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RESEARCH

Gastroprotective Effects of Taxifolin on Ethanol-Mediated Gastropathy *in vivo*: Role of Anti-Apoptotic, Antioxidant, and Anti-Inflammatory Mediators

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Abstract
Taxifolin is a naturally occurring bioflavonoid that has been used as a therapeutic agent for several Inflammatory bowel disorders due to its notable antioxidant and anti-inflammatory properties. However, the role of taxifolin in ethanol-induced gastropathy and gut health remains unclear. Here, we investigated the acute toxicity and gastroprotective effects of taxifolin on ethanol-induced gastric ulcers and depicted its related molecular pathways. Sprague male rats were pretreated with either 10% Tween 20, 30 mg/kg lansoprazole, or 30 mg/kg and 60 mg/kg taxifolin before intragastric ethanol delivery to induce ulcers. The results indicated an increased safety margin of taxifolin in rats ingested with up to 500 mg/kg. Our data demonstrated the significant gastroprotective potential of Taxifolin (30 and 60 mg/kg) by strengthening gastric defense factors (increasing mucin secretion, up-regulating mucopolysaccharides, and maintaining gastric pH), reducing gastric ulcer area by 74.07% and 77.69%, respectively, compared to ulcer controls. Moreover, taxifolin supplementation ameliorated gastric tissue alterations, denoted by fewer hemorrhagic/lesion areas, less epithelial cell loss, and reduced submucosal edema with leucocytes. Taxifolin pretreatment enhanced the production of antioxidants (glutathione peroxidase, catalase, and superoxide dismutase), as well as lowered lipid peroxidation marker (MDA) and pro-inflammatory mediators (TNF-α and interleukin-6). The anti-apoptotic effects of taxifolin were evidenced by increased HSP 70 and reduced Bax protein levels in gastric tissues. These findings present taxifolin as a potent inhibitor of gastric ulcer, which could be a new natural source for bioformulation.

Keywords Taxifolin · Gastric ulcer · Immunohistochemistry · Antioxidant · Inflammation

Introduction

A peptic ulcer is the most common gastrointestinal disorder associated with gastric morbidity that can progress into bleeding or perforation if not managed properly. As the most incidence gastric disorder, peptic ulcer affects at least 10% of individuals worldwide during their lifetime [1]. In 2021, the global incidence and prevalence of peptic ulcer cases increased by 11.1% and 8.8%, respectively, compared to the 1990 data [2]. A peptic ulcer is recognized as a deep lesion initiated from the muscularis mucosa in the gastrointestinal tract and passes through the GIT mucosal thickness. The initiation, development, progression/pathogenesis, and recurrence of peptic ulcer have been linked with several pivotal factors such as aging, increased alcohol intake, drugs, sedentary lifestyle, spicy food, and infections (commonly *H. pylori*) [3].

Heavy alcohol consumption has become a global health threat since more than 43% of the population drinks alcohol. Alcohol overuse has been related to more than 200 illnesses, disability, and approximately 2.6 million deaths globally according to 2019 statistics. Scientists confirmed that heavy alcoholism increases the chances of acquiring liver steatosis/fibrosis, especially among obese and NAFLD cases [4].

Extended author information available on the last page of the article

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Abusive alcohol consumption is an unhealthy, risky behavior that can ameliorate gastric defense barriers and promote gastric mucosal injury, which has been used as a model to study the gastroprotective effects of a potential therapeutic medicinal plant or its bio compounds [5]. Ethanol-mediated mucosal injury is linked with the reduction of endogenous antioxidants, including SOD, CAT, GPx, nitric oxide (NO), and prostaglandin E2 (PGE2) levels that are essential to balance free radicals and to avoid oxidative stress, which is parallel with up-regulation of pro-inflammatory mediators, interleukin-6 (IL-6), IL-1β, and tumor necrosis factor α (TNF-α), all of which provoking a diverse immune and inflammatory responses that changes the mucosal integrity [6]. Moreover, aggressive factors such as alcohol can disrupt the cellular homeostatic rate of apoptotic and cell proliferative processes that can directly regulate gastric sore formation and healing. Alcohol is considered a major regulator of pro-apoptotic proteins, including p53 and members of the Bcl-2 family (Bax and Bcl-2), which is a crucial stimulating factor of the intrinsic pathway by permeabilizing the mitochondrial membrane and cytochrome C release. Therefore, scientific efforts are focusing on finding therapeutic agents that can attenuate ethanol-mediated apoptotic actions, a bio-compound with promoting potential on anti-apoptotic proteins, such as HSP 70, to strengthen cellular integrity and regulate cell proliferation [7]. Despite numerous pharmaceutical innovations, the current employed treatment strategies in the clinics are mainly limited to proton pump inhibitors (lansoprazole), prostaglandin analogues (misoprostol), and histamine H2 receptor antagonists (ranitidine), which are accompanied by several adverse reactions over long periods [8, 9]. Therefore, searching for a novel gastroprotective bio-compound could fill the gap with a safer margin than synthetic chemicals.

Taxifolin is an isoflavanone that consists of two phenyl groups (ring A and ring B) joined together by a heterocyclic ring (ring C) (Fig. 1). As a dihydroquercetin, taxifolin is abundantly present in olive oil, onions, grapes, and citrus fruits, as well as in extracts of *Pinus roxburghii*, *Cedrus deodara*, *Siberian larch*, and *Larix sibirica* [10]. Taxifolin is commonly added to numerous food products as a natural antioxidant owing to its two aromatic rings and two phenolic groups (OH) at the meta- and para-position, respectively [11]. In the last decades, taxifolin-rich extracts have been accredited as a novel food and authorized by many countries, including the United States, the United Kingdom, and China, as well as the European Commission [12, 13]. Recent studies have shown numerous health benefits/pharmaceutical potentials of taxifolin, including anti-oxidant [14], anti-inflammatory [15], anti-microbial [16], and anticancer effects [17]. A brief study highlighted anti-ulcer effects of taxifolin in the aspirin-induced ulcer model, supported by macroscopic and biochemical (only Glutathione, MDA, and Cox-1) examinations [18]. However, literature data on its possible toxic effects and potential gastroprotective effects

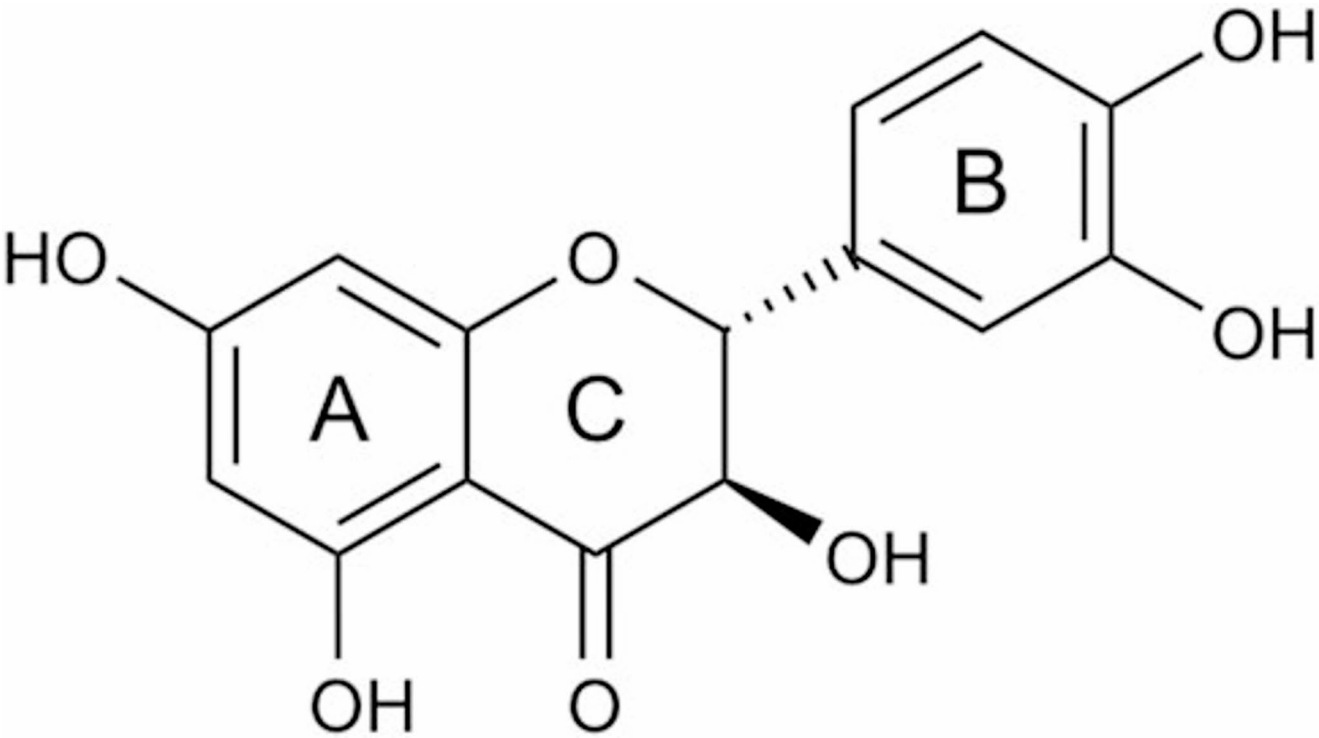

Fig. 1 Taxifolin structure appeared with two phenyl groups (A, B) rings linked by a heterocyclic ring (C)

are scarce. Therefore, this study was geared to unveil the acute toxicity and gastroprotective potentials of taxifolin in ethanol-mediated ulcerative animal model through different histopathological and biochemical approaches.

Materials and Methods

Acute Toxicity Experiment

The present animal procedures complied with the standards of **ARRIVE** [19]. Rats (aged 7–8 weeks; 180–200 g) were provided by the Erbil Polytechnic University. The experimental trials were approved by the ethical committee of Erbil Polytechnic University (No. 43, 4/5/2025). Sprague Dawley rats were arbitrarily aligned into 3 groups (6 males and 6 females in each) in a mesh-wired cage during a 7-day adaptation procedure. All rats underwent overnight fasting followed by oral treatments; group A had 10% Tween 20; group B received 250 mg/kg Taxifolin; group C rats had 500 mg/kg Taxifolin. Following an additional 3–4 h of fasting after treatment, food was provided, and rats were checked regularly for any possible incidence of toxicity for the next 14 days. On day 15, rats were injected with an intraperitoneal injection of 1 mL of anesthesia (3 mg/kg xylazine and 30 mg/kg ketamine) and underwent euthanasia. The blood samples were drawn for relevant bio-contents, and the kidneys/liver were dissected for histological examination (A.j. Jabbar and Abdul-Samad Ismail, [20].

Gastroprotective Experiment

Experimental Design

The Sprague Dawley rats (180–200 g, aged 7–8 weeks) were provided by Erbil Polytechnic University. Thirty male rats were placed in 5 cages and provided with standard food and tap water during a one-week adaptation period. After that, rats were fasted for 24 h, and then pretreated differently; normal control (A) and positive ulcer control rats (B) received 1 mL of 10% Tween 20; the reference group (C) received 30 mg/kg lansoprazole (dissolved in 10% Tween 20); the prevention rat groups (D and E) received single oral dosage of 30 and 60 mg/kg Taxifolin (Solarbio, Beijing, China, Cat. No.: ST8050), dissolved in 10% Tween 20, respectively. After 1 h, rats in the positive ulcer, reference, and prevention groups received 1 mL of absolute ethanol, while normal control rats received normal saline. One hour later, all rats were anesthetized, and their blood samples were obtained by cardiac puncture after formalin anesthesia [21]. The dissected stomachs were opened at the greater cavity, and their contents were collected and then divided into two parts for histopathological (10% formaldehyde) and biochemical examinations (Fig. 2). The collected blood

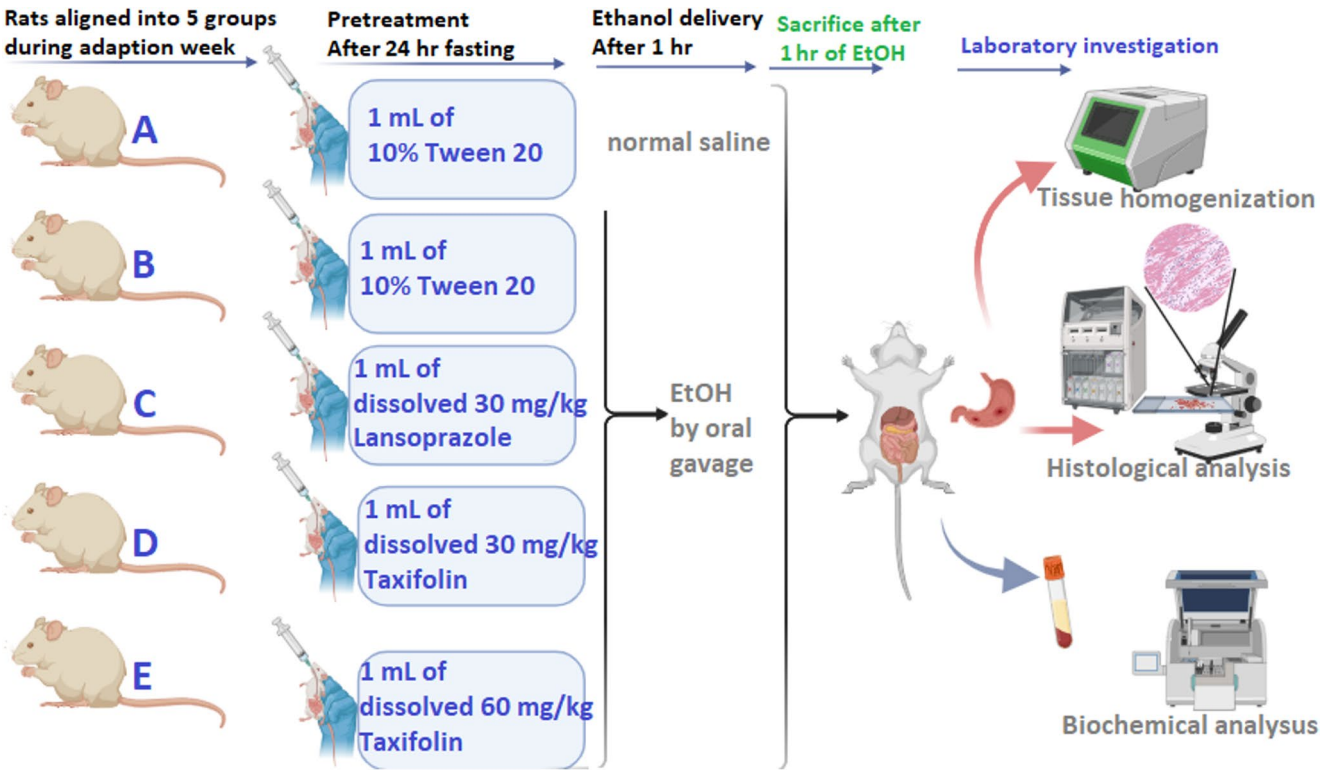

Fig. 2 Experimental design for examining Taxifolin's anti-ulcer effects

samples were centrifuged for 10 min at 2500× g, and the obtained clean serum was stored at − 20 ◦C for later analysis [22].

Gross and Ulcer Score Study

The stomachs were dissected, opened at the greater curvature, the mucus was collected by scraping a clean slide against the surface lining, and they were weighed using an electric balance. The stomachs were washed with ice-cold saline. The clean stomachs were imaged at the mucosal lesion areas (red/dark erosion lines), and the macroscopic damage (using Image J software) was screened by a blinded examiner. The lesion/ulcer area (mm) was measured along its greatest length, and for the patches, five lesion areas were counted as equivalent to 1 mm of ulcer. The lesion area in each rat was measured in mm, and the group means (n = 6) were determined as the ulcer index for statistical comparison [23]. The ulcer inhibition percentage was estimated relative to the scores of ulcer areas from ulcer control rats using the following Eq. 1.

$$Inhibition\ \%\ (I\%)\ =\ UI\ control - UI\ treated/UI\ control\ X\ 100 \quad (1)$$

Assessment of Gastric Contents

The gastric contents were collected after dissecting at the greatest curvature and immediately drained into centrifuge tubes. The gastric mucosa of rats was gently scraped using a glass slide, and the mucus content was weighed using a precision electronic balance. The obtained mucus content was examined for the hydrogen ion intensity using a digital pH metre (titration with 0.1 N NaOH). The total stomach acidity (TSA) of stomach contents was determined by mixing every sample with distilled water (1 ml) and phenolphthalein (2–3 drops) and then titrating the solution mixture with NaOH (0.01 N) until a pink color appears [24]. Equation 2 was employed to determine the TSA:

$$\mathrm{TSA} = \frac{V\ (NaOH) \times\ N \times\ 100\, mEq/L}{0.1} \quad (2)$$

Moreover, to estimate the acidic mucopolysaccharides (mucin) in gastric juice, the Alcian blue binding capacity (ABC) procedure was employed [25]. Briefly, the stomach's glandular part was weighed and poured into a 10 mL of 0.1% w/v Alcian blue solution for 2 h. After removal of the excess dye using a sucrose solution, the Alcian blue dye adherent to the gastric wall was extracted using 4 mL magnesium chloride (MgCl2) and Diethyl ether to have an emulsion texture. The emulsion mixture was centrifuged at 5000 rpm, and the supernatant was examined in a spectrophotometer at 580 nm and the results were expressed as mg/gram of glandular gastric tissues. The quantity of Alcian blue was estimated by linear regression and a calibration curve that was predetermined using various concentrations of Alcian blue [26].

Histological Analysis

Stomach tissues were sliced, fixed in a 10% (v/v) formalin, and paraffin-embedded, as detailed previously [24]. Paraffin-embedded sections at 5 µm were colored with hematoxylin and eosin (H&E) and Periodic Acid-Schiff (PAS) for histopathological examination. The pathological alterations in stomach tissue layers were screened using a trinocular light microscope (N-PW300AT, Zeedo, Jinhua, China). The hemorrhagic areas, epithelial cell disruption, submucosal edema, and mucosal changes were recorded [24].

Apoptotic Protein Quantification

The stomach tissues were buffer-washed (PBS) and homogenized at 5000 rpm for 5 min at 4 °C to have a mammalian protease inhibitor (cocktail) for apoptotic protein evaluation, as previously detailed [27]. Briefly, after homogenization, the tissue mixture (1000 g) was centrifuged at 1200 rpm for 10 min at 4 °C, and the supernatant was transferred to a fresh Eppendorf tube for further processing. Subsequently, the tissue lysate was diluted with diluent buffer and examined for the immunocontent using ELISA commercial anti-HSP 70 (1:100 dilution, Vitro master diagnostica, Sevilla, Spain) and anti-Bax (1:50 dilution, Vitro master diagnostica, Sevilla, Spain) kits. The same procedure was repeated for the standard preparation. The procedures were conducted following the manufacturer's recommendations.

Antioxidants of Tissue Homogenates

The intensity of SOD, CAT, GPx, and MDA in supernatants of gastric tissue homogenates was evaluated using available ELISA kits from Solar Bio Co. (Beijing, China). All the procedures were conducted according to the producer's recommendations [28].

Estimation of Cytokines

The concentration of pro-inflammatory and anti-inflammatory mediators (TNF-α, IL-6, and IL-10) in serum samples of experimental rats exposed to ethanol-mediated gastropathy was determined using commercial ELISA kits (Cat. No. SEKR-0009, SEKR-0005, and SEKR-0006, respectively) from Solar Bio Co. (Beijing, China) [29].

Statistics

The obtained data from multiple experimental groups were handled using One-way ANOVA with a post hoc Tukey's test. The GraphPad Prism v9.0 software was used to design figures (GraphPad Software, Inc., San Diego, CA, USA). The results are presented as Mean ± SEM, presenting as ✱, $p > 0.05$; ✱✱, $p > 0.01$; ✱✱✱, $p > 0.001$; ✱✱✱✱, $p > 0.0001$; ns, non-significant.

Results

Acute Toxicity

The two-week toxicity trial showed an increased safety margin of taxifolin in rats ingested with up to 500 mg/kg of taxifolin according to biochemical and histological evaluations. The observational process did not find any abnormal behavior/physiological changes or mortality during or after the trial. Rats ingested with oral dosages of 250 and 500 mg/kg did not exhibit any toxicity indications such as gastrointestinal issues (vomiting, diarrhea, saliva leakage), respiratory distress, behavior changes (lethargy, tremors, seizures), physical changes (eye/fur color), convulsions, or any movement disabilities. Throughout the trial, the water and food intake of supplemented rats was similar to that of normal saline-treated rats. The histopathological evaluation of the obtained liver and kidneys denoted regular tissue architecture without any signs of tissue layer distortion, hemorrhage, tubular necrosis, vacuolation, hydropic degeneration, or necrotized fatty hepatic changes. Moreover, liver and kidney functional parameters in serum samples were found to be non-significantly varied between taxifolin and normal saline-treated rats (available on request). Overall, the above data serve as scientific evidence to support the safe ingestion of taxifolin up to 500 mg/kg in animal models (Fig. 3).

Assessment of Gastroprotective Activity

Macroscopic Views

A gross evaluation of dissected stomachs revealed different levels of mucosal lesions, bleeding, and hemorrhages, which appeared as longitudinal dark/red lesions in various diameters/depth, severe congestion, sharply defined, slightly irregular, or flat edges, as seen in the ulcer control rats. Normal control rats exhibited a pink mucosal layer, normal folding, with the absence of observable gastric surface injury. However, pre-treatment with taxifolin (30 and 60 mg/kg) exhibited mild to moderate congested mucosal lesions, fewer hemorrhagic areas, and no indications of surface bleeding, with high-dose taxifolin being more efficient than its low dose (Fig. 4).

Effect of Taxifolin on Gastric Defense Factors and Ulcer Estimations

The intragastric ethanol delivery significantly weakened gastric defense barriers, reduced mucus secretion, and altered gastric pH/acidity. Normal control rats exhibited sufficient mucus content, maintained gastric pH, and increased Alcian blue binding capacity (ABC) compared to ulcer control and taxifolin-treated rats. Ulcer controls exhibited severe gastric tissue injury due to altered gastric barriers, which reduced mucus secretion by 70.70%, lowered gastric pH by 55.48%, lowered Alcian binding capacities by 75.21%, and increased TSA by 198.63%, compared to normal control rats. Lansoprazole or taxifolin pretreatment (30 and 60 mg/kg) strengthened gastric defense barriers, denoted by up-regulation of mucus weight by 1.79-, 1.55-, 1.68-folds; up-regulated gastric pH by 2.30, 2.03, and 211-folds; reduced total stomach acidity by 1.96-, 1.28-, and 1.52-folds; heightened ABC by 3.66-, 2.34-, and 3.10-folds, compared to ulcer controls. Pre-ingestion with lansoprazole or taxifolin (30 and 60 mg/kg) led to significant ulcer inhibitory percentages by 78.26, 74.17, and 77.69%, respectively) in comparison to the ulcer control's zero value (Table 1). The present data evidenced significant modulatory potentials of taxifolin on gastric defense factors, attenuating ethanol-mediated gastropathy in rats.

Same letters on values within the same column mean significance at $P < 0.05$. Ethanol oral delivery caused significant down-regulation of gastric defense barriers, which enhanced gastric tissue penetrations. While taxifolin ingestion strengthened gastric defense barriers, it also limited ethanol-mediated gastric tissue damage.

Histopathological Examination Using H&E Stain

The histopathological investigation was conducted to highlight the morphological alteration in the gastric tissues exposed to ethanol-mediated tissue injury, as shown in Fig. 5. The normal control rats had usual tissue architecture with a normal gastric mucosa, gastric pits/cavity, squamous epithelial layer, gastric glands, muscularis mucosae/submucosa, with the absence of noticeable abnormal indications. Absolute ethanol oral delivery provoked signification coagulative necrosis of the whole mucosal thickness, intense mononuclear cell infiltration, congested blood vessels, hemorrhage lesions, and

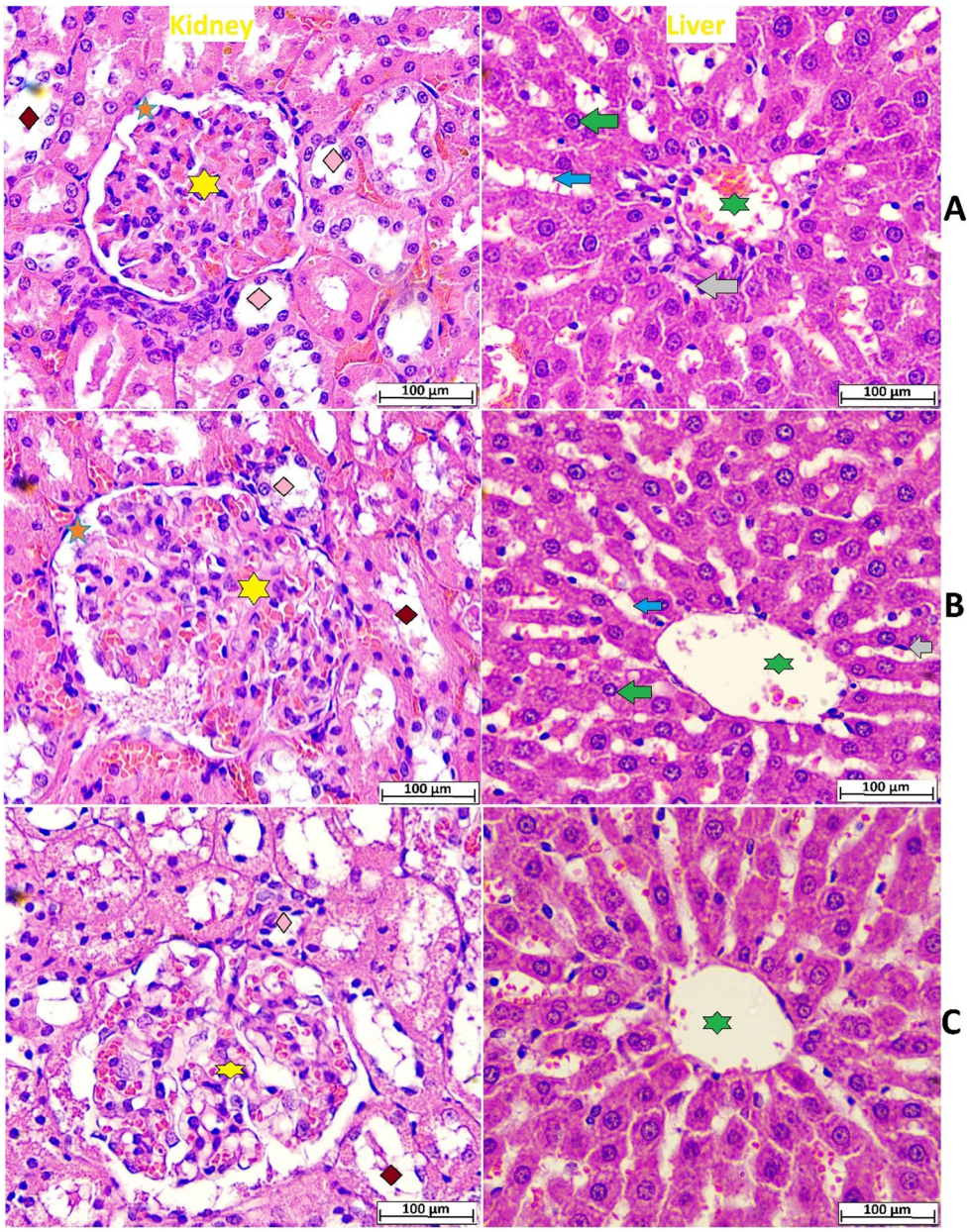

Fig. 3 Structural tissue views of the liver and kidneys of rats employed in the acute toxicity trial. Group A had normal saline; groups B and C were treated with 250 and 500 mg/kg of taxifolin, respectively. Green star, central vein; gray arrow, Kupffer cells; green arrow, hepatocyte; blue arrow, sinusoids; yellow star, glomerulus; orange star, Bowman's space; pink diamond, proximal convoluted tubules; brown diamond, distal convoluted tubules (H & E staining, 40x). There were no significant changes in the liver/kidney tissue components between normal saline and taxifolin-treated rats

aggregation in all gastric mucosa layers as well as excessive eosinophilic edema in the submucosa, and disruption of the mucosal surface epithelium. In contrast, taxifolin pretreatment dilated the ethanol-mediated tissue injury, characterized by wide gastric pits, less inflammatory/leukocyte infiltration, congested blood vessels, intact histological morphology of the gastric glands, mucosal epithelium, and overall mucosal layer. The taxifolin-treated rats did not exhibit any signs of RBC extravasation.

The present gastroprotective trial detected different levels of muco-substances (glycoproteins), glycogen, and mucins in the stomachs based on the employed PAS staining assay (Fig. 6). Normal control rats showed a strong magenta (reddish-purple) color on their epithelial cells and gastric glands as an indication of rich-carbohydrate structures. Gastric tissues of ulcer controls are marked with an eroded mucosal layer with faint and weak color intensity of PAS reaction, denoting reduced mucin/glycoprotein concentrations, which enhanced ethanol-mediated mucosal injury. In contrast, lansoprazole or taxifolin (30 and 60 mg/kg)-treated rats had mild to moderate PAS reaction on their surface epithelium and mucosal layers, as an indication of enhanced the production of mucin/glycoprotein by the mucosal gland, strengthening gastric defensive barriers by creating a protective layer on the gastric layers to lubricate/trap microbes, as well as prevent corrosive chemicals (ethanol) from reaching underlying tissues.

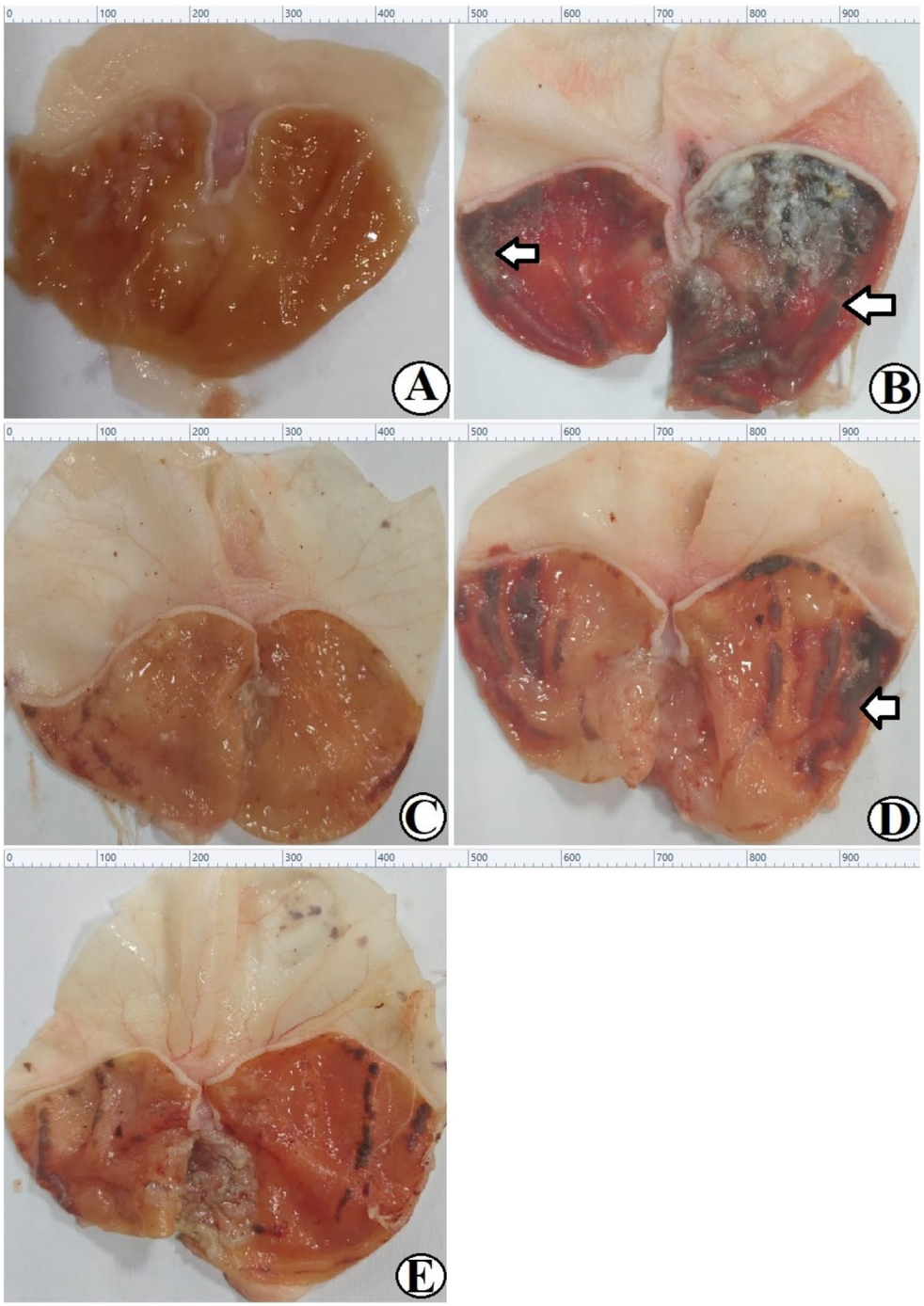

Fig. 4 Effect of taxifolin pre-treatment on the macroscopic views of rats' stomach linings exposed to pre-treatments + absolute ethanol. Normal control rats (**A**) had 10% Tween 20 + normal saline. Ulcer control rats (**B**) had 10% Tween 20 + ethanol; reference rats (**C**) had 30 mg/kg lansoprazole + ethanol; groups **D** and **E** rats were pretreated with 30 and 60 mg/kg taxifolin, respectively + ethanol. According to gross indications, ethanol oral ingestion provoked significant hemorrhage/lesions as well as edema in the gastric mucosal and submucosal layers with visible blood vessels bulging on the stomach surface. In contrast, taxifolin oral delivery resisted ethanol-mediated gastric injury and limited gastric tissue penetration, shown by higher gastric folds and lower oval or round-shaped open sores/lesions, as well as less congested areas

Table 1 Effect of taxifolin on the gastric parameters of rats exposed to ethanol-mediated gastropathy

Groups	Volume (ml)	pH	Ulcer index	Inhibition (%)	TSA (mEq/L/100 g)	Mg Alcian blue/g tissues
Normal control	3.14 ± 0.53^{a}	6.29 ± 0.40^{a}		-	21.23 ± 0.8	586.33 ± 6.3
Ulcer control	0.92 ± 0.12^{d}	2.80 ± 0.34^{b}	6.25	-	63.4 ± 4.4	145.3 ± 4.2
Lansop.+EtOH	1.65 ± 0.30^{b}	6.45 ± 0.53^{a}	1.36	78.24^{a}	32.22 ± 3.5	532.5 ± 5.3
Taxifolin 30 mg/kg+EtOH	1.43 ± 0.43^{c}	5.70 ± 0.45^{d}	1.62	74.07^{b}	49.20 ± 4.2	340.3 ± 4.6
Taxifolin 60 mg/kg+EtOH	1.55 ± 0.30^{b}	5.93 ± 0.30^{a}	1.40	77.69^{a}	41.56 ± 4.5	451.6 ± 5.4

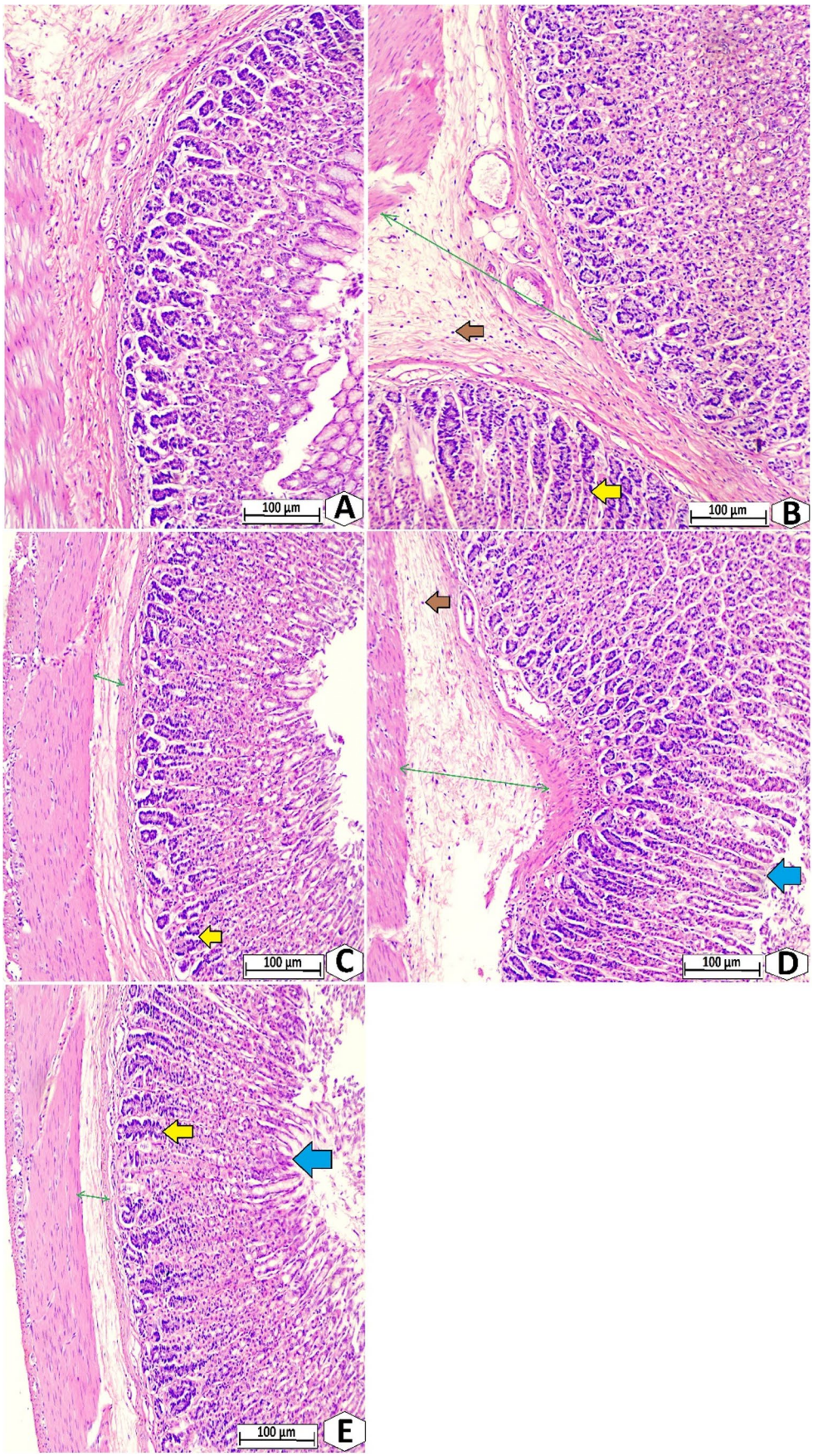

Fig. 5 Effect of taxifolin pretreatment on the microscopic appearance (H&E, 10x) of gastric tissues exposed to pretreatments and absolute ethanol. Normal control rats (**A**) had 10% Tween 20 + normal saline. Ulcer control rats (**B**) had 10% Tween 20 + ethanol; reference rats (**C**) had 30 mg/kg lansoprazole + ethanol; groups **D** and **E** rats were pretreated with 30 and 60 mg/kg taxifolin, respectively + ethanol. Gastric tissues of ulcer control rats exhibited increased epithelial distortion (blue arrow), mucosal penetration, and submucosal edema (double head arrow), damaged gastric glands (yellow arrow), and numerous inflammatory cell infiltrations (brown arrow) into the mucosal layers. While taxifolin pretreatment (30 and 60 mg/kg) dilated ethanol-mediated mucosal damage and submucosal edema, as well as reduced leukocyte infiltration, lessened congested blood vessels, and preserved the histological architecture of the mucosal epithelium

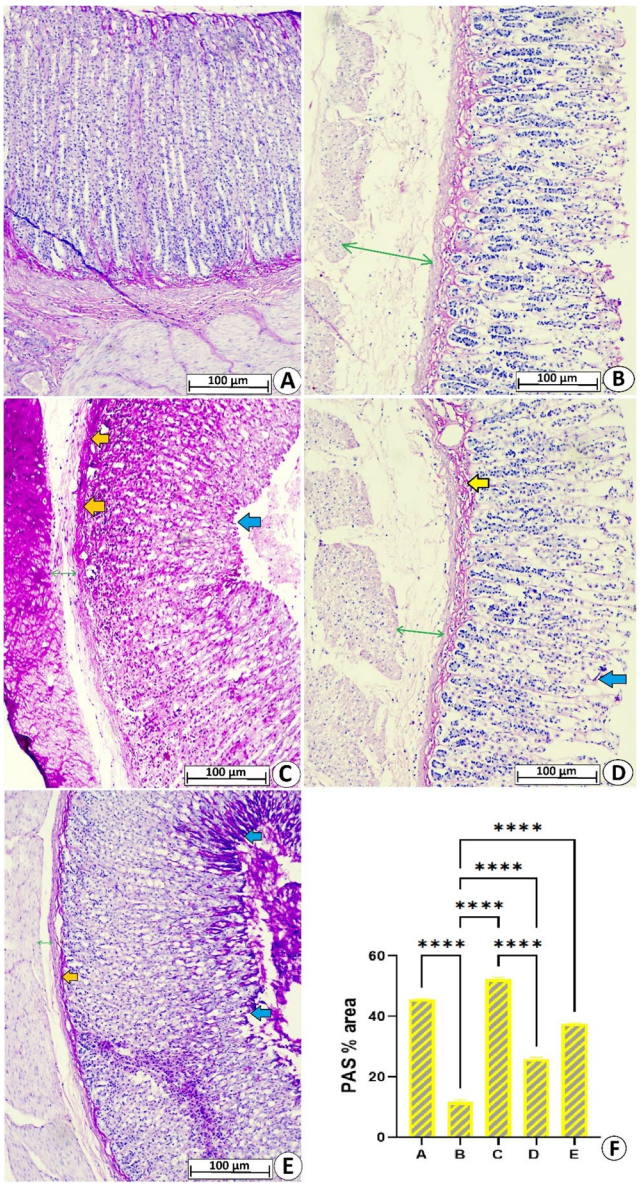

Fig. 6 Effect of taxifolin on the glycoprotein contents (PAS stain intensity, 10x) in stomach tissues after exposure to pretreatments and absolute ethanol. Normal control rats (**A, F**) had 10% Tween 20 + normal saline. Ulcer control rats (**B, F**) had 10% Tween 20 + ethanol; reference rats (**C, F**) had 30 mg/kg lansoprazole + ethanol; groups **D** and **E** rats were pretreated with 30 and 60 mg/kg taxifolin, respectively, + ethanol. Gastric tissues of ulcer control rats exhibited reduced glycoprotein concentration (yellow arrow) and increased epithelial distortion (blue arrow), mucosal penetration, submucosal edema (green double head arrow), and numerous inflammatory cell infiltrations into the mucosal layers. Rats pre-ingested with 30 and 60 mg/kg taxifolin exhibited faint to moderate PAS intensity in their gastric epithelium and gastric mucosal areas near muscularis mucosa, denoting improved production of mucin/glycoprotein defense barrier against ethanol-mediated gastric tissue penetrations. mage J software was employed to quantify glycoprotein as the positively stained area (%). Data considered significant ($n = 6$) at $p < 0.001$, ****

Apoptotic Protein Contents

The present immunohistochemical procedure examined gastric tissues for the amount of HSP 70 protein, which is an essential stimulator of cell proliferation at the margin of the gastric ulcer, provoking gastric ulcer healing by enhancing growth factor expression and promoting angiogenesis actions in the granulation tissue. Normal control rats exhibited reduced HSP 70 proteins in their tissue, which indicated limited or a lack of any proliferation/angiogenesis actions since they were not exposed to any stress factors (ethanol). Ulcer control rats showed reduced intensity (21.5 ng/mL) of this protein compared to normal control and other treated rats, which not only delayed the ulcer healing process, but also exacerbated the mucosal penetration and lesion formation. Notably, lansoprazole and both doses of taxifolin (30 and 60 mg/kg) led to significant stimulation of immunoreaction of HSP 70 proteins in gastric tissues, which were significantly higher by 62%, 13.16%, and 39.53%, respectively, compared to the detected intensity of ulcer controls (Fig. 7). Such positive modulation of HSP 70 protein not only enhanced cell proliferation and angiogenesis, but also resisted apoptotic actions at ulcer margins, altogether resulting in faster ulcer healing.

The immunohistochemical assay also examined the gastric tissue homogenates for the amount of Bax proteins, which are considered pro-apoptotic proteins that activate the intrinsic pathway of apoptosis by traveling to the mitochondria, oligomerizing, and altering mitochondrial permeability, altogether provoking apoptosis in the ulcer area. Normal control rats exhibited reduced intensity of Bax proteins, denoting a lack of any apoptotic actions. In contrast, ulcer control rats showed increased Bax protein concentration, higher by 83.82% compared to normal control rats. Moreover, lansoprazole or taxifolin pretreatment (30 and 60 mg/kg) showed a mild to moderate suppression of Bax protein, which was lower by 73.08%, 65%, and 72.79% compared to the value of ulcer control. Such down-regulation of Bax protein limited apoptotic cell death at ulcer margins, all of which contributed to the gastric mucosal protection from ethanol-mediated injury (Fig. 8).

Effect of Taxifolin on Oxidative Stress

The oxidative stress marker and antioxidants were significantly different between pretreated and ulcer control rats. As presented in Fig. 9, normal control rats highlighted

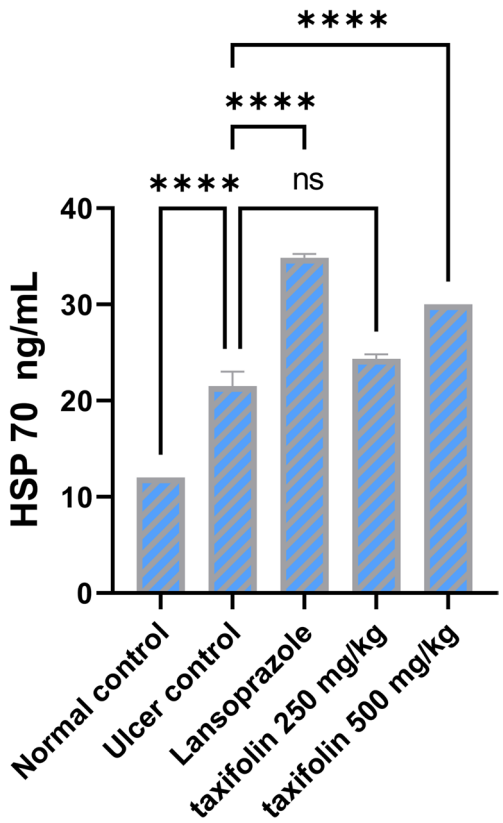

Fig. 7 Effect of taxifolin on HSP 70 concentration in gastric tissues of rats exposed to pretreatments and absolute ethanol. Normal control rats had 10% Tween 20 + normal saline. Ulcer control rats had 10% Tween 20 + ethanol; reference rats had 30 mg/kg lansoprazole + ethanol; supplemented rats pretreated with 30 and 60 mg/kg taxifolin, separately, + ethanol. Ulcer control rats exhibited reduced intensity of HSP 70 proteins, which is significantly lower than that of other pretreated rats. Lansoprazole or taxifolin supplementation enhanced production of HSP 70 protein, which enhanced proliferation and angiogenesis, lowered mucosal apoptosis, and promoted cellular repair/survival by enhancing the refolding of partially damaged active proteins. ****, $p > 0.0001$; ns, non-significance

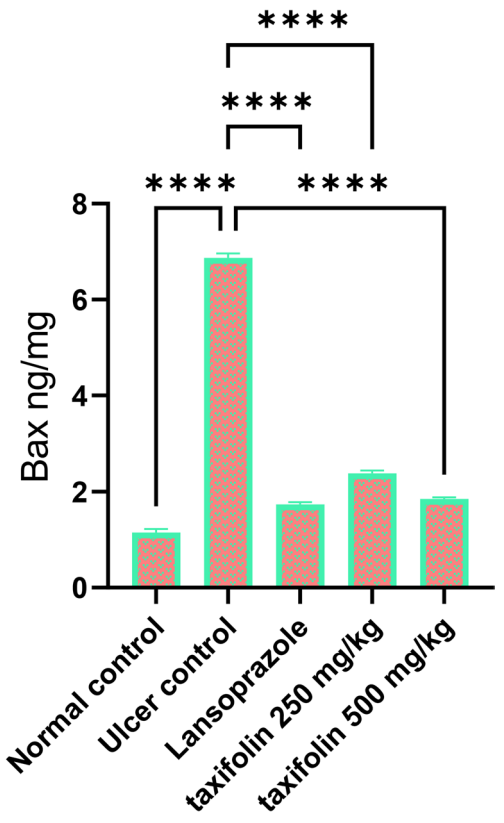

Fig. 8 Effect of taxifolin on the Bax protein intensity in the stomachs of rats that received pretreatments and absolute ethanol. Normal control rats had 10% Tween 20 + normal saline. Ulcer control rats had 10% Tween 20 + ethanol; reference rats had 30 mg/kg lansoprazole + ethanol; supplemented rats pretreated with 30 and 60 mg/kg taxifolin, separately, + ethanol. Ulcer control rats had up-regulated Bax proteins, which provoked the apoptotic actions and further gastric cell death. Lansoprazole or taxifolin supplementation limited the production of Bax protein, which reduced apoptotic actions at the ulcer margin, lowering gastric cell death and enhancing pathways associated with cellular repair/survival. ****, $p > 0.0001$

with increased antioxidant enzymes (CAT, 55 nmol/min/mg; SOD, 33.5 U/mg; GPx, 24.67 pg/ml) and decreased lipid peroxidation marker MDA (13.10 nmol/mg) in their stomach homogenates. Ulcer control rats experienced severe oxidative stress conditions, denoted by increased MDA levels (61.03 nmol/mg) and reduced antioxidants (SOD, 12.32 U/mg; CAT, 11.66 nmol/min/mg; GPx, 6.15 pg/ml). In contrast, Lansoprazole or taxifolin supplementation (30 and 60 mg/kg) maintained a healthy balance of ROS level in gastric tissues, shown by increased SOD (18.65, 15.70, 14.45 U/mg, respectively); CAT (41.33, 36.92, 39.68 nmol/min/mg); GPx (44.20, 29.17, 37.83 pg/ml). Lipid peroxidation (MDA) markers were found significantly lower (25.67, 36, 25.05 nmol/mg) in lansoprazole or taxifolin (30 and 60 mg/kg)-treated rats, respectively, compared to ulcer control rats. The data evidenced significant antioxidant (ROS regulator) potential of taxifolin, which is essential to promote angiogenesis, improve gut integrity, and stimulate cell proliferation, as important cell survival pathways to restore ethanol-mediated tissue injury.

Effect of Taxifolin on Inflammation

In this gastroprotective trial, we evaluated three biomarkers of inflammation in serum samples of rats exposed to ethanol-mediated gastropathy. As shown in Fig. 10, ulcer control rats manifested a severe inflammatory condition, denoted by an increase in TNF-α by 280.56% and IL-6 by 658.08%, while exhibiting a decrease in IL-10 by 79.75% relative to normal control rats. However, lansoprazole or.

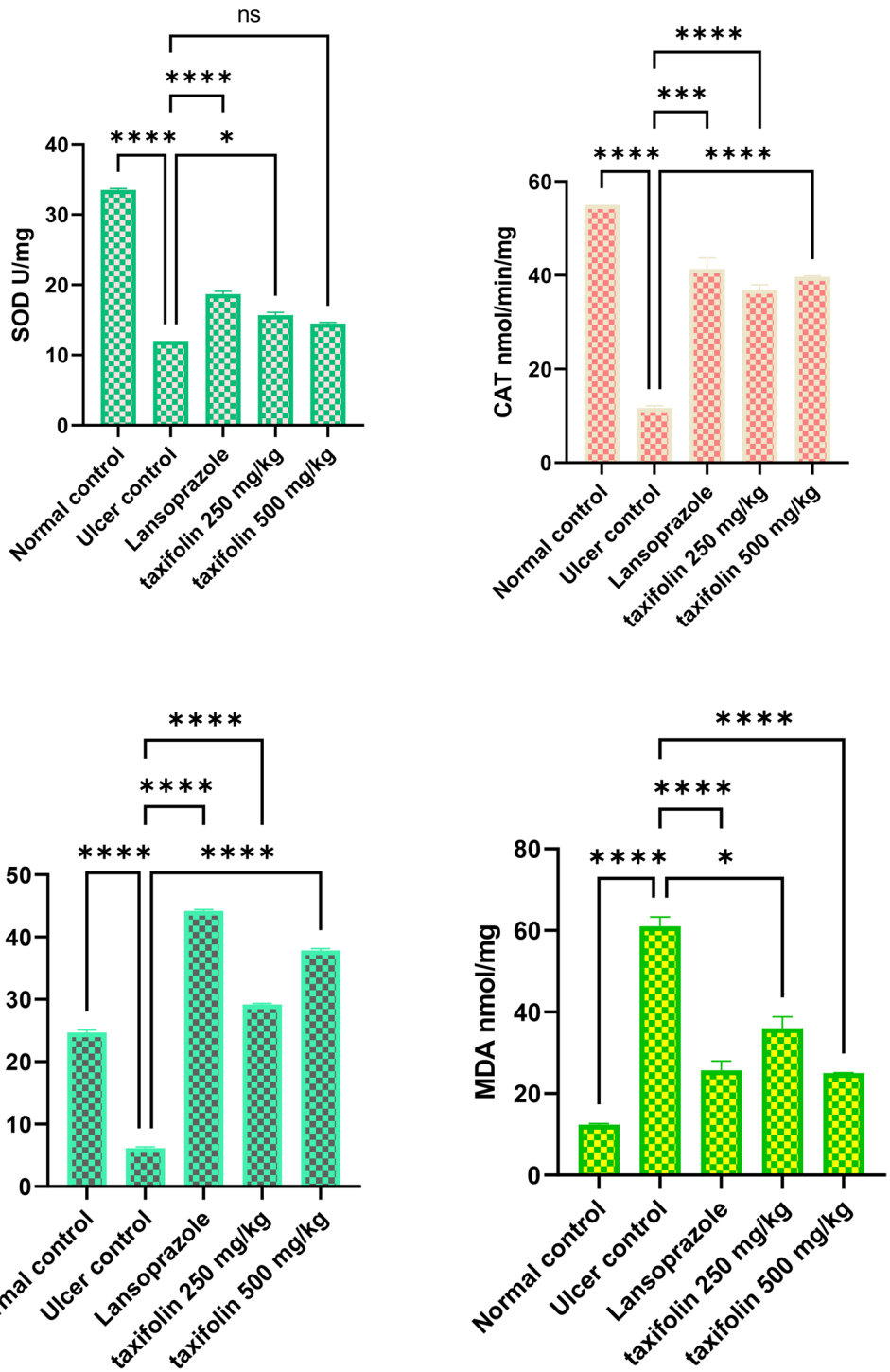

Fig. 9 Effect of taxifolin on oxidative stress markers and antioxidants in the gastric tissues exposed to pre-treatment and absolute ethanol. Normal control rats had 10% Tween 20 + normal saline. Ulcer control rats had 10% Tween 20 + ethanol; reference rats had 30 mg/kg lansoprazole + ethanol; supplemented rats pretreated with 30 and 60 mg/kg taxifolin, separately, + ethanol. Ulcer control rats experienced a severe oxidative stress as a result of absolute ethanol ingestion, shown by lower antioxidants and higher MDA levels, which exacerbated gastric tissue injury. Interestingly, taxifolin supplementation maintained a healthy balance of ROS/antioxidant molecules in gastric tissues, ameliorating ethanol-mucosal injury and submucosal edema. ✻, $p > 0.05$; ✻✻✻, $p > 0.001$; ✻✻✻✻, $p > 0.0001$; ns, non-significant

taxifolin supplementation (30 and 60 mg/kg taxifolin) showed mild to moderate anti-inflammatory potentials, shown by a decrease in TNF-α by 54.73%, 37.46%, and 61.04%; IL-6 by 69.46%, 30.79% and 57.17%, respectively, relative to ulcer control rats. Moreover, lansoprazole or taxifolin (30 and 60 mg/kg taxifolin) treatment increased production of IL-10 by 328.91%, 110.84%, and 169.75% relative to the value of ulcer controls (Fig. 10).

Discussion

Plants and their natural ingredients can have toxic effects, especially if they are eaten in large amounts in repeated doses; therefore, safety evaluation of these natural resources is crucial before considering them as a therapeutic for human ailments. The present trial evaluated the safety indications of single-dose delivery of up to 500 mg/kg taxifolin in male

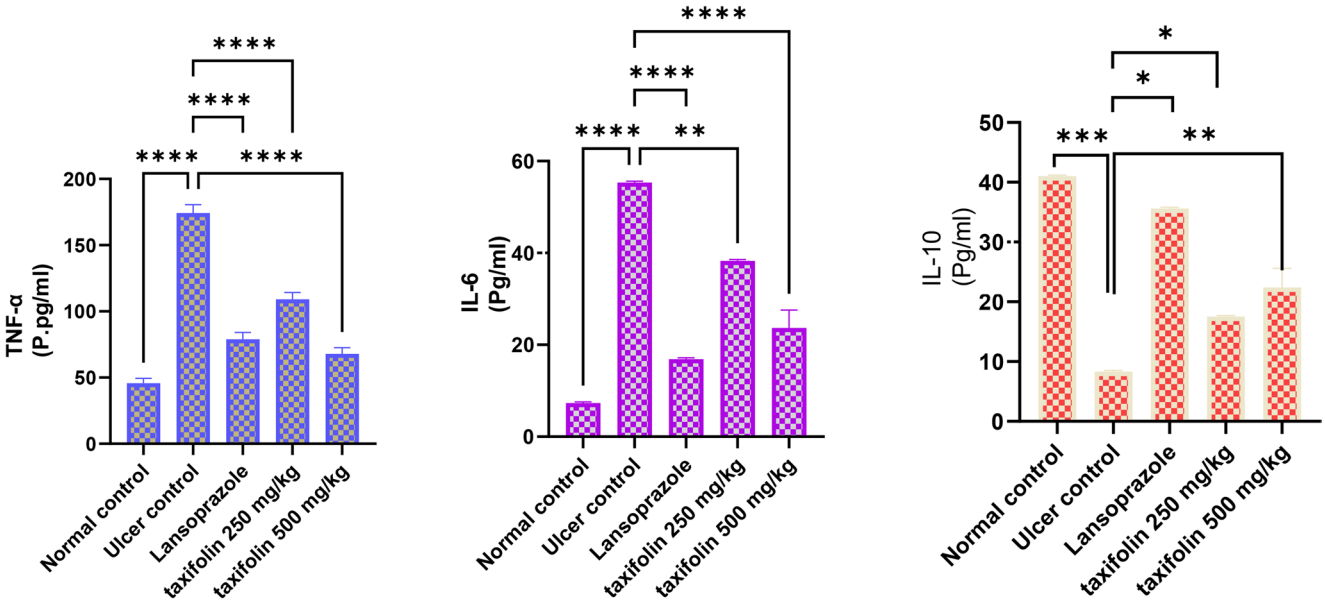

Fig. 10 Effect of taxifolin on serum inflammatory mediators in rats exposed to ethanol-induced gastric ulceration. Normal control rats had 10% Tween 20 + normal saline. Ulcer control rats had 10% Tween 20 + ethanol; reference rats had 30 mg/kg lansoprazole + ethanol; supplemented rats pretreated with 30 and 60 mg/kg taxifolin, separately, + ethanol. Ulcer controls exhibited a severe inflammation rate, shown by elevated TNF-α and IL-6 and lower IL-10, which created a prolonged inflammatory loop that worsened gastric hemorrhage and mucosal lesions. In contrast, lansoprazole or taxifolin pretreatment ameliorated ethanol-induced gastropathy, shortening the inflammatory response and leukocyte infiltrations that accelerated ulcer healing. ✱, $p > 0.05$; ✱✱, $p > 0.01$; ✱✱✱, $p > 0.001$; ✱✱✱✱, $p > 0.0001$; ns, non-significant

and female rats following OECD standards [30], which did not result in any toxicity indications, abnormal behavior, or mortality. Concomitantly, a large body of literature data has shown increased safety margin in different in vitro [10], in vivo [31, 32], and clinical trials [33]. Accordingly, oral taxifolin treatment did not show any toxic signs, yet a notable therapeutic efficacy in different health-conditioned humans [34, 35]. From the human and animal studies, it was concluded that taxifolin can be added to pre-packed foods to enhance immunity and enhance brain activity due to its antioxidant, anti-inflammatory, and anti-fatigue effects, making a novel dilatory additive [10, 12, 36].

Gastric ulcers are a global health issue that could be initiated by notorious/aggressive factors such as alcohol overuse. Ethanol has been labelled as an "aggressive factor" that can initiate or exacerbate gastritis and delay ulcer healing [37, 38]. Ethanol overconsumption enhances the intensified ulcer index, as seen in our study; ulcer controls exhibited a noticeable gastric mucosal lesion/hemorrhagic line extended longitudinally in various depths and widths. Moreover, ethanol provokes ulcerative inflammation, tissue necrosis, and disrupts epithelial cells, which could be linked with increased intensity of pro-inflammatory mediators (cytokines and chemokines) that mediated leukocyte infiltration near ulcer areas [39]. In the current trial, taxifolin supplementation resisted ethanol-mediated gastropathy, shown by preserved tissue architecture, increased mucin content, provoked production of muco-polysaccharides, and lower ulcer index compared to ulcer controls. Such gastroprotective potentials of taxifolin could be linked to its antioxidant potentials that were repeatedly confirmed by previous researchers [40, 41]. A previous study by Schlickmann et al. highlighted increased gastroprotective effects of taxifolin (1.14 mg/kg, orally) (extracted *from Mimusops balata* fruits) in HCl-induced gastric ulcer in mice based on 62% reduction in lesion area. These results were further supported by in vitro increased inhibitory action of taxifolin at 10 and 100 µg/ml on proton pump activity (H+, K+ -ATPase activity) with 32% and 41% lower percentage than vehicle rats, while very comparable to that 44% of the omeprazole group, but the underlying mechanism was not declared [42].

Similarly, anti-ulcer effects of gastro-mucoadhesive microparticles containing taxifolin have been linked with its antioxidant potentials (modulating Myeloperoxide/myeloperoxidase and glutathione levels), while promoting production of stomach mucin levels as well as its anti H+/K + -ATPase (in silico) and *anti-H. pylori* effects (MIC = 625 µg/mL) [43]. A preliminary study unveiled significant gastroprotective potentials of taxifolin (50 mg/kg) in aspirin-mediated gastric ulcer, shown only by macroscopic and biochemical indications [18].

The gastric ulcer healing involves many cellular processes, including the initiation of blood vessels (angiogenesis), inflammatory response, and cell proliferation. New vascular formation during ulcer healing is essential as regenerated blood vessels supply more oxygen/nutrients to the

injury site. As an anti-apoptotic protein, HSP 70 is normally expressed tremendously near ulcer areas passively through leaking from necrotic cells and by active routes, through the exocytosis pathway. HSP 70 supports ulcer healing through up-regulation of growth factors and prostaglandins, down-regulates protein denaturation/aggregation, activates cell proliferation, increases binding capacity for receptors (toll-like receptors) that aid in stimulating innate immune response, and strengthens gastric mucosal barriers. Such a pro-proliferative activity protein was found to be notably low in our ulcer control rats, which is condiment with previous findings [44]. Aggressive factors such as ethanol can increase the generation of ROS/free radicals in gastric tissues, which causes increased intensity of pro-apoptotic factors (Bax) and apoptosis activation, all of which are mediated by acute hemorrhagic gastric lesions as found in ulcer controls [45]. Conversely, pretreatment with taxifolin improved production of HSP 70 and decreased Bax concentration in gastric tissues, which ameliorated ethanol-mediated apoptotic tissue injury. Such modulatory potentials of taxifolin on apoptotic proteins could be linked with its antioxidant and anti-inflammatory potentials, as declared previously [46]. Taxifolin's anti-apoptotic effects were confirmed by its regulation of Bcl2/Bax/Caspase-3 signaling pathway, which has been considered as the main underlying pathway of its hepatoprotective potentials in rats supplemented with 25 and 50 mg/kg TXF for 3 months [47]. Accordingly, taxifolin reduced Bax proteins and up-regulated Bcl-2 protein expression, which is considered the main underlying tissue protective pathways in liver ischemia-reperfusion injury in an animal model [48]. Algefare et al. have shown a significant anti-apoptotic potential (Bax and caspase-3) of taxifolin supplementation (25 and 50 mg/kg), which was regarded as the main mechanistic event of its tissue-protective effects in Cd-induced nephrotoxicity animal model [32].

Reactive oxygen species are generated as a result of several metabolic processes in aerobic organisms. These radical molecules are mainly eliminated by the antioxidant defense components, such as SOD, CAT, and GPx. Microbial pathogens and aggressive factors such as alcohol can exacerbate ROS generation, resulting in oxidative stress and severe inflammatory/immune response in the gut. Several mechanisms have been proposed as the underlying pathway of oxidative injury by ethanol, including ethanol's proapoptotic effects that cause mitochondrial damage/death and subsequent increased ROS formation. Excess ROS generation facilitates lipid peroxidation in the gastric cell membrane, thereby increasing MDA formation and alleviating gastric defense barriers, as seen in the ulcer control rats [49]. Such an altered redox state in gastric tissues was resisted in rats pretreated with taxifolin. Accordingly, literature data show different levels of antioxidant potentials of taxifolin-rich extracts in different in vitro and in vivo trials [34, 50, 51]. A more recent in vivo study has demonstrated a strong antioxidant potential of taxifolin, which was considered a main protective factor against liver ischemia-reperfusion injury animal model [48]. Concomitantly, a preliminary gastroprotective effect of taxifolin (50 mg/kg) in aspirin-mediated gastric ulcer has been linked with its antioxidant potentials that balance ROS generation and strengthen gastric defense barriers [18]. Unver et al. have reported significant antioxidant potentials of taxifolin (50 mg/kg), shown by down-regulation of oxidants MDA, myeloperoxidase (MPO), and 8-hydroxy-2 deoxyguanosine (8-OHdG), while up-regulating total glutathione in the cisplatin-Induced Pulmonary Damage animal model [52]. Cerrah et al. have indicated significant gastroprotective effects of taxifolin in the aspirin-induced gastric ulcer model, which mainly attributed to its modulatory effects on oxidant/antioxidant molecules [18].

Inflammation is one of the major contributors to ethanol-mediated gastropathy. Heavy alcoholism has been linked with up-regulated ROS formation and oxidative stress, both of which activate several inflammatory pathways, such as the NF-κB pathway and up-regulation of signal/chemicals, including pro-inflammatory chemokines and cytokines, TNF-α, MPO, IL-1β, and IL-6. As a simultaneous action, increased ROS molecules enhance activation of inhibitor Kappa B (IκB) kinase (phosphorylation of inhibitors of IκB) that mediates proteasomal breakdown of IκBα and stimulates the NF-κB pathway. Activation of the NF-κB mechanism is considered a central mechanism of inflammation initiation, which follows the translocation of free NF-κB into the nucleus and recruitment of immune cells, as well as the transcriptional activation of numerous pro-inflammatory mediators and enzymes like iNOS and COX-2 [53]. In the present trial, ethanol ingestion stimulated a significant inflammation in gastric tissues (increased TNF-α and IL-6 generation), exacerbating the gastric tissue injury. Interestingly, taxifolin pretreatment suppresses the ethanol-mediated inflammatory cytokine release, denoted by lower TNF-α, IL-6, and higher serum IL-10 cytokines. Such anti-inflammatory potentials of taxifolin have been verified by researchers, showing significant suppression action on the NF-κB pathway, mitogen-activated protein kinase (MAPK), and decreased Trap, C-Fos, MMP-9, Cathepsin K, Nfatc1, and RANK expression; as well as down-regulation of IL-6, IL-1β, and TNF-α cytokines in lipopolysaccharide-induced bone loss in vivo [54]. Concomitantly, researchers have correlated the anti-inflammatory potentials of taxifolin with its different biological potential, including the amelioration of LPS-mediated inflammation in vitro/in silico study [15] and its anti-diabetic effects in streptozotocin-induced diabetic rats [55]. The possible underlying mechanism of the gastroprotective effects of taxifolin is hypothesized in Fig. 11.

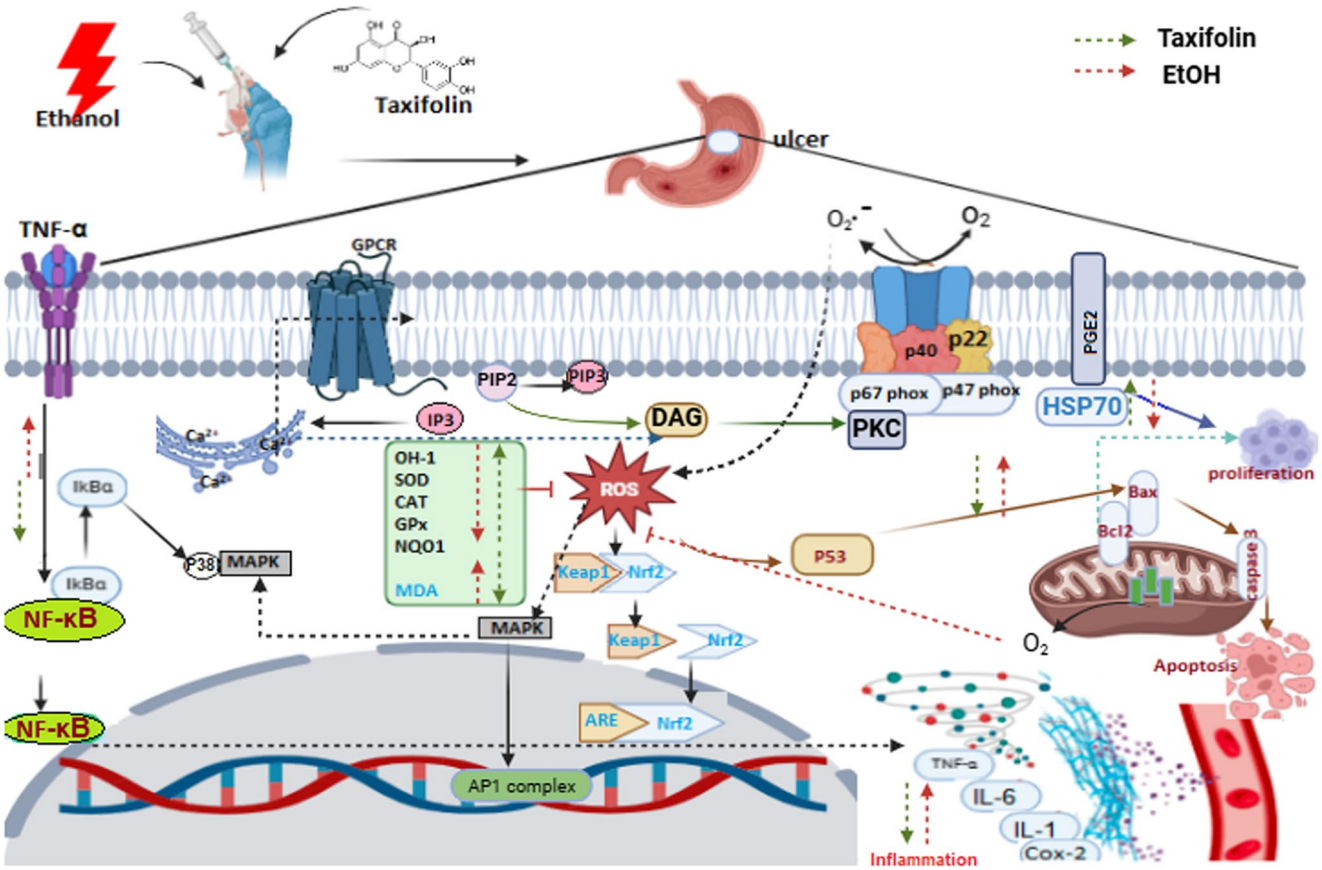

Fig. 11 The possible underlying mechanism of the gastroprotective actions of taxifolin. DAG, diacylglycerol; PIP2,3, phosphatidylinositol 4,5-bisphosphate; NQO1, quinone oxidoreductase 1. Taxifolin ameliorated ethanol-mediated gastric injury through down-regulation of pathways associated with oxidative stress, inflammation, and cellular apoptosis. The figure was created with BioRender.com

Conclusion

The study aimed to unveil the gastroprotective potential of taxifolin as well as its acute toxicity effects in an animal model. Taxifolin supplementation did not cause any toxic damage, pathophysiological changes, or mortality in rats ingested with up to 500 mg/kg taxifolin. Pretreatment with taxifolin (30 and 60 mg/kg) showed a noticeable attenuation of ethanol-mediated mucosal injury, evidenced by the improvement of gastric defense factors (increasing mucus/mucopolysaccharides secretion), endogenous antioxidants (increasing SOD, CAT, and GPx and lowering MDA), as well as down-regulated pro-inflammatory mediators (IL-6 and TNF-α). Moreover, the anti-apoptotic effects of taxifolin were confirmed by down-regulated Bax and up-regulated HSP 70 proteins, which improved cellular integrity and promoted cell proliferation. Due to the present limitations (lack of funds and well-equipped facility), future studies (e.g., NF-κB pathway, PCR, or COX-2 regulation) are needed to confirm its anti-ulcer potential in large in vivo/clinical trials before considering it as a viable option for gastroprotective therapeutics.

Abbreviations

SOD	superoxide dismutase
CAT	catalase
Keap-1	kelch-like ECH-associated protein 1
MDA	malondialdehyde
Bax	Bcl-associated X
HSP-70	Heat Shock Protein 70
TNF-α	tumor necrosis factor-α

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Data Availability All relevant data are contained within the article.

Declarations

Competing interests The authors declare no competing interests.

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