeprazole were purchased from Sigma Aldrich (St Louis, MO, USA). All other reagents and solvents were analytical grade.

HPLC analysis of the crude extract

Chromatographic analysis of *B. dracunculifolia* extract was performed using Shimadzu (Kyoto, Japan) HPLC equipment: an SCL-10A*vp* controller, three LC-10AD pumps, SPD-M10A*vp* diode array detector and Class-VP version 5.02 software controller. A Shim-Pack CLC-ODS (M), Shimadzu column (4.6 mm × 250 mm, particle diameter 5 μm, pore diameter 100 Å) was used.

Hydroalcoholic crude extract samples were dissolved in methanol (5.0 mg mL^{-1}) and filtered through a 0.45 μm filter before injecting 15 μL onto the HPLC system. A gradient starting with 0.8% acetic acid, 0.3% ammonium acetate, 5.0% methanol/water and 25% acetonitrile, and finishing with 100% of acetonitrile, over 60 min (flow rate 1.0 mL min^{-1}), was used to separate the major compounds. Veratraldehyde was used as the internal standard.

The phenolic compounds were identified by comparison with the authentic chromatographic standards obtained from the compounds library of the Pharmacognosy Laboratory of the School of Pharmacy of Ribeirão Preto, Brazil.

Animals

Male Wistar rats weighing 200–250 g were provided by the Central Animal House of the West University of Santa Catarina (UNOESC), Campus of Videira. The animals were housed in groups of five, in standard cages at room temperature (25 ± 3°C) in a 12:12 hour light–dark cycle, with both food and water ad libitum. Twelve hours before the experiments, animals were transferred to the laboratory and were maintained with only water ad libitum. Animals were housed and cared for in accordance with the Federal Government legislation on animal care. Experiments were authorised by the Ethical Committee for Animal Care of the University of the West of Santa Catarina, Brazil.

Ethanol-induced ulcer

The experiment was performed according to the method of Morimoto et al (1991). After 12 h of fasting, rats were randomly divided into five groups of six animals. Animals in the first group were given 1 mL vehicle (1% Tween-80 aqueous solution); the second group were treated with omeprazole (30 mg kg^{-1}). The remaining three groups received 50, 250 or 500 mg kg^{-1} *B. dracunculifolia* extract dissolved in 1% Tween-80 aqueous solution. All treatments were administered orally by gavage. One hour after treatment, all rats received 1 mL 99.5% ethanol to induce gastric ulcer. Animals were killed 1 h later by cervical dislocation. The stomachs were removed, opened along the greater curvature and rinsed gently with water to remove the gastric contents and blood clots, and were scanned later. The images obtained were analysed by specific software (developed by Dr Eros Comunello, Universidade do Vale do Itajaí, São José, SC, Brazil). Ulcers were classified as level I – ulcer area < 1 mm^2; level II – ulcer area 1–3 mm^2 or level III – ulcer area > 3 mm^2. The ulcerative lesion index was calculated as 1 × (number of level I ulcers) + 2 × (number of level II ulcers) + 3 × (number of level III ulcers). The percentage of inhibition was calculated as 100 – ($IU_{treated} \times 100/IU_{control}$) where $IU_{treated}$ and $IU_{control}$ are the ulcerative index values (as calculated above) for the treated and control groups, respectively. We also calculated the total area of lesions and the percentage of lesion area in relation to the total stomach area.

NSAID-induced ulcer

The experiment was performed according to the method of Nwafor et al (2000) with a few modifications. After 12 h of fasting, rats were randomly divided into five groups of six animals. Rats in the first group were given 1 mL vehicle (1% Tween-80 aqueous solution). The second group were given cimetidine (100 mg kg^{-1}). The other three groups were given 50, 250 or 500 mg kg^{-1} *B. dracunculifolia* extract dissolved in 1% Tween-80 aqueous solution. All treatments were administered orally by gavage. One hour after treatment, all rats received

indometacin (100 mg kg^{-1}) to induce gastric ulcer and were killed 4 h later by cervical dislocation. The stomachs were removed, opened along the greater curvature and rinsed gently with water to remove gastric contents and blood clots, and were scanned later. The images obtained were analysed using the parameters described above.

Stress-induced ulcer

The method described by Basile et al (1990) was used in this assay. Rats were dosed in the same was as for NSAID-induced ulcer, described above. Thirty minutes later, each animal was placed in a tube and immersed vertically up to the neck region in current water at 25°C for 17 h, after which it was killed by cervical dislocation. The stomachs were removed, opened along the greater curvature, and then washing gently with water to remove gastric contents and blood clots, and were scanned later. The images obtained were analysed using the parameters described above.

Measurement of gastric secretion

The assay was performed using the method of Shay et al (1945) with a few modifications. Animals were divided into groups of six. After 24 h of fasting, rats were anaesthetised with tyopental sodium (10 mg kg^{-1} i.p.), the abdomen was incised, the pylorus ligated and treatment was administered intraduodenally. Rats were dosed in the same way as for NSAID-induced ulcer, described above. Four hours later, rats were killed by cervical dislocation, the abdomen was opened and another ligature placed at the oesophageal end of the stomach. The stomach was then removed and the gastric contents collected and centrifuged at 3000 rpm (8*g*) at 25°C for 10 min. The amount of gastric juice acid (mL) and the pH values were determined. Total acid secretion in the gastric juice was determined in the supernatant volume by titration to pH 7.0 using 0.01 M NaOH solution, and phenolphthalein as indicator.

Statistical analysis

Data are reported as mean ± standard error of the mean (s.e.m.) and were compared using one-way analysis of variance followed by Dunnett's pairwise test; $P < 0.05$ was considered significant.

Results

HPLC analysis of extract

HPLC analysis of the *B. dracunculifolia* hydroalcoholic extract allowed the identification of the following compounds: caffeic acid, *p*-coumaric acid, ferulic acid, aromadendrin-4′O-methyl ether, isosakuranetin, artepelin C and baccharin (Figure 1).

Effect of *B. dracunculifolia* hydroalcoholic extract on the ulcer models

The effects of *B. dracunculifolia* extract on the ulcer models used in this work are summarised in Table 1.

In the ethanol-induced ulcer model, treatment with *B. dracunculifolia* extract (50, 250 and 500 mg kg^{-1}) and omeprazole (30 mg kg^{-1}) significantly reduced the lesion index, the total lesion area and the percentage of lesion, compared with the negative control group ($P < 0.05$). The percentage inhibition of ulcers was 79.9 ± 6.5, 92.7 ± 7.1, 95.0 ± 6.3 and 98.9 ± 9.3 for the *B. dracunculifolia* 50, 250, 500 mg kg^{-1} treatment groups and positive control (omeprazole), respectively.

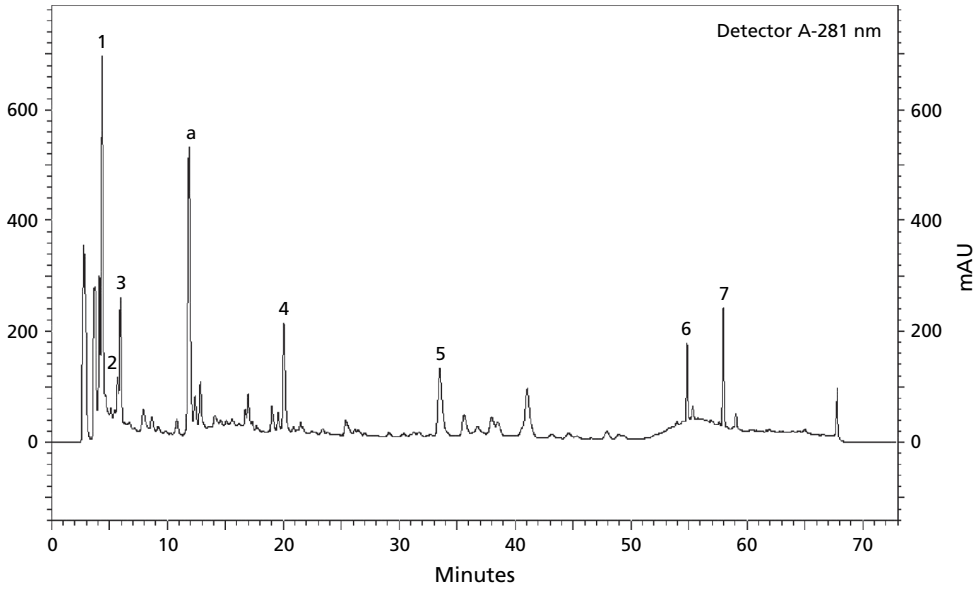

Figure 1 HPLC profile of *Baccharis dracunculifolia* hydroalcoholic extract. a = internal standard (veratraldehyde); 1 = caffeic acid; 2 = *p*-coumaric acid; 3 = ferulic acid; 4 = aromadendrin-4′O-methyl ether; 5 = isosakuranetin; 6 = artepelin C; 7 = baccharin.

Table 1 Effects of *Baccharis dracunculifolia* extract and omeprazole or cimetidine, administered orally, on ethanol-, indometacin- and stress-induced gastric ulcers in rats

Method	Treatment (p.o.)	Dose ($mg\,kg^{-1}$)	Total area of lesion (mm^2)	% of lesion area	Ulcer index	Inhibition (%)
Ethanol	Control	–	40.75 ± 3.93	10.15 ± 2.4	45.25 ± 5.05	–
	Omeprazole	30	0.81 ± 0.08*	0.11 ± 0.06*	0.80 ± 0.08*	98.9 ± 9.3*
	B. dracunculifolia extract	50	11.3 ± 3.60*	2.00 ± 0.54*	17.23 ± 3.21*	79.9 ± 6.5*
		250	5.8 ± 1.54*	0.71 ± 0.10*	10.65 ± 2.75*	92.7 ± 7.1*
		500	2.8 ± 0.24*	0.58 ± 0.09*	5.45 ± 1.28*	95.0 ± 6.3*
Indometacin	Control	–	60.61 ± 4.32	6.83 ± 1.50	60.60 ± 5.81	–
	Cimetidine	100	1.55 ± 0.64*	0.16 ± 0.09*	6.20 ± 1.29*	97.6 ± 8.3*
	B. dracunculifolia extract	50	37.45 ± 2.53*	3.79 ± 0.19*	37.40 ± 1.16*	44.5 ± 3.2*
		250	17.78 ± 4.32*	1.72 ± 0.36*	21.20 ± 2.55*	74.8 ± 4.3*
		500	12.72 ± 2.56*	1.67 ± 0.47*	19.60 ± 2.43*	75.6 ± 5.6*
Stress	Control	–	131.31 ± 10.70	13.96 ± 2.32	117.60 ± 19.50	–
	Cimetidine	100	11.40 ± 1.27*	1.26 ± 0.16*	27.80 ± 4.61*	76.4 ± 6.0*
	B. dracunculifolia extract	50	26.11 ± 6.28*	2.66 ± 0.69*	40.80 ± 8.16*	65.3 ± 3.2*
		250	16.05 ± 5.12*	1.71 ± 0.62*	35.20 ± 9.21*	70.1 ± 4.6*
		500	14.45 ± 3.32*	1.69 ± 0.32*	29.66 ± 6.39*	74.8 ± 5.1*

Results are mean ± s.e.m. for six rats. Statistical comparison was performed using one-way analysis of variance, followed by Dunnett's test. *$P < 0.05$ in comparison with negative control group.

In the indometacin-induced ulcer model, treatment with *B. dracunculifolia* extract (50, 250 and 500 $mg\,kg^{-1}$) and cimetidine (100 $mg\,kg^{-1}$) significantly reduced all the parameters evaluated compared with the control group ($P < 0.05$). In this model, the percentage inhibition of ulcers was 44.5 ± 3.2; 74.8 ± 4.3, 75.6 ± 5.6 and 97.6 ± 8.3 for for the *B. dracunculifolia* 50, 250, 500 $mg\,kg^{-1}$ treatment groups and positive control (cimetidine), respectively.

Regarding the stress-induced ulcer model, significant reductions in lesion index, total lesion area and percentage of lesions were observed in animals treated with *B. dracunculifolia* extract (50, 250 and 500 $mg\,kg^{-1}$) and cimetidine (100 $mg\,kg^{-1}$) compared with the negative control group ($P < 0.05$). The percentage inhibition of ulcers was 65.3 ± 3.2, 70.1 ± 4.6; 74.8 ± 5.1 and 76.4 ± 6.0 for the groups treated with 50, 250, 500 $mg\,kg^{-1}$ of *B. dracunculifolia* and positive control (cimetidine), respectively.

The results obtained indicate that *B. dracunculifolia* extract produced a dose-dependent gastroprotection in all the ulcer-induction models studied in this work.

Effect of *B. dracunculifolia* hydroalcoholic extract on gastric secretion

The results are summarised in Table 2. In the model of gastric secretion measurement using ligated pylorus, treatment with *B. dracunculifolia* extract (50, 250 and 500 $mg\,kg^{-1}$) and cimetidine (100 $mg\,kg^{-1}$) reduced the volume of gastric juice and total acidity and raised the gastric pH significantly ($P < 0.05$) compared with the control group.

Discussion

Considering that green propolis extract has antiulcer activity (Reis et al 2000; Barros et al 2006) and that *B. dracunculifolia* is the main botanical source visited by honeybees to collect resinous material for its production (Marcucci et al 1998), this research was undertaken to evaluate the antiulcer activity of *B. dracunculifolia* extract. Antiulcer activity was evaluated

Table 2 Effect of *Baccharis dracunculifolia* hydroalcoholic extract, administered intraduodenally, on the biochemical parameters of gastric juice obtained from a rat ligated-pylorus model

Treatment	Dose ($mg\,kg^{-1}$)	Gastric pH	Gastric juice volume (mL)	$[H^+]$ ($mEq\,L^{-1}$ per 4 h)
Control	–	1.78 ± 0.14	2.89 ± 0.49	90.24 ± 10.46
Cimetidine	100 mg/kg	6.00 ± 1.01*	0.72 ± 0.06*	28.03 ± 1.35*
B. dracunculifolia extract	50 mg/kg	2.65 ± 0.14*	0.88 ± 0.28*	34.66 ± 3.19*
	250 mg/kg	2.96 ± 0.07*	0.79 ± 0.09*	32.22 ± 2.63*
	500 mg/kg	5.17 ± 0.90*	0.53 ± 0.20*	30.78 ± 9.64*

Results are mean ± s.e.m. for six rats. Statistical comparison was performed using one-way analysis of variance, followed by Dunnett's test. *$P < 0.05$ in comparison with negative control group.

using ethanol-, indometacin- and stress-induced ulcers, the most commonly used experimental models for the evaluation of antiulcer activity in animals. The effects of *B. dracunculifolia* extract on gastric secretion were evaluated in a ligated-pylorus model.

It should be taken into consideration that, in most cases, the aetiology of ulcers is unknown, but it is generally accepted that ulceration results from an imbalance between acid and pepsin production and the maintenance of mucosal integrity through endogenous defence mechanisms (Wallace 2001). This study demonstrates that *B. dracunculifolia* extract protected the gastric mucosa against ulcer development in the three models of ulcer induction. Moreover, the protective activity was higher in the ethanol-induced ulcer model, in which inhibition of 79.9, 92.7 and 95.0% in groups treated with 50, 250, 500 mg kg^{-1} of *B. dracunculifolia*, respectively, was reported.

The formation of gastric mucosal lesions by necrotising agents such as ethanol has been reported to involve the depression of the gastric defence mechanisms (Kinoshita et al 1995). Oral treatment with ethanol causes focal hyperaemia, oedema, necrosis and submucosal haemorrhage, as well as circulatory disturbances (Oates & Hakkinen 1988). Formation of gastric mucosal lesions by ethanol administration involves several mechanisms that reduce gastric blood flow, thereby contributing to the development of haemorrhage and necrosis, and to the solubilisation of mucus constituents in stomach. These actions result in an increased flux of sodium and potassium ions, increased pepsin secretion, and a loss of hydrogen ions and histamine into the lumen (Szabo 1987). Oral treatment with ethanol clearly resulted in the expected characteristic zone of necrotising mucosal lesions in the control group. Treatment with *B. dracunculifolia* extract significantly decreased the lesion index, the total lesion area and the percentage of lesion. These results indicate that *B. dracuncuilifolia* extract displays an antiulcerogenic effect relating to cytoprotective activity, since it significantly reduced ethanol-induced ulcer.

NSAIDs such as aspirin and indometacin are known to induce ulcers by inhibition of prostaglandin synthetase through the cyclooxygenase pathway (Rainsford 1987). In the stomach, prostaglandins have a vital protective role, where they stimulate the secretion of bicarbonate and mucus, maintain mucosal blood flow and regulate mucosal cell turnover and repair (Hayllar and Bjarnason 1995). Thus, the supression of prostaglandin synthesis by NSAIDs results in increased susceptibility to mucosal injury and gastroduodenal ulceration. *B. dracunculifolia* extract significantly reduced mucosal damage in the indometacin-induced ulcer model. These results suggest the possible involvement of prostaglandins and/or mucus in the antiulcer effect of the extract.

Stress plays an important role in the aetiopathology of gastroduodenal ulceration (Govindarajan et al 2006). The vagus nerve stimulates stomach acid secretion via interaction of acetylcholine at muscarinic receptors. Activation of muscarinic receptors starts a sequence of events that results in increased gastric acid secretion (Clapham 1995). According to some authors, these receptors are located at parietal cells and histamine secretory cells. Therefore, the increase in acid secretion is a consequence of acetylcholine activity on histamine cells and parietal cell activity (Schubert 2000). It is important to consider that vagal activity up-regulates in stressful situation. Some antiulcer drugs, such as cimetidine, ranitidine and famotidine, block H2 histamine receptors. In the current study, *B. dracunculifolia* extract inhibited the production of stress-induced ulcers. This finding indicates that *B. dracunculifolia* extract may either enhance gastric mucosal defensive factor or act as a H2-receptor antagonist.

In this work, we also evaluated the activity of *B. dracunculifolia* extract on gastric secretion in a rat ligated-pylorus model, a model that allows changes of the parameters relative to the gastric content to be investigated. The gastric distention produced by accumulated secretion seems to influence the secretion of gastric acid in this model, possibly by increasing the release of gastrin hormone, and consequently further increasing acid secretion (Nagy et al 1968). A significant decrease in gastric fluid volume, a decrease in acid output and an increase in gastric pH were observed after intraduodenal administration of *B. dracunculifolia* extract compared with the control, indicating that the extract possesses antisecretory activity. Moreover, these results showed that the antiulcer activity of this extract not only relates to local neutralisation of gastric contents, but was also effective after the absorption of the extract, indicating a systemic effect. In addition, these results corroborate the possible anti-histaminic activity observed in the stress-induced ulcer model.

Analysis of the chemical composition of the *B. dracunculifolia* extract used in this study revealed the presence of mainly cinnamic acid derivates and flavonoids. It is well known that many flavonoids display antisecretory and cytoprotective properties in different experimental models of gastric ulcer (Martin et al 1998). The protection mediated by flavonoids seems to be related to an increase in microcirculation, probably caused by stimulation of afferent nerves and release of nitric oxide (NO) (Zayachkivska et al 2005). Oxidative damage is considered to be a common factor in the pathogenesis of ulcers in different experimental and clinical models (Sairam et al 2002), and extracts containing cinnamic acid derivates have been shown to have antioxidant activity (Tapia et al 2004). Thus, the phenolic components of *B. dracunculifolia* ethanol extract may play an important role in the displayed antiulcer activity.

Plants belonging to the *Baccharis* genus are reported in the literature as possessing anti-inflammatory activity (Abad et al 2006). Moreover, *B. dracunculifolia* is widely used in folk medicine for the treatment of inflammation, hepatic disorders and stomach ulcers (Menezes 2005). Therefore, it could be advantageous to administer a *B. dracunculifolia* phytotherapic along with an NSAID in the treatment of chronic inflammatory conditions such as rheumatoid arthritis that are associated with peptic ulcer or chronic gastritis.

Conclusions

The results of this study show that *B. dracunculifolia* hydroalcoholic extract displays gastroprotective activity, as it significantly inhibited the formation of ulcers induced in different animal models, and decreased gastric secretion. This effect may be attributed, at least in part, to cinnamic acid derivates and flavonoids present in the extract, because these compounds have been reported to display anti-ulcer activities. These results

were similar to the results observed in studies undertaken with green propolis extract. Further investigations are required to allow the use of *B. dracunculifolia* as a phytotherapic preparation for the treatment of gastric ulcer. The results obtained demonstrate that *B. dracunculifolia* displays a good antiulcer activity, which corroborates the use of this plant in folk medicine, contributing to its pharmacological validation.

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