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Preventing ethanol-induced stomach ulcers in rats using *Senecio perralderianus* leaf extract

Prevención de úlceras estomacales inducidas por etanol en ratas utilizando extracto de hoja de *Senecio perralderianus*

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ABSTRACT

Senecio perralderianus belongs to the family of Asteraceae and is only found in Algeria. Some species of this family are used to heal gastrointestinal issues in conventional medicine for their antioxidant and anti-inflammatory properties. This research was performed in order to determine if methanolic extract from the leaves of *S. perralderianus* had any protective effects on gastroenteritis brought on by alcohol consumption. Wistar rats were fed with 100% ethanol orally to induce gastric ulcer, and pre-treated with 50, 100, and 200 mg·kg^{-1} of the extract in addition to 5 mg·kg^{-1} of Ranitidine as a positive reference drug. The extract had shown a positive effect to protect ethanol-induced gastric ulcers with a protection percentage of 71 to 88%. In addition, pretreatment of rats significantly increased levels of GSH, CAT, and SOD *in vivo* as non-enzymatic and enzymatic antioxidants, and also reduced the level of lipid peroxidation. Histopathological sections, which showed the action of the therapeutic extract, substantially confirmed these findings on the reduction of the inflammation zone and the reduction of immune cell filtration caused by ethanol toxicity with increased extract dosages compared to Ranitidine. The antiulcer activity is due to inhibition of oxidative stress and gastritis. It is associated with a total polyphenol, flavonoids, chlorophyll (a, b), and carotenoids substantial amounts.

Key words: *Senecio perralderianus*; methanol extract; gastric ulcer; oxidative stress

RESUMEN

Senecio perralderianus pertenece a la familia Asteraceae y se encuentra únicamente en Argelia. Algunas especies de esta familia se utilizan para curar problemas gastrointestinales en la medicina convencional por sus propiedades antioxidantes y antiinflamatorias. Esta investigación se llevó a cabo para determinar si el extracto metanólico de las hojas de *S. perralderianus* tenía efectos protectores sobre la gastroenteritis causada por el consumo de alcohol. Las Wistar ratas fueron ingeridas por vía oral con etanol al 100 % por vía oral para inducir úlcera gástrica y fueron pretratadas con 50; 100 y 200 mg·kg^{-1} del extracto, además de 5 mg·kg^{-1} de Ranitidina como fármaco de referencia positivo. El extracto había demostrado un efecto positivo para proteger las úlceras gástricas inducidas por el etanol con un porcentaje de protección del 71 al 88 %. Además, el pretratamiento de ratas aumentó significativamente los niveles de GSH, CAT y SOD *in vivo* como antioxidantes no enzimáticos y enzimáticas, y también redujo el nivel de peroxidación de lípidos. Las secciones histopatológicas, que mostraron la acción del extracto terapéutico, confirmaron sustancialmente estos hallazgos sobre la reducción de la zona de inflamación y la disminución de filtración de células inmunes causada por la toxicidad del etanol con dosis de extractos aumentadas en comparación con la Ranitidina. La actividad antiúlcera se debe a la inhibición del estrés oxidativo y la gastritis. Se asocia con un total de polifenoles, flavonoides, clorofila (a, b), y carotenoides cantidades sustanciales.

Palabras clave: *Senecio perralderianus*; extracto de metanol; úlcera gástrica; estrés oxidativo

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INTRODUCTION

Many diseases and health problems can affect the digestive system and the nature of its work (related to digestion). These health problems can affect various parts of the system, especially the large intestine, micro intestines, stomach, oesophagus, and digestive accessories. They range in severity from severe or minor disorders of short duration, such as mild cases of heartburn, to severe or chronic disorders that can be life-threatening in some cases, such as perforating ulcers.

Duodenal and gastric ulcers are also the most common chronic diseases for years, these two primary forms of gastrointestinal ulcers represent the general term for open contractions in the upper part of the digestive tract, mainly affecting the duodenum's first segment (bulb) and the stomach's mucosa, where the involvement of acid and pepsin in the disease is essential [1]. This accompanies many different symptoms, which in some cases can be very alarming, causing many people to suffer, such as abdominal bloating, diarrhea, and constipation [2]. Chlorhydro-peptic aggressiveness and defensive processes (mucosal barrier) are out of balance, which causes peptic ulcers at a specific point [3]. This disruption is caused by many internal and external causal factors that modulate the aggression/defence balance, including smoking, stress, diet and alcohol [4]. For this reason, many people are turning to herbal remedies, which has led to several studies in recent years on how herbs used in traditional medicine affect biology to protect the gastrointestinal tract, increasing the antiulcer and anti-inflammatory culinary and medicinal plant activities.

Complications of peptic ulcer, however, did not decrease, according to systematic reviews and meta-analyses (18 European, American and Palestinian studies, more than 1,000 people per study). Older population comorbidities, more frequent consumption of ulcer medications may help [1, 5]. In Algeria, some botanical and natural products are used to treat inflammatory diseases, including gastric ulcers and diarrhea [6]. The genus *Senecio*, where 18 species, including 5 endemic species, are recorded to Algeria [7]. According to locals, *Senecio perralderianus*, in folk medicine; used to treat cough, asthma and bronchitis [8]. *S. perralderianus* is found only in Algeria at an altitude of 1,900 m in the mountain ranges of Babor in the Northern tip of Sétif and in the mountains of Djurdjura between the States of Tizi-Ouzou, Bouira and Bejaia (Kabylie mountain range), both mountains are located in Northern Algeria [9]. However, to the present knowledge, no report is available on anti-inflammatory and antioxidant properties of *S. perralderianus*. In this regard, this study's goal is to perform a further assessment the antiulcer effect of the methanolic extract of *S. perralderianus* using *in vivo* and *ex vivo* methods. An investigation was conducted on *S. perralderianus* extract's ability to prevent ethanol-induced stomach ulcers by calculating the ulcer surface, studying tissue sections and examining the content of gastrointestinal mucus, proteins and glutathione, lipid peroxidation and catalase activity.

MATERIALS AND METHODS

Animals

The Wistar rats (*Rattus norvegicus*) weighing around 150 and 155 g were used in the *in vivo* experiments. Before the experiment, they were starved for 17 hours (h) and they were deprived of water for about 1 h before the experiment.

Plant material

The harvest of the medicinal plant *S. perralderianus* was carried out in spring of 2019 (March) by Dr. Benchikh A. and Dr. Mamache W (FIG. 1), from the mountain ranges of Babor in the Northern tip of Setif at an altitude of 1,536 and 1,900 m and was identified by Pr. Laouer H. (University of Setif 1). The impurities were removed, the leaves were isolated and dried for ten days in the open air and in the dark.

FIGURE 1. Botanic aspect of *Senecio perralderianus*. The plant appears in small tall of 4 to 15 cm, not very leafy, with a very frail appearance, it is characterised by composite flowers and alternate, toothed leaves

Methanolic extract preparation

Through maceration, the methanolic extract was produced of 150 g of plant powder with 1 L of 80% methanol. During 72 h, the mixture was mixed daily in the dark at room temperature. After filtration, the filtrate was vacuum-concentrated using a BUCHI rotavap at 40°C. The resulting extract was followed full drying at 37°C [10].

Ethanol-induced gastric injury

One hour after administering the test solution, ethanol (100%) was administered orally to promote ulcers in the stomach [11]. Four distinct sets of male Wistar rats were established (n=8 each). The dose of 50 mg·kg^{-1},100 mg·kg^{-1} and 200 mg·kg^{-1} (dissolved in 0.9% NaCl) of plant extract were ingested one hour prior to gavage with 0.5 mL of ethanol. Untreated rats (negative control group) were received only 0.9% NaCl in the same manner. Rats received Ranitidine 5 mg·kg^{-1} in addition to ethanol were considerate as positive control group. 30 min later, animals were cervical dislocated and killed. The stomach was cut out after a ventro-medial laparotomy, then, the stomach was excavated and opened following the larger curvature, flushed with 0.9% NaCl, and spread out on a tray. The Image J 1.52o software (Wayne Rasband, NIH, USA) was used to identify the lesion area.

Percentages of ulceration (%) and protection are calculated as follows:

$$Ulceration\ (\%) = \frac{Ulcerated\ area}{Total\ area}$$

$$Protection\ (\%) = \frac{Ulceration\ \ negative\ \ control\,(\%) - Ulceration\ \ tratment\ \ (\%)}{Ulceration\ \ negatice\ \ control\ \ (\%)}$$

Preparation of histological sections

For classical histological studies, the preparation of thin sections for observation under light microscopy (OPTIKAB353A, OPTIKA s.r.l., Italy) is performed in several steps: sampling, fixation, post-fixation, dehydration and circulation, coating, sectioning, handling, staining, final assembly and observation under the microscope.

The fixative liquid used to immerse the specimen in current practice is 10% formalin aldehyde for 24 h, after which the sectioned hip is placed in it (24 h). The specimen was passed through alcohol baths of increasing concentration (from 50° alcohol to 100° absolute alcohol), then through xylene baths for thinning or toluene, then through kerosene for impregnation (58°C) for 24 h. Inclusion (Coating) the sample is bathed in molten kerosene is poured into a small metal mold (KARTELL LABWARE® 2923, Italy) (heated to 56 °C) therefore became liquid and then infiltrates the entire piece. After cooling to obtain a hard kerosene block then roughing (demoulding and trimming to have a parallel edge cutting font, then passed the block to the microtome, which can produce slices with a thickness of 5 µm, arranged regularly strips (ribbon shape).

After having undergone a dehydration (by alcohol baths of increasing degrees then toluene baths), the colored sections are mounted between slide and lamella with a synthetic resin whose refractive index is close to that of glass.

Ex vivo antioxidant activity

After sacrifice, in order to produce a 10% (w/v) homogenate, the glandular section of the stomach part was weighed and homogenized in a 50 mM (Tris-HCl) solution (pH 7.4). The resulting homogenate was centrifuged for 15 min at 4000 G (Sigma 3-30K, Germany), and the supernatant was collected and kept at -20 °C until it was utilized for the following parameters: estimated total protein content, lipid peroxidation (MDA), reduced glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) activity.

Total gastric protein content

The total gastric protein content was assessed according to Gornall, Bardawill [12] method, Using a biuret kit (BIOLABO LP87016, Italy). Briefly, 1 mL of the Biuret reactant was combined with 25 µL of the standard (BSA) or stomach homogenate, and the resulting mixture was incubated for 10 min in the dark at room temperature. The absorbance was then measured at 540 nm. Using this equation, concentration of total protein was estimated:

$$Total\ protein\ (mg.mL^{-1}) = \left(\frac{Abs\ assay}{Abs\ standard}\right) \times 100$$

n: concentration of used standard.

Estimation of lipid peroxidation

The lipid peroxidation of gastric tissue was evaluated by measuring the content of Malon dialdehyde (MDA) formed using the Ohkawa, Ohishi [13] method of. The principle of this reaction is that MDA reacts with Thio barbituric acid (TBA) in acidic medium at high temperature to form a coloured pink complex of MDA-TAB. Briefly, TCA (20%) and 0.250 mL of TBA (0.067%) are combined with 0.125 mL of tissue homogenate. The mixture was heated for 15 min in 100°C, immediately cooled in an ice bath, and then centrifuged for 15 min at 1,006 G (Sigma 3-30K, Germany) while 4 mL of *n*-butanol was added. The clear fraction of the supernatant's absorbance was measured in comparison to a blank (Shimadzu™ UV 1800 Spectrophotometer, Japan). Using the molecular absorption coefficient, the MDA concentration was determined (ε of MDA-TBA: 156 $mM^{-1}{\cdot}cm^{-1}$). Results are presented as nmol of MDA/g tissue

Determination of reduced glutathione

Using Ellman [14] approach, the reduced glutathione (GSH) content was determined. In this test, GSH is being oxidized by 5,5'-dithiobis (2-nitrobenzoic) acid (DTNB) (Ellman reagent). To form 2-nitro-5-thiobenzoic acid (TNB), which is highly coloured and significantly absorbs at 412 nm. 10 mL of phosphate buffer solution (pH 8, 0.1 M) were used to dilute 50 µL of tissue homogenate. After 5 min of incubation (at laboratory temperature), the absorbance of 3 mL of the diluted homogenate solution mixed with 20 µl of DTNB (0.01 M) was measured (Shimadzu™ UV 1800 Spectrophotometer, Japan). The MDA concentration was estimated using the coefficient of molecular absorption (εNBT: 13.6.103 $M^{-1}{\cdot}cm^{-1}$). Results are presented as nmol of GSH/g tissue.

Estimation of catalase activity

With slight adjustments, the Clairborne [15] technique was used to assess catalase (CAT) activity. The idea behind this test is based on how hydrogen peroxide breaks down when catalase is present. In a quartz cuvette (Bitomic, USA), 50 µL of homogenate was combined with 2.9 mL of H_2O_2 (19 mM) in a phosphate buffer solution (50 mM, pH 7.4). Using the molecular absorption coefficient (εH_2O_2: 43.6 $M^{-1}{\cdot}cm^{-1}$), the rate of H_2O_2 breakdown was measured spectrophotometrically (Shimadzu™ UV 1800 Spectrophotometer, Japan) at 240 nm every 15 s for 1 min. The enzyme activity was then reported as nmol of $H_2O_2{\cdot}min^{-1}{\cdot}mg^{-1}$.

Superoxide dismutase (SOD) activity.

Based on Gao, Yuan [16] report, SOD activity was estimated by the ability of the enzyme to prevent pyrogallol auto-oxidation. 5 µL of the supernatant was mixed with 10 µ of pyrogallol and 1 mL of Tris HCl buffer solution (pH 8.2, 50 mM). Measurement the rise in absorbance at 420 nm (Shimadzu™ UV 1800 Spectrophotometer, Japan) every 30 s for one min in comparison to the control was applied. SOD activity is defined as using the molecular absorption coefficient (ε pyrogallol: 2.47 $mM^{-1}{\cdot}cm^{-1}$).

Statistical analyses

All samples were analyzed 3 times (*ex vivo*), whereas 40 animals (8 rats in each group) were used for *in vivo* experiments. Results were expressed as mean ± SD or SEM of *ex vivo* or *in vivo* tests, respectively, and were analyzed by ANOVA one-way followed by Tukey's test with GraphPad Prism Software (V 8.0). Multiple comparisons of variances ANOVA were used to analyse the results. *P* value <0.05 or less was taken as significantly different.

RESULTS AND DISCUSSION

Anti-ulcer activity

Macroscopic analysis showed that animals that received 100% ethanol showed consistent macroscopic lesions manifested by loss of

normal color and mucus and the presence of petechiae, hemorrhages. This damage can be mitigated by administering different doses of extract. Pretreatment of rats with *S. perralderianus* leaves methanol extract at different doses reduced ethanol-induced damage (FIG. 2).

These results were confirmed by histopathology analysis. In rats, haemorrhagic lesions of the gastric mucosa, infiltration, and signs of inflammation were reduced in rats treated at doses of 100–200 mg·kg^{-1} of the extract (FIG. 3).

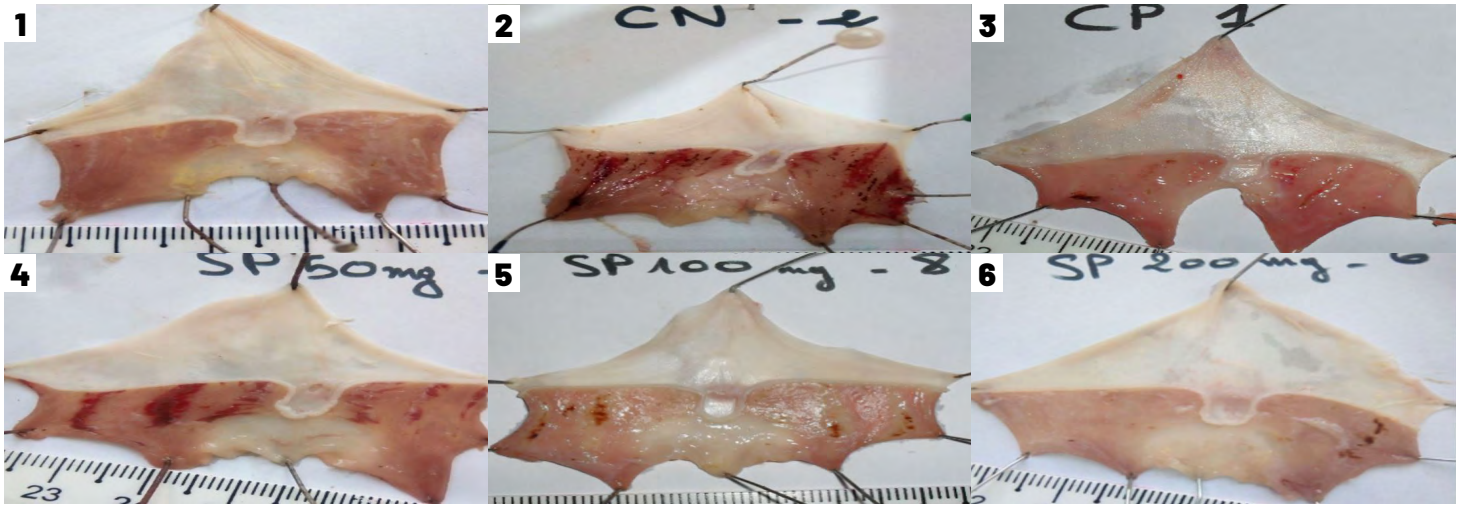

FIGURE 2. Effect of *Senecio perraldarianus* on appearance of gastric mucosa in ethanol-induced gastric ulcer. 1: Negative group; 2: Ethanol 100%; 3: Ranitidine 5 mg·kg^{-1}. 6, 5, 4: extract (200, 100 and 50 mg·kg^{-1})

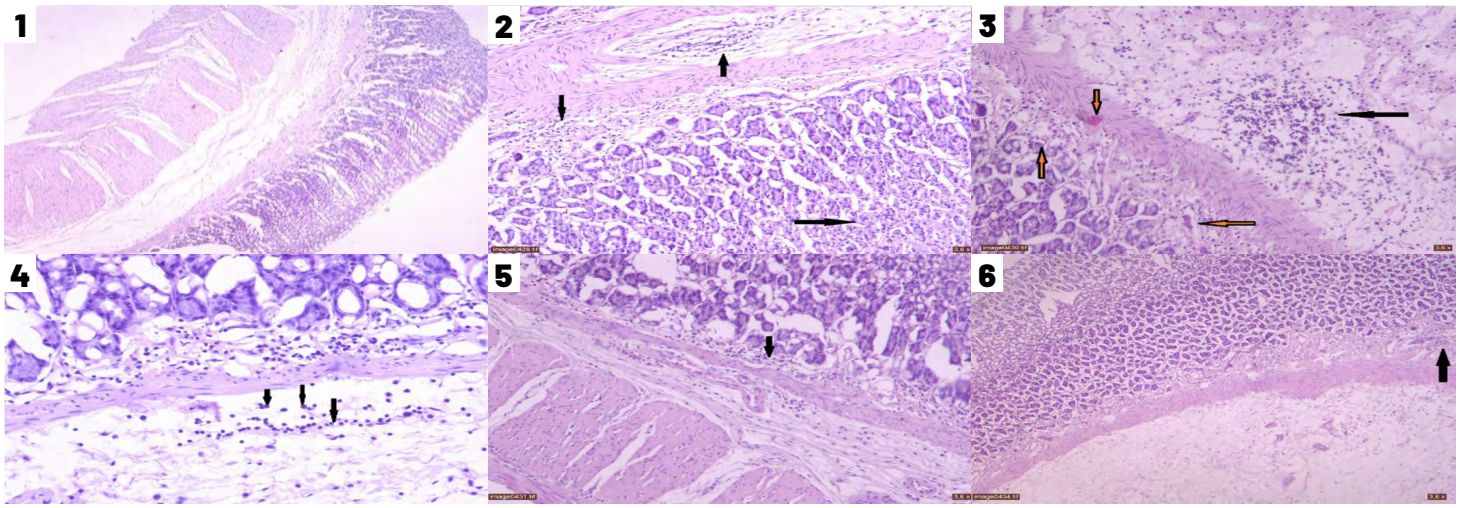

FIGURE 3. Histopathological evaluation of protective effect of *Senecio perralderianus* extract against gastric ulcer induced by the ethanol (magnification x 100).1: Negative group, 2: Ethanol 100%, 3: Ranitidine 5 mg·kg^{-1}, 6, 5, 4 the extract: (200, 100 and 50 mg·kg^{-1}). Red arrow: epithelial barrier damage. Black arrow: infiltration of inflammatory cells. Orange arrow: erythrocytes

Oral administration the extract with different doses of induces significant protection ranging from 71 to 88% and comparable to that of Ranitidine 5 mg·kg^{-1} (79.25 ± 3.87%, P>0.05, (FIG. 4) a protection of 88.22 ± 3.44% and 71.48 ± 3.45 (n=8) was observed following the use of 200 and 100 mg·kg^{-1}, respectively. No significant difference was recorded when comparing the different types of extracts.

Induction of ulcer by ethanol by oral administration causes destruction of gastric wall and significant inflammatory infiltration; acute gastritis in muscular mucosa and submucosa, appearance of inflammatory cells (polynuclear, neutrophils). Observation of histological sections in the presence of extract showed that the 200 mg·kg^{-1} dose induced a decrease in migration of lymphocytes and immune cells in comparison with the 50-100 mg·kg^{-1} doses, and similar to that of Ranitidine (FIG. 3).

The ethanol gavage model in rodents has been widely used to test the efficacy of drugs and explore the mechanism of gastric ulcer. Because consuming ethanol damages the body (ulceration), animal models typically employ ethanol to cause stomach ulcers [11]. Superoxide anions

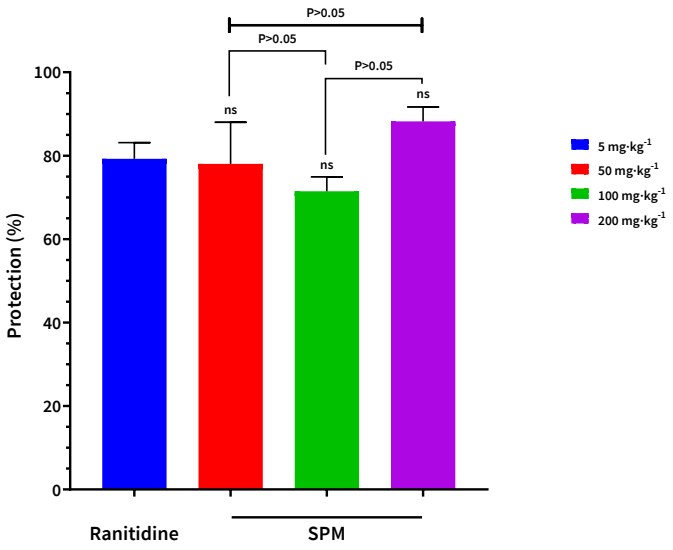

FIGURE 4. Effect of *Senecio perralderianus* extract (SPM) on the gastric mucosa in the gastric ulcer induced by the ethanol. ns: not significant, (n=8)

and hydro peroxide radicals, which are by-products of metabolism of the ethanol, are responsible for these effects [17]. In the present study, administration of absolute ethanol to rats induces macroscopic lesions of gastric tissue, such as petechiae, hemorrhages. These lesions are probably related to the depletion of venous and arterial mucus in the gastric mucosa, leading to hemorrhage, inflammation, and shrinkage of tissue lesions [18]. *S. brasiliensis* has ulcer reducing activity due to the presence of alkaloids (senecionine, seneciphylline), Prostaglandin [19]. Oral administration of ethanol resulted in the induction of a severe inflammatory reaction marked by a large migration of inflammatory cells. This response may be due to pepsin secretion and increased PGE2 synthesis, leading to leukocyte recruitment by increased levels of various pro-inflammatory cytokines, and increased expression of COX2 and nuclear factor κB [20, 21].

In this study, the anti-inflammatory results may be due to the amount of phenolic compounds such as the presence of quercetin and caffeic acid in the genus *Senecio* [22]. Quercetin decreases the production levels of NO, PGE2, TNF-α, IL-6, IL-1β and causes increased in production of IL-10 and TGF-β. Similarly, it inhibits inflammatory reaction by reducing COX-2i and NOS enzymes expression, reducing cellular ROS, and inhibiting the activation of the NF-κβ signaling pathway in the macrophages [23, 24]. The caffeic acid can act on multiple cellular protective mechanisms, leading to anti-inflammatory and antioxidant effects by decreasing IL-1β and NF-κB production and contrasting oxidative/nitrosative damage [25].

When calculating the total protein value, it did not find a significant effect, but other experiments have announced a gastro protective effect against ethanol induced ulcer such as the plant *S. candicans* [26].

Ex vivo antioxidant activity

In rat stomach homogenate, oxidative stress indicators such as lipid peroxidation, SOD, CAT, and GSH were assessed. Lipid peroxidation and MDA content were decreased following the use of the deferent dose of the extract as dose dependent manner. Furthermore, pre-treatment of rats by the different doses of SPM progressively decreased gastric lipid peroxidation, this activity becoming significant from the 200 mg·kg^{-1} dose only to reach 6.39 ± 1.56 nmole·g^{-1} of tissue (P<0.0003, n=8). Ranitidine 5 mg·kg^{-1} showed a weak effect when compared with the 100-200 mg·kg^{-1} doses (P<0.05) and (P<0.0001, n=8), respectively (FIG. 5). Treatment of rats with SPM extract with deferent doses induces an increase in GSH level for the 50 mg·kg^{-1} dose only 42.12 ± 2.7 µmol.mg^{-1} (P≤0.02, n=8). This content decreases to 28.53 ± 2.74 (P<0.05) and 31.36 ± 1.4 (P>0.05) and µmol·mg^{-1} for the 200 and 100 mg·kg^{-1}, respectively. Similarly, a GSH content is obtained with Ranitidine is comparable to that of 100 and 200 mg·kg^{-1} (P>0.05) but lower than that of the 50 mg·kg^{-1} dose (P≤0.04) (FIG. 6).

Treatment of rats with extract induced a slight (P>0.05) and non-dose dependent increase in catalase activity to 50.78 ± 2.45 nmol·mg^{-1}·min^{-1} for the 200 mg·kg^{-1} dose. The catalase activity observed with the extract

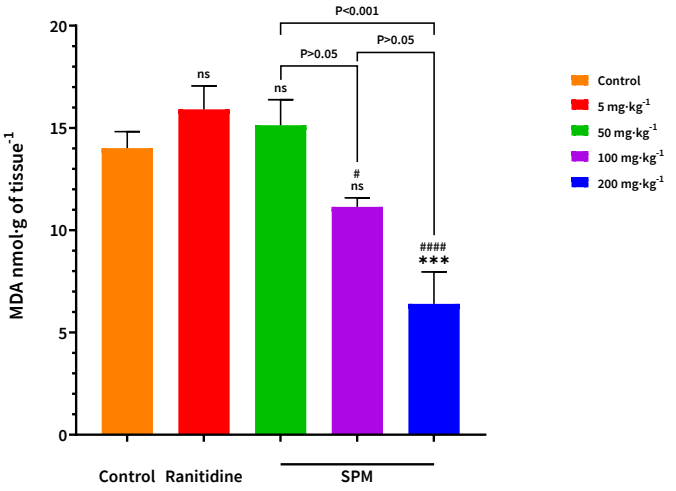

FIGURE 5. Effect of *Senecio perralderianus* extract on lipid peroxidation. Results are represented as mean % ± SEM (*P≤0.003) *vs* Control, 200 and 100 mg·kg^{-1} dose (# P≤0.05) *vs* Ranitidine, ns: not significant**

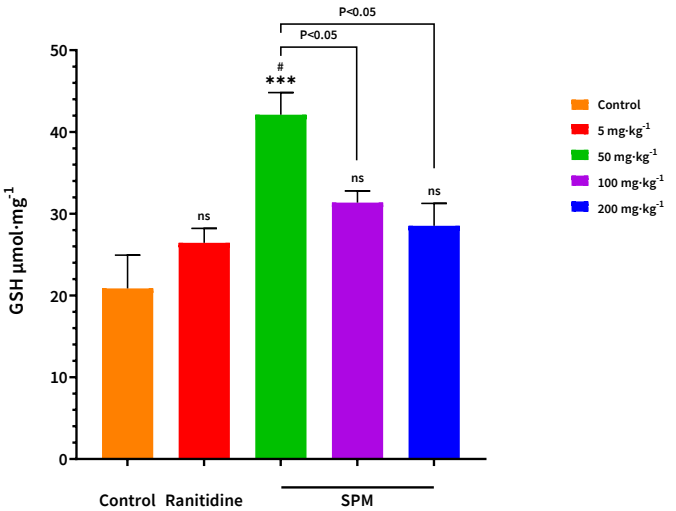

FIGURE 6. Effect of *Senecio Perralderianus* on GSH level. The results are represented as mean % ± SEM (*P≤0.002) vs Control, dose 50 mg·kg^{-1} (# P≤0.05) *vs* Ranitidine, ns: not significant, (n=8)**

doses was comparable to that obtained with Ranitidine ($P>0.05$). No significant effect was recorded when comparing the different doses of extract (FIG. 7).

The result revealed a significant increase ($P\leq0.0208$) in SOD activity upon treatment with Ranitidine and ethanol. The SOD activity observed with extract doses is decreased to 19.56 ± 2.75 and 15.55 ± 2.23 nmol·mg^{-1}·min^{-1} (n=8) for 100 and 200 mg·kg^{-1}, respectively. No significant difference is recorded when comparing the different extract doses ($P>0.05$) (FIG. 8).

The results of this study reveal that ethanol ingestion induces significant oxidative stress, which results in increased lipid peroxidation and decreased intracellular antioxidants such as GSH, CAT or SOD. On the other hand, administration of different doses of *S. perralderianus* resulted in an increase in CAT activity, an increase in GSH content and a significant decrease in gastric lipid peroxidation. However, the plasma MDA content was elevated following pre-treatment with ethanol extract of *S. Serratuloides* in the arterial hypertension model [27]. In the CCl_4-induced oxidative model conducted by Okoro and Kadiri [28] using the aqueous extract of *S. Biafrae* roots demonstrated an increase in GSH content, an intensification in the enzymatic activity of CAT and SOD; with a strong reduction in MDA content in the time, suggesting an *in vivo* antioxidant activity. Moreover, in the streptozocin-induced diabetes model the ethanolic extract of *S. petasitis* showed a remarkable increase for CAT and a decrease in MDA content [29]. Based on the previous results, the antiulcer activity of methanol extract extract was probably related to its *ex-vivo* antioxidant activity.

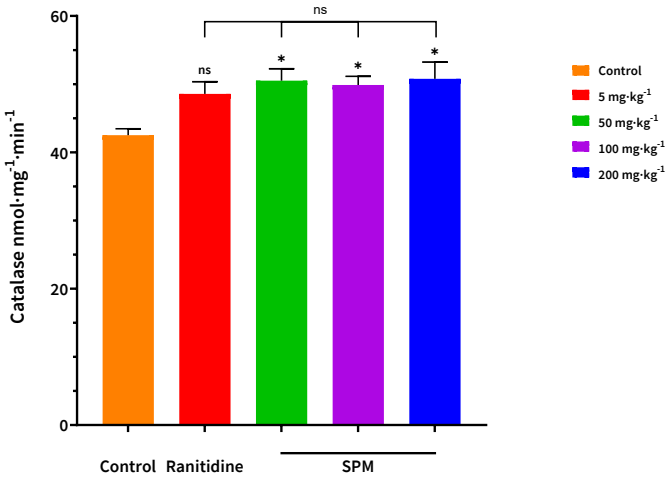

FIGURE 7. Effect of *Senecio perralderianus* extract on catalase activity. ns: not significant, (n=8)

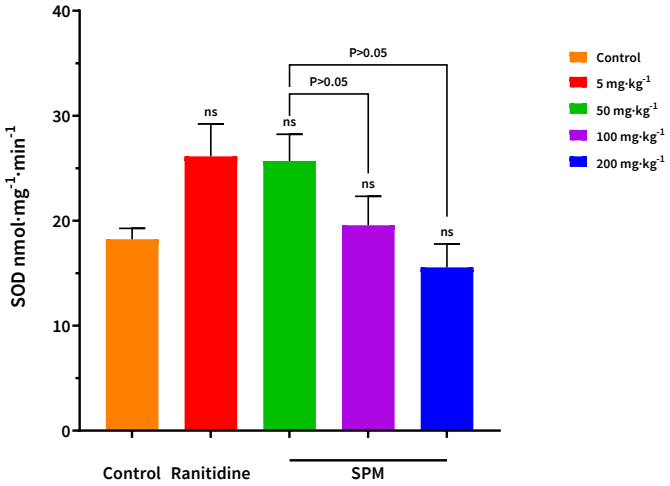

FIGURE 8. Effect of methanolic extract of *Senecio perralderianus* on SOD activity. Results are represented as mean % ± SEM, ns: not significant, (n=8)

Previous studies have shown the significant role of natural flavonoids of flavanol type against ulcer, in this context quercetin, kaempferol, rutin (sophorin) are the best examples, the latter possess the aglycone form, all sharing the same basic structure formed by two aromatic rings connected by three carbons, its most often meet in the form of glycosides, and are known by their antiulcer property [30, 31]. Furthermore, polyphenols such as ellagic acid, gallic acid, caffeic acid in the same activities [32, 33, 34] these compounds are the major constituents of the studied plants of the genus *Senecio* [22, 35].

CONCLUSIONS

The results exhibited that different doses of extract of *S. perralderianus* reduced ethanol-induced gastric ulcer due to its anti-inflammatory and antioxidant effects, and has a comparable anti-ulcer effect to Ranitidine. Compared to the negative reference, the oxidative markers in digestive system of treated rats showed an increase in a non-concentration dependent manner, such as GSH, CAT, SOD, as well as a reduction in MDA levels. The anti-inflammatory activity showed that *S. perralderianus* has a marked inhibitory effect on reducing the infiltration of mononuclear inflammatory cells in mucosal areas.

Conflict of interest statement

We declare that there is no conflict of interest.

Ethical approval

This study was following European Union Guidelines (2010/63/EU) approved by the Committee of the Algerian Association of Experimental Animal Sciences (88-08/1988).

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