Conjecturas

Effects gastroprotective of the hydroalcoholic extract from *Sonchus oleraceus* in mice

Efeitos gastroprotetores do extrato hidroalcoólico de *Sonchus oleraceus* em camundongos

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ABSTRACT

Sonchus oleraceus L., (Asteraceae), is native of Europe and largely distributed in Brazil. However, despite the extensive traditional use, the gastroprotective pharmacological mechanism has not yet been investigated. In this context, the present study aimed to evaluate the involvement of inflammatory and stress oxidative markers in the gastroprotective effect of hydroalcoholic extract of *S. oleraceus* (HES) in mice. Thus, mice (*Mus musculus*) were pre-treated with HES (3, 30, or 300 mg/kg, p.o) and after 1 h submitted to gastric ulcers with a non-steroidal anti-inflammatory (indomethacin, 100 mg/kg). After euthanasia, areas lesions were quantified and biochemical analyses were performed. In the animals that received HES (30 or 300 mg/Kg), was observed a reduction in lesion area (70.3% and 57.4%, respectively; $p < 0.01$), compared to the vehicle (Veh, water), and the protective effect of the gastric mucosa was confirmed in histological analyzes (HE). In addition, it was observed that the HES (30 or 300 mg/Kg) prevented the depletion CAT and SOD and showed a significant decrease in MPO when compared with the Veh group. The results of this study contribute to the elucidation of the gastroprotective mechanism of *S. oleraceus*, and validation of the popular use of the species.

Keywords: antiulcer; medicinal plants; serralha.

RESUMO

A espécie *Sonchus oleraceus* L., (Asteraceae), é nativa da Europa e amplamente distribuída no Brasil. No entanto, apesar do amplo uso tradicional, o mecanismo farmacológico gastroprotetor ainda não foi investigado. Nesse contexto, o presente estudo teve como objetivo avaliar o envolvimento de marcadores inflamatórios e de estresse oxidativo no efeito gastroprotetor do extrato hidroalcoólico de *S. oleraceus* (HES) em camundongos. Assim, camundongos (*Mus musculus*) foram pré-tratados com HES (3, 30 ou 300 mg/kg, p.o) e após 1 h submetidos a úlceras gástricas com anti-inflamatório não esteroidal (indometacina, 100 mg/kg). Após a eutanásia, as áreas lesionadas foram quantificadas e análises bioquímicas foram realizadas. Nos animais que receberam HES (30 ou 300 mg/Kg), foram observadas, redução da área da lesão (70,3% e 57,4%, respectivamente; $p < 0,01$), em relação ao veículo (Veh, água), e o efeito protetor da mucosa gástrica foi confirmado em análises histológicas (HE). Além disso, observou-se que o HES (30 ou 300 mg/Kg) preveniu a depleção de CAT e SOD e apresentou diminuição significativa da MPO quando comparado ao grupo Veh. Os resultados deste estudo contribuem para a elucidação do mecanismo gastroprotetor de *S. oleraceus* e validação do uso popular da espécie.

Keywords: antiúlcera; plantas medicinais; serralha.

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INTRODUCTION

Gastric ulcer (UG) is a chronic disease, characterized by the presence of necrotic lesions involving all layers of the stomach mucosa, even reaching the muscular layer (ZANOTELLI *et al*., 2020). The etiology is complex and multifactorial however, it is known that the disease is caused by the imbalance of the aggressor mechanisms (gastric acid, pepsin, reactive and oxidizing free radicals) and mucosal protectors (gastric mucus, bicarbonate, prostaglandin - PG, and blood flow). Furthermore, it is important to emphasize that the main causes of UG involve the presence *Helicobacter pylori* bacterium, hypersecretion of hydrochloric acid, and NSAIDs (AMIRSHAHROKHI; KHALILI, 2017; ATHAYDES *et al*., 2019).

The treatment of UG is based on the suppression of secretion of gastric acid, using mainly proton pump inhibitors (PPI) and antagonists type 2 histamine receptors (H2-RAs). In recent years, several studies have linked antisecretory drugs with serious adverse effects, such as atrophic gastritis, a precursor of gastric cancer, increased, decreased calcium absorption, and increased osteoporotic fractures. More recently, it has also been hypothesized that the use of PPIs can cause kidney disease and dementia. These drugs have the potential for rebound acid hypersecretion after drug withdrawal (DACHA *et al*., 2015; SILVA *et al*., 2020).

In the context, there has been an intensification of studies that seek to identify safe and effective alternative resources, with a particular focus on the anti-ulcerative potential of natural products (CALIXTO, 2019; KUNA *et al*., 2019). In addition, there is an increase in the use of alternative therapies supported by policies within the scope of the Unified Health System (SUS), especially the use of medicinal plants and phytotherapics (ZENI *et al*., 2017; ROMAN JUNIOR *et al*., 2022).

Sonchus oleraceus L., (Asteraceae), is a species native to Europe that has presented a global distribution. The leaves are widely consumed in some regions of Asia, Europe, and Oceania as a dietary supplement owing to their high nutritional value. In traditional chinese medicine (TCM), for example, it is used for treating tumors, inflammatory diseases, and infections (CHEN *et al*., 2019). In Brazil, the plant it is known as serralha, chicory-brava, and serralheira, and the aerial parts are popularly used as depuratives, laxatives, and in the treatment of cardiovascular and gastrointestinal problems (YIN *et al*., 2007; MAWALAGEDERA *et al*., 2016). These activities are

probably related to the presence of several phenolic compounds, having flavonoids as major compounds. In pharmacological tests for the plant, there are descriptions of intense antioxidant action and strong anti-inflammatory potential (VILELA *et al*., 2010; LI *et al*., 2020).

However, despite the wide popular use and the therapeutic potential of its constituents, the gastroprotective mode of action of the plant has not yet been elucidated. Thus, the aim of this study is to evaluate the involvement of inflammatory markers and oxidative stress in the gastroprotective effect of the hydroalcoholic extract of *S. oleraceus* on NSAID-induced ulcers in mice.

METHODOLOGY

Plant material

The aerial parts of *S. oleraceus* were collected in Chapecó (SC), Brazil, with latitude and longitude of 27° 01'55.14 'S and 52° 47 '29.42' 'W, in September 2017. The plant was identified by Prof. Adriano Dias de Oliveira do Herbarium Curator of the University Community of the Region of Chapecó (Unochapecó) where a voucher was deposited (nº 3701).

Preparation of extracts of *Sonchus oleraceus*

Samples of S. oleraceus were dried at room temperature (25 ± 5°C), crushed in a knife mill (Ciemlab®, CE430), selected in a sieve (425 µm), identified, and stored protected from light. The hydroalcoholic extract (HES) was produced by maceration (5 days) at room temperature using the dried and milled leaves (500 g) and 70% ethanol (1:20, w/v). HES was funnel filtered Büchner and concentrated by evaporation under reduced pressure (40°C), freeze-dried, weighed (55.9 g; 11% yield), and stored at -20°C.

Quantification of flavonoids

The number of total flavonoids was measured using the Woisky and Salatino method (1998) with adjustments. Briefly, 1 mL HES (in MeOH) (1000 µg/mL) was added to 1 mL of 2% AlCl3 (in MeOH) and after 60 min the readings of the spectrophotometers were carried out at 365 nm. To produce the calibration curve, the quercetin was diluted in methanol as standard (10, 15, 20, 25 and 30 µg/mL), and the readings were performed in triplicate. The quantification was determined in milligrams per gram of extract.

Animals

Male Swiss mice (20 - 35 g) were supplied by Central Animal House of Unochapecó and kept cages under laboratory conditions standard (12-hour light/dark cycle, temperature 22 ± 2°C), with free access to food (Biobase®, Águas Frias/SC, Brazil) and water. Food was removed 12 hours before the experiments and water were provided ad libitum in raised floor cages with raised mesh to prevent coprophagia. All experiments were performed after approval by the Institutional Animal Ethics Committee of Unochapecó (protocol number 020/17), following the International Principles for Research on Animals Biomedical Involving Animals (CIOMS / WHO, 2002).

Indomethacin-induced gastric ulcer

The methodology applied was described by Nwafor et al. (2000). After 12 hours of fasting, mice (n= 6/group) were pretreated orally with vehicle (Veh: solution saline plus 1% tween-80, 1 mL/kg), carbenoxolone (CBX: 200 mg/kg) and HES (3, 30 or 300 mg/kg). After 6 h, all animals, except the naive group, received an oral dose 80 mg/kg indomethacin (80 mg/kg). The mice were euthanized six hours later, the stomach removed through the opening along the greatest curvature, washed with saline and evaluated macroscopically to measure the injured areas. The percentage of the lesion area (mm2), in relation to the total area of the stomach was measured using the EARPs® software. The samples of stomach were stored at -80°C for analysis.

Histological evaluation

Tissue samples from stomachs from all groups were evaluated microscopically as previously described (DE-FARIA et al., 2012). The samples of gastric ulcers were fixed in Alfac (85% ethanol to 80%; 10% formaldehyde and 5% acetic acid) for 24 hours. Afterward, the gastric tissues were dehydrated with alcohol and xylene, embedded in paraffin, sectioned to 5 mm, and stained with hematoxylin/eosin (HE). The material was analyzed, and the images obtained with a stereomicroscope with 10x magnification.

Biochemical analysis of gastric tissue

The ulcerated tissue samples were homogenized with a phosphate buffer of 200 mM potassium (pH 6.5). The obtained homogenate was used to determine the content reduced glutathione (GSH) (SEDLAK; LINDSAY, 1968). The remaining material was

centrifuged (20 min, 9000 x g, 4°C) and the supernatant was quantified for superoxide dismutase (SOD) (MARKLUND; MARKLUND, 1974), catalase (CAT) (AEBI, 1984) and glutathione-S-transferase (GST activities) (HABIG; PABST; JAKOBY, 1974). Rates of subcellular fraction homogenates were centrifuged at 11000 x g for 20 min at 4°C. O resulting precipitate was used to determine MPO activity as described by Young et al. (1989).

RESULTS AND DISCUSSION

The ulcerogenic agent used in the research was indomethacin, whose harmful effect on gastric is known, presenting itself as an adverse reaction. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) with no specificity for cyclooxygenases enzymes (COX 1 or 2). Its use is related to the appearance of gastric lesions due to inhibition of COX-1, which in turn decreases the production of prostaglandins (PGE2), one of the factors related to the protection of the gastric mucosa (LI et al., 2020). It also increases the acid secretion and pepsin activity, thus decreasing the mucus strength and the secretion of bicarbonate, consequently, there is an increase in lipid peroxidation and production of radicals free in the gastric mucosa, leading to an increase in toxic oxygen radicals (superoxide and oxygen peroxide), in addition to the damage caused to the gastric mucosa, performs the recruitment of leukocytes and leukotrienes, increasing tissue inflammation (KURNIJASANTI; PUTRI, 2017).

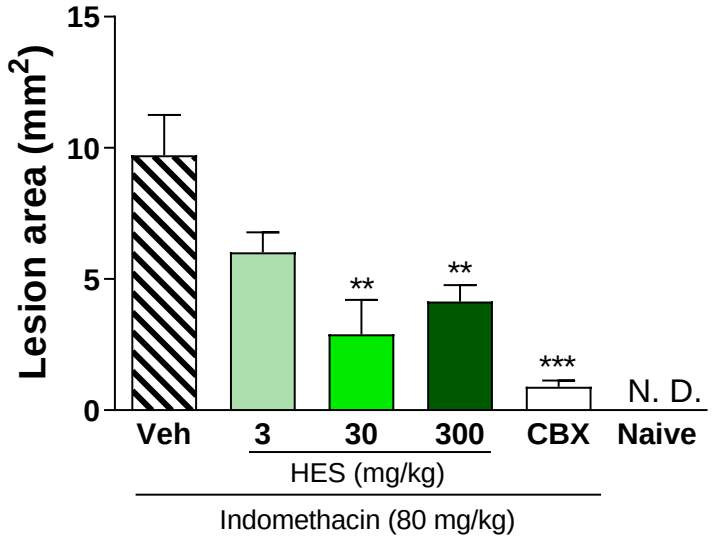
In this study, as expected, mice that received indomethacin and were treated with solution saline (Veh) showed a high lesion area. On the other hand, the HES (30 and 300 mg/kg) reduced the ulcerated area by 70.3% and 57.4% ($p < 0.01$) compared to Veh. The group CBX showed reduction in lesion area of 90.8% (Figure 1A).

The gastroprotective effects of HES (30 and 300 mg/kg) were corroborated by histological analyzes of hematoxylin/eosin staining (Figure 1B), that have showed greater mucosal preservation gastric when compared to vehicle. Thus, preventing submucosal edema, hemorrhagic injury and the loss of common epithelial cells (SOUZA et al., 2018; BOUTEMINE et al., 2018). This gastroprotective effect can be explained in part, by the presence in HES of a large number of polyphenolic compounds. In this study, using the spectrometric analysis (UV/Vis) through the calibration curve (quercetin, 10 - 30 µg/mL; $y = 0.0614x - 0.0384$; $R^2 = 0.9973$), the HES showed a high amount of flavonoids (67.0

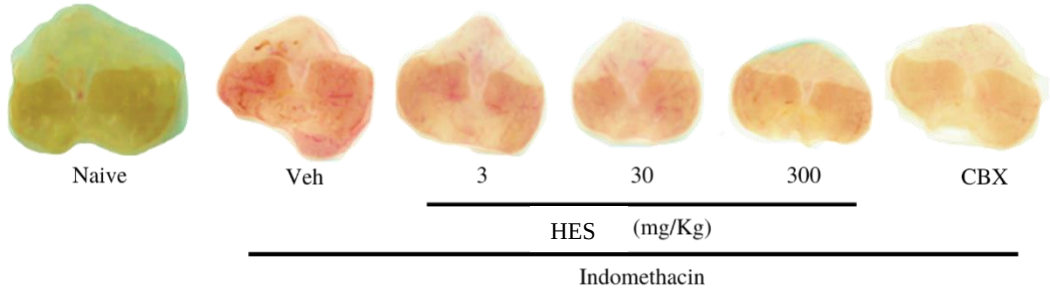
mg/g; 6.7%). These molecules protect the gastrointestinal mucosa from lesions observed in several experimental gastric ulcer models and against different necrotic agents. Several mechanisms of action may be involved in this protective effect, including anti-secretory, healing, anti-inflammatory, and antioxidant activity (MOTA et al., 2009; MOUSA et al., 2019).

Figure 1. Effect of the hydroalcoholic extract from *Sonchus oleraceus* (HES, 3 – 300 mg/kg) and carbenoxolone (CBX; 200 mg/kg) on the indomethacin-induced ulcer (mean ± SEM; n = 6). (A) Mice induced with indomethacin and treated with saline (Veh). One-way ANOVA followed by Tukey test. $^{**}p < 0.01$ and $^{***}p < 0.001$ compared to vehicle ulcerated (Veh) group; N.D: not detected. (B) Representative macroscopic images of stomachs of from each group. (C) Representation of histological analyzes by Hematoxylin/eosin (HE).

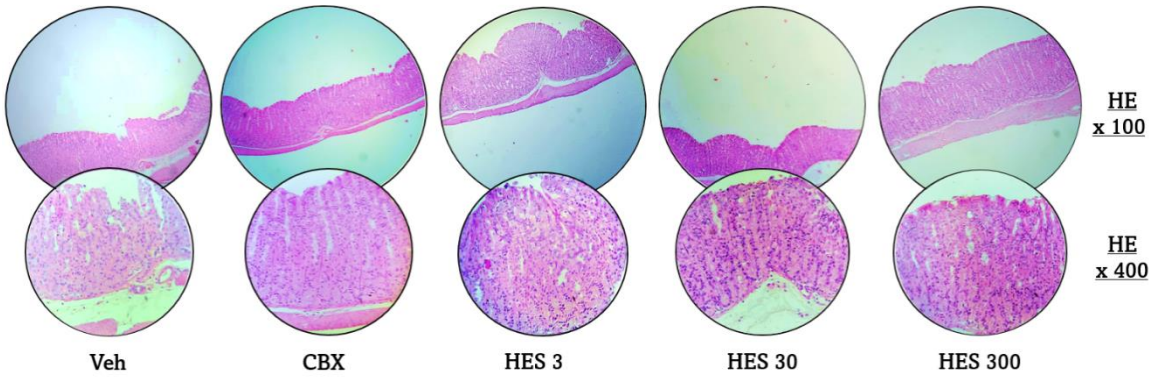
1A



1B



1C



The assessment of GSH levels, as well as enzymatic activities of SOD, CAT, and MPO were measured in stomach tissues ulcerated by indomethacin (Table 1). The HES (30 and 300 mg/kg) showed the ability to avoid the depletion of enzymatic activities of CAT and SOD ($p < 0.005$) compared to Veh. In addition, HES (3, 30, and 300 mg/kg) decreased tissue MPO activity compared to the vehicle group ($p < 0.001$). Results are similar to the carbenoxolone group (CBX). GSH levels were not decreased by HES and CBX.

Table 1. Results of HES in SOD, CAT, MPO, and GSH assays.

Treatments (mg/kg)	GSH	SOD	CAT	MPO
Veh (water)	3074 ± 67.9	31.54 ± 5.629	2.206 ± 0.335	0.165 ± 0.012
HES 3	3614 ± 275.3$^{\#\#}$	54.48 ± 4.095	2.984 ± 0.061$^{\#}$	0.049 ± 0.020 ***
HES 30	3068 ± 166.1	61.47 ± 4.939*	20.49 ± 3.267*	0.061 ± 0.017***
HES 300	3132 ± 145.1	61.80 ± 6.001*	20.90 ± 2.913*	0.076 ± 0.011***
CBX 200	3752 ± 61.4$^{\#}$	67.60 ± 6.238**	28.27 ± 2.913**	0.069 ± 0.007***
Naive	2303 ± 386.7	68.11 ± 5.862*	25.75 ± 0.207*	0.080 ± 0.016*

Note: Carbenoxolone (CBX, 200 mg/kg); hydroalcoholic extract of *S. oleraceus* (HES 3, 30 or 300 mg/kg); reduced glutathione (GSH, µg/mg of tissue); superoxide dismutase (SOD, U/mg of protein); catalase (CAT, µmol/min/mg of protein), myeloperoxidase (MPO, mD.O/mg of protein). Values are expressed as means ± SEM (n = 8). One-way ANOVA followed by Tukey's test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ *versus* vehicle-treated group. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ *versus* naive group.

Antioxidant mechanisms correspond to the organisms' protection systems against the oxidative stress process, aiming to maintain the cellular redox state, either by delaying, removing, or preventing damage, through antioxidant mechanisms divided into primary and secondary (mode of action) and in enzymatic and non-enzymatic (LOCATELI et al., 2020). The non-enzymatic antioxidant system is composed of products produced in the organism, such as bile pigments, urate, metal transport proteins (such as metallothionein), and the tripeptide glutathione (GSH), the main intracellular antioxidant compound (MEURER et al., 2022). The enzymatic antioxidant system is composed of the enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione-S-transferase (GST). These antioxidant compounds have been used as oxidative stress biomarkers (BARBOSA et al., 2014).

The antioxidant and anti-inflammatory activity demonstrated by HES is important because it several authors have shown that agents with potential antioxidants, that can restore these enzymatic pathways have shown great potential for protecting the stomach against injurious agents (KWIECIEN et al., 2014; VECCHIA et al., 2022). The chronic use of NSAIDs and alcohol consumption (risk factors) for example, contribute significantly to the onset of UG, forming lesions that destroy deeply the gastric mucosa. Such a tissue destruction process triggers several mechanisms cellulars, including the intense activity of the MPO enzyme, which, in turn, provides oxidative parameters in inflammatory conditions (SANTANA et al., 2015; BENVENUTTI et al., 2020).

HES at all doses, decreased MPO activity. Despite its great importance in the immune system, MPO is associated with the cause or progression of various diseases, due to its property of accentuating inflammation and damaging tissue (KHAN et al., 2018; VECCHIA et al., 2022). Studies show that NSAID-induced gastric ulcers in rats increase the production of concentrations of MPO activity, which may be associated with increased neutrophil infiltration in damaged tissues, used as a marker for inflammation and neutrophil infiltration (SILVA et al., 2013; OLIVEIRA et al., 2022).

Thus, the results obtained in this work demonstrate that the HES, in addition, to promoting the increase of antioxidant enzymes, reduced MPO activity in tissue stomachs of animals treated with Indomethacin indicating a reduction in infiltration neutrophilic. This effect corroborates the statement of Ateufack et al. (2015), which the damage to the gastric mucosa is related to increased neutrophil infiltration in ulcerated tissues. these

neutrophils inhibit ulcer healing, just as lipid peroxidation acts through the release of cytotoxic factors. Infiltrated and activated neutrophils represent a source of species reactive oxygen, nitrogen species, and pro-inflammatory cytokines (DEGER et al., 2006).

CONCLUSION

The hydroalcoholic extract of *S. oleraceus* leaves has gastroprotective effects mediated via an enhancement of antioxidant defenses, in parallel with a reduction in the inflammatory process. These effects are at least in part, promoted the activity of flavonoids presents HES. We accordingly believe that the findings of this study make an important contribution and advance our current understanding of the pharmacological mechanisms for gastroprotective molecules. In addition, this study contributes to the popular use of plants and in the prospection of new gastroprotective agents.

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