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Gastroprotective activity of *Solanum torvum* leaves in the ethanol-induced gastric injury model in Wistar rats and possible mechanism of action

Actividad gastroprotectora de las hojas de *Solanum torvum* en el modelo de lesión gástrica inducida por etanol en ratas Wistar y posible mecanismo de acción

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ABSTRACT

Peptic ulcer disease is one of the most common gastrointestinal disorders affecting the population. Currently, proton pump inhibitors are the most commonly used medications for the treatment of this condition. However, their long-term use is associated with adverse effects, so the search for new drugs is essential. The objective of this study was to evaluate the gastroprotective activity of *Solanum torvum*. Extracts (hexane, dichloromethane, and methanol), fractions of the methanolic extract, and a mixture of *S. torvum* compounds were evaluated in a model of ethanol-induced gastric injury in Wistar rats. The inhibitors L-NAME and indomethacin, or the sulfhydryl blocker NEM, were used to determine their mechanism of action. The methanolic extract was the most active, achieving 75.1 ± 4.5% gastroprotection at 100 mg/kg. From the column chromatography fractionation of this extract, fraction F3 was the most active, giving 78.5 ± 8.79% gastroprotection. About the mixture of compounds isolated from this fraction, the maximum effect was reached at the 100 mg/kg dose, achieving 83.07 ± 3.86% gastroprotection. Regarding the possible mechanism of action, it seems that only nitric oxide is involved.

Keywords: Cytoprotection, gastroprotection, medicinal plants, peptic ulcer, *Solanum torvum*

RESUMEN

La enfermedad ulcerosa péptica es uno de los trastornos gastrointestinales más comunes que afectan a la población. En la actualidad, los inhibidores de la bomba de protones constituyen los medicamentos más empleados para el tratamiento de esta patología. No obstante, su empleo a largo plazo está asociado a efectos adversos, por lo que la búsqueda de nuevos fármacos es esencial. El objetivo del estudio consistió en evaluar la actividad gastroprotectora de *Solanum torvum*. Los extractos (hexano, diclorometano y metanólico), fracciones del extracto metanólico y mezcla de compuestos de *S. torvum* se evaluaron en un modelo de lesiones gástricas inducidas por etanol en ratas Wistar. Para su mecanismo de acción, se utilizaron los inhibidores L-NAME e indometacina o el bloqueador de los grupos sulfhidrilos NEM. El extracto metanólico fue el más activo, alcanzando un 75.1 ± 4.5% gastroprotección a 100 mg/kg. Del fraccionamiento por cromatografía en columna de este extracto, la fracción F3 fue la más activa, dando un 78.5 ± 8.79 % de gastroprotección, en cuanto a la mezcla de compuestos aislada de dicha fracción el efecto máximo se alcanzó con la dosis de 100 mg/kg lográndose un 83.07 ± 3.86% de gastroprotección. Respecto al posible mecanismo de acción, al parecer solo el óxido nítrico se encuentra implicado.

Palabras clave: Citoprotección, gastroprotección, plantas medicinales, *Solanum torvum*, úlcera péptica

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1. INTRODUCTION

Peptic ulcer disease affects a large part of the world's population. It is now generally agreed that gastric lesions develop when the delicate balance between some gastroprotective (prostaglandin, bicarbonate, nitric oxide, and growth factors) and aggressive factors (acid, pepsin, and *Helicobacter pylori*) is lost (Sánchez-Mendoza *et al*., 2024). The current treatment for peptic ulcers primarily involves medications that inhibit gastric acid secretion by H_2-receptor antagonists and proton pump inhibitors. Additionally, acid-independent therapies such as sucralfate and bismuth are used. However, there are reports of issues such as tolerance development, the incidence of relapses, and side effects, that raise questions about their overall effectiveness (Meng *et al*., 2019).

Proton pump inhibitors are used to treat various acid-related disorders, like gastroesophageal reflux disease, peptic ulcers, and *H. pylori* infections. However, studies have shown that long-term use of these inhibitors can cause irreversible side effects, including a reduction in the absorption of vitamin B12, which can lead to issues such as dementia, neurological damage, anemia, hypergastrinemia (Abreu *et al*., 2015), acute myocardial infarction (Shah *et al*., 2015), pancreatic cancer (Peng *et al*., 2018), kidney diseases, bone fractures, and impaired absorption of other micronutrients.

There is a growing interest in alternative therapies and the use of natural substances, particularly those derived from plants. In traditional medicine, several plants have been used to treat digestive disorders (Ardalani *et al*., 2020). From a medicinal perspective, the Solanaceae family is one of the most important angiosperm families. There are approximately 2,000 species of *Solanum* in the world, mainly found in tropical and subtropical areas, with a small number in temperate regions (Edmonds & Chweya 1997). It is estimated that 21 species of the genus are used in traditional medicine (Hu *et al*., 1999). *S. torvum* belongs to the Solanaceae family, and among the major chemical constituents are steroids, steroid saponins, steroid alkaloids, and phenols (Zubaida *et al*., 2013), it has demonstrated several biological activities, including antimicrobial properties against *Bacillus subtilis* and *Staphylococcus aureus*, among others. Additionally, it has shown antiviral effects against Herpes simplex virus type 1 (Arthan *et al*., 2002), and immunosecretory activity in the pulmonary mucosa of mice (Israf *et al*., 2004). It has exhibited analgesic and anti-inflammatory activity in rats by its performance in pain models such as acetic acid-induced abdominal writhing test, pressure test, and carrageenan-induced paw edema (Ndebia *et al*., 2006); in addition, both aqueous and methanolic extracts demonstrated hypotensive activity in isolated rat aorta rings and exhibited antiplatelet properties (Nguelefack *et al*., 2008).

Research has highlighted the antioxidant and antidiabetic effects of *S. torvum* in mice. In acute toxicity studies conducted on rats, the methanolic extract of the fruits showed no adverse effects (Gandhi *et al*., 2011). Additionally, *S. torvum* can inhibit the growth of *H. pylori*, a bacterium linked to an increased risk of developing duodenal or gastric ulcers, as well as gastric adenocarcinomas (Hsu *et al*., 2010).
In this study, we decided to evaluate the gastroprotective effect of *S. torvum* through a bioassay-guided study, employing the absolute ethanol-induced gastric ulcer experimental model in Wistar rats, as there is currently no report regarding the compound or compounds

responsible for this activity. Furthermore, we discuss the role of endogenous nitric oxide (NO), sulfhydryl groups, and prostaglandins in the gastroprotection of *S. torvum*.

2. MATERIALS AND METHODS

The study was approved by the Internal Committee for the Care and Use of Lab Animals (CICUAL, according to the initials in Spanish) of the Escuela Superior de Medicina, Instituto Politécnico Nacional, with registration number ESM-CICUAL-01/ 14-02-2024.

2.1. Animals

Experiments were conducted with male Wistar rats (180–220 g) from the vivarium of the Autonomous Metropolitan University, Xochimilco campus, Mexico City. Animal care and handling were in accordance with the official Mexican regulations for laboratory animals (NOM-062-ZOO-1999) and international standards. Unless otherwise specified, rats were randomly assigned to individual cages with wire mesh floors and deprived of food 18 h before the experiment. Animals had free access to water throughout the experiment. All experiments were conducted with nine animals per group.

2.2. Drugs and Compounds

The mixture of compounds (suspended in 0.05% tween 80), carbenoxolone (the reference drug, dissolved in water), L-NAME (N^G-nitro-L-arginine methyl ester, dissolved in saline solution), NEM (N-ethylmaleimide, dissolved in saline solution) and indomethacin (dissolved in saline solution containing 5 mM $NaHCO_3$) were prepared immediately before use. All the above drugs were purchased from Sigma Aldrich Co. (St. Louis, MO, USA).

2.3. Plant materials and extract preparation

During August 2023, *S. torvum* leaves were collected in Ocosingo, Chiapas, Mexico. The plant was registered in the Flora Department of the Chip Herbarium, belonging to the Botanical Garden of the Secretariat of Environmental Protection, Housing and Natural History of the State of Chiapas, Mexico. A specimen from the original collection is available under receipt number HEM12852. *S. torvum* leaves were shade-dried at room temperature (22 ± 2 °C) for three weeks and subsequently ground. 5.6 kg of ground leaves were placed in a glass container, to which 20 L of hexane were added. This solvent remained in contact with the plant material for three days at room temperature (22 ± 2 °C). On the third day, it was filtered and concentrated. This operation was repeated twice to obtain the hexane extract. Subsequently, a stream of air was passed over the plant residue to eliminate hexane residues; once it was dried, it was treated with dichloromethane (20 L) and finally with methanol (20 L) to obtain the respective extracts.

2.4. Ethanol-induced gastric lesions

According to Robert's 1979 method, gastric lesions were induced by administering 1 mL of absolute ethanol intragastrically (Robert, 1979). According to the corresponding experiment, extracts, fractions, compounds, carbenoxolone, or vehicle were administered orally (p.o.), and

thirty minutes later, ethanol (1 mL, p.o.) was administered. Two hours later the animals were sacrificed in a CO_2 chamber, and their stomachs were dissected and filled with 10 mL of 2% formaldehyde for five minutes to fix the inner stomach layer. After this period, we proceeded to open the stomach through the greater curvature. The damaged area (mm^2) was measured with the help of a stereoscopic microscope equipped with a metric grid. The ulcer index (UI) was calculated by summing the area of all lesions in the corpus of each stomach. The percentage of gastroprotection (% GP) was determined using the following formula:

$$\%GP = \frac{UIC - UIT}{UIC} \times 100$$

Where: UIC is the average ulcer index of the control group.
UIT is the ulcer index of each treated animal (Sánchez-Mendoza *et al*., 2011).

150 g of methanolic extract was subjected to separation by silica gel column chromatography with significant changes in polarity. Three fractions were obtained: F1, F2, and F3 using 2.5 L of 100% hexane, ethyl acetate, and methanol as solvents, respectively. The F1 fraction had a very low yield, which made it impossible to conduct evaluations with it. Meanwhile, fractions F2 and F3 were evaluated at a dose of 100 mg/kg.

Since fraction F3 was the most active, 50 g were separated by column chromatography using dichloromethane (100%), dichloromethane/methanol mixtures (9.75:0.25, 9.5:0.5, 9.25:0.75, and 9:1), and methanol (100%), obtaining 80 fractions of 50 mL each. From the fractions 50 to 60 that were eluted with dichloromethane/methanol (9:1), a white solid of 2.5 g was obtained. Afterwards, the compound obtained was evaluated in the model of gastric lesions at doses of 3, 10, 30, and 100 mg/kg.

2.5. Assessment of NO in the possible mechanism of action of the mixture of compounds

To determine the participation of NO in the gastroprotective effect of the mixture of compounds, L-NAME (70 mg/kg) was administered intraperitoneally, and thirty minutes later, either the mixture of compounds or the carbenoxolone (100 mg/kg, p.o.) to the corresponding group (Vera-Arzave *et al.*, 2012). After thirty minutes, absolute ethanol was administered and two hours later the animals were sacrificed to determine the UI. In this evaluation, two control groups were included, the first one received only the vehicles plus ethanol, while the second was administered L-NAME and ethanol.

2.6. Assessment of prostaglandins in the possible mechanism of action of the mixture of compounds

To demonstrate the role of endogenous prostaglandins in the gastroprotection of the mixture of compounds, a dose of 10 mg/kg of indomethacin was administered subcutaneously (s.c.). Seventy-five minutes later, either of the mixture of compounds or carbenoxolone (100 mg/kg) was given orally to the corresponding group. Thirty minutes later, absolute ethanol was

administered, and the methodology described was followed until the UI was determined. In this evaluation, two control groups were comprised. The first group (vehicle control) received only the vehicles plus ethanol, while the second group (indomethacin control) received indomethacin and ethanol.

2.7. Assessment of sulfhydryl groups in the possible mechanism of action of the mixture of compounds

To investigate the participation of the sulfhydryl groups in the gastroprotection of the mixture of compounds, NEM (10 mg/kg) was administered s.c. and thirty minutes later, the mixture of compounds or carbenoxolone was administered orally. Then, after thirty minutes, absolute ethanol was administered, and two hours later, the animals were sacrificed. The procedure was continued until the UI was reached. Two control groups were included in this evaluation: one received only the vehicles plus ethanol, and the other received NEM and ethanol.

2.8. Statistics

The results are presented as the standard error of the mean (SE) for nine rats per group. To evaluate significant differences, the Kruskal-Wallis test was used followed by Dunn's multiple comparisons test. The differences were statistically significant with a value of $p \leq 0.05$.

3. RESULTS

3.1. Evaluation of the gastroprotective activity of the extracts

The results of the evaluation of hexane, dichloromethane, and methanol extracts of *S. torvum* are shown in Table 1. As can be seen, the hexane and methanol extracts were active. The highest activity was observed with the latter, which showed a dose-dependent gastroprotective effect, reaching its maximum effect at 100 mg/kg. The dichloromethane extract exhibited no activity at the three doses analyzed. The above results indicate that both low and high-polarity compounds are involved in the gastroprotective effect of *S. torvum*.

3.2. Evaluation of the fractions of methanolic extract

Regarding the outcomes of the evaluation of the methanolic extract fractions, F3 was proven to be the most active fraction, achieving 78.5 ± 8.79% gastroprotection (Table 2). Since fraction F3 had a greater gastroprotective effect, it was subjected to silica gel column chromatography. Upon eluting fractions 50 to 60 with a mixture of dichloromethane/methanol (9:1), 2.5 g of a white powder was obtained. Subsequently, a dose-response curve was constructed using the powder. The results are shown in Figure 1a, as can be seen, all doses evaluated (3, 10, 30, and 100 mg/kg) had a significant gastroprotective effect relative to the control and the effect was dependent on the dose. The highest activity was obtained at 100 mg/kg, obtaining a gastroprotection of 83.07 ± 3.86%. The white powder obtained from fraction F3 was analyzed by thin-layer chromatography and resulted in a mixture of three compounds. Carbenoxolone was used as a reference drug, it also had a dose-dependent effect (Fig. 1b) and reached a maximum effect at 100 mg/kg (63.51± 9.40% gastroprotection).

Table 1. The gastroprotective effect of *S. torvum* extracts on ethanol-induced ulceration in rats.

Treatment	Dose (mg/kg)	n	UI (mm^2)	Gastroprotection (%)
Control	--	9	84.1 ± 8.9	--
Hexanic extract	10	9	44.0 ± 4.9*	35.0 ± 7.2
	30	9	41.4 ± 4.4*	38.8 ± 6.5
	100	9	37.5 ± 3.6*	44.6 ± 5.4
Dichloromethane extract	10	9	70.9 ± 9.0	19.1 ± 8.8
	30	9	66.0 ± 5.5	15.2 ± 7.6
	100	9	61.2 ± 6.5	21.3 ± 8.3
Methanolic extract	10	9	47.6 ± 9.0*	49.2 ± 10.8
	30	9	29.0 ± 9.6*	65.4 ± 11.4
	100	9	18.8 ± 4.0*	75.1 ± 4.5

Results of the evaluation of hexane, dichloromethane and methanol extracts of *S. torvum* on ethanol-induced gastric lesions in rats. Kruskal-Wallis test followed by Dunn's multiple comparisons. *$p < 0.05$ vs. control group; UI = Ulcer index.

Table 2. Methanol extract fractions protect rats from ethanol-induced injuries.

Treatment	Dose (mg/kg)	n	UI (mm^2)	Gastroprotection (%)
Control	---	10	84.0 ± 8.8	---
F2 (Ethyl acetate)	100	9	41.0 ± 8.1*	53.9 ± 9.66
F3 (Methanol)	100	9	19.1 ± 7.0*	78.5 ± 8.79

Evaluation of the fractionation of methanolic extract of *S. torvum* on ethanol-induced gastric lesions in rats. Kruskal-Wallis test followed by Dunn's multiple comparisons. *$p < 0.05$ vs control group; UI = Ulcer index.

3.3. Participation of NO in the mechanism of action of the mixture of compounds

When determining the participation of nitric oxide, the UI obtained in rats pretreated with L-NAME plus mixture of compounds (146.5 ± 10.6 mm^2) was statistically different from the control group with vehicle (91.60 ± 7.61 mm^2). However, when comparing the value of the control group with L-NAME (130.3 ± 7.7 mm^2) with the value of L-NAME plus mixture of compounds (146.5 ± 10.6 mm^2) they did not differ statistically, indicating that nitric oxide participates in the gastroprotective mechanism the mixture of compounds. As for carbenoxolone, pretreatment with L-NAME inhibited its gastroprotective effect (Fig. 2a),

indicating that nitric oxide also participates in its mechanism of action. This result is consistent with the findings reported in the literature (Sánchez-Mendoza *et al*., 2018).

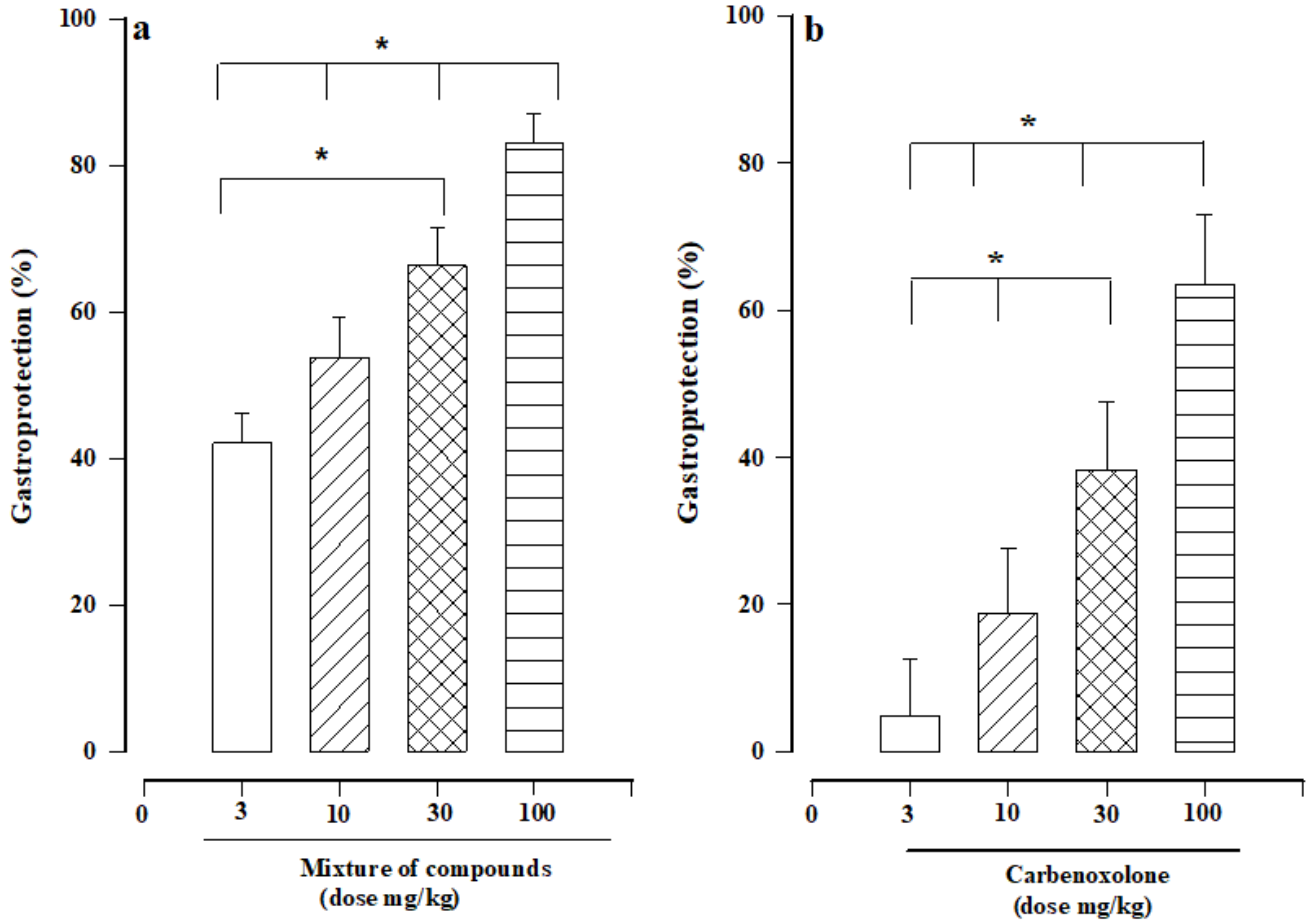

Fig. 1. Gastroprotective effect of mixture of compounds (a) and carbenoxolone (b). Bars represent the mean ± SE (n = 9). *p < 0.05, based on the Kruskal-Wallis test followed by Dunn's multiple comparison.

3.4. Participation of prostaglandins in the mechanism of action of the mixture of compounds

Preadministration of indomethacin (10 mg/kg) did not significantly affect the gastroprotective function of mixture of compounds, since its UI (32.42 ± 5.67 mm²) did not differ significantly from mixture of compounds (19.38 ± 3.87 mm²). However, a significant discrepancy was observed between the vehicle control group (87.64 ± 6.34 mm²) and the indomethacin control group (112.68 ± 4.127 mm²). These results indicate that prostaglandins are not associated with the gastroprotective effect of the mixture of compounds. Since the gastroprotective effect of carbenoxolone (81.23 ± 5.29 mm²) was reversed in the presence of indomethacin, as seen in Figure 2b, the results are consistent with those reported in the literature.

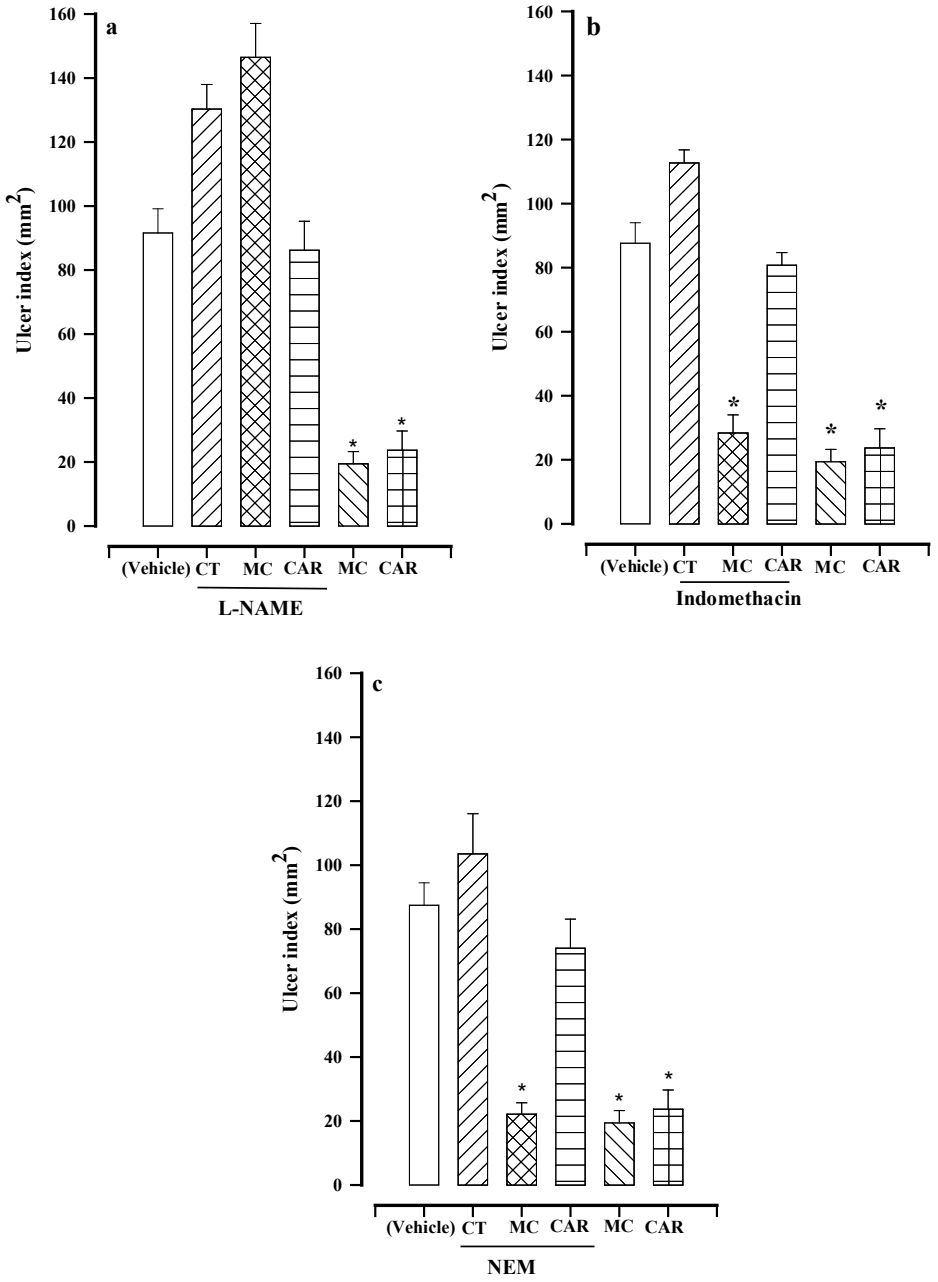

Fig. 2. Effect of mixture of compounds (MC, 100 mg/kg) and carbenoxolone (CAR, 100 mg/kg) on gastric lesions induced by ethanol in rats pretreated with N^G-nitro-L-arginine methyl ester (L-NAME) (70 mg/kg) (a), indomethacin (10 mg/kg) (b) or N-ethylmaleimide (NEM) (10 mg/kg) (c). CT = the control group for the distinct inhibitors. Bars represent the mean ± SE (n = 9). *p < 0.05 vs the respective vehicle, based on the Kruskal−Wallis test followed by Dunnett's.

3.5. Participation sulfhydryl groups in the mechanism of action the mixture of compounds

Regarding the involvement of sulfhydryl groups, the UI obtained in rats pretreated with NEM (a sulfhydryl blocker, 10 mg/kg) and mixture of compounds (22.1 ± 3.6 mm^2) did not exhibit a statistically significant difference compared to the UI achieved in the group treated only with mixture of compounds (19.4 ± 3.9 mm^2). However, it was significantly different from the vehicle control group (87.5 ± 7.0 mm^2) and the NEM control group (103.5 ± 12.6 mm^2). This suggests that sulfhydryl groups are not involved in the mechanism of action of the mixture of compounds. As for carbenoxolone, sulfhydryl groups affect its mechanism of action. Preadministration of NEM reversed its protective effect (Fig. 2c), which is consistent with what has been reported.

4. DISCUSSION

Any treatment for peptic ulcer disease should focus not only on inhibiting acid secretion by parietal cells, but also on increasing mucosal protective factors such as prostaglandin synthesis, increased nitric oxide, and microcirculation (Meng *et al*., 2019). There has been a longstanding interest in finding natural molecules that can protect gastric mucosa from acid. Many plants are currently being used by various communities to treat such diseases. *S. torvum* is used in a Chiapas community for gastritis and peptic ulcer problems. A report on this plant regarding this property was carried out in 2008 by Nguelefack and collaborators, where they reported that the methanolic and aqueous extracts have gastroprotective activity (Nguelefack *et al*., 2008). Until now, it was unknown which types of compounds, and their mechanisms could explain the gastroprotective effect of the plant.

In the present study, it was found that methanol extract showed the highest gastroprotective activity (Table 1). Additionally, it was found that hexane extract also demonstrated a gastroprotective effect, albeit to a lesser extent. This suggests that *S. torvum* contains active compounds of both low and high polarity.

A white powder was obtained from the sub fractionation of F3, and it showed slightly more effective gastroprotective activity than carbenoxolone, and a dose's dependent. Thin-layer chromatography analysis of the white powder revealed that it was a mixture of compounds, probably steroid glycosides, which could be responsible for the gastroprotective activity since *S. torvum* contains this type of compounds and some of them have been shown to have gastroprotective activity, although this hypothesis requires to be corroborated (Vieira Júnior *et al*., 2015; Lu *et al*., 2009).

Nitric oxide plays an important role in maintaining the integrity of the gastric mucosa. NO is synthesized by nitric oxide synthase (NOS). It has been shown that there are three types of NOS in the gastrointestinal tract: neuronal, endothelial, and inducible (which manifests itself in pathological states). However, only neuronal and endothelial NOS participate in maintaining the integrity of the gastrointestinal mucosa by regulating blood flow in the gastric mucosa. On the other hand, it has been shown that NO could activate cyclooxygenase and thus promote the synthesis of prostaglandins (Liang *et al*., 2021).

The present study demonstrates that the gastroprotective effect of mixture of compounds was reversed by the administration of L-NAME, a nonspecific inhibitor of nitric oxide synthase; this indicates nitric oxide's involvement in its mechanism of action. Such protection is probably caused by the increase in NO production by the mixture of compounds, as do some steroidal glycosides that exert gastric protection through this mechanism (Fan *et al*., 2016; Matsuda *et al*., 2003). However, this hypothesis still needs to be corroborated.

Prostaglandins, primarily PGE_2 are produced from arachidonic acid by cyclooxygenases (COX), which are present throughout the gastrointestinal tract. They are known to regulate various functions within the gastrointestinal tract, including acid and bicarbonate secretion, mucus production, and mucosal blood flow. These actions contribute significantly to the safeguarding of gastric mucosa (Takeuchi & Amagase 2018). Indomethacin, a non-specific COX inhibitor was unable to reverse the gastroprotective effect of the mixture of compounds (Fig. 2b). Based on the observed results, prostaglandins do not appear to be involved in the mechanism of action of the compound mixture.

The mucous strengthens the mucosa barrier against harmful agents also has an important role in gastric protection. Accordingly, the literature reports that endogenous nonprotein-sulfhydryl compounds are the key agents in mucosal protection against ethanol-induced gastric injury. The endogenous nonprotein-sulfhydryl compounds bind the free radicals formed from ethanol action and are also involved in controlling the production and nature of mucus and in recycling antioxidants (Rozza *et al.,* 2011). Following pretreatment with NEM in the current contribution, there was no significant change in the protection furnished by the mixture of compounds against ethanol-induced gastric lesions (Fig. 2c). Thus, the mechanism of action of gastroprotection does not involve sulfhydryl groups. Contrarily, the effect of carbenoxolone was reversed by NEM pretreatment, coinciding with published results.

5. CONCLUSION

A mixture of compounds responsible for the gastroprotective activity of *S. torvum* was isolated from fraction 3 of the methanolic extract. Nitric oxide is suggested to be involved in the possible mechanism of action. In the future, we will attempt to isolate the compound(s) responsible for this biological activity.

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AUTHOR CONTRIBUTIONS

María Elena Sánchez-Mendoza was responsible for conceptualization, writing of original draft preparation, writing review, and editing. **Yaraset López-Lorenzo** analyzed the data and supported the methodology. **Jazmín García Machorro** provided assistance with the methodology, writing, and revision of the publication. **Guillermo García-Castillo** provided assistance with the methodology, writing, and revision of the publication. **Danna Brigith Vera-Carrillo** provided assistance with the methodology, writing, and revision of the publication. **Jesús Arrieta** was responsible for the conceptualization, acquisition of funds, design, writing, preparation of the initial draft, revision, and editing of the writing.

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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