



Antiulcer mechanisms of *Vernonia condensata* Baker: A medicinal plant used in the treatment of gastritis and gastric ulcer



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ABSTRACT

Ethnopharmacological relevance: The leaves from *Vernonia condensata* Baker are broadly used in folk medicine for the treatment of gastric ulcers and dyspepsia. The Brazilian Public Health System (SUS) describes this species as having the potential to serve as a new herbal product with therapeutic benefits. **Aim of the study:** The purpose of the study was to evaluate the gastroprotective activity and gastric healing properties of a crude ethanolic extract from leaves of *V. condensata* (CEEV) in different animal models.

Materials and methods: In order to assess the gastroprotective potential of CEEV, ulcer models were established using ethanol and indomethacin. The gastric healing effect was then evaluated in the acetic acid-induced ulcer model, where the tissue was used to assess oxidative levels (reduced glutathione and lipid hydroperoxide levels, as well as superoxide dismutase and catalase activity), inflammatory [myeloperoxidase (MPO)] parameters, and mucin content. Furthermore, the ligature pylorus model, with and without secretagogue stimuli, was employed to investigate the mechanism of action of CEEV. In addition, H^+K^+ -ATPase activity, MPO activity, and antioxidant activity through the DPPH assay were examined through *in vitro* trials. Phytochemical analyses were also performed. The ethanol/HCl-induced gastric ulcer method was employed to verify the gastroprotective effect of the main compound in CEEV.

Results: CEEV (30 and 300 mg/kg, p.o) exhibited gastroprotective activity and prevented both gastric lesions induced by ethanol or indomethacin in rats. The gastric healing effect of CEEV (300 mg/kg, p.o. taken twice a day for a duration of seven days) was confirmed by examining the macroscopic and microscopic appearance of chronic gastric ulcers induced by acetic acid in rats. The restorative effect of CEEV was accompanied by a significant increase in mucin content (PAS staining) and by a reduction in oxidative stress and inflammatory parameters at the site of the ulcer. Moreover, CEEV (300 mg/kg), administered via an intraduodenal route, significantly reduced the volume, pH, total acidity and pepsin activity of gastric content in the pylorus ligature model in rats. The gastric acid antisecretory effect of CEEV was maintained even in the presence of cholinergic and gastrinergic, but not histaminergic, stimuli. *In vitro*, CEEV (1–10 μ g/ml) was able to scavenge free radical DPPH, but did not promote inhibitory effects on MPO or H^+K^+ -ATPase activity. Phytochemical analysis of CEEV indicated that luteolin is the main compound present in the extract. However, luteolin (1, 3 and 10 mg/kg, p.o or 1 mg/kg, i.p.) did not promote gastroprotection against ethanol/HCl in mice. It is also important to mention that oral administration of CEEV did not produce any sign of acute toxicity in animals.

Conclusions: *V. condensata* extract demonstrates gastroprotective effects through the inhibition of gastric secretion via cholinergic and gastrinergic pathways. Furthermore, it exhibits cytoprotective effects, involving antioxidant activity, an increase in mucin content and inhibition of neutrophil migration. Thus, this medicinal plant may be a suitable natural source for the prevention and treatment of gastric lesions.

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1. Introduction

Gastric ulcers are prevalent throughout the world, and are considered to be a global health problem (Thorsen et al., 2013). The etiology of the gastric ulcer is not completely understood, but it has been established that it may result from an imbalance

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between the protective factors and aggressive factors in the gastric mucosa (Laine et al., 2008). Among the defensive factors we can include mucus and bicarbonate production, cellular regeneration and adequate blood flow, while the main aggressive factors comprise gastric acid, pepsin secretion, and reactive oxygen species (Malfertheiner et al., 2009). Furthermore, the gastric ulcer may be triggered by a *Helicobacter pylori* infection (Calabuig et al., 2009), stress, or chemical agents (excessive alcohol intake or chronic treatment with non-steroidal anti-inflammatories) (Lemos et al., 2011).

The classic antiulcer treatment regime consists of acid suppressant drugs, mainly type-2 histamine receptor antagonists (H₂-RAs) and proton pump inhibitors (PPIs) (Sheen and Triadafilopoulos, 2011). However, in cases of ulcers initiated by *H. pylori* infection, it is necessary to utilize an approach consisting of antibiotics and inhibitors of gastric secretion (Malfertheiner et al., 2009).

Nevertheless, research for the development of new antiulcer drugs is necessary due to the following key points: 1. There is a diversity of significant side effects presented by drugs that are currently available (increased susceptibility to pneumonia and bone fractures, thrombocytopenia, iron and vitamin B12 deficiencies, hypergastrinemia, and cancer) (Dacha et al. 2015); 2. Several drug-drug interactions exist (Sheen and Triadafilopoulos, 2011); and 3. Frequent ulcer recurrence in patients has been observed following treatment (Kangwan et al., 2014). In view of this, natural products are considered attractive sources for potential new treatments of gastric ulcer.

Vernonia condensata Baker (Asteraceae) (syn.: *Vernonia amygdalina* Delile, *Vernonanthura condensata* (Baker) H. Rob., *Vernonia bahiensis* Toledo and *Vernonia sylvestris* Glaz.) is commonly known in Brazil as “boldo baiano”, “alumã” (Lorenzi and Matos, 2008), “figatil”, or “necroton” (Da Silva et al., 2013). The leaves from *V. condensata* are traditionally used by the population for a multitude of purposes including its analgesic, anti-inflammatory, antipyretic, antianemic and antibacterial effects, as well as a tonic for the liver. Its main use however, is as an antiulcerogenic agent, also used for the treatment of dyspepsia (Lorenzi and Matos, 2008). Its traditional use for gastric ulcer treatment is so prevalent, that in a quick Internet search using the terms “úlceras” (Portuguese for ulcer) and “boldo-baiano (vernonia)” more than 2000 websites were found describing the antiulcer properties of this plant. Moreover, *V. condensata* was included in a list called “Renisus,” which contains plant species with the potential to advance in the therapeutic industry and generate herbal medicines of interest to the Brazilian Public Health System (SUS). In addition, this species is also included in “Formulário de Fitoterápicos da Farmacopeia Brasileira (Brazilian Pharmacopeia)”. In this compendium, *V. condensata* is indicated as an antiulcer agent and a treatment for dyspepsia (Brasil, 2009; Brasil, 2011).

Frutuoso et al. (1994) evaluated the gastroprotective activity of a polar fraction of *Vernonia condensata*. In this study, the authors found significant gastroprotective activity on the indomethacin induced ulcer model. However, the mechanisms involved in the effect, as well as the gastric healing activity in a chronic gastric ulcer model or antisecretory properties of *Vernonia condensata* remained unknown. Based on this, the aim of this study was to evaluate the activity of *Vernonia condensata* in different animal models to further elucidate the various gastric healing mechanisms of this species.

2. Materials and methods

2.1. Plant material

The leaves from *Vernonia condensata* were collected in Itajaí city, at the UNIVALI (Universidade do Vale do Itajaí) in the state of Santa Catarina, Brazil, at May 2014 (S26°55'2"; W48°39'58"), and identified by Renê Artur Ferreira. A voucher specimen was deposited at the Barbosa Rodrigues Herbarium (Itajaí/SC) under number 55,272. The vegetal material (1270 g) was dried at room temperature and then crushed (184 g) and macerated with ethanol 99.6% at room temperature for 7 days. After, the macerate was filtered and the solvent removed by rotatory evaporator under reduced pressure, yielding 8 g (4.34%) of crude ethanolic extract of *Vernonia condensata* (CEEV).

2.2. Phytochemical analysis

2.2.1. Preliminary phytochemical analysis

Phytochemical screening were done to detect the presence of alkaloids, triterpenes, steroids, saponins, flavonoids, tannins, coumarins and anthraquinones according the methods proposed by Randau et al. (2004). Besides, thin layer chromatography (TLC) was used to evaluate the chemical composition of *V. condensata* extract. Were used as mobile phase hexane:acetone (7:3) and chloroform:methanol (8:2) and specific chromophores as revelators, anisaldehyde for terpenoids and ferric chloride for phenolic compounds. For comparison were used different patterns solutions of terpenes and flavonoids.

2.2.2. Estimation of total phenolic content

The content of total phenols was determined using the Folin–Ciocalteu reagent according to the method described by Arnous et al. (2001). About 50, 100, 150 and 200 µg/ml of CEEV or an infusion prepared with 3 g of dry leaves of *V. condensata* in 150 ml of water were mixed with 0.5 ml of distilled water. After, 2.5 ml of Folin–Ciocalteu reagent (1:10 dilution) and 2.0 ml of sodium carbonate (7.5% w/v) were added and the tubes were incubated at 45 °C for 15 min. The absorbance was determined at 760 nm in spectrophotometer. The total polyphenol concentration was calculated from a calibration curve, using tannic acid as a standard. Results were expressed as tannic acid equivalents (TAE) in µg.

2.2.3. High-performance liquid chromatography (HPLC) analysis

High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-20 AC chromatographer equipped with a quaternary pump, scan spectrum photo diode array automatic detector and SIL-20A injector. The LC Solution[®] software was used to record the chromatograms and measure the peak areas. The scan range detection was performed at a range of wavelengths from 190 nm to 400 nm. The mobile phase were vacuum filtered through 47 mm diameter and 0.45 mm porosity regenerated cellulose membrane and ultrasound degassed. For the analysis 1 mg of extract and 0.1 mg of standards were dissolved in 1 ml of methanol (HPLC grade). Chromatographic separation was accomplished on a C18 Phenomenex column (250 × 4.5mm, 5 µm). HPLC grade methanol (A) and water (B), both containing 0.1% formic acid, were used as chromatographic eluents in gradient mode. The following elution program was used: 0–25 min, 10–90% B; 25–30 min, 90% B; 30–32 min, 90–10% B. The flow rate was set at 0.9 ml/min, and the column temperature was controlled at 35 °C. The injection volume was 10 µl.

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