

Anti-ulcer potential of the Ethanolic Extract of leaves of *Solanum Violaceum* in Wistar albino rats

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Abstract

The study evaluates the possible gastroprotective of Ethanolic extract of leaves of *Solanum violaceum* [EESV] using two different gastric ulcer models. Gastric ulcers in Wistar albino rats were induced by Ethanol (1ml/200gm) and Indomethacin (30mg/kg) induced ulcer. Various parameters like Ulcer index, Acid volume, Total acidity, p^H, Total protein, Glutathione, Catalase and Superoxide dismutase were evaluated. Omeprazole (20mg/kg) and Ranitidine (60mg/kg) were used as the standard drug. *Solanum violaceum* was administered at two dose levels, 250 mg/kg and 500 mg/kg body weight. Statistical analysis was done by ANOVA followed by Dunnet's Multiple Comparison test, P<0.05 was considered statistically significant. Oral administration of Omeprazole and *Solanum violaceum* at 250 and 500 mg/kg produced significant (p<0.01 & p<0.001) decrease in ulcer index, total acidity, acid volume, severity of ulceration in the ethanol-induced ulcer model as well protection against Indomethacin induced ulcerations compared to control. It also shows significant (P<0.001) increase p^H and antioxidant parameters like Glutathione, Total protein, Catalase, Superoxide dismutase compared to control in both methods. Furthermore, histopathological studies have shown that pretreatment with the ethanolic extract of leaves of *Solanum violaceum* reduces (92%) ethanol and indomethacin-induced hemorrhagic necrosis in rats.

Keywords: *Solanum violaceum*, Ethanol, Indomethacin, Omeprazole, Ranitidine.

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1. Introduction

Solanum violaceum belongs to the family Solanaceae and which is used as folkloric for the medicinal treatment. It is a tropical herb and branched shrub, naturally grown on roadsides, follow land and forest edges throughout the country. The whole plant or different parts of the plant has been used in various diseases e.g.; asthma, dry cough, flatulence, helminthiasis, dysuria, toothache, pruritus, asthma, indigestion, ulcer and diabetes, etc[1].

Ulcers, a common gastrointestinal “disorder”, is an open sore or lesions of the skin or mucous membrane characterized by sloughing of inflamed dead tissue[2,3].

Peptic ulcer is a chronic, heterogeneous recurrent disease [4] of multifactorial etiology. It is denoted by the

disorder of mucosal integrity of the oesophagus, stomach, or duodenum [5].

Peptic ulcer disease (PUD), which comprises gastric and duodenal ulcers, is the most prevalent gastrointestinal disorder and requires a well-targeted therapeutic strategy. The pathophysiology of PUD involves an imbalance between aggressive (acid, pepsin and *Helicobacter pylori*) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide and growth factors [6,7].

People who take NSAIDs, smoke, cigarettes, excessive intake of alcohol, or use cocaine, high intake of spicy foods or coffee, food poisoning, presence of

Helicobacter pylori or secondary due to pathological conditions such as Zollinger-Ellison syndrome are at increased risk of developing PUD. The U.S peptic ulcer disease affects between 3.5 and 7.5 million people with approximately one-half million new cases diagnosed every year. Despite improvements in therapy widespread use of NSAIDs and low dose aspirin, the economic burden of PUD remains a significant issue. Due to the effectiveness as well as the potential side effects of modern drugs, patients are often led to explore complementary or alternative medicines such as herb and medicinal botanicals in particular[8,9].

No documented reports are available so far on the evaluation of the leaves of this plant for possible gastroprotective activities. Therefore, to justify the traditional claim, the objective of the study to assess gastroprotective and antioxidant effect of ethanolic extract of leaves of *Solanum violaceum* in Wistar albino rats.

2. Materials and methods

This study was performed in Postgraduate studies in the Department of Pharmacology, Bharathi College of Pharmacy, Bharathinagara, Mandya, and Karnataka, India.

2.1 Collection and preparation of plant extract:

The fresh leaves of *Solanum violaceum* were collected from local area of Bharathinagara, Mandya District, and Karnataka. The leaves were identified and authenticated by Botanist Dr. Gurukar Mathews, Head of the Department, Bharathi College of Post-Graduation and Research Centre, Bharathinagara, Maddur (Tq), Mandya (Dist), Karnataka state.

After collection, the fresh leaves were separated and washed thoroughly with running tap water, cut into small pieces and shade dried. The dried leaves of *Solanum violaceum* were then pulverized separately into coarse powder by a mechanical grinder. The extraction of 100g of powdered leaves of *Solanum violaceum* was carried out by hot extraction process by using Soxhlet apparatus with ethanol was used as solvent for 72 hours at 50°C. The distillates were collected and distilled separately to yield the concentrated extracts. These extracts dried using rotary vacuum evaporator to get crude extract. It turned into a sticky concentrate of greenish-black colour (yield= 11.3%). It was kept in a desiccator over anhydrous calcium chloride until used. The phytochemical test was carried out according to the standard procedure indicates the presence of alkaloids, carbohydrates, flavonoids, tannins, etc [10]

2.2 Animals

The experiments were performed on healthy Wistar albino rats of either sex (180-200 g) were procured from the Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India The animals were housed in

separate group (six rats in each cage) in clean sanitized polypropylene cages. They feed with free access to standard pellet diet and water *ad libitum*. The animals were maintained under day and night 12:12 hr cycles and with the maintenance of room temperature at 25±2°C. All experimental procedures were performed in accordance with the Institutional Animal Ethics Committee (IAEC) constituted as per the direction of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Permission and approval for animal studies were obtained from the Institutional Animal Ethics Committee (IAEC) of Bharathi College of Pharmacy, Mandya. Bharathi Education Trust. (Approval no.BCP/IAEC/PCOL/02/2019).

2.3 Acute Oral Toxicity Study

An acute toxicity study was carried out to check the toxic effects for ethanolic extract of Leaves of *Solanum violaceum* on female mice (This is because literature surveys of conventional LD₅₀ tests show that generally females were slightly more sensitive and single sex of animals is used to reduce variability and means of minimizing the number of animals used). The study was performed as per Organization for Economic Cooperation and Development (OECD) and acute oral toxicity was done by up and down procedure (OECD guideline-425)[11].

2.4 Ethanol-induced gastric ulceration [12,13]

The Wistar albino rats were divided into five groups (n=6). The rats fasted for 24 hrs before the start of the experiment. Group I served as a Normal control, which received distilled water [0.025% carboxy methyl cellulose (CMC)], group II served as disease control which received ethanol at the dose of 1ml/200g, whereas animals in group III received the reference drug Omeprazole (20mg/kg p.o). Rats in group IV and V received the EESV at 250 and 500mg/kg p.o. doses. The animals were administered with ethanol at the dose of 1 ml/200g orally after the last dose of EESV and reference drug. After 1h, the animals were sacrificed under ether anesthesia followed by cervical dislocation and the stomach was excised along the greater curvature and examined grossly. Scoring of the ulcer is made according to the severity of ulcer as follows: 0= Normal stomach, 0.5= Red coloration, 1= Spot ulcer, 1.5=Hemorrhagic streak, 2= Deep ulcer, 3= Perforation.

2.5 Indomethacin-induced gastric ulcer in rats [12,14]

The Wistar albino rats were fasted for 18 h and deprived of water for 12h. They will be divided into five groups (n=6). The animals in group I served as a Normal control which received [0.025% distilled water carboxy methyl cellulose (CMC)]. Group II served as disease control which received indomethacin (30 mg/kg p.o), whereas animals in group III received the reference drug Ranitidine (60mg/kg p.o.). Animals in groups IV and V

were administered with EESV at the 250 and 500mg/kg b.w. p.o. doses, 1h before the Indomethacin (30mg/kg p.o) administration after the last dose of EESV and reference drug. After 6 hrs animals were sacrificed under ether anesthesia followed by cervical dislocation and stomach was excised along the greater curvature, and examined grossly. Scoring of the ulcer is made according to the severity of ulcer as follows: 0= Normal stomach, 0.5= Red coloration, 1= Spot ulcer, 1.5=Hemorrhagic streak, 2= Deep ulcer, 3= Perforation.

2.6 Determination of Ulcer Index

After scoring Ulcer according to their severity, the mean ulcer score for each animal was expressed as ulcer index. Ulcer index was measured by using the following formula:

$$\text{Ulcer Index (UI)} = \text{UN} + \text{US} + \text{UP} \times 10^{-1}$$

Where UI = Ulcer Index.

UN = Average number of ulcers per animal.

US = Average number of severity scores.

UP = Percentage of animals with ulcers.

% Inhibition of Ulceration

Percentage inhibition of ulceration was calculated as below:

$$\% \text{ Inhibition of Ulceration} = \frac{(\text{Ulcer index Control} - \text{Ulcer index Test}) \times 100}{\text{Ulcer index Control}}$$

2.7 Methods for Biochemical estimation like acid volume, pH, total acidity and total protein in gastric juice

2.7.1 Collection of gastric juice

Gastric juice was collected from ethanol and indomethacin-induced gastric ulcer in rats mentioned earlier. The collected gastric juice was centrifuged for 1000 rpm for 10 minutes and the volume of gastric juice was measured. This gastric juice was used for biochemical estimations as follows.

2.7.2 Determination of Total Acidity

The stomachs were removed and the content was subjected to centrifugation at 3000 rpm for 10 min. The total acidity of the gastric secretion was determined by titration with 0.01 N NaOH and phenolphthalein as indicator.

2.7.3 Determination of pH

pH of the gastric secretion was recorded with calibrated pH meter.

2.7.4 Total protein [15]

This method is based on the formation of colored complex of proteins on addition of Folin Ciocalteu reagent that can be measured at 610nm using Bovine serum albumin as the standard. To 0.1ml of gastric juice, 0.9 ml of 90% alcohol was added and centrifuged at 3000 rpm for 10 minutes. The supernatant was discarded and precipitated was dissolved in 1 ml of 0.1N NaOH. From the above

solution 0.05 ml was taken in a test tube, to which 4 ml of freshly prepared alkaline mixture was added and allowed to stand for 10 minutes. To the above reaction mixture 0.4 ml of phenol reagent was added allowed to stand for further 10 minutes for the reaction to complete. The blank absorbance was measured at 610 nm using distilled water as 0.1 ml in steps 2 & 3. The amount of protein was calculated using the formula:

$$\text{Protein} = \frac{\text{O.D of sample} \times \text{concentration of standard (mg/ml)}}{\text{O.D of standard}}$$

2.7.5 Biochemical estimation:

Animals were sacrificed the stomach tissue is washed thoroughly and rinsed with ice. Then tissue was gently blotted between the folds of a filter paper and weighed in an analytical balance. 10% homogenate was prepared in 0.05M phosphate buffer (pH 7) using a homogenizer at 4°C. The homogenate was centrifuged at 3000rpm for 10min. The supernatant was used for the estimation of GSH, Catalase and SOD.

2.7.5.1 Glutathione:

The sulfhydryl group of glutathione reacts with DTNB (5, 5'-dithiobis-2-nitro benzoic acid) which produces a yellow coloured 5-thio-2-nitrobenzoic acid (TNB) compound. Measurement of the absorbance of TNB at 412 nm provides an accurate estimation of glutathione in a sample. Briefly, 0.5 ml of homogenate was mixed with 0.1 ml of 25% TCA to precipitate proteins and centrifuged at 4000 rpm for 5 min. The 0.3 ml of the supernatant was mixed with 0.5 ml of 0.1M phosphate buffer (pH 7.4) and 0.2 ml of 10 mM DTNB. This mixture was incubated for 10 min and the absorbance was measured at 412 nm against appropriate blanks. The glutathione content was calculated by using extension coefficient $13.6 \times 10^4 \text{M}^{-1} \text{cm}^{-1}$. The values are expressed as units /mg protein. 1 unit of enzyme is the amount necessary to decompose 1 μmole of NADPH per minute.[16]

$$\text{GSH} = \frac{\Delta \text{Abs at } 412 \text{nm}}{13.6 \times 10^{-3} \times \text{total protein} \times \text{total volume}}$$

2.7.5.2 Catalase:

The catalase activity was assayed by H_2O_2 decomposition method In the incubation mixture 0.1ml of sample, 1.9 ml of 0.5 M phosphate buffer and 1ml of 11mM of H_2O_2 solution was added to initiate the reaction, and the absorption was measured immediately at 0, 1, 2 mins at 240 nm. Control/blank was 0.1ml sample and 2.9ml of phosphate buffer. Activity of catalase was calculated using the mmoles (mM) extinction coefficient $40 \text{cm}^{-1} \cdot \mu\text{moles}$ of H_2O_2 decomposed/min/mg protein.[17,18]

$$\text{Catalase (U/mgprotein)} = \frac{\Delta A / \text{min} \times 1000 \times 3}{40 \times \text{mg protein in sample}}$$

2.7.5.3 Super oxide dismutase:

0.01ml of the tissue homogenate was mixed with 0.2 ml of 0.1M EDTA (containing 0.0015% NaCN), 0.1ml of 1.5mM NBT and phosphate buffer (67mM, pH7.8) In a total volume of 2.6ml. After adding 0.05ml of riboflavin, the absorbance of the Solution was measured against distilled water at 560nm using UV spectrophotometer.

All the tubes were illuminated uniformly for 15min and absorbance of the blue colour Formed was measured again. Percent of inhibition was calculated after comparing. Absorbance of sample with the absorbance of control (the tube containing no enzyme activity). The volume of the sample required to scavenge 50% of the generated superoxide an ion was considered as a unit of enzyme activity and expressed in U/mg Protein. The % inhibition of the sample is calculated using the following formula. [19,20]

$$\% \text{ inhibition} = \frac{\text{Absorbance of test} - \text{Absorbance of blank}}{\text{Absorbance of test}} \times 100$$

2.8 Histopathological Examination:

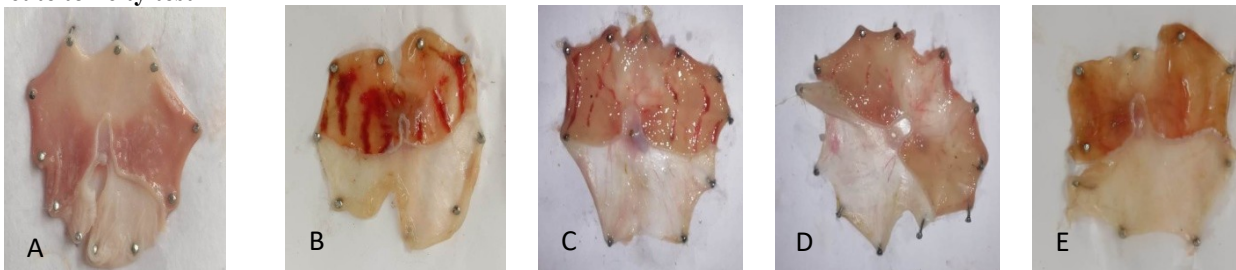
Histopathological section was done by fixing stomach tissues in 10% formalin for 24hr. The formalin fixed specimens was embedded in paraffin and section (3-5 μ m) and stained with hematoxylin and eosin dye. The slides were then examination using light microscopy.

2.9 Statistic analysis

All the values were expressed as mean \pm SEM. Statistical comparisons were performed by one way ANOVA followed by Dunnett compare all columns versus control column using Graph Pad Prism version 5.0. *P<0.05, **P<0.01, ***P<0.001 was considered as significant compared to disease control.

3. Result

3.1 Acute toxicity test



(A) Normal control rat; (B) Disease control rat (Ethanol); (C) EESV Low dose; (D) EESV high dose; (E) Standard drug (Omeprazole 20 mg/kg)

From this study, it was found that both the extracts of *Solanum violaceum* were safe at 2000 mg/kg with no mortality. (1/8th and 1/4th) of this dose i.e. 250 mg/kg and 500 mg/kg were used in the anti-ulcer study.

Fig 1: Photographs showing effect on Ethanol-induced gastric ulcers

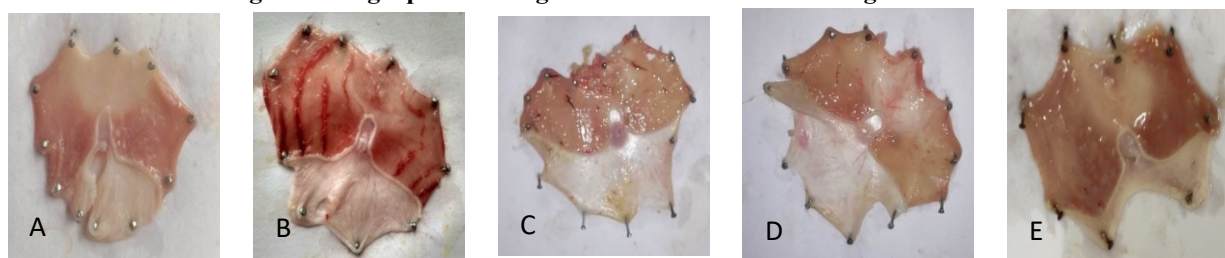


Fig 2: Photographs showing effect on Indomethacin induced gastric ulcers

(A) Normal control rat; (B) Disease control rat (Indomethacin); (C) EESV Low dose; (D) EESV high dose; (E) Standard drug (Ranitidine 60 mg/kg)

3.2 Ethanol-induced gastric ulceration

Table 1: Effect of ethanolic extract of leaves of *Solanum violaceum* in ethanol-induced acute gastric ulcers rats

Treatment	Dose (mg/kg p.o)	Ulcer index	% protection
Disease control	80% 1ml/200g	11.05 \pm 0.112	-
EESV low dose	250	5.9416 \pm 0.068	46.46 \pm 0.538
EESV high dose	500	4.525 \pm 0.058	59.02 \pm 0.917
Omeprazole	20	2.683 \pm 0.395	75.92 \pm 3.496

Each group consists of six animals, Data is presented in mean \pm SEM. Here Significant at P < 0.05*, 0.01** and 0.001***, as compared to Negative control group. Ns= no significant EESV=Ethanolic Extract of *Solanum violaceum*.

Table 1 shows the ulcer index and percent protection from ulcer in the ethanol-induced ulcer model. The extract of the plant showed significant protection from ulcers (59.02%) at a dose of 500mg/kg ($p < 0.01$) compared with the controls. The standard drug, Omeprazole, also showed a significant protective effect against ulcers (75.92%) at a dose of 20 mg/kg when compared with the control groups ($p < 0.01$). The formulation also significantly reduced the volume and total acidity and increased the pH of the gastric fluid, providing its anti-ulcer activity. As compared to normal rats, ethanol induced gastric ulceration

was found to reduced Glutathione, total protein, SOD and catalase in the ulcerated control group, thus leading to oxidative stress. Administration of ethanolic extract of leaves of *Solanum violaceum*, at the doses of 250 and 500 mg/kg, brought about a significant increase in the activities of antioxidant enzymes namely, SOD and catalase. An increase in the levels of glutathione along with the enhancement total protein was also observed at 500mg/kg of the dose levels of ethanolic extract of leaves of *Solanum violaceum*. (Table 2)

Table 2: Effect of ethanolic extract of leaves of *Solanum violaceum* in ethanol-induced acute gastric ulcers rats

Treatment	Dose (mg/kg p.o)	pH	Acid volume(ml)	Total acidity (mEq/l)	Total protein (mg/ml)	Glutathione (U/mg)	Catalase (U/mg)	SOD (U/mg)
Normal control	Distilled water(0.025% CMC)	5.20±0.21	0.40±0.10	13.67±1.54	0.75±0.0548	1.433±0.182	32.44±3.37	7.741±0.341
Disease control	80% 1ml/200g	3.21±0.22***	5.00±0.48***	37.50±2.24***	0.263±0.0375***	0.231±0.023***	19.28±3.347*	4.578±0.372***
EESV low dose	250	4.35±0.39*	3.08±0.38**	29.00±1.15**	0.465±0.0623*	0.771±0.037*	31.316±3.582*	5.73±0.226*
EESV high dose	500	5.68±0.20***	2.40±0.28***	19.83±2.00***	0.72±0.0673***	0.878±0.034**	43.016±4.575***	6.778±0.256***
Omeprazole	20	5.93±0.25***	1.61±0.24***	13.00±1.59***	0.83±0.0423***	1.317±0.204***	46.866±2.272***	7.653±0.249***

Each group consists of six animals, Data is presented in mean±SEM. Here Significant at $P < 0.05^*$, 0.01^{**} and 0.001^{***} , as compared to Negative control group. Ns= no significant EESV=Ethanolic Extract of *Solanum violaceum*.

3.3 Indomethacin-induced gastric ulcer in rats

The ulcer index and percent protection against ulcers in the Indomethacin induced gastric ulcer in rats model are shown in Table 3. The extract of the plant showed significant protection against ulcer (61.17%) at a dose of 500 mg/kg ($p < 0.01$) when compared with the control animals. The standard drug, ranitidine, also showed significant protective effects against ulcers (78.65%) at a dose of 60mg/kg when compared with the control group ($p < 0.01$). Total acidity and acid volume were also significantly decreased at a dose of 500 mg/kg of the

extract, as shown in Table 4 when compared with the control animals. The pH and total protein were significantly increased when compared with the control groups. Indomethacin administration was found to decrease SOD, Catalase and reduced glutathione in the disease control group when compared to normal rats. Administration of ethanolic extract of leaves of *Solanum violaceum* significantly decrease acid volume and increased the levels of SOD, Catalase, Total protein and glutathione at the dose of 500mg/kg shown in Table 4.

Table 3: Effect of ethanolic extract of leaves of *Solanum violaceum* in indomethacin-induced acute gastric ulcers rats

Treatment	Dose (mg/kg p.o)	Ulcer index	% protection
Disease control	30	11.116±0.1073***	-
EESV low dose	250	5.691±0.0639***	48.78±0.692***
EESV high dose	500	4.3166±0.0934***	61.17±0.614***
Ranitidine	60	2.2716±0.1308***	78.65±1.679***

Each group consists of six animals, Data is presented in mean±SEM. Here Significant at $P < 0.05^*$, 0.01^{**} and 0.001^{***} , as compared to Negative control group. Ns= no significant EESV=Ethanolic Extract of *Solanum violaceum*.

Table 4: Effect of ethanolic extract of leaves of *Solanum violaceum* in indomethacin induced acute gastric ulcers rats

Treatment	Dose (mg/kg p.o)	pH	Acid volume(ml)	Total acidity (mEq/l)	Total protein (mg/ml)	Glutathione (U/mg)	Catalase (U/mg)	SOD (U/mg)
Normal control	Distilled water (0.025% CMC)	5.30±0.25	0.30±0.05	12.17±0.94	0.75±0.0548	1.217±0.142	32.44±3.691	7.65±0.348
Disease control	30	3.65±0.47*	5.58±0.24***	36.83±1.68***	0.263±0.0375***	0.288±0.041***	19.28±3.347*	3.59±0.4306***
EESV low dose	250	5.11±0.44*	4.36±0.35**	28.50±2.33**	0.465±0.0623*	0.778±0.055*	37.76±3.183***	5.116±0.4667*
EESV high dose	500	5.51±0.34**	2.58±0.15***	19.33±1.82***	0.72±0.0673***	0.925±0.024**	47.88±2.534***	5.521±0.417***
Ranitidine	60	6.48±0.17***	2.01±0.14***	12.33±1.25***	0.83±0.0423***	1.317±0.190***	50.416±3.381***	7.26±0.556***

Each group consists of six animals, Data is presented in mean±SEM. Here Significant at $P < 0.05^*$, 0.01^{**} and 0.001^{***} , as compared to Negative control group. Ns= no significant EESV=Ethanolic Extract of *Solanum violaceum*.

4. Discussion

Although in most cases the etiology of ulcer is unknown, it is generally accepted that it results from an imbalance between aggressive factors and the maintenance of the mucosal integrity through the endogenous defense mechanism²¹. To regain the balance, different therapeutic agents including herbal preparations are used to inhibit gastric acid secretion or to boost the mucosal defense mechanism by increasing mucus production.

The present study was undertaken to evaluate the anti-ulcerogenic effect of *Solanum violaceum*, a herbal drug formulation consisting of plants that are mentioned in Indian system of medicine (Ayurveda) for their remedial properties.

The antiulcer effect of *Solanum violaceum* was tested against gastric lesions included by ethanol and indomethacin, the experimental models related to lesion pathogenesis with production of reactive species. *Solanum violaceum* prevented the mucosal lesions induced by ethanol and indomethacin. *Solanum violaceum* was also found to increase the pH and decrease the acid volume.

These effects of *Solanum violaceum* treatment on the parametrs that influence the initiation and induction of

ulceration may be considered as highly desirable property of anti-ulcerogenic agent.

Reactive oxygen species are involved in the pathogenesis of ethanol induced and indomethacin induced [22] gastric mucosal injury *in vivo*. Results in the present study also indicated 'similar alterations in the antioxidant status after ethanol and indomethacin induced ulcers. Preventive antioxidants, such as superoxide dismutase and catalase enzymes are the first line defense against reactive oxygen species. Reduced glutathione is a major low molecular weight scavenger of free radicals in the cytoplasm [23].

Administration of *Solanum violaceum* resulted in a significant increase in the SOD, catalase and glutathione levels as compared to the control animals, which suggests its efficacy in preventing free radical-induced damage.

4.1 Histopathological investigation

The Histopathological investigation of the gastric mucosa (Fig. 3 & 4) of the rats revealed that the ethanol and indomethacin treatment caused hemorrhagic necrosis. Pretreatment with the ethanol extract of leaves of *Solanum violaceum* reduced ethanol and indomethacin induced hemorrhagic necrosis in the rat stomach in both models.

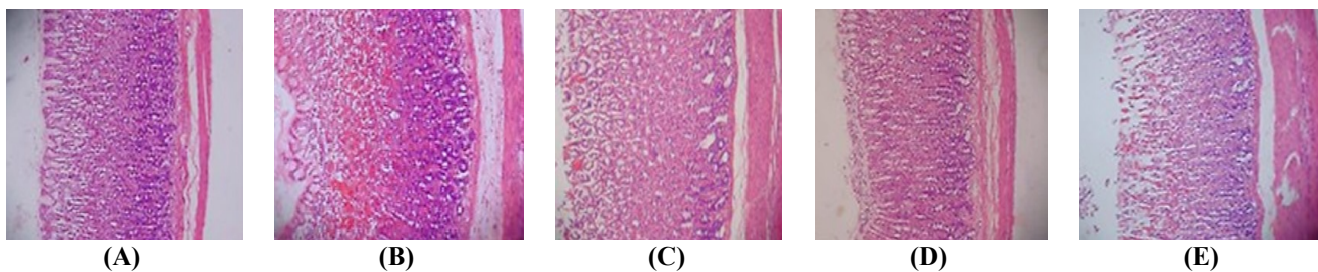


Fig 3: Histopathology of stomach

(A) Normal control group showing its normal appearance. (B) Disease control group treated with 80 %1ml/200gm ethanol. (C) EESV Low dose. (D) EESV high dose (E) Standard (omeprazole 20 mg/kg).

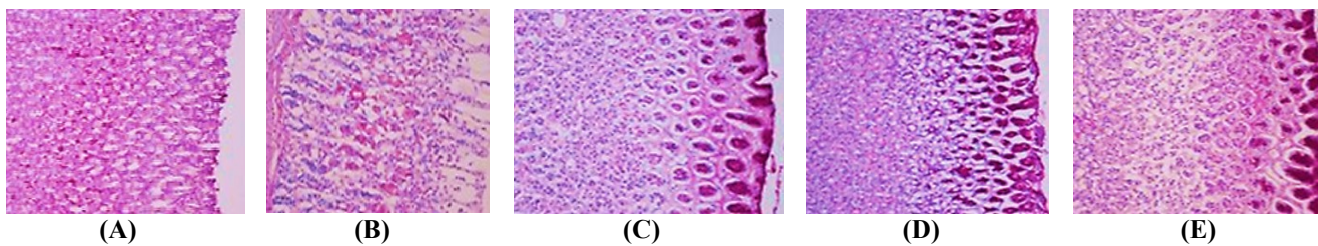


Fig 4: Histopathology of stomach

(A) Normal control group showing its normal appearance. (B) Disease control group treated with Indomethacin 30 mg/kg. (C) EESV Low dose. (D) EESV high dose (E) Standard (Ranitidine 60 mg/kg).

5. Conclusion

The result of our study indicates that the ethanolic extract of leaves of *Solanum violaceum* produces significant cytoprotective effects against ethanol and indomethacin-induced ulcers ($p < 0.01$). Thus, the ethanolic extracts of leaves of *Solanum violaceum* can be used as a source for antiulcer drugs.

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Conflict of interest statement

We declared that we have no conflict of interest.

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