Research Article

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GASTROPROTECTIVE EFFECT OF *VETIVERIA ZEZANIOIDES* IN EXPERIMENTAL ANIMALS

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ABSTRACT

The aim of the study was to evaluate gastroprotective effect of *Vetiveria zizanioides* in experimental animals. The ethanolic extract of roots of *Vetiveria zizanioides* (VZ) was screened for gastroprotective activity by using Aspirin+ pylorus ligation induced peptic ulcers in rats in which ulcer index, gastric wall mucus, antioxidant enzyme level like SOD, GSH, Catalase, & LPO in stomach were determined. It was found that animals belonging to VZ group reduced the ulcer index, increased mucus content as well as restored the antioxidant parameters in stomach and increased pH of gastric juice, decreased gastric volume and total acidity significantly as compared to ulcerated group of animals. VZ showed significant gastroprotective activity which may be due to increase in mucus secretion as well as free radicals scavenging activity in stomach.

Key words: Gastroprotective, *Vetiveria zizanioides,* Aspirin+ pylorus ligation, ulcer index.

INTRODUCTION

Peptic ulcer is one of the most prevailing gastrointestinal disorders worldwide occurring due to increased acid secretion and acid related disorders caused by stress, NSAID's and H. Pylori infection [1,2]. The modern approach to control gastric ulceration is to prevent excess gastric acid secretion, to provide gastro protection, to block apoptosis and to increase erosion healing by stimulating proliferation of epithelial cells for [3]. Drugs used to control peptic ulcer are the anti-secretary drugs like proton pump inhibitors (omeprazole, lansoprazole) and H_2-receptor blockers like ranitidine, famotidine. [4, 5]

Remedies from Ayurvedic or traditional medicinal system can be the alternative approach in recent days to overcome the adverse effects of drugs like NSAID's. The use of medicinal plants like Aloe, *Terminalia Chebula, Ginseng, Capsicum* [6,7], *Rubia cordifolia* [8], *Capparis zeylanica* [9], *Argyreia speciosa*[10], *Jasminum grandiflorum* [11] , *Heliotropium indicum*[12] as drug therapy to treat ulcers has proved to be clinically effective and less relatively toxic than the existing drugs and also reduces the offensive factors serving as a tool in the prevention of peptic ulcer.

Traditionally, *Vetiveria zizanioides* belonging to family Poacea is a tufted perennial occurring in large clumps arising from a much branched "rootstock". The root decoction of *Vetiveria zezanioides* has been used as cooling in high fever, inflammation, sexual diseases. Traditionally roots of *Vetiveria zizanioides* used for ulcers [13,14,15]. *Vetiveria zizanioides* have the tremendous medicinal potential as it possesses antioxidant[16], anti-microbial[17], sedative & hypnotic [18], free radical scavenging activity [19]. It has been also reported that flavonoids, terpenoids and tannins shown to possesses antiulcer activity[20].

Taking into consideration of traditional claims, reported pharmacological activities and chemical constituents, the present study was planned to evaluate gastroprotective activity of *Vetiveria zizanioides* roots Aspirin+ pylorus ligation induced peptic ulcers in rat.

MATERIAL AND METHODS

Procurement and Authentication of plant

The root powder of *Vetiveria zizanioides* was purchased and authenticated from Endeavour exports, Nisha Bhavan, Marthandam, Tamil Nadu, India.

Extraction

Dried and coarsely root powder of *Vetiveria zizanioides* (500g) was defatted with petroleum ether and the marc remaining was extracted successively by 95% ethanol in Soxhlet extractor. Solvent was evaporated in rotary evaporator under reduced pressure to produce ethanolic extract of *Vetiveria zizanioides* roots (VZ) [11].

Phytochemical evaluation

Phytochemical evaluation of ethanolic extract of *Vetiveria zizanioides* roots for terpenoid, saponin, flavonoid, glycosides, tannins and protein was performed[21].

Procurement of animals

The Wistar rats of either sex were purchased from National Toxicology Centre, Pune. They were housed in group of five under standard laboratory conditions of temperature (25 ± 2°C) and 12/12 hr light/dark cycle. Animals had free access to standard pellet diet (Amrut laboratory animal feed, Sangali-Maharashtra.) and water *ad libitum*. The distribution of animals in the groups, the sequence of trials and the treatment allotted to each group were randomized, throughout the experiment. Laboratory animal handling and experimental procedures were performed in accordance with the guidelines of CPCSEA and experimental protocol was approved by Institutional Animal Ethics Committee (198/99/CPCSEA) with protocol number DYPIPSR/IAEC/12-13/P-06.

Acute toxicity study

Albino rats of either sex weighing 200-250 gm were used in the study. Acute oral toxicity study was performed as per Organization for Economic Co-operation and Development (OECD)-423 guidelines[22]. The animals were divided in 4 groups (n=3) and were fasted overnight prior to drug administration. Following the period of fasting, the animals were weighed and the test substance was administered. The animals were administered with test extract at the dose of 5, 50, 300 and 2000 mg/kg body weight orally. The animals were observed for 5 min every 30 min till 2 h and then at 4, 8 and 24 h after treatment for any behavioural changes/mortality. They were further observed daily for 7 days for mortality. No mortality up to 7 days after treatment was observed with the ethanolic extract of *Vetiveria zizanioides* roots at the dose of 2000 mg/kg, p.o. and therefore they were found safe up to dose of 2000 mg/kg. Thus the animal doses were selected on the basis of acute oral toxicity study.

Aspirin+ pylorus ligation induced peptic ulcers in rat

The rats were divided into six groups (n=6). Group I served as normal control and received 1% w/v sodium carboxy methyl cellulose alone. Group II served as ulcerated control and received ethanol (1ml/200g, p. o.). Group III served as standard and received Ranitidine (50mg/kg, p.o.) daily for 7 days. Groups IV, V and VI served as test and received ethanolic extract of *Vetiveria zizanioides* 100, 200 and 400 mg/kg, p. o. respectively, daily for 7 days. From days 5th to 7th day group II to VI received aspirin (200 mg/kg, p.o) 2 hrs after the administration of respective drug treatment. On 8th day, animals were anaesthetized with ketamine hydrochloride (50 mg/kg i.p) and the abdomen of each animal was opened by small midline incision below the xiphoid process and pylorus portion of stomach was slightly lifted out and ligated. Precaution was taken to avoid traction to the pylorus or damage to its blood supply .The stomach was placed carefully in the abdomen and the wound was suture by interrupted sutures. Four hours after pylorus ligation the rats were sacrificed and the stomach was removed. The gastric content was collected and centrifuged. The volume, pH, and total acidity of gastric fluid were determined. The stomach was then incised along the greater curvature and observed for ulcers. The number of ulcers was counted using a magnifying glass and the diameter of the ulcers was measured using a vernier caliper. [23]

Ulcer score and percentage protection

The number of ulcers was counted using a magnifying glass and the diameter of the ulcers was measured using a vernier caliper[24]. Ulcer index was determined. The ulcer index was expressed as sum of scores given to ulcerative lesions as described below

Score 1: Maximal diameter of 1 mm
Score 2: Maximal diameter of 1-2 mm
Score 3: Maximal diameter of 2-3 mm
Score 4: Maximal diameter of 3-4 mm
Score 5: Maximal diameter of 4-5 mm
Score 10: An ulcer over 5 mm in diameter
Score 25: A perforated ulcer

$$\% \text{ protection} = \text{UI control} - \text{UI treated} \times 100 / \text{UI control}$$

UI= Ulcer Index

Determination of mucin content

After the collection of gastric juice, the glandular portion was excised and opened down along the lesser curvature. The reverted stomach was soaked for 2 h in 0.1% alcian blue (0.16M sucrose buffered with 0.05M sodium acetate). The uncomplexed dye was removed by two successive washes of 15 and 45 min in 0.25M sucrose solution. The dye complexed with mucus was diluted by immersion in 10 ml of 0.5M magnesium chloride for 2 h. The resulting blue solution was shaken briefly with equal volume of diethyl ether and the optical density of aqueous phase was measured at 605 nm. The mucin content of the sample was determined from the standard curve obtained with different concentrations of mucin[25].

Determination of Gastric Acidity

The junctions between the stomach and the esophagus and the duodenum and pylorus were secured before the stomach was isolated. Then 3 ml of distilled water was introduced into the stomach and the organ was carefully shaken. The gastric juice was then collected and centrifuged for 10 min at 3000 rpm. The supernatant was the taken and diluted 10 times. Following this, a few drops of phenolphthalein was added to the solution. Titration was done using 0.01 M NaOH solution until the color of the test solution changed to light pink, indicating pH 7.0. The volume of sodium hydroxide (NaOH) needed for titration was used in the calculation to derive the hydrogen ion concentration[26]. The total acidity is expressed as mequiv/l using the following formula:

$$n \times 0.01 \times 40 \times 1000$$

Where, n = volume of NaOH quantified, 40 is the molecular weight of NaOH, 0.01 is normality of NaOH and 1000 is the factor represented in litre.

Estimation of pepsin

Aliquots of 20 µl of the gastric content were incubated with 500 µl of albumin solution (5 mg/ml in 0.06 N hydrochloric acid) at 370C for 10 min. The reaction was stopped with 200 µl of 10% trichloroacetic acid and the samples were centrifuged at 1500 g for 20 min. The supernatant was alkalinized with 2.5 ml of 0.55 M sodium carbonate and 400 µl of 1.0 N folin's reagent was added to the tubes, which were incubated for 30 min at room temperature. The absorbance of the samples was determined by spectrophotometry at 660 nm. The concentration of pepsin is determined by a standard curve.[27]

Volume and pH of gastric juice

The gastric content of each stomach obtained from the pylorus ligation induced ulcers was drained into a centrifuge tube after an incision with a fine pair of scissors. After the centrifugation of gastric content at 2500 rpm for 20 min at 40C, the volume of the supernatant (ml) and pH value were measured. The volume was expressed as ml/100g/4hr. [23]

Evaluation of antioxidant enzymes

The stomach was weighed and then further processed for antioxidant enzymes, in which the stomach was homogenised in chilled Tris buffer (10 mM pH 7.4) at concentration of 10% (w/v). The homogenate were centrifuged at 10,000 x at 0^0c for 20 min using Remi C-24 high speed cooling centrifuge. The clear supernatant was used for the assay of lipid peroxidation (MDA content) [28], Superoxide dismutase (SOD) [29], Catalase (CAT) [30] and reduced glutathione (GSH) [31].

Statistical Analysis

The values expressed as mean ± SEM from 6 animals. The result were subjected to statistical analysis by using one way ANOVA followed by Dunnett's test to verify the significant difference if any among the groups. P<0.05* and P<0.01** were considered significant.

RESULTS

Phytochemical evaluation: The yield after the ethanolic extraction was found 7.4 %w/w. In phytochemical evaluation VZ showed the presence of terpenoids, saponins, flavonoids, glycosides, tannins and proteins was found to be absent.

Selection of Dose: Dose of the ethanolic extract of *Vetiveria zizanioides* was selected based on acute oral toxicity study (423). VZ was found to be safe up to the dose level 2000mg/kg. There was no behavioural abnormality and zero mortality was recorded till 48 h post treatment with no signs of acute toxicity. Therefore $1/10^{th}$ of the dose 2000mg/kg of VZ was selected i.e., 200mg/kg as middle dose in rats. The dose regime for VZ in rats was 100, 200, 400 (mg/kg. p. o.)

Effect of VZ on ulcer index, percentage protection

In aspirin + pylorus ligation induced peptic ulcer method, aspirin has induced ulcerative condition in rats. Ulcerated control group showed significant (p< 0.01) increase in ulcer index as compared to normal control group. (Figure 1)

Ranitidine treated groups showed significant (p< 0.01) decrease in ulcer index as compared to ulcerated control. Ranitidine offered 92.40 % protection in aspirin + pylorus ligation induced peptic ulcers. (Graph 1 & 2)

Animals treated with the VZ at the dose of 100mg/kg (p< 0.05), 200 and 400 mg/kg (p< 0.01) showed significant decrease in ulcer index as compared to ulcerated control and offered 65.18%, 79.74% and 88.60% ulcer protection respectively.

Group-I (NC):-Sodium carboxy methyl cellulose (1%, 10ml/kg p. o.);**Group-II (UC):-**Sodium carboxy methyl cellulose (1%, 10ml/kg p. o.) + Aspirin (200mg/kg, p.o.); **Group- III (Standard):-**Ranitidine (50mg/kg) + Aspirin (200mg/kg, p.o.; **Group-IV (VZ 100):-** The ethanolic extract of *Vetiveria zizanioides* roots (100mg/ kg,p. o.) + Aspirin (200mg/kg, p.o.); **Group-V (VZ200):-** The ethanolic extract of *Vetiveria zizanioides* roots (200mg/ kg, p.o.)+ Aspirin (200mg/kg, p.o.); **Group-VI (VZ 400):-**The ethanolic extract of *Vetiveria zizanioides* roots (400mg/ kg, p.o.)+ Aspirin (200mg/kg, p.o.)

Effect of VZ on gastric volume, pH and total acidity

Ulcerated control group showed significant (p< 0.01) increase in gastric volume, total acidity and decrease in pH as compared to normal control group.

Ranitidine treated group showed significant (p< 0.01) decrease in gastric volume, total acidity and showed significant (p< 0.01) increase in pH as compared to ulcerated control group.

Animals treated with the ethanolic extract of *Vetiveria zezanioides* at the dose of 100mg/kg did not show significant decrease in gastric volume as compared to ulcerated control group but showed significant(p< 0.01) increase in pH and decrease in total acidity as compared to ulcerated control group.

Animals treated with the ethanolic extract of *Vetiveria zezanioides* at the dose of 200 and 400 mg/kg showed significant (p< 0.01) decrease in gastric volume as compared to ulcerated control; while showed significant (p< 0.01) increase in pH and decrease total acidity as compared to ulcerated control. (Table 1)

Effect of VZ on gastric wall mucus and peptic activity

Ulcerated control group showed significant (p< 0.01) increase in peptic activity and decrease in gastric wall mucus in comparison to normal control group.

Ranitidine treated group showed significant (p< 0.01) decrease in peptic activity and increase gastric wall mucus in comparison to ulcerated control.

Animals treated with the ethanolic extract of *Vetiveria zizanioides* at the dose of 100mg/kg did not show significant decrease in peptic activity and increase gastric

wall mucus in comparison to ulcerated control group. The ethanolic extract of *Vetiveria zizanioides* at the dose of 200 and 400 mg/kg showed significant ($p< 0.01$) decrease in peptic activity and increase in gastric wall mucus in comparison to ulcerated control group. (Table 2)

Effect of VZ on Antioxidant enzyme levels in stomach

In stomach, Ulcerated control showed significant ($p< 0.01$) decrease in catalase, glutathione, superoxide dismutase and increase in lipid peroxidation levels as compared to normal control.
Ranitidine treated group showed significant increase ($p< 0.01$) in superoxide dismutase (SOD), glutathione (GSH)and catalase (CAT) level and decrease in lipid peroxidation levels (LPO) as compared to ulcerated control group.
Animals treated VZ at the dose of 100 mg/kg did not restored increased the lipid peroxidation and decreased glutathione level; while significantly ($p< 0.01$) increased in superoxide dismutase and catalase levels as compared to ulcerated control group
Animals treated with VZ at the dose of 200 mg/kg did not restored increased the lipid peroxidation as compared to ulcerated control group; while significantly ($p< 0.01$) increased glutathione, superoxide dismutase and catalase levels as compared to ulcerated control group.
Animals treated with VZ at the dose of 400 mg/kg showed significant ($p< 0.01$) decrease in lipid peroxidation level and a significant ($p< 0.01$) increase glutathione, superoxide dismutase and catalase levels as compared to ulcerated control group. (Table 3)

DISCUSSION

The main reason behind occurrence of gastric ulcer is disruptions of the gastric mucosal defence and repair systems. To restore the balance between these two different therapeutic agents including herbal preparations are useful to inhibit the gastric acid secretion or to improve the mucosal defence mechanism [32].

Aspirin, a nonsteroidal anti-inflammatory drug (NSAID) is one of the drug that induces gastroduodenal ulceration by suppression of prostaglandin synthesis. The prostaglandin stimulates the secretion of bicarbonate and mucus, maintaining mucosal blood flow regulating mucosal cell turnover and repair. Therefore, decrease in prostaglandin results in increase susceptibility to mucosal injury and gastroduodenal ulceration.[33]

By administration of NSAIDs, the free carboxyl group in NSAID forms an electrostatic strong bond with the positively charged zwitter ion present in phospholipid of mucus layer, increases the phospholipid solubility, and neutralizes its surface activity. Therefore, disrupt tissue's the hydrophobic protective lining of the mucus gel layer [34]. In pyloric ligation, accumulation of gastric juice interferes with gastric blood circulation and thus induces ulceration [35]. It has reported that in the pathogenic effects of aspirin plus pylorus-ligated ulcer, there was increase in gastric acid secretion, followed by increase in gastric volume, low pH, increase in free and total acidity which in turn cause damage to gastric mucosa, alteration in permeability, gastric mucus depletion, increase in the pepsin and protein content, and generation of free radical production [36].

In the present study, VZ has offered protection against ulcer by showing decrease the ulcer index in dose dependent manner. VZ has also significantly increased the pH of gastric juice and decreased the gastric volume and total acidity when compared with ulcerated control group. This indicated that VZ contains some active components which reduce the gastric acidity may be due to down regulating the activity of acid secreting cell. Thus contributing in the acid neutralization, may be responsible for the gastroprotective effect in peptic ulcer. The same effect was observed by Sini *et al*, 2011. VZ in the group of rats treated with aspirin showed significant increase gastric wall mucus in comparison to ulcerated control group. This may be due to decrease in leakage of protein content into the gastric juice which further strengthening the mucosal barrier and increase in its resistance to the damaging effect of aspirin.

Generally, chief cells in the stomach releases pepsinogen which is activated by hydrochloric acid (HCl) into pepsin that degrades food proteins into peptides. Ingestion of food stimulates secretion of hormone gastrin and the vagus nerve which in turn triggers the release of both pepsinogen and HCl in stomach. In the present study Aspirin + pylorus ligation induced increase in secretion of gastric acid and pepsin followed by their accumulation in stomach, which further increased peptic activity [8]. It was observed that pre-treatment with VZ reversed the increased peptic activity by decreasing gastric acid and pepsin secretion associated with aspirin which may further contribute in the treatment of peptic ulcers.

Apart from acid and pepsin related factors, reactive oxygen species (ROS) induces damage due to ulcer. SOD converts the reactive superoxide radical to H_2O_2, which if not scavenged by Catalase (CAT) leads to lipid peroxidation by generation of hydroxyl radicals. Hence decrease in SOD and CAT levels may lead to increase in accumulation of these ROS therefore results in increased lipid peroxidation and tissue damage. Glutathione is scavenger of free radicals in the cytoplasm that inhibits free radical mediated lipid peroxidation and thus inhibits formation of ulcer [10]. This free radical scavenging activity is impaired in acute and chronic ulceration in gastric mucosa [11]. In stomach homogenate, VZ significantly restored the level of SOD, GSH, CAT and decreased lipid peroxidation as compared to ulcerated control group.

During Preliminary photochemical evaluation VZ showed presence of terpenoids, saponins, flavonoids, glycosides, tannins and proteins. Flavonoids [36] and glycosides [37] are known to possess anti-ulcer and anti-oxidant activities. Thus, the presence of these phytoconstituents in the ethanolic extract of *Vetiveria zizanioides* may further contribute in in the management of ulcer.

Table 1: Effect of VZ on gastric volume, pH and total acidity

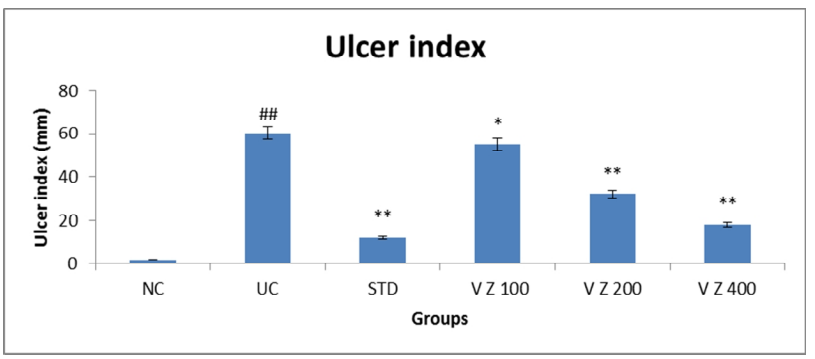
Groups (n= 6)	Gastric Volume (ml/ 100 g)	pH	Total acidity (meq/ ltr /4hr)
Group- I (NC)	2.98 ± 0.021	5.82 ± 0.021	988.12 ±0.021
Group- II (UC)	7± 0.930##	1.12± 0.021##	2300± 57.735##
Group III (Standard)	3.12± 0.009**	6.25± 0.036**	900± 57.735**
Group-IV (VZ 100)	6.10± 0.028	2.18± 0.018**	2000.12± 57.735**
Group- V (VZ 200)	5.18± 0.009**	3.45± 0.028**	1100.11± 0.023**
Group- VI (VZ 400)	3.15± 0.018**	6.1± 0.057**	1012± 2.129**

Table 2: Effect of VZ on gastric wall mucus and peptic activity

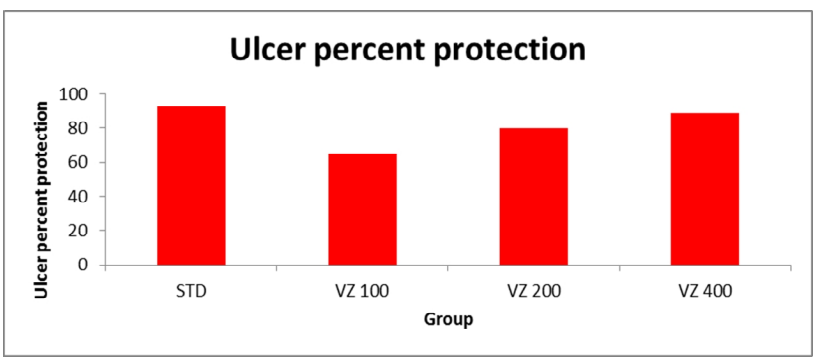
Groups (n=6)	Gastric wall mucus (µg Alcian blue/ gm tissue)	Peptic activity (µmoles Tyrosine/ ml)
Group- I(NC)	82.11 ± 0.020	11.00 ± 0.816
Group- II(UC)	69.12± 0.021##	25.22 ± 0.021##
Group-III(Standard)	80.11± 0.005**	10.12±0.021**
Group- IV(VZ 100)	70.33± 1.745	24.22±0.021
Group- V(VZ 200)	76.11± 0.020**	15.00± 0.216**
Group- VI(VZ 400)	79.82± 0.021**	11.12± 0.021**

Table 3: Effect of VZ on Antioxidant enzyme levels in stomach

Groups (n= 6)	LPO (nmoles MDA/g tissue)	SOD (Units/g tissue)	GSH (µmoles/g tissue)	Catalase (µmolesH_2O_2 consumed / g tissue)
Group- I (NC)	7.74 ± 0.018	10.12±0.021	7.3 ±0.173	12.40 ± 0.115
Group- II (UC)	17.12±2.984##	5.4±0.057##	2.0 ±0.288##	8.14 ± 0.018##
Group- III(Standard)	8.88 ± 0.051**	9.2±0.010**	6.4 ± 0.126**	11.40 ±0.018**
Group- IV (VZ 100)	16.12 ± 0.021	6.2±0.115**	2.2 ± 0.288	9.14 ± 0.018**
Group- V (VZ 200)	13 ± 0.930	7.4±0.115**	4.5 ± 0.288**	10.19 ±0.023**
Group- VI (VZ 400)	9.01 ± 0.023**	8.3±0.006**	5.9 ± 0.301**	10.89 ±0.023**



Graph 1: Effect of VZ on ulcer index



Graph 2: Effect of VZ on ulcer percentage protection

Data was expressed as mean ± SEM, where n=6; statistical analysis done byANOVA followed by Dunnett'stest, where ## = p< 0.05when NC compared with UC; *= p<0.05, **= p<0.01whereGroup VZ 100, 200 & 400 Compared with UC.

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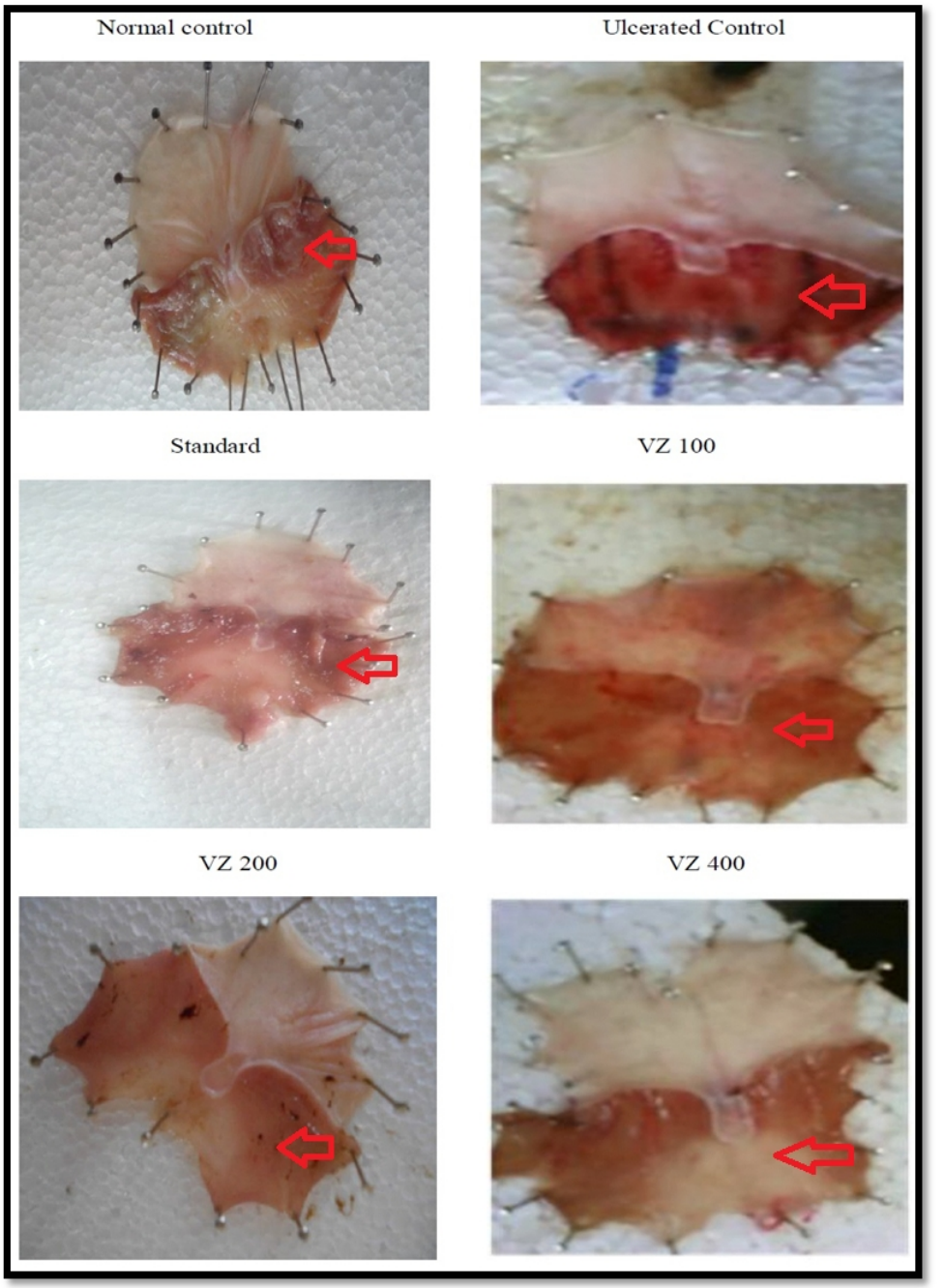

Figure 1: Evaluation of Ulcer Index in stomach of rats (Red arrow indicating Ulcer index)

CONCLUSION

Thus from the results obtained in the present investigation we conclude that the ethanolic extract of *Vetiveria zizanioides* roots may prove to be useful in preventing peptic ulcer owing to its ability to increase mucosal defence mechanism due to gastroprotective and antioxidant effect in stomach. Thus our studies establish a significant antiulcer and cytoprotective effect of VZ. However, further more studies are required to establish its exact mechanism of action and the active principles involved in its antiulcer effect.

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