IJBPAS, December, 2021, 10(12): 4564-4577

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

EVALUATION OF ANTIULCER AND ANTI-OXIDANT ACTIVITY OF *Hylocereus undatus* FRUIT (HAHU) IN WISTAR RATS

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Received 21st Feb. 2021; Revised 20th Mar. 2021; Accepted 19th April. 2021; Available online 1st Dec. 2021

https://doi.org/10.31032/IJBPAS/2021/10.12.5772

ABSTRACT

Peptic ulcer is common illness where there occurs erosion in gastric mucosa further penetrating within the lining of the stomach, duodenum (beginning of the small intestine) or oesophagus. Pathogenesis of ulcer disease includes an imbalance between gastric offensive factors like acid, pepsin secretion, Helicobacter pylori (*H.pylori*), bile salts, ethanol, lipid peroxidation, nitric oxide (NO) and defensive factors like prostaglandins (PG'S), gastric mucus, blood flow, mucosal cell shedding, cellular renovation, glycoproteins, mucin secretion, and antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT) and glutathione levels. Modern management methods of ulcer include inhibition of gastric acid secretion, promoting gastro protection, blocking apoptosis and stimulation of epithelial cell-proliferation for effective healing. In this experimental study wistar rats were assessed of gastric ulcer by 2 methods-ethanol induced and pylorus ligated Shay rat model. Rats were divided into six groups I, II, III, IV, V each of which contains five animals. Group I -Control, Group II - Pylorus ligated/Ethanol induced (negative control), Group III - Pylorus ligated/Ethanol induced and treated with Omeprazole (positive control), Group IV- Pylorus ligated/Ethanol induced and treated with test drug HAHU 200mg, Group V-

Pylorus ligated/Ethanol induced and treated with test drug HAHU 400mg. The treatment protocol was followed for 14 days. Animals were sacrificed on 15th day, gastric mucosal were observed.

Findings suggest that Group III, Group IV, Group V showed significant protection against gastric ulcer induced by Ethanol and pylorus ligation in rat models. They have Antioxidant and Antiulcer activity and can be utilized in near future to provide gastric protection.

Keywords: Antiulcer, Anti-Oxidant, *Hylocereus undatus*

INTRODUCTION

Peptic ulcers are craters or open sores in the lining of the upper gastrointestinal tract (GIT). They include duodenal ulcers (those that are located in the top of the small intestine or duodenum) and gastric ulcers (those found in the stomach). Damage of mucosa which normally protects the oesophagus, stomach and duodenum from gastric acid and pepsin leads to peptic ulcer, **[1]** modern management despite being effective it also causes various side effects. Herbal drugs have been tried for their ulcer protective effect experimentally and clinically and triumphed as a diverse popular therapy emerging as an alternative to the available synthetic drugs **[2]**. Dragon fruit which is rich in vitamins are reported to contain β-amyrin, flavonoids, ascorbic acid, terpenoids and tannins these helps the digestive process, prevents colon cancer and diabetes, neutralize toxic substances such as heavy metal, and helps to reduce cholesterol levels and high blood pressure. The red-fleshed varieties contain lycopene, which is a natural antioxidant known to fight cancer, heart disease, and lower blood pressure. Pitaya fruit is a potential fruit for betacyanin extraction **[3]**. Regularly consuming the dragon fruit can help against asthma and cough. Dragon fruit is rich in fiber, Vitamin C and minerals. Dragon fruit is also rich in Phyto albumins which are highly valued for their antioxidant properties. Antioxidants prevent the formation of cancer-causing free radicals. The flesh and peel of dragon fruits are both rich of polyphenols and are good sources of antioxidants. However, there is no information in the literature about the anti-ulcer effects of the Fruit *Hylocereus undatus*. Therefore, this study aims to investigate the Antiulcer and Antioxidant activities of the Fruit *Hylocereus undatus* against ethanol-induced and pylorus ligated ulcers in rats.

MATERIALS AND METHODS

Extract preparation: Fruit of *Hylocereus undatus* is washed, cut into pieces and then dried under shade. Dried plant material is extracted with Ethanol and water at ratio of 4:1 using Soxhlet technique for 12 hrs. The extracts were collected and allowed it to concentrate to obtain solid mass. After

concentration, the dried extracts were scraped, collected and yield of extracts were calculated. Extract was stored at 4°C until use for further analysis.

Drugs and chemicals: Ethanol 5ml/kg, Omeprazole 20mg/kg, Fruit *Hylocereus undatus* was purchased and extracted for its constituent.

Experimental Animals: Wistar rats of either sex of comparable weight were obtained. Thirty healthy wistar rats for each method were divided into 5 groups consisting of 6 animals in each group. Rats were housed in cages at 25±2˚c and relative humidity 50-55% with 12 hrs light and dark cycle for entire duration of the experiment. Animals were provided standard animal feed and water ad libitum.

Experimental grouping:

Method I-Ethanol Induced Gastric Ulcer Model

Group I was treated with normal saline. Group II was induced with ethanol on 14^{th}day. Group III was treated with Omeprazole (20mg/kg p.o) 30 min prior to induction of gastric ulcer on the 14^{th}day and Group IV and V were treated with HAHU 200mg/kg p.o and HAHU 400mg/kg p.o respectively for 14 days. After fasting for 24hrs, the gastric ulcer was induced to all the groups using ethanol except group I and sacrificed 4 hours treatment **[4, 5]**. The stomach was cut open along with the greater curvature and the contents drained into small beaker, centrifuged and subjected to assess antiulcer activity. The inner surface of stomach was examined for ulcer index. Physical parameters and biochemical investigations were then performed.

Method II-Pylorus ligation induced (Shay rat) gastric ulcer model

Group I was treated with normal saline. Group II was treated with pylorus ligation on 16thday. Group III was treated with pylorus ligation and omeprazole (20mg/kg p.o) administered 30 min prior to the test on 16thday. Group IV and V were treated with (HAHU) 200mg/kg and 400mg/kg p.o respectively for 14days. Group II, III, IV and V were fasted for 24hrs, care being taken to avoid coprophagy. On 16thday pylorus ligation was performed. Rats were anaesthetized with the help of anesthetic ether; the abdomen was opened by a small midline incision below the xiphoid process. Pylorus portion of the stomach was slightly lifted out and ligated, avoiding traction to the pylorus or damage to its blood supply **[5, 7]**. The stomach was replaced carefully and the abdominal wall was closed by interrupted sutures. Rats were sacrificed by an over dose of anesthetic ether after 4 hours of pylorus

ligation. The abdomen was opened, cardiac end of the stomach was dissected out and the contents were drained into a glass tube. The inner surface of stomach was examined for ulcer index. Physical parameters and biochemical investigations were then performed.

Sample Analysis: Gastric mucosa was scraped for evaluation of gastric injury. Gross gastric mucosal lesions were examined using a magnified lens. Gastric lesions severity was measured using 1 to 5 scoring system. The Ulcer index for each group was taken as the mean lesion score of all the rats in that group **[8]**. The percentage ulcer inhibition (% UI) was calculated by the equation **[8]**.

%UI = [(UI of ulcer control − UI of treated) / (UI of ulcer control)] × 100%.

Other parameters like free acidity, total acidity, gastric volume was determined

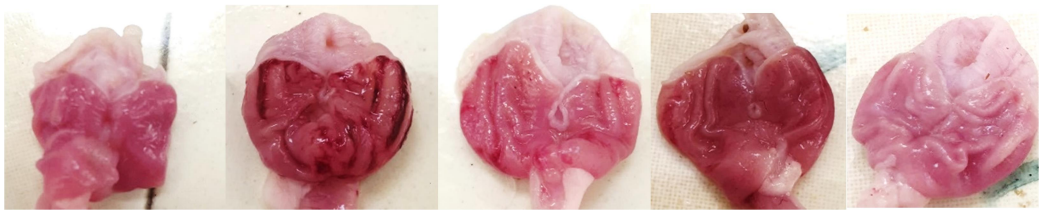
Antioxidant parameters like SOD, Total protein was assessed, also SGOT and SGPT was assessed.

Histopathological analysis: After the study period, the rats were anaesthetized. Stomach was dissected out perfused with chilled saline to remove blood and blood clots and fixed in 10% w/v formalin saline. Paraffin blocks were prepared and tissue was stained with hematoxyline and eosin, and subjected to routine histopathology. The photographs were taken under 100× magnification.

Statistical analysis: Data were expressed as mean± standard error mean (SEM) of six replicated determination and then analyzed by Graph pad prism – Version 8 computer software program. Significance was calculated by one-way ANOVA followed by Dunnett's multiple comparison tests.

RESULTS AND DICUSSIONS

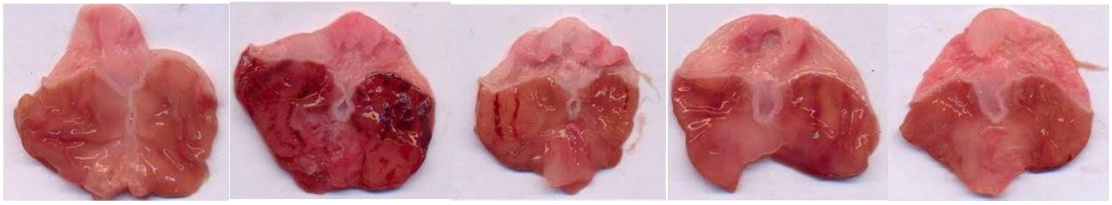
GROSS EVALUATION OF RAT STOMACH IN ETHANOL INDUCED GASTRIC ULCERMODEL (Figure 1)



GROUP I **GROUP II** **GROUP III** **GROUP IV** **GROUP V**

Figure 1: Photographs of rat stomach showing Antiulcer effect of *Hylocereus undatus* on Ethanol induced ulcer models as; Group I –Control, Group II –Ethanol induced, Group III –Ethanol+ Omeprazole, Group IV-Ethanol+ HAHU 200mg, Group V-Ethanol+ HAHU 400mg

GROSS EVALUATION OF RAT STOMACH IN PYLORUS LIGATIONINDUCED GASTRIC ULCERMODEL (Figure 2)



GROUP I GROUP II GROUP III GROUP IV GROUP V

Figure 2: Photographs of rat stomach showing Antiulcer effect of *Hylocereus undatus* on Pylorus ligated ulcer models as; Group I -Control, Group II - Pylorus ligated, Group III - Pylorus ligated + Omeprazole, Group IV- Pylorus ligated + HAHU 200mg, Group V- Pylorus ligated + HAHU 400mg

HISTOPATHOLOGICAL SECTION OF RAT STOMACH IN ETHANOLINDUCED GASTRIC ULCERMODEL

GROUP I shows Normal mucosa with no ulcer is seen. GROUP II shows Disruption, necrosis of gastric epithelium, degradation of mucosal epithelial cells, neutrophilic infiltration in between the gastric glands and submucosal blood vessels revealed congestion. GROUP III shows Multifocal mild erosion, degeneration of gastric glands, very mild neutrophilic and mononuclear cells infiltration in the gastric gland region. GROUP IV shows Multifocal mild erosion, degeneration of gastric glands, very mild neutrophilic and mononuclear cells infiltration in the gastric gland region. GROUP V shows Mild multifocal erosion with comparatively lesser disruption **(Figure 3)**.

HISTOPATHOLOGICAL SECTION OF RAT STOMACH IN PYLORUS LIGATED INDUCED GASTRIC ULCER MODEL

GROUP I shows Normal mucosa with no ulcer. GROUP II shows multifocal erosion, disruption, necrosis of gastric epithelium, degradation of mucosal epithelial cells, neutrophilic infiltration in between the gastric glands and submucosal blood vessels revealed congestion. GROUP III shows multifocal mild erosion, degeneration of gastric glands, very mild neutrophilic and mononuclear cells infiltration in the gastric gland region. GROUP IV shows multifocal mild erosion, disruption, degeneration, necrosis of gastric epithelium, very mild submucosal oedema GROUP V shows Mild multifocal erosion with comparatively lesser disruption **(Table 1, Figure 4, 5)**.

Effect of HAHU on Ethanol induced gastric ulcer model:

There was significant (p<0.0001) increase in ulcer index, % inhibition, Total protein, SGOT, SGPT in Group II, III, IV when compared to Group I. There was significant (p<0.0001) decrease in ulcer index, total protein, SGOT, SGPT in Group III, IV, V when compared to Group II.There was significant (p<0.0001) increase in ulcer index, SGOT, SGPT in Group IV, V when compared to Group III **(Table 2)**.

Effect of HAHU on Pylorus ligation induced gastric ulcer model:

There was significant (p<0.0001) increase in ulcer index, % inhibition, free acidity, total acidity, gastric volume, Total protein, SGOT, SGPT in Group II, III, IV when compared to Group I.There was significant (p<0.0001) decrease in ulcer index, total protein, SGOT, SGPT in Group III, IV, V when compared to Group II.There was significant (p<0.0001) increase in ulcer index, SGOT, SGPT in Group IV, V when compared to Group III **(Figure 6)**.

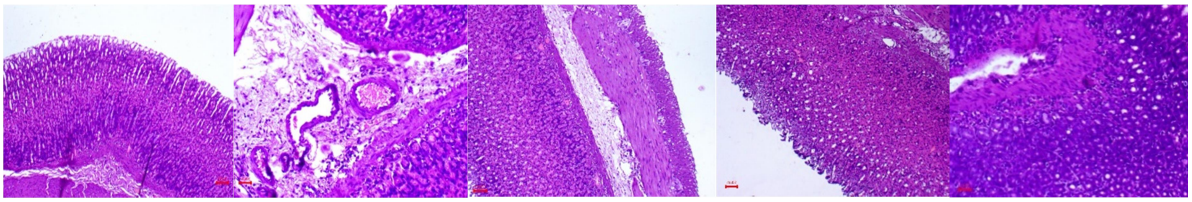


Figure 3

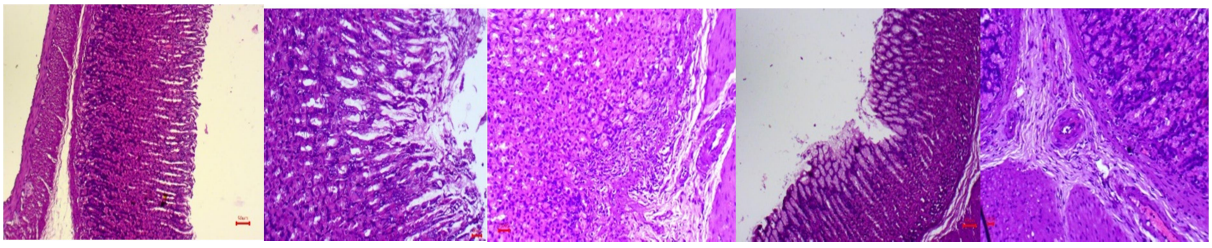


Figure 4

Table 1: Effect of HAHU on Ethanol induced gastric ulcer model

GROUPS	ULCER INDEX	% INHIBITION	SOD mmol/min/mg/tissue	TOTAL PROTEINmg/dL	SGOT IU/L	SGPT IU/L
GROUP I Treated with normal saline	0±0	0±0	90.73±0.184	2.862±0.022	99.01±0.940	53.03±0.783
GROUP II Ethanol (5ml/kg p.o)	8.291±0.132 a****	0±0 ns	21.51±0.176 a****	6.363±0.132 a****	168.14±1.92 a****	123.9±1.526 a****
GROUP III Ethanol (5ml/kg p.o) and treated with omeprazole (20mg/kg p.o)	2.401±0.118 a****b****	73.03±0.198 a*****b****	8278±0.215 a*****b****	5.399±0.082 a****b****	129.89±1.30 a***b**	70.083±1.301 a****b****
GROUP IV Ethanol (5ml/kg p.o) and treated with HAHU (200mg/kg p.o)	6.543±0.101 a****b****c****	45.97±0.162 a*****b****c****	61.58±0.249 a*****b****c****	5.839±0.034 a****b***c***	152.16±1.54 a****b ns c****	91.031±0.723 a****b****c ns
GROUP V Ethanol (5ml/kg p.o) and treated with HAHU (400mg/kg p.o)	3.49±0.064 a*****b****c****	64.57±0.347 a*****b****c****	78.61±0.188 a*****b****c****	4.840±0.0285 a****b****c****	131.73±1.54 a***b**c ns	72.191±1.134 a****b****c****

The values are expressed as mean ± SEM of 6 animals. Comparisons were made between:
Group I vs Group II, III, IV, V is considered as"a"
Group II vs Group III, IV, V is considered as"b"
Group III vs Group IV, V is considered as "c"
Statistical significance test for comparison was done by One way ANOVA followed by Dunnett's test. Symbols represent statistical significance * p<0.05, ** p<0.01, *** p<0.001, ****p<0.0001, ns –non significant

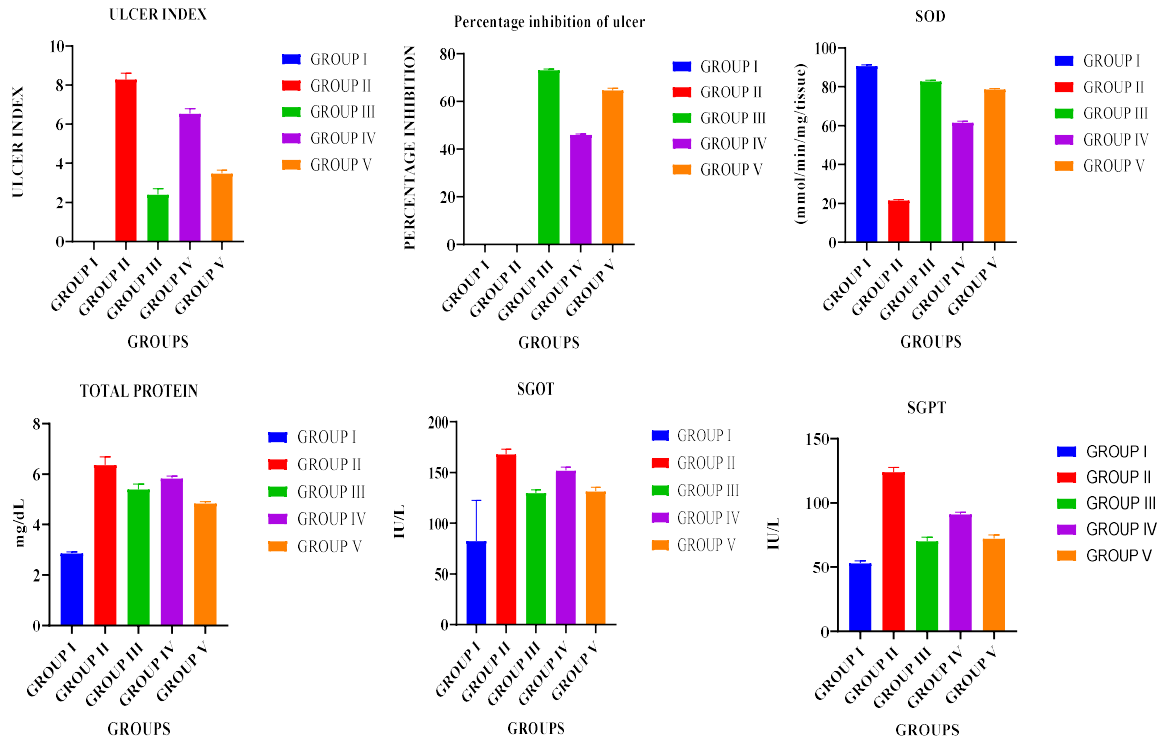


Figure 5: Effect of HAHU on Ethanol induced gastric ulcer model

Table 2: Effect of HAHU on Pylorus ligation induced gastric ulcer model

GROUPS	ULCER INDEX	% INHIBITION	TOTAL PROTEIN(mg/dL)	SGOT (IU/L)	SGPT (IU/L)
GROUP I-Treated with normal saline	0±0	0±0	2.623±0.023	101.73±0.878	55.35±0.281
GROUP II-Pylorus ligated	15.551±0.066a****	0±0 a ns	6.181±0.122 a****	152.658±1.606 a****	96.94±0.815 a****
GROUP III-Pylorus ligatedand treated with omeprazole (20 mg/kg)	4.79±0.04 a****b****	64.681±0.082 a****b****	5.304±0.077 a****b****	115.82±0.490 a****b****	61.73±0.849 a****b****
GROUP IV-Pylorus ligated and treated with HAHU 200mg/kg	11.635±0.069 a****b****c****	40.756±0.113 a****b****c****	5.637±0.307 a****b****c**	134.36±1.084 a****b****c****	75.25±0.796 a****b****c****
GROUP V-Pylorus ligated and treated with HAHU 400mg/kg	6.9±0.061 a****b****c****	61.978±0.085 a****b****c****	4.938±0.0267 a****b****c**	120.231±0.798 a****b****c*	60.211±0.967 a***b****c ns

GROUPS	Free Acidity (mEq/L)	Total Acidity (mEq/L)	Gastric volume (ml)
GROUP I-Treated with normal saline	11.015±0.060	32.883±0.142	2.23±0.025
GROUP II-Pylorus ligated	25.153±0.129 a****	63.928±0.117 a****	6.495±0.038 a****
GROUP III-Pylorus ligatedand treated with omeprazole (20 mg/kg)	15.73±0.100 a****b****	45.393±0.049 a****b****	5.916±0.043 a****b****
GROUP IV-Pylorus ligated and treated with HAHU 200mg/kg	19.773±0.144 a****b****c****	55.841±0.084 a****b****c****	5.025±0.059 a****b****c****
GROUP V-Pylorus ligated and treated with HAHU 400mg/kg	17.823±0.075 a****b****c****	42.94±0.133 a****b****c****	3.603±0.032 a****b****c****

The values are expressed as mean ± SEM of 6 animals. Comparisons were made between:
Group I vs Group II, III, IV, V is considered as"a"
Group II vs Group III, IV, V is considered as"b"
Group III vs Group IV, V is considered as "c"
Statistical significance test for comparison was done by One way ANOVA followed by Dunnett's test.Symbols represent statistical significance * p<0.05, ** p<0.01, *** p<0.001, ****p<0.0001, ns –non significant.

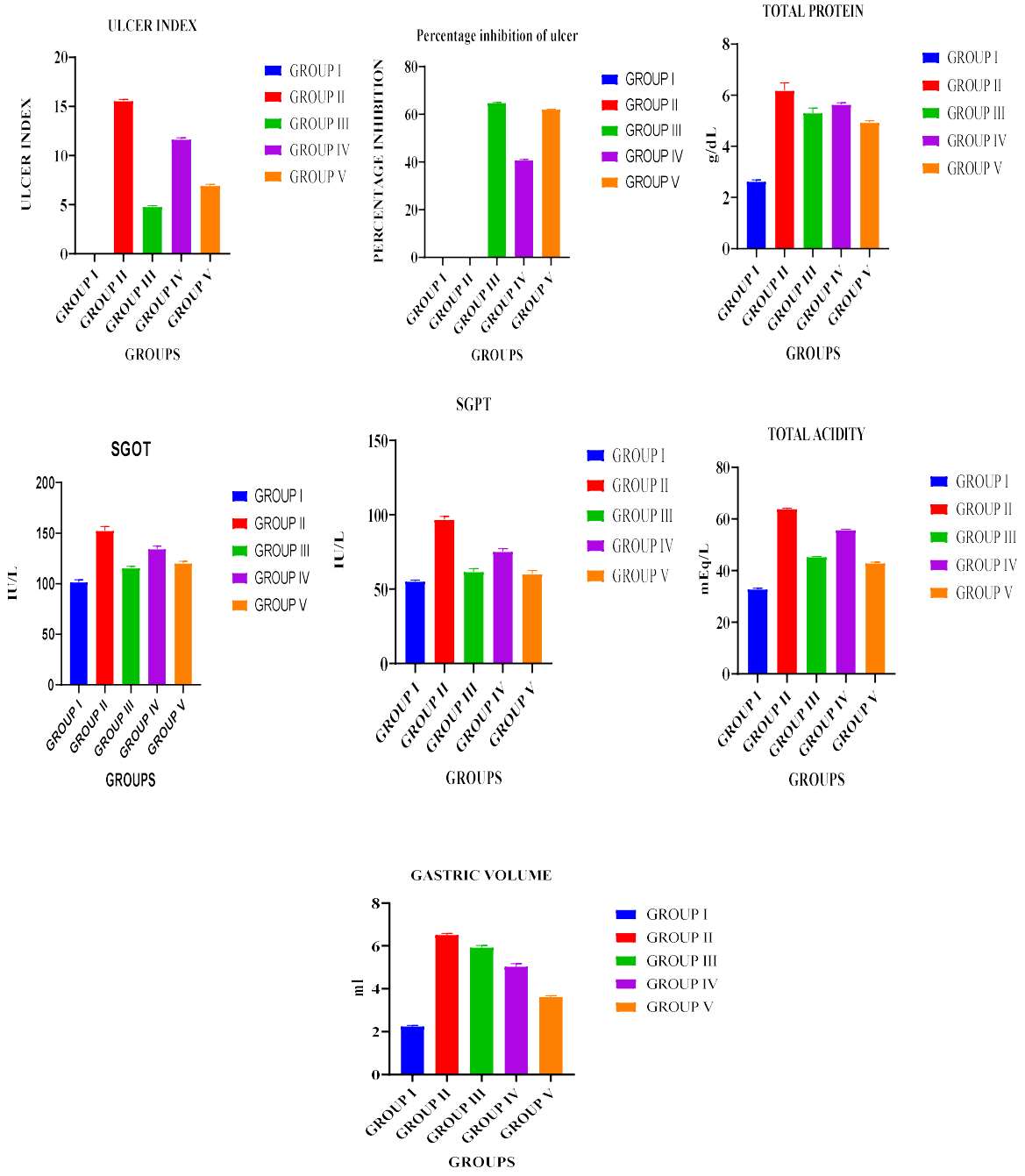

ULCER INDEX
ULCER INDEX
GROUPS
GROUP I
GROUP II
GROUP III
GROUP IV
GROUP V
Percentage inhibition of ulcer
PERCENTAGE INHIBITION
GROUPS
TOTAL PROTEIN
g/dL
GROUPS
SGOT
IU/L
GROUPS
SGPT
IU/L
GROUPS
TOTAL ACIDITY
mEq/L
GROUPS
GASTRIC VOLUME
ml
GROUPS

Figure 6

DISCUSSION

Omeprazole is a proton pump inhibitor which has been widely used as an acid inhibitor agent for the treatment of disorders related to gastric acid secretion. Omeprazole inhibits acid secretion by acting on the hydrogen-potassium exchanger (H^+, K^+ - ATPase) for the apical plasma membrane of the gastric mucosa **[9]**. Omeprazole is highly selective for the proton pump and undergoes catalyzed conversion into active form within the acid forming space. The active inhibitors react with SH (thiol) group of the proton pump, resulting in inhibition of acid formation **[10]**. The HAHU treated groups showed antiulcer activity comparable toomeprazole. The antiulcer activity of HAHU was Proved in ulcer models like Ethanol induced and pylorus ligation induced.

Ethanol induced ulcer:

High concentrations of ethanol can reduce peptic activity with its ability to inhibit pepsinogen activation to pepsin. This causes destruction of stomach tissues,oral administration of absolute ethanol within the animal model is destructive to stomach tissue, because it penetrates rapidly and easily into the gastric mucosa, producing gastric lesions. Such lesions characterized by extensive submucosal edema, hemorrhage, desquamation of epithelial cells and infiltration of inflammatory cells, which are typical characteristics of alcohol injury **[11]**.

The oxidative damage arises from an imbalance of antioxidant defense mechanisms, which causes oxidative stress and further leads to cell damage. There is decreased level of SOD in induced group due to the increase in generation of reactive free radicals which can create an oxidative stress in the cell. As SOD converts the reactive superoxide radical to H_2O_2 which is further converted into water and oxygen, can cause LPO by the generation of hydroxyl radicals and cause tissue damage. In the present study, HAHU showed increase level of SOD compared to ethanol induced group which indicates antioxidant activity of HAHU.

It is observed that HAHU reduces ulcer index and increased formation of ulcer inhibition compared to Ethanol induced group which suggests the possible role of HAHU in strengthening of gastric mucosa. The increase in the total protein level of the gastric juice in anethanol induced groups indicates the damage to the gastric mucosa as a result of which plasma protein leaks into gastric juice. HAHU treated groups showed significant reduction in protein concentration, which indicates strengthening of the gastric mucosa, therefore it prevents the entry of

plasma protein into gastric juice. Liver enzymes such as SGPT and SGOT play a vital role in indicating the damage caused in tissue or cells. It is also observed that liver enzymes such as SGOT and SGPT levels are increased which is due to the damage of gastric mucosa in the ulcer induced models, whereas it showed decrease in SGOT and SGPT levels in HAHU treated groups indicates antiulcer activity.

Pylorus ligation induced ulcer:

The pylorus ligated rat model is used (Shay rat) as acute ulcer model in the stomach. The activation of the Gastrointestinal reflex circuits in the vagus nerve by stimulation of pressure receptors in the antral gastric mucosa in pylorus ligation model is believed to increase gastric secretion**.**

Effect of the accumulated gastric juice is believed to be responsible for producing ulcer in the pylorus ligated rats. Pylorus ligated ulcers are thought to be caused due to increase in presence of acid and pepsin in the stomach. Increase in mucus secretion, bicarbonates and prostaglandin synthesis by the gastric mucosal cells can prevent gastric ulceration by several mechanisms including reduction of the stomach wall friction during peristalsis, alter mucosal blood flow and acting as an effective barrier to the back diffusion of hydrogen ions **[12]**. HAHU treated groups showed significant decreases in total acidity, free acidity and gastric volume indicating the lower production of acid pepsin, which shows both gastric secretory and gastric cytoprotective effect. The increase in the total protein level of the gastric juice in a pylorus ligated groups indicates the damage in gastric mucosa as a result of which plasma protein leaks into gastric juice. HAHU treated groups showed significant reduction in protein concentration, which indicates strengthening of the gastric mucosa, therefore it prevents the entry of plasma protein into gastric juice. It is also observed that liver enzymes such as SGOT and SGPT level are increased which indicates injury caused to stomach tissue, cell membrane gets damaged, these enzyme leak into blood stream causing damage to the gastric mucosa in the ulcer induced model whereas it showed in SGOT and SGPT levels are decreased in HAHU treated groups indicates antiulcer activity.

In the present study, the histopathological reports have shown hemorrhage and congestion in Ethanol induced gastric ulcer group. Whereas HAHU treated groups showed normal gastric mucosa. Also, in the histopathological reports of pylorus ligation induced ulcer

group showed hemorrhage, inflammation and congestion. Whereas HAHU treated groups showed normal gastric mucosa which may be due to active compound like flavonoids, β-amyrin and tannins.

Flavonoids and tannins have shown to be present in the HAHU treated groups. These constituents may be responsible for the decrease in the acid secretion. It is suggested that, these active compounds would be able to stimulate mucus, bicarbonate and the prostaglandin secretion and counteract with the deteriorating effects of reactive oxidants in gastrointestinal lumen. So, the antiulcer activity of HAHU may be attributed to its flavonoid content.

Therefore, it is concluded that HAHU has an antiulcer activity which may be due to the protection and strengthening of the mucosal defensive factor like mucus, bicarbonate andprostaglandin.

SUMMARY AND CONCLUSION

Ethanol induced gastric ulcer in wistar rats which were treated with HAHU showed significant decrease in ulcer index, Total protein, SGOT and SGPT which indicates the antiulcer activity of *Hylocereus undatus* fruit. HAHU treated groups showed significant increase in Percentage inhibition of ulcer, SOD and Total protein which indicates the antioxidant activity of *Hylocereus undatus.*

Pylorus ligation induced gastric ulcer treated with HAHU showed significant decrease in Ulcer index, Free acidity, Total acidity, Gastric volume, SGOT and SGPT which showed its antiulcer and antioxidant activity. Increase in the Percentage inhibition of ulcer showed cytoprotective activity of *Hylocereus undatus.*

The histopathological studies suggested that no haemorrhage, inflammation and congestion of the stomach were seen in HAHU treated group which indicate the healing of the ulcer in the stomach.

In conclusion, the present study provided preliminary data for the first time that the Fruit *Hylocereus undatus* possess significant antiulcer activity in animal models. It has a gastric antisecretory and acid neutralizing effect that are comparable to standard drug Omeprazole. The antiulcer activity is probably due to the presence of bioactive compounds like Flavonoids, Tannins. These compounds protect and strengthen the mucosal barrier which may be responsible for the antiulcer activity.

Further studies are required to confirm the exact molecular level mechanism underlining the ulcer healing and protecting property of the extract and to identify the chemical constituents responsible for it.

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