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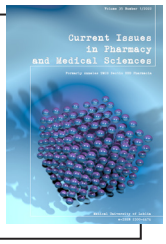

Gastroprotective effect of an Algerian hydroalcoholic *Punica granatum* L. peel extract against ethanol/HCl-induced gastric mucosal injury in Wistar rats

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ABSTRACT

Ulceration represents a significant pathological condition, and research into effective treatment is imperative. The present study sought to evaluate the gastroprotective effect of pomegranate hydroalcoholic peel extract (PGPE) on an ulcer model induced by acidified ethanol (HCl/ethanol) in Wistar rats. The experimental animals were divided into six groups. Group 1 was a negative control that was treated with distilled water. Group two was utilized as the positive control, receiving a treatment of acidified ethanol (20/80; v/v) with the objective of inducing ulceration. Groups three to six were administered 0.75, 1.50, and 3.0 g/kg of PGPE, along with 0.10 g/kg of omeprazole, which served as the reference pharmaceutical agent. Rats were administered acidified ethanol via oral gavage one hour later. A substantial increase in pH and an increase in gastric mucus were observed, accompanied by a decrease in gastric mucosal damage, in animals fed with PGPE. The histopathological results indicated significant destruction of the gastric mucosa in the ulcer control group. However, gastroprotective effects were observed in rats pretreated with plant extract. Current research suggests that PGPE has potential antiulcer effects, possibly through its high antioxidant activity, possibly due to its bioactive constituents. The results obtained from this study offer valuable insights into the nutritional composition of the products under scrutiny. It is recommended that further preclinical and clinical trials be conducted to evaluate the natural active agents and effectiveness of this plant.

INTRODUCTION

Peptic ulcer disease is a common disorder of the gastrointestinal system and is characterized by an imbalance between aggressive factors, such as gastric acid and pepsin, Helicobacter pylori infection and defensive mechanisms, including gastric mucus, bicarbonate secretion, and prostaglandins, leading to inflammation, mucosal injury, and tissue damage [1-3]. Ethanol is a well-known harmful agent associated with various pathological conditions and is widely used in experimental models to induce acute gastric injury. Ethanol or HCl/ethanol-induced gastric ulcers result from destruction of the gastric mucosa, leading to increased mucosal permeability, bleeding, and hemorrhagic lesions caused by excessive production of free radicals that damage gastric epithelial cells. This injury is accompanied by vascular constriction, congestion, inflammation, and tissue necrosis [4,5].

Due to the adverse effects associated with many synthetic antiulcer drugs, herbal medicines are increasingly considered as alternative therapeutic agents. Several natural products have been reported to exhibit antiulcer activity through their beneficial effects on gastric mucosal defense mechanisms [6].

Pomegranate (*Punica granatum* L.) is a widely consumed fruit in tropical and subtropical regions and belongs to the family Punicaceae. It is extensively cultivated in the Mediterranean region and represents an economically important

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crop worldwide [7]. Traditionally, *P. granatum* has been used in various folk remedies and is currently recognized for its antimicrobial, antiviral, and anticancer properties, which has attracted considerable scientific interest [8]. Both the pulp and peel of pomegranate are rich in antioxidants, with phenolic compounds, particularly flavonoids and anthocyanins, being identified as the major contributors to its antioxidant potential [7,9].

Recent studies have also emphasized the value of plant by-products as sustainable sources of bioactive compounds. In this context, Zeghad *et al.* [10] evaluated the antioxidant and photoprotective properties of *P. granatum* peel extracts, demonstrating high levels of total phenolics and flavonoids associated with strong antioxidant activity and significant UV absorption. Moreover, the pomegranate pericarp has been reported to contain high concentrations of phenolic compounds such as punicalagins, gallic acid, catechin, quercetin, rutin, flavones, flavonones, and anthocyanidins. Flavonoids, in particular, have shown pronounced antiulcer activity in experimental animal models [11].

To the best of our knowledge, there are no reports demonstrating the gastroprotective or antiulcer activity of *P. granatum* L. peel cultivated in Algeria. Therefore, the present study aimed to evaluate the antiulcerogenic potential of a hydroalcoholic extract of pomegranate peel and to investigate its healing effects on experimentally induced gastric ulcers in rats.

MATERIALS AND METHODS

Plant material and preparation of the extract

Peels of *P. granatum* L. fruits were collected from Skikda, Algeria, in autumn 2020. The plant material was authenticated by qualified botanists, and a voucher specimen (No. F184/2020) was deposited after taxonomic identification. The peels were air-dried at room temperature in the dark for two weeks and then ground using a blender. The powdered material was macerated in methanol/water (70:30, v/v) at room temperature for 24 h, followed by ultrasonic extraction (Fisher Scientific FB 15046, Leicestershire, England; >20 kHz) for 30 min. The extraction was performed twice, and the combined extracts were filtered. The filtrate was concentrated under reduced pressure at 40°C using a rotary evaporator (Büchi, Switzerland). The resulting crude extract was lyophilized (Christ Alpha 2-4 LD Plus, Osterode am Harz, Germany) and stored at -25 °C until further use [8].

Drugs and chemicals

All chemicals and reagents were of analytical grade and purchased from Merck (Darmstadt, Germany). Omeprazole, used as the reference drug, was obtained from a commercial pharmaceutical company (Constantine, Algeria).

Preliminary phytochemical screening

Preliminary phytochemical analysis of the hydroalcoholic peel extract of *P. granatum* L. was performed according to Zeghad *et al.* [9] to detect the presence of flavonoids, tannins, saponins, alkaloids, quinones, terpenoids, coumarins, and steroids.

Phytochemical screening

Test for tannins

Tannins were detected using the ferric chloride ($FeCl_3$) test. Briefly, 1.5 g of dried, powdered plant material was macerated in 10 mL of 80% methanol for 15 min with continuous agitation. The extract was then filtered and transferred into dry test tubes. The addition of a 1% $FeCl_3$ solution produced a blue-black coloration, indicating the presence of gallic tannins, or a greenish-brown coloration, indicative of catechin tannins.

Test for flavonoids

Flavonoids were detected by treating 1 mL of the hydroalcoholic extract with a few drops of concentrated hydrochloric acid, followed by the addition of small magnesium turnings. The development of an orange to purplish-red coloration confirmed the presence of flavonoid compounds.

Test for saponins

Saponins were identified using the foam test. Five milliliters of the extract were diluted with distilled water and shaken vigorously in a test tube. The formation of a stable froth exceeding 1 cm in height and persisting for at least 15 min indicated the presence of saponins.

Test for alkaloids

Alkaloids were screened using Mayer's reagent. The methanolic extract was acidified with a few milliliters of 50% hydrochloric acid. Upon the addition of Mayer's reagent, the formation of a yellowish-white precipitate indicated a positive reaction for alkaloids.

Test for quinones

Approximately 1 g of dried, powdered plant material was extracted with 15-30 mL of petroleum ether, followed by agitation and maceration for 24 h. The extract was filtered and concentrated using a rotary evaporator. A few drops of 0.1 N sodium hydroxide (NaOH) were added to the aqueous phase. The appearance of a yellow, red, or violet coloration indicated the presence of free quinones.

Test for terpenoids

Terpenoids were detected by mixing 0.5 mL of the crude extract with 2 mL of chloroform, followed by the careful addition of 3 mL of concentrated sulfuric acid. The formation of a reddish-brown coloration at the interface confirmed the presence of terpenoid compounds.

Test for steroids

One gram of the plant extract was dissolved in a few drops of glacial acetic acid, followed by the careful addition of concentrated sulfuric acid. The appearance of a green coloration at the interface indicated the presence of steroidal compounds.

Test for coumarins

Coumarins were detected by adding 3 mL of 10% sodium hydroxide (NaOH) to the aqueous plant extract. The development of a yellow coloration indicated a positive reaction for coumarins.

Experimental animals

The study was conducted after obtaining approval from the Animal Ethics Committee of the Laboratory of Pharmacology and Toxicology, Institute of Veterinary Sciences, Constantine 1 University. Adult Wistar albino rats, weighing 242-300 g and aged 4-5 weeks, were used in the present study. Animals were housed in standard polypropylene cages under controlled environmental conditions (24 ± 2°C) with a 12 h light/dark cycle. They were acclimatized for seven days prior to experimentation and had ad libitum access to standard pelleted food and water. All experimental procedures were carried out in accordance with the guidelines outlined in the *Guide for the Care and Use of Laboratory Animals* (2011). The experimental protocol was approved by the Ethical Committee of the Laboratory of Pharmacology and Toxicology, Institute of Veterinary Sciences, Constantine 1 University.

Acute toxicity test

An acute toxicity test was performed by randomly dividing 36 rats into six groups (n = 6). Groups I and II served as the negative and positive control groups, respectively, while the remaining four groups received treatment. Animals were deprived of food and water overnight prior to the experiment. The control group received distilled water, whereas the treated groups were administered PGPE reconstituted in distilled water at sequential oral doses of 0.5, 2.5, 5.0, and 10 g/kg via oral gavage.

Animals were continuously observed for the first 30 min after administration and then periodically for 24 h. Subsequently, observations were conducted once daily for 14 days. Mortality, changes in general behavior, and alterations in physiological activities were recorded [9-14]. Body weight was measured on days 7 and 14. At the end of the observation period, all animals were sacrificed under appropriate anesthesia, and major internal organs (heart, liver, kidneys, lungs, and spleen) were carefully examined for gross pathological changes [14].

Induction of gastric ulcer by ethanol/HCl

For gastric ulcer induction, male Wistar rats were randomly divided into six groups (n = 6 per group). Animals were fasted for 48 h, with free access to distilled water until 2 h before the start of the experiment. The administered volume was standardized at 5 mL/kg for all experimental groups.

The negative control group (Group I) received distilled water only by oral gavage. The positive control group (Group II) was administered acidified ethanol/HCl (20/80, v/v). Treated groups (Groups III, IV, and V) received *Punica granatum* L. peel extract at doses of 0.75, 1.5, and 3.0 g/kg, respectively. Group VI received the commercial standard omeprazole® (0.10 g/kg) [15].

Sixty minutes after pretreatment, all animals,except those in the negative control group, were administered acidified ethanol/HCl (20/80, v/v) to induce gastric ulceration [16]. One hour after ulcer induction (at the end of the experiment), animals were euthanized by inhalation of chloroform in a closed chamber to ensure rapid and humane death.

All experimental procedures involving animals were conducted in accordance with institutional and international ethical guidelines for the care and use of laboratory animals. Following sacrifice, the stomachs were excised, opened along the greater curvature, and examined for the presence and extent of ulcerative lesions.

Measurement of gastric pH

Gastric contents were collected by opening the stomachs along the greater curvature. The contents were centrifuged, and the resulting supernatants were used to determine the pH of gastric juice using a digital pH meter. Titration was performed with 0.1 N NaOH solution [17].

Measurement of gastric mucus

The stomachs were gently rinsed with normal saline. Gastric mucus was carefully scraped from the mucosal surface using glass slides and collected into separate tubes. The amount of mucus was weighed using an electronic balance [17].

Ulcer measurements

Gastric ulcers were identified by the presence of elongated hemorrhagic bands along the gastric mucosa. The stomachs were examined macroscopically, photographed, and digitally recorded for further analysis. Ulcer areas were measured using ImageJ software by determining the length (mm) and width (mm) of each lesion. The method described by Sobreira *et al.* [18] was used to calculate the ulcer area.

The percentage of ulcer inhibition (I%) was calculated according to the method of Abdulla *et al.* [19] using the following formula:

$$I\% = \frac{(UA\_control - UA\_treated)}{UA\_control} \times 100$$

Histological examination of gastric tissue

After sacrifice, the stomachs were excised and rinsed with 0.9% sodium chloride (physiological saline). The glandular portions were cut into small sections and fixed in 10% buffered formalin. Tissue dehydration was performed using a graded ethanol series (60%, 75%, and 100%), followed by clearing in xylene. Samples were processed using an automated tissue processor (Leica, Wetzlar, Germany) and embedded in paraffin wax.

Paraffin blocks were sectioned at a thickness of 5 µm using a microtome. The sections were mounted on glass slides, stained with hematoxylin and eosin (H&E), and examined under a light microscope for histopathological evaluation. Observations focused on parameters such as hemorrhage, necrosis, congestion, and edema, following standard histological procedures [20].

Statistical analysis

Data are presented as mean ± standard deviation (SD). Statistical comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's honestly significant difference (HSD) post hoc test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Preliminary phytochemical screening

The preliminary phytochemical composition of the hydroalcoholic *P. granatum* L. peel extract is presented in Table 1. The analysis revealed a wide range of phytochemical constituents, including flavonoids, phenolic compounds, and tannins.

Table 1. Phyto-components of *Punica granatum* L. peel extract

Phytochemicals	Presence/Absence
Tannins	+
Flavonoids	+
Saponins	+
Alkaloids	+
Quinones	+
Terpenoids	+
Coumarins	+
Steroids	+

Acute toxicity

The hydroalcoholic peel extract of *P. granatum* L. did not cause any mortality within 24 h at any of the tested doses. No behavioral changes were observed in animals treated with the pomegranate hydroalcoholic peel extract at a dose of 10,000 mg/kg (per os). Moreover, no significant differences in body weight (gain or loss) were recorded, and no mortality was observed during the 14-day observation period, indicating the absence of acute toxicity at the maximum tolerated dose (10 g/kg). According to previous studies, substances with an oral LD_{50} greater than 5.0 g/kg are considered nontoxic [21]. Furthermore, no macroscopic abnormalities were detected upon examination of the internal organs.

Gastroprotective activity

The gastroprotective effects of the pomegranate peel extract against acidified ethanol-induced gastric lesions are summarized in Table 2 and Figure 1. Pretreatment with PGPE at doses of 0.75, 1.50, and 3.00 g/kg, as well as with the reference drug omeprazole (0.10 g/kg), resulted in a marked reduction in gastric ulcer area (176.75 ± 28.88, 96.25 ± 25.86, 32.75 ± 10.05, and 186.75 ± 77.26 mm², respectively) compared with the ulcer control group (522.75 ± 268.95 mm²).

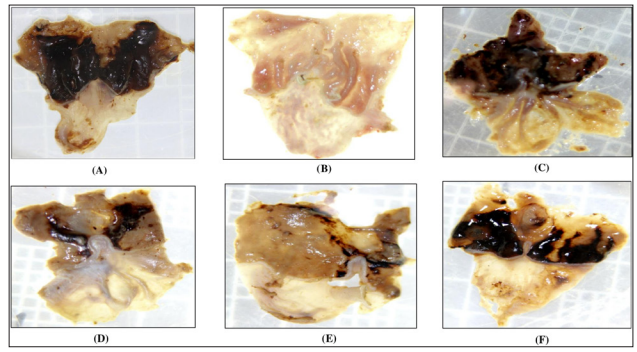
All tested doses of PGPE and omeprazole demonstrated a highly significant antiulcer effect ($p < 0.0001$) in a dose-dependent manner, with inhibition percentages of 62.29 ± 10.37%, 79.73 ± 6.77%, 93.32 ± 1.10%, and 63.05 ± 9.20%, respectively, compared with the ulcer control group (Group II). The antiulcer effect of PGPE at 0.75 g/kg (62.29 ± 10.37%) was comparable to that of omeprazole (63.05 ± 9.20%). In contrast, higher doses of PGPE (1.50 g/kg, $p < 0.05$; 3.00 g/kg, $p < 0.01$) exhibited significantly greater gastroprotective effects than omeprazole.

As shown in Table 2, ulcerated animals (group II) produced less mucus from the gastric mucosa. Animals pretreated with PGPE at doses of 1.50 g/kg ($p < 0.05$) and 3.00 g/kg ($p < 0.0001$) showed a significant increase in mucus content compared to the ulcer control group and the group pretreated with PGPE and omeprazole. The pH increased markedly compared to the ulcer control group. The results showed that the gastric mucosal folds were flattened in animals pretreated with PGPE. The group pretreated only with distilled water (the ulcer control group) showed more lesions in the stomach. Complete ulcer formation was observed due to the presence of severe hemorrhagic lineage. Pretreatment with PGPE at 1.50 and 3.00 g/kg reduced gastric lesion formation (Fig. 1, D and E).

Table 2. Gastroprotective activity of *Punica granatum* L. peel hydroalcoholic extract against acidified ethanol (HCl/Ethanol)-induced gastric lesions in rats

Groupe	Affectation	Gastric pH	Mucus weight (g)	Ulcer areas (mm²)	Inhibition of ulcer areas (%)
Group I	Distilled water	5.48 ±0.41 [c, e]	3.10 ±0.21 [c, f]	-	-
Groupe II	Ulcer Positive group	1.69 ±0.22 [d]	0.82 ±0.07	522.75 ±268.95	-
Groupe III	*Punica granatum* (0.75g/kg)	3.03 ±0.54 [a]	1.07 ±0.07	176.75 ±28.88 [c]	62.29 ±10.37
Groupe IV	*Punica granatum* (1.50g/kg)	4.57 ±0.13 [c, d]	1.43 ±0.19 [a]	96.25 ±25.86 [c, d]	79.73 ±6.77
Groupe V	*Punica granatum* (3.00g/kg)	5.75 ±0.41 [c, f]	3.44 ±0.32 [c, f]	32.75 ±10.05 [c, e]	93.32 ±1.10
Groupe VI	Omperazol® (0.10 g/kg)	3.41 ±0.38 [b]	0.95 ±0.10	186.75 ±77.26 [c]	63.05 ±9.20

Values are expressed as mean ± SD
[a] - p<0,05, statistically significant as compare to ulcer control
[b] - p<0,01, statistically significant as compare to ulcer control
[c] - p<0,0001, statistically significant as compare to ulcer control
[d] - p<0,05, statistically significant as compare to Omperazole
[e] - p<0,01, statistically significant as compareto Omperazole
[f] - p<0,0001, statistically significant as compare to Omperazole

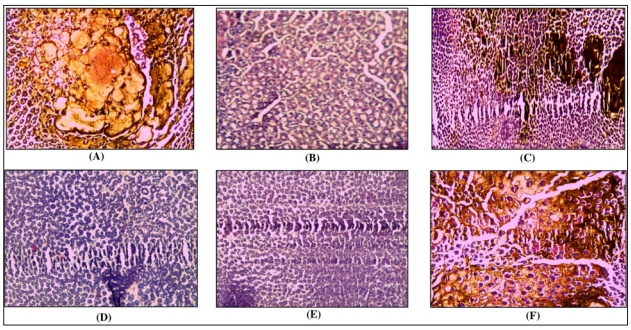


Images were taken using a digital camera. (A) Rats receiving only ulcerogenic agent, (B) Rats receiving distilled water, (C) Rats receiving ulcerogenc agent+Punica granatum L. peel extract (0.75g/kg), (D) Rats receiving ulcerogenc agent+ Punica granatum L. peel extract (1.50/kg), (E) Rats receiving ulcerogenc agent+ Punica granatum L. peel extract (3.00/kg), (F) Rats receiving ulcerogenc agent+commercial standard (Omperazol) (0.10/kg)

Figure 1. Macroscopic analysis of ulcers induced by acidified ethanol (HCl/Ethanol)

Histopathological studies

Histopathological examination demonstrated severe gastric mucosal damage in rats treated with acidified ethanol, as evidenced by disruption of the normal mucosal architecture, disorganization of gastric glands, epithelial cell loss, necrosis, hemorrhage, and congestion, compared with the normal control group. Pretreatment with PGPE at doses of 1.50 and 3.00 g/kg provided significant, dose-dependent protection against ethanol-induced gastric injury. Animals treated with the lower dose of PGPE (0.75 g/kg) and with omeprazole exhibited partial protection, characterized by reduced submucosal edema and less pronounced mucosal damage (Figure 2C, E).



Stomachs were observed under an optical microscop (X10). Images were taken using a digital camera. (A) Rats receiving only ulcerogenic agent, (B) Rats receiving distilled water, (C) Rats receiving ulcerogenc agent+Punica granatum L. peel extract (0.75g/kg), (D) Rats receiving ulcerogenc agent+ Punica granatum L. peel extract (1.50/kg), (E) Rats receiving ulcerogenc agent+ Punica granatum L. peel extract (3.00/kg), (F) Rats receiving ulcerogenc agent+commercial standard (Omperazol) (0.10/kg).

Figure 2. Histological examinations of stomachs in treated and untreated groups

DISCUSSION

Oral administration of acidified ethanol is detrimental to gastric tissue, as it disrupts the gastric mucosal barrier and vasculature, leading to hemorrhagic injuries, increased mucosal fragility, excessive submucosal edema, and damage to gastric epithelial cells. Mucus secretion constitutes an important defensive mechanism that protects gastric tissues from the direct action of digestive enzymes. Peptic ulcer disease remains a global health challenge affecting populations worldwide. It is widely accepted that ulcers develop when mucosal integrity is compromised due to an imbalance between endogenous defensive mechanisms and aggressive factors [22]. Various therapeutic agents, including plant extracts, may be used to restore this balance.

The results of the present study demonstrated that PGPE exerted significant antiulcer effects and provided marked protection of the gastric mucosa. Previous studies have shown that certain phytoconstituents, such as phenolic compounds and flavonoids, play an important role in mediating antiulcer activity [23-25]. Therefore, the observed prophylactic and healing effects of pomegranate peel extract on gastric ulcers may be attributed to its antioxidant activity [7] and its rich phytochemical composition [26].

To date, there are limited reports specifically addressing the antiulcer potential of *P. granatum* L. peel extracts grown in Algeria. Although the precise mechanisms underlying the gastroprotective effects of PGPE remain to be fully elucidated, several plant-derived constituents, including flavonoids, tannins, terpenoids, and saponins, have been widely recognized as potent gastroprotective agents [27]. In particular, flavonoids, tannins, and triterpenoids exhibit well-documented cytoprotective and antiulcer activities [22, 27]. The prevention of ulceration by tannins is considered due to its vasoconstriction activities [28]. It is further reported that pomegranate contains excess polyphenols, anthocyanins and tannins with gastroprotective properties [29]. Pomegranate tannins have a protective effect on gastric ulcers. Its antiulcer effect is associated with increased free and adhering mucus production in the gastric wall [30,31]. This inhibits the formation of oxygen free radicals, reduces depletion of glutathione peroxidase and superoxide dismutase, and keeps nitric oxide levels at normal levels [30, 31]. In another study, the inhibitory effect of gastric mucosal injury was evaluated *in vivo*, administration of pomegranate peel 70% methanolic extract showed gastroprotective activity through its antioxidant nature. The antioxidant level in the treated group of rats increased and remained within the normal range. All histopathological examinations of the stomachs of animals where the ulcer was caused showed severe erosions of the gastric mucosa, neutrophil infiltration and submucosal swelling; that was normal in treated groups [31]. The results of our study depict that PGPE gastric mucosa is significantly prevented from acidified ethanol-induced gastric ulcers, and the protective effect of the gastric mucosa was enhanced when the dose was increased (in a dose-dependent manner). The antiulcer results of PGPE can be attributed to several compounds found in the plant, including punicic acid, anthocyanins, anthocyanins, ellagic acid, ellagitannins (including punicalagin), flavonoids, estrogenic flavonols, and flavonoids [26]. These results are supported by previously published data explaining that gastroprotective effects are associated with the presence of phenolic, flavonoids and other antioxidant constituents that may have anti-ulcer effects. Thus, ulcer prevention/ protection effect of PGPE can undoubtedly be attributed to phytochemical, having antioxidant nature [30,31]. The present study found that PGPE has a promising phytochemical that may be used for treatments of ulcers. There is further need for investigation to know the active ingredients of plants that have gastroprotective roles with strong antioxidant effects.Despite these promising findings, the present study has certain limitations. The assessment of gastroprotective effects was primarily based on macroscopic and histopathological evaluations, which, although informative, do not fully elucidate the underlying molecular mechanisms. The inclusion of inflammatory and apoptotic markers, such as NF-κB and p53, would provide deeper insights into the biological pathways involved in PGPE-mediated gastroprotection. Future investigations are therefore warranted to incorporate relevant biochemical and molecular assays to comprehensively evaluate the anti-inflammatory and cytoprotective mechanisms of pomegranate peel extract.

In conclusion, the findings of this study suggest that PGPE represents a promising natural source of bioactive compounds with significant antiulcer potential. Further studies aimed at isolating and characterizing the active constituents, as well as validating their efficacy through advanced mechanistic and clinical investigations, are strongly recommended.

CONCLUSION

In conclusion, the hydroalcoholic *P. granatum* L. peel extract (PGPE) exhibited significant antiulcer and gastroprotective effects against HCl/ethanol-induced gastric injury in rats. These protective effects are likely associated with the extract's free radical scavenging capacity and its rich phytochemical composition.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

N.Z. contributed to the study methodology, data analysis, and interpretation of results. N.Z. and E.A. were responsible for manuscript structuring and writing. M.H.G., A.M., H.S., and A.B. contributed to manuscript revision and supervision. All authors have read and approved the final version of the manuscript.

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