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ANTI - ULCER POTENTIAL OF THE ETHANOLIC EXTRACT OF LEAVESOF *SOLANUM VIOLACEUM*ORTEGA IN WISTAR ALBINO RATS

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Solanum violaceum Ortega, Ethanol, Indomethacin, Omeprazole, Ranitidine.

ABSTRACT

Solanum violaceum Ortega (Solanaceae) is a medicinal plant traditionally used to treat various ailments, including ulcers. In order to establish pharmacological properties of the leaf of *Solanum violaceum*Ortega, studies were performed on antiulcer activity of the plant's ethanol extract.The ethanol extract of leaves of *Solanum violaceum* Ortega (EESV) was prepared in the doses of 250 and 500 mg/kg. Antiulcer activity of EESV was evaluated by ethanol and indomethacin-induced gastric ulcer. Acute toxicity was also carried out.EESV, at the dose of 2000 mg/kg, did not cause any signs of toxicity to rats when given orally. Oral administration of EESV exhibited antiulcer activity ($p < 0.05$) in all models used. However, the dose-dependent activity was observed in the ethanol and indomethacin induced gastric ulcer model. Histological studies supported the observed antiulcer activity of EESV,in ethanol and indomethacin induced ulcer, EESV increased the gastric wall mucus secretion.

INTRODUCTION

Solanum violaceum Ortega 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 diseaseseg; 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 aetiology. 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 *Helicobactor*

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 wide spread 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 gastro protective activities. Therefore, to justify the traditional claim, the objective of the study to assess gastro protective and antioxidant effect of ethanolic extract of leaves of *Solanum violaceum*Ortega in Wistar albino rats.

Materials and methods: This study was performed in Postgraduate studies in Department of Pharmacology, Bharathi college of Pharmacy, Bharathinagara, Mandya, and Karnataka, India.

Collection and preparation of plant extract: The fresh leaves of *Solanum violaceum*Ortega were collected from local area of Bharathinagara, Mandya District, and Karnataka. The leaves were identified and authenticated (no. BCK.Bot.24.6) 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*Ortega was then pulverized separately into coarse powder by a mechanical grinder. The extraction of 100g of powdered leaves of *Solanum violaceum*Ortega were carried out by hot extraction process by using Soxhlet apparatus with ethanol was used as solvent for 72 hours at 50^0C. 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].

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 maintained of room temperature at 25±2ºC. Allexperimental 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 was obtained from the Institutional Animal Ethics Committee (IAEC) of Bharathi college of Pharmacy, Mandya. Bharathi Education Trust. (Approval no. BCP/IAEC/PCOL/02/2019).

Acute Oral Toxicity Study: An acute toxicity study was carried out in order to check the toxic effects for ethanolic extract of Leaves of *Solanum violaceum*Ortega on female mice (This is because literature surveys of conventional LD 50 tests show that generally females were slightly more sensitive and single sex of animals is used in order 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].

1. Ethanol induced gastric ulceration [12,13]: The wistar albino rats were divided into five groups (n=6). The rats were fasted for 24 hrs prior to start of 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 theEESV 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 anaesthesia followed by cervical dislocation and stomach was excised along the greater curvatureand 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=Haemorrhagic streak, 2= Deep ulcer, 3= Perforation.

2. 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 fivegroups (n=6). The animals in group I served as a Normal control which received[0.025% distilled watercarboxy methyl cellulose (CMC)]. Group IIserved as disease control which receivedindomethacin (30 mg/kg p.o), whereas animal in group III received the reference drug Ranitidine (60mg/kg p.o). Animals in group 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 last dose of EESV and reference drug. After 6 hrs animals were sacrificed under ether anesthesia followed by cervical dislocation and stomach wasexcised 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.

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 following formula:

Ulcer Index (UI) = UN + US + UP X 10-1

Where, UI = Ulcer Index.

UN = Average number of ulcers per animal. US = Average number of severity score. UP = Percentage of animals with ulcers. % Inhibition of Ulceration

Percentage inhibition of ulceration was calculated as below: % Inhibition of Ulceration = (Ulcer index Control-Ulcer index Test) ×100/Ulcer index Control.

Methods for Biochemical estimation like acid volume, p^H, total acidity and total protein in gastric juice

Collection of gastric juice: Gastric juice was collected from ethanol and indomethacin induced gastric ulcer in rats mentioned earlier. The collectedgastric 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.

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.

Determination of pH : P^H of the gastric secretion was recorded with calibrated pH meter.

Total protein[15]: This method is based on the formation of coloured complex of proteins on addition of Folin Ciocalteau 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 solution0.05 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 step 2 & 3. The amount of protein

was calculated using the formula: Protein =O.D of sample × concentration of standard (mg/ml) /O.D of standard

Biochemical estimation: Animals were sacrificed the stomach tissue is washed thoroughly and rinsed with ice. Thentissue were 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 4ºC.The homogenate was centrifuged at 3000rpm for 10min. The supernatant was used for the estimation ofGSH,Catalase and SOD.

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 anaccurate estimation of glutathione in a sample. Briefly, 0.5 ml ofhomogenate w a s 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 x 10^4M^-1 cm^-1. The values are expressed as units /mg protein. 1 unit of enzyme is the amount necessary to decompose 1 μmole of NADPH perminute.[16]

GSH= ΔAbs at 412nm/13.6 X 10^{-3} X total protein X total volume

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 sampleand 2.9mlofphosphatebuffer.Activityofcatalasew ascalculatedusingthemmoles (mM) extinction coefficient 40cm-1.μmoles of H_2O_2 decomposed/min/mg protein.[17,18]

Catalase(U/mgprotein)= ΔA/min x1000 x 3/ 40 x mg protein in sample

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 for15min 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 as1unit of enzyme activity and expressed in U/mg Protein.

The % inhibition of the sample is calculated using the followingformula.[19,20]

%inhibition = Absorbance of test - Absorbance of blank X 100/ Absorbance of test

Histopathological Examination: Histopathological section was done by fixing stomach tissues in 10% formalin for24h. The formalin fixed specimens was embedded in paraffin and section (3-5μm)and stained with haematoxylin and eosin dye. The slides were then examination using light microscopy.

STATISTICALANLYSIS: All the values were expressed as mean ± SEM. Statistical comparisons were performed by one way ANOVA followed by Dunnett's 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.

RESULT:

Acute toxicity test: From this study, it was found that both the extracts of *Solanum violaceum*Ortega 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.

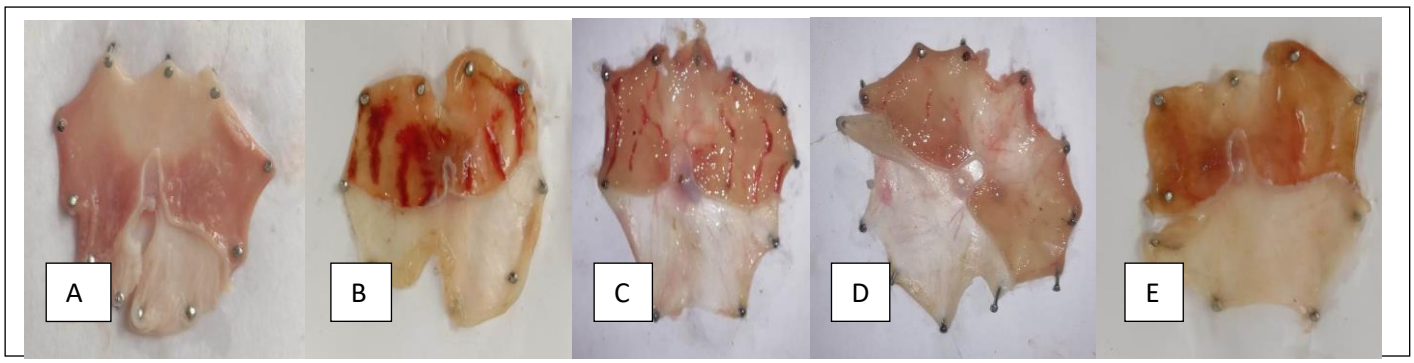

Fig 1: Photographs showing effect on Ethanol induced gastric ulcers

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

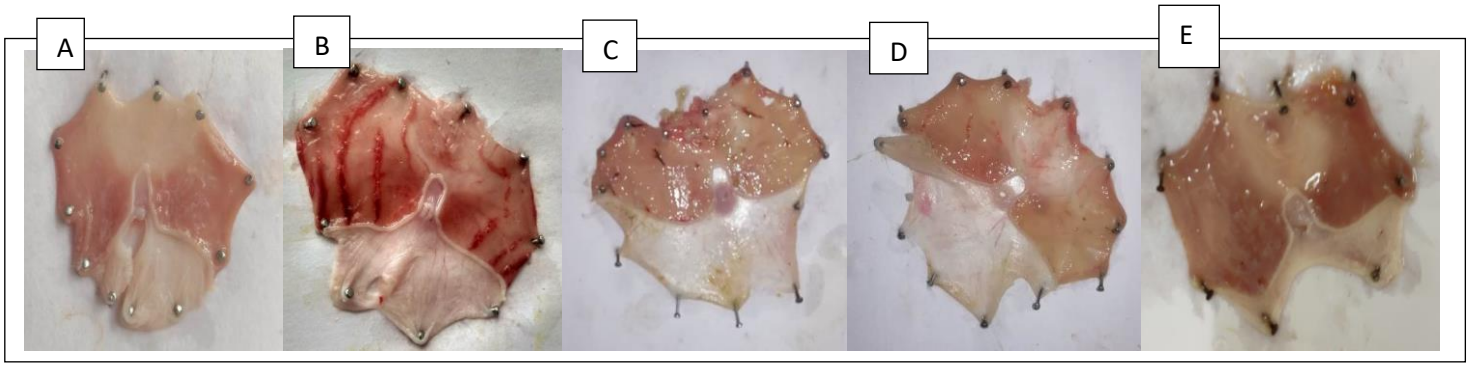

Fig 2: Photographs showing effect on Indomethacin induced gastric ulcers

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

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

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

Each group consist 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* Ortega.

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

Treatment	Dose (mg/kg p.o)	P^H	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 consist 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* Ortega.

Table 3: Effect of ethanolic extract of leaves of *Solanum violaceum*Ortega 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 consist 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*Ortega.

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

Treatment	Dose (mg/kg p.o)	P^H	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 consist 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* Ortega.

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 p^H 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*Ortega, 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 the dose levels of ethanolic extract of leaves of *Solanum violaceum* Ortega (Table 2)

Indomethacin-induced gastric ulcer in rats: The ulcer index and percent protection against ulcers in the Indomethacin induce 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 p^H 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.

DISCUSSION:

Although in most of the 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 defence mechanism[21]. To regain the balance, different therapeutic agents including herbal preparations are used to inhibit the gastric acid secretion or to boost the mucosal defence mechanism by increasing mucus production. The present study was undertaken to evaluate the anti-ulcerogenic effect of *Solanum violaceum*Ortega, an herbal drug formulation consisting plants that are mentioned in Indian system of medicine (Ayurveda) for their remedial properties. The antiulcer effect of *Solanum violaceum*Ortega was tested against gastric lesions included by ethanol and indomethacin, the experimental models related to lesion pathogenesis with production of reactive species. *Solanum violaceum*Ortega prevented the mucosal lesions induced by ethanol and indomethacin. *Solanum violaceum*Ortega was also found to increase the $p^H$and decrease the acid volume. These effects of *Solanum violaceum*Ortega treatment on the parameters 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 defence against reactive oxygen species. Reduced glutathione is a major low molecular weight scavenger of free radicals in the cytoplasm[23]. Administration of *Solanum violaceum*Ortega 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.

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

CONCLUSION:

Preliminary phytochemical evaluation of EESV revealed the presence of tannins, carbohydrate, sterols, flavonoids, glycosides, alkaloids and triterpenes in both the extracts. Acute oral toxicity studies recorded no mortality with either of the extracts even at the dose level of 2,000 mg/kg body weight. Anti-ulcer activity have been confirmed that EESV extracts in experimental animals, with different ulcer models. In ulcer, both the extracts at low and high doses produced a significant anti-ulcer activities ($P < 0.05$*, 0.01** and 0.001***). Phytochemical constituents such as tannins, flavonoids and triterpenes are already reported for their anti-ulcer activity and both the extracts contained the above mentioned constituents. Thus, this finding confirms the traditional use of *Solanum violaceum* Ortega in the treatment of gastric Ulcer. Further studies are required to confirm the exact mechanism underlying for the ulcer healing and protecting property of the extract.

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Authors Contribution Statement:
Dr. Palaksha MN: Conceived of the presented idea, verified the analytical methods, contributed to the interpretation of the results, encouraged to investigate and supervised the findings of this work. Supervised the research Designed experiments and co-wrote the paper. Miss. Mamatha BS: Conceived of the presented idea, developed the theory and performed the computations, carried out the experiment, developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Designed and directed the project and also wrote the paper. Miss. Nandini KN: Contributed to sample preparation, contributed to the interpretation of the results, Performed transporter experiments, and performed the measurements. Miss. Lekhana AR: Performed transporter experiments, contributed to sample preparation, performed the measurements, contributed to the interpretation ofthe results. Dr. Palaksha M.N, Miss. Mamatha BS, Miss Nandini KN and Lekhana AR are all contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript.

Conflict of interest statement: We declared that, we have no conflict of interest.

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