



Original Article

Gastroprotective and Antioxidant Effects of Ethanolic Extract of Smilax Zeylanica in Indomethacin-Induced Gastric Ulcer in Albino Wistar Rats

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ABSTRACT

Background: Considering NSAIDs, such as indomethacin, produce oxidative stress, prostaglandin suppression, and cyclooxygenase inhibition, PUD remains a major issue for health care systems worldwide. The development of safer medications is necessary since current medications, are helpful but also carry a risk of negative effects.

Objective: To evaluate the free-radical scavenger and gastroprotective properties of the ethanol-based extract of Smilax zeylanica leaves in an albino Wistar rat model of gastric ulcer caused by indomethacin.

Methods: Male Wistar rats of adult age were divided into five groups, including control, ulcer control, standard drug (omeprazole, 20 mg/kg), and two groups receiving ethanolic extract of Smilax zeylanica leaves (100 and 200 mg/kg) for 14 days. The ulcer index, preventive index, levels of SOD, NO, GSH, MDA and histamine were evaluated, and histopathological analysis was performed.

Results: Histamine levels, oxidative damage biomarker levels, and ulcer severity have all significantly increased after using indomethacin. By raising the concentration of NO and GSH, lowering the concentration of MDA and histamine in a dose-dependent way, and boosting the protective index, the pretreatment of Smilax zeylanica extract was shown to have a substantial impact on both the ulcer index and the ulcer count. By demonstrating that a dosage of 200 mg/kg had effects comparable to those of omeprazole, microscopic investigations validated the extract's protective efficacy.

Conclusion: The ethanol extract of Smilax zeylanica exhibits a remarkable gastroprotective activity, as well as its antioxidant properties, indicating its possible use as the natural product for treating peptic ulcer diseases caused by NSAIDs.

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Introduction

Millions of individuals worldwide are affected with peptic ulcer disease, which is still severe medical condition. The worldwide Burden of Disease Study

reports that while age-adjusted prevalence and mortality rates declined, the worldwide prevalence rate of PUD rose from over six million cases during 1990 to over eight million in 2019 [1-4]. This situation illustrates that PUD still has an important clinical and economic impact

in developing countries with limited access to healthcare facilities.

NSAIDs, which are commonly used to treat pain and inflammation, are important risk factors for ulcerogenesis. The main NSAID indomethacin damages the stomach by inhibiting COX enzymes, which stops prostaglandin formation and compromises the gastric mucosa's protective qualities. Additionally, NSAIDs cause stomach hypermotility, increased gastric mucosal permeability, an increase in polymorphonuclear neutrophil infiltration, and the production of active oxygen, all of which result in oxidative stress and gastric mucosal death [5-8]. The combination of these processes explains the high rate of NSAID-induced gastrointestinal diseases in clinical practice and animal studies.

At present, the treatment of PUD mainly incorporates the use of PPIs and H2RAs. Though both classes of drugs are helpful for suppressing gastric acid production, they come with their limitations. PPIs have been associated with multiple negative effects such as osteoporosis, renal damage, micronutrient deficiency, and a higher chance of bacterial infection, while H2RAs can cause the occurrence of tachyphylaxis, gynecomastia, and concerns related to contamination [9-14]. These issues prompt the need for safer and organic alternatives that would be able to perform gastroprotection without side effects and drawbacks.

Medicinal plants have been shown to be significant in gastrointestinal health due to their phytochemical composition and their mechanism. *Smilax zeylanica* L. which is a climbing plant from the family Smilacaceae is prevalent in South and Southeast Asia and has been used in traditional medicine for ailments like rheumatism, syphilis, and gastrointestinal disorders. Phytochemical studies have shown that the plant contains flavonoids, tannins, and many phenolic compounds which are known to have antioxidant and anti-inflammatory properties. The extract from the plant is also shown to have free radical scavenging ability in vitro experiments [15-20].

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Smilax zeylanica is well known for its many pharmacological properties, including anti-inflammatory, antimicrobial, cytoprotective, and immunomodulatory properties, which have also led to its use in phytotherapy [21-24]. This is particularly important in view of the role of oxidative stress, pro-inflammatory mediators, and microorganisms and bacteria such as *Helicobacter pylori* in the pathogenesis of peptic ulcer disease [25-26]. The benefit of using natural antioxidants in the treatment of peptic ulcer disease and their influence on restoring the action of antioxidant enzymes like SOD, catalase, and glutathione peroxidase is well documented [27-35].

Several author studies confirmed that plant-derived substances possessing pharmacological potential in the treatment of peptic ulcers, such as flavonoids, tannins, and saponins, display gastroprotective properties by improving mucus secretion, stabilizing cell membranes, and scavenging reactive oxygen species [36-41]. Moreover, the fact that plant-derived compounds show a beneficial synergistic effect makes it possible to affect several mechanisms of action, such as inhibition of prostaglandin synthesis, regulation of nitric oxide level, and downregulation of pro-inflammatory cytokines [42-44].

Based on these properties of *Smilax zeylanica*, the present study came into existence with the aim of evaluating the anti-ulcer effect of ethanol extracted leaves of the plant against indomethacin-induced gastric injury in albino Wistar rats. The reason for this study is due to the belief that the antioxidant and cytoprotective activities of the plant will help in reducing the oxidative damage and mucosal injury caused by NSAIDs.

Literature Gap

While a number of studies have pointed to the roles of oxidative stress and inflammatory mediators in NSAID-related gastric damage, present treatment methods, which use PPIs and H2RAs, remain limited due to side effects and inferior mucosal protection [45-47]. At the same time, studies in medicinal plant research pointed to evidence of antioxidant and cytoprotective effects, based on the molecules of flavonoids, tannins, and saponins with anti-inflammatory and free radical scavenging activity [48-54]. At the same time, despite the use of *Smilax zeylanica* in traditional medicine for gastrointestinal disorders, there are still no systematic studies focusing on its gastroprotective properties, and reports are mostly limited to in vitro experimental designs regarding antioxidant and cytotoxic activities [21,55]. This means that studies in animals are required to show whether ethanolic extracts of *Smilax zeylanica* have been able to

maintain the integrity of the mucosa, restore the oxidative stress markers, and offer protection comparable to that of other anti-ulcer drugs.

Materials and Methods

Animals

Adult Wistar male rats weighing 150 to 180 grams were taken from the institutional animal facility and kept under regulated environmental conditions (temperature of $25 \pm 2^\circ\text{C}$, humidity 50%–60%, and a photoperiod of 12 hours of light and dark) for 14 days before being used for the experiments [56]. All the experiments were performed after receiving permission from the Institutional Animal Ethics Committee (IAEC/04/18/2026) and in accordance with the CCSEA guidelines.

Plant Material and Extraction

Fresh leaves from the plant, *Smilax Zeylanica*, were acquired and botanically identified by the botanist. Following collection, the leaves were shade-dried and then shredded and then subjected to Soxhlet extraction using 50% ethanol for 72 hours. After the extraction, the concentrate was subjected to rotary evaporation using a rotary evaporator at temperatures between $40\text{--}45^\circ\text{C}$, to yield a semi-solid mass after evaporation. The resulting residue was stored at 4°C until it was used for preparing the dosing suspension at concentrations of 100mg/mL and 200mg/mL. Ethanolic extraction was selected because it gives a lot of phytoconstituents like flavonoids, saponins, and tannins that are known to have antioxidant and cytoprotective properties [57,58].

Experimental Design

The animals were divided randomly into five groups ($n = 6$) where Group I acted as the normal control group which was given normal saline (10 mL/kg). Group II acted as the ulcer control and the rats were given indomethacin (20 mg/kg) after fasting. Group III received standard treatment as pre-treatment with omeprazole (20 mg/kg) for 14 consecutive days. Groups IV and V received an ethanolic extract of *Smilax zeylanica* at doses of 100 mg/kg and 200 mg/kg (p.o.), respectively, and for the same period. After 15 days, all the groups except the control group were treated with indomethacin (20 mg/kg). After three hours of treatment, the rats were sacrificed under light induction anaesthesia and the stomach tissues were collected for evaluation [59-62].

Assessment of Ulcer Index and Preventive Index

The stomachs were opened along the greater curvature, rinsed with cold saline, and examined under a

magnifying lens (10 $\times$). Ulcer incidence and severity were recorded, and the ulcer index was calculated following the method of Szabo and Hollander (1989). The preventive index was determined by comparing ulcer scores of treated groups with those of the ulcer control [63,64].

Biochemical Estimations

At the end of the study, blood samples were collected from the retrobulbar sinus under light urethane anaesthesia using a fine capillary tube. Approximately 1–2 mL of blood was drawn into heparinized tubes and centrifuged at 3,000 rpm for 10 minutes at 4°C to separate plasma. After blood collection, animals were sacrificed, and stomach tissues were excised, washed in cold saline, and homogenized in phosphate-buffered saline (PBS). The homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C , and the supernatants were used for biochemical assays [65,66].

Nitric Oxide (NO) Estimation

Nitric oxide (NO) levels were estimated indirectly by measuring nitrite, a stable metabolite, using the Griess reagent method. Briefly, 100 μL of gastric mucosal homogenate was mixed with an equal volume of Griess reagent (1% sulphanilamide and 0.1% naphthylethylenediamine dihydrochloride in 2.5% phosphoric acid), incubated for 10 minutes at room temperature, and absorbance was read at 540 nm. Sodium nitrite standards were used to construct a calibration curve, and results were expressed as μmol nitrite per gram of tissue [67].

Reduced Glutathione (GSH) Estimation

Reduced glutathione (GSH) was quantified using Ellman's method. A 0.5 mL aliquot of gastric homogenate was combined with 2 mL of 0.3 M phosphate buffer (pH 8.4) and 0.5 mL of Ellman's reagent (DTNB). After 10 minutes of incubation at room temperature, absorbance was measured at 412 nm. Values were calculated against a standard curve prepared with glutathione and expressed as μmol GSH per gram of tissue [68].

Malondialdehyde (MDA) Estimation

Malondialdehyde (MDA), a marker of lipid peroxidation, was determined using the Thio barbituric acid reactive substances (TBARS) assay. Gastric homogenate (0.2 mL) was mixed with 0.2 mL of 8.1% sodium dodecyl sulphate, 1.5 mL of 20% acetic acid (pH 3.5), and 1.5 mL of 0.8% Thio barbituric acid. The mixture was heated at 95°C for 60 minutes, cooled, and centrifuged at 10,000 rpm for 10 minutes. Absorbance

of the supernatant was measured at 532 nm, and MDA concentration was calculated using a standard curve prepared with 1, 1, 3, 3-tetramethoxypropane, expressed as nmol MDA per gram of tissue [69].

Histamine Estimation

Histamine content in gastric mucosa was measured using an EIA kit. The tissue samples were treated with antibodies specific to histamine, followed by enzyme-conjugated secondary antibody with the same specificity. The last step was addition of the substrate, which started the reaction that changed the colour in relation to the amount of histamine. The absorbance value was found at 650 nm, while histamine levels were found using the standard curve based on the known content of histamine in the samples [70].

Results

Macroscopic and Ulcer Parameters

Indomethacin use resulted in severe stomach ulcers in the glandular part of the stomach, signified by many bleeding wounds and mucosal wear. Pre-administration of the extract from *Smilax zeylanica* had a significant

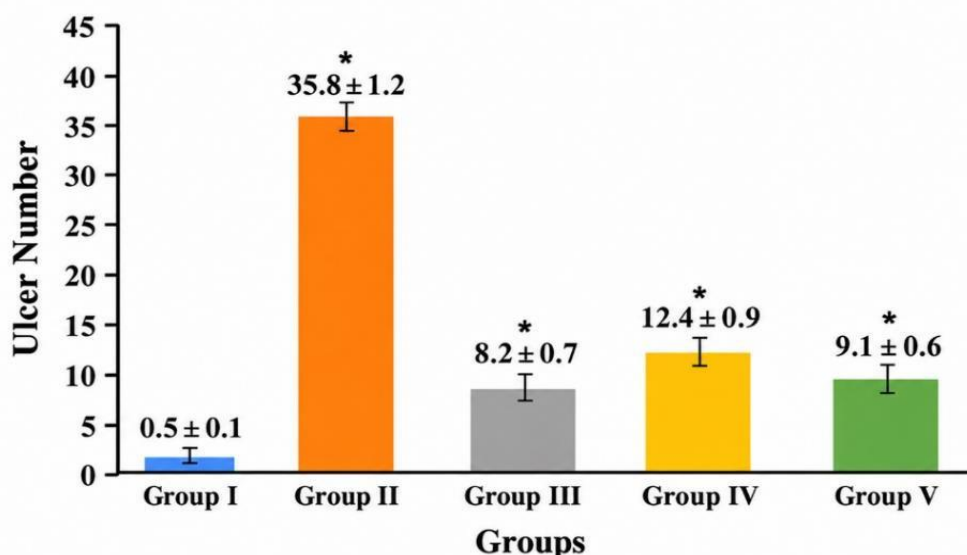
impact on the total number of ulcers and ultramodern severity in a dose-response manner. The group of 100 mg/kg had moderate protection while in a group of 200 mg/kg the preservation of the mucosa was virtually total. In quantitative terms, number of ulcers and ulcer index increased in the ulcer control group compared to the normal rats. Both doses of *Smilax zeylanica* led to reduction in these parameters, the higher dose being more effective. Preventive index was also increased significantly in the groups treated confirming gastroprotective properties of the extract (**Fig. 1**).

Superoxide Dismutase Activity

SOD activity increased significantly in indomethacin-induced ulcers compared to the normal control group, suggesting oxidative panic. The initial treatment with *Smilax zeylanica* extract led to a dose-dependent return of SOD activity to normal. Compared to the 100 mg/kg dose, the 200 mg/kg dose showed a larger reduction in SOD activity, nearing levels similar to those of the omeprazole-treated control group. This implies that the extract is able to counteract this oxidative imbalance by restoring the enzymatic antioxidant defence (**Table 1**).

Table 1: Impact of *Smilax zeylanica* on SOD activity in indomethacin-induced gastric ulcer in albino Wistar rats.

Group	Treatment	Superoxide Dismutase (U/ml)
Group I	Normal control (Saline)	1.2
Group II	Indomethacin 20 mg/kg	15.4
Group III	Omeprazole 20 mg/kg	9.8
Group IV	<i>S. zeylanica</i> extract 100 mg/kg	12.1
Group V	<i>S. zeylanica</i> extract 200 mg/kg	19.6



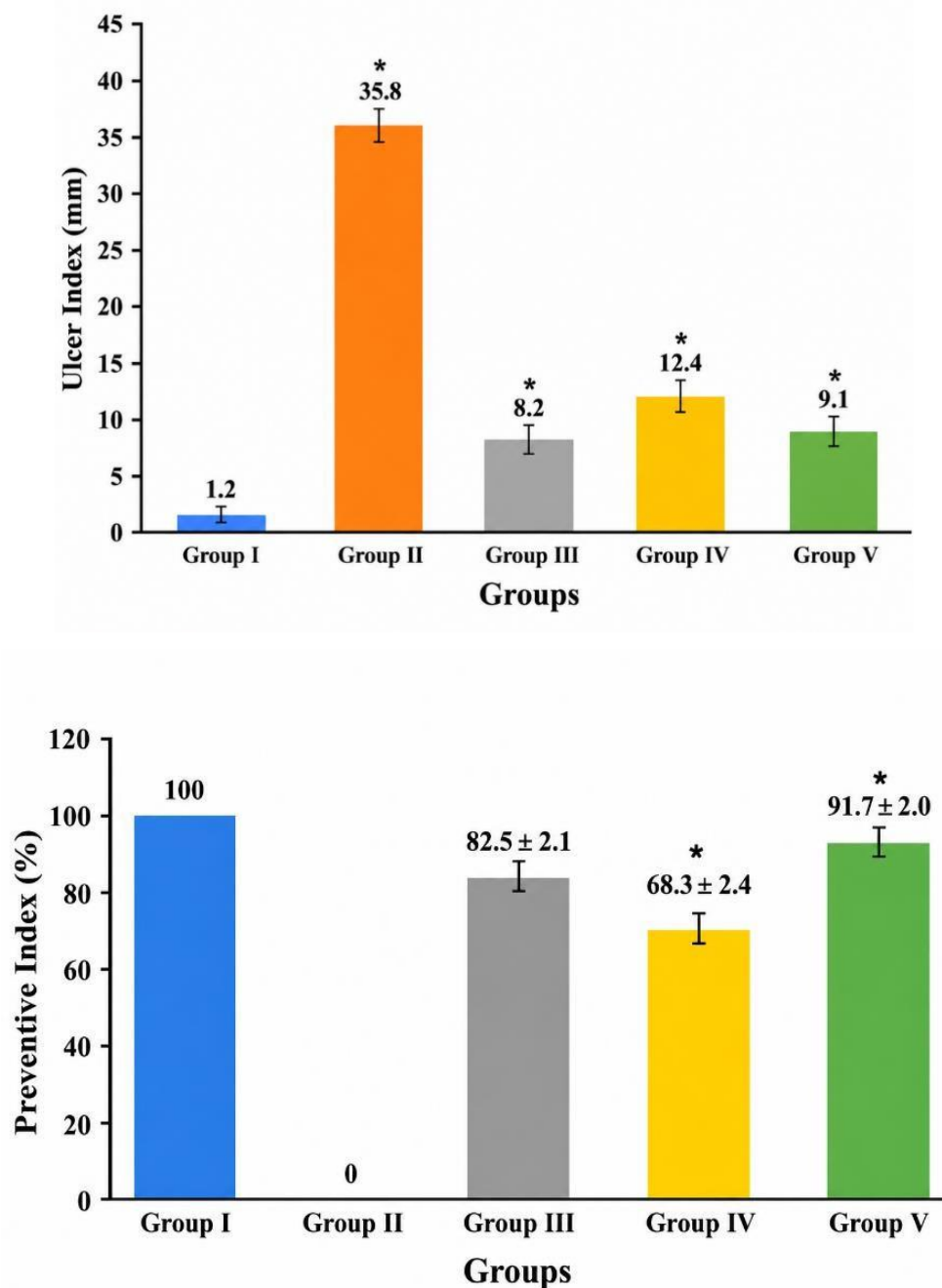


Figure 1: *Smilax zeylanica* ethanolic extract's impact on indomethacin-induced stomach ulcer metrics in albino Wistar rats: (A) ulcer number, (B) ulcer index, and (C) preventive index.

Biochemical Markers of Oxidative Stress and Inflammation

Indomethacin had a significant effect on the increase of MDA and histamine levels as well as the decrease of NO and GSH amounts in the stomach mucosa. The

Smilax zeylanica extract was shown to have the ability to normalize these indicators in a dose-related manner, while the extract in the amount of 200 mg/kg normalized the values of biochemistry similar to that of omeprazole, showing its effectiveness as an antioxidant and an anti-inflammatory agent (**Table 2**).

Table 2: Influence of *Smilax zeylanica* on gastric mucosal biochemical markers in indomethacin-induced gastric ulcer in Wistar rats.

Parameters group	GSH ($\mu\text{mol/g}$ tissue)	% of control ulcer	NO ($\mu\text{mol/g}$ tissue)	% of control ulcer	MDA (nmol/g tissue)	% of control ulcer	Histamine (ng/g tissue)	% of control ulcer
Group I: Normal control (saline)	5.68 ± 0.36	433.59	154.28 ± 3.56	417.22	11.08 ± 0.51	10.87	1.01 ± 0.053	10.48
Group II: Ulcer control (indomethacin 20 mg/kg, i.p.)	$1.31 \pm 0.056^*$	100	$36.96 \pm 2.04^*$	100	$102.43 \pm 5.21^*$	100	$9.42 \pm 0.47^*$	100
Group III: Omeprazole (20 mg/kg, p.o.)	$2.12 \pm 0.073^*$	161.83	$67.51 \pm 2.74^*$	182.72	$55.25 \pm 3.56^*$	53.94	$2.58 \pm 0.23^*$	27.39
Group IV: <i>Smilax zeylanica</i> extract (100 mg/kg, p.o.)	$1.71 \pm 0.038^*$	130.53	$45.21 \pm 2.07^*$	122.38	$76.83 \pm 2.47^*$	75.02	$4.55 \pm 0.35^*$	48.30
Group V: <i>Smilax zeylanica</i> extract (200 mg/kg, p.o.)	$2.38 \pm 0.041^*$	181.68	$61.34 \pm 2.18^*$	165.95	$60.22 \pm 2.86^*$	58.79	$3.40 \pm 0.29^*$	36.10

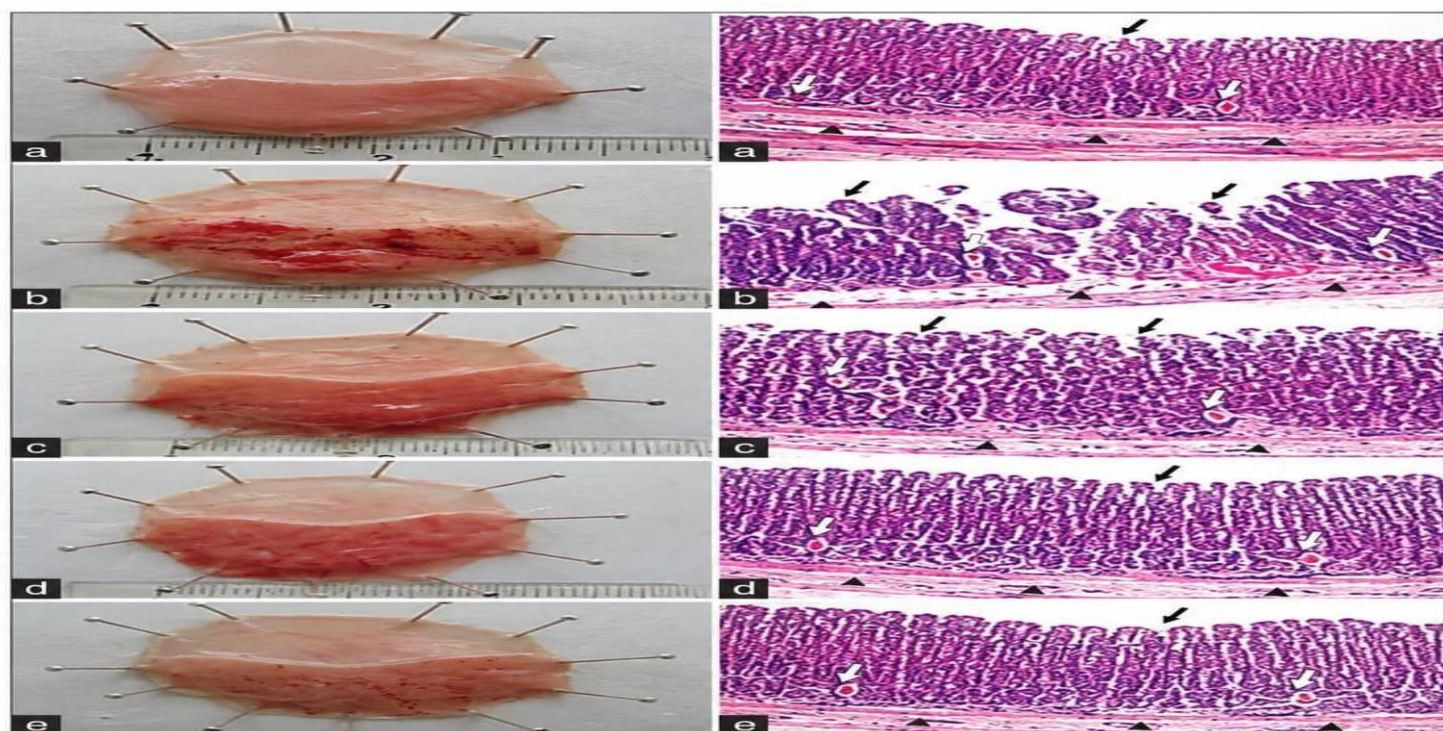


Figure 2: Histopathological examination of *Smilax zeylanica* on stomach tissues in indomethacin-induced gastric ulcer in Wistar rats.

The ulcer control group (b) shows severe epithelial damage and inflammation due to indomethacin-induced oxidative stress. Omeprazole (c) and *Smilax zeylanica*-treated groups (d, e) exhibit progressive mucosal recovery, with the 200 mg/kg extract (e) showing almost complete restoration of normal histoarchitecture. The normal control (a) maintains intact mucosa, serving as baseline reference.

Conclusion

The study presented shows that the ethanolic extract from the leaves of *Smilax zeylanica* possesses impressive properties concerning gastroprotection and antioxidation against gastric ulceration caused by indomethacin in treatment in albino Wistar rats. Pre-treatment with the extract reduced the indices of ulcers and ulceration, improved the preventive index and restored the squamous levels of nitric oxide and glutathione, and reduced the values of malondialdehyde and histamine. Histopathological results confirmed that the mucosal integrity was preserved with the respective dose of 200 mg/kg having the same degree of protection as omeprazole. The findings emphasize that *Smilax zeylanica* can be used as a nature remedy against gastric ulcers having both cytoprotective and antioxidant effects as well as fewer side effects than standard medications. The results give a good reason for continuing with the further research.

Funding

None.

Conflict of Interest

None.

Author Contributions

All the authors contributed to the study.

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