Research Article CODEN: IJPRNK ISSN: 2277-8713
Solanki HD, IJPRBS, 2013; Volume 2(6): 594-610 IJPRBS

INTERNATIONAL JOURNAL OF
PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

# ULCER PREVENTIVE (ANTIULCER) ACTIVITY OF *HELICTERES ISORA* FRUIT EXTRACTS.

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**Accepted Date: 24/12/2013; Published Date: 27/12/2013**

**Abstract:** Peptic ulcer disease is a deep gastrointestinal erosion disorder, involves the entire mucosal thickness and even penetrates the muscular mucosa. Numerous natural products have been evaluated as therapeutics for the treatment of same. The antiulcer activity of various extracts of Helicteres isora lin. fruit was evaluated in pyloric ligation and ethanol induced gastric ulcer in albino rats. The fruit extracts were prepared by cold maceration process with alcohol and N-butanol separately. Oral administration of alcohol and N- butanol extracts of H. isora lin fruits were evaluated for antiulcer activity and compared with the standard drug, pentoprazole. From the results, it can be concluded that the N-butanolic extract of H. isora lin fruits showed dose-dependent antiulcer activity. These results lend scientific support for the plant as folk medicine.

**Keywords:** Helicteres isora, ulcer index, Pentoprazole

***PAPER-QR CODE***

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**Access Online On:**

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**How to Cite This Article:**

Solanki HD, IJPRBS, 2013; Volume 2(6): 594-610

## INTRODUCTION

Peptic ulcer has been one of the most important and frequent disease of mankind. It is the result of imbalance between aggressive and defensive factors involved in the gastric mucosa. The healthy mucosa withstands acid attack and prevents back diffusion of $H^+$ into the mucosa. The specific biological mechanisms involved in mucosal defense include a mucus coat provided by surface epithelial cells that secrete mucus and bicarbonate, maintenance of adequate mucosal blood flow and production of prostaglandins by mucosa. Among the aggressive factors, it is generally accepted that increased gastric acid secretion, reduced gastric mucosal blood flow (GMBF), increased gut motility, degranulation of mast cells and inhibition of prostaglandin biosynthesis are important factors causing gastric erosions.

The plant remedies had widespread use in the treatment of this disease for thousands of years. In spite of the recent progress by the invention of $H_2$-receptor antagonists and proton pump inhibitors, peptic ulcers still continue to become the major problem of population. As the progress in chemical and biological methods in the last two decades, increasing number of studies are carried out in order to evaluate the potential of plant remedies and to discover leading molecules for the treatment of peptic ulcer disease.

Research in this field has made significant contribution in understanding the mechanism of mucosal protection and role of mucus in recovery of the upper gastrointestinal tract from acute damage.

The problems encountered in the experimental evaluation of an antiulcer drug arise in part from the lack of complete understanding of the physiological and biochemical mechanisms involved in the formation of ulcers. It is not possible from a single model to study the genesis of ulcers as well as understand exact mechanism of antiulcer effect. Therefore, a number of experimental procedures are generally employed to evaluate the antiulcer activity of different extracts of *H. isora* dried fruit. [1]

## MATERIAL AND METHODS:

The fruits of *Helicteres isora* were bought from the local market and identified by comparing its morphological characteristics described in different standard text and floras. The authenticated dried fruits of *H. isora* were crushed, powdered and shifted from 40 # sieve. Dried powder of *H. isora* was extracted with 50 % alcohol and N-butanol. The alcohol extract was concentrated under reduced pressure to yield dry solid and N-butanol extract was concentrated under reduced pressure and air dried. The suspension of these dried extracts were prepared using 1% Na-CMC and further used for animal study.

**Animals**

Wistar albino rats of either sex (150-200 g) were selected for the study. The animals were housed under standard conditions. Experiment complied with the guidelines of ethics committee for animal experimentation. Rats were fasted for 24 h with water ad libitum.

**1.1. Ethanol-induced gastric ulcers in rats.** [2]

Group-1: Only 1 % Na CMC as vehicle

Group-2: Pantoprazole (20 mg/kg, p.o.)

Group-3: Alcoholic extract (100 mg/ kg, p.o.)

Group-4: N-butanol extract (50,100 & 200 mg/kg, p.o.)

Gastric lesions in rats were induced by oral administration of 1 ml of 95 % alcohol. All the treated animals were given the test extracts 1 h before the alcohol administration. Two hrs after the alcohol administration, rats were sacrificed, abdomen opened, and stomachs were removed. All stomach preparations were opened through the greater curvature and ulcer indices were determined [3]. Stomach tissues were processed to measure the gastric wall mucus content [4].

**1.2. Ethanol-induced gastric mucosal lesion in indomethacin-pretreated rats** [5]

Group-1: Indomethacin + 1 % Na CMC

Group-2: Indomethacin + alcoholic extract (100 mg/ kg, p.o.)

Group-3: Indomethacin + N-butanol extract (100 mg/kg, p.o.)

To investigate the involvement of endogenous prostaglandins for the gastroprotective activity of alcoholic and N-butanolic extracts of H. isora, indomethacin (70 mg/kg, s.c.) injected 75 min before the treatment of groups with 1% Na CMC, alcoholic extract (100 mg/kg, p.o.), N-butanol extract (100 mg/kg, p.o.). One hour after drug treatment, 1 ml of 95 % alcohol was administrated orally. Two hours after alcohol treatment animals were sacrificed and gastric mucosal lesions were measured [2].

**1.3. Ethanol-induced and pylorus ligated gastric mucosal lesions in rats** [6]

The animals of various groups received treatment as follows.

Group-1: Pylorus ligation +1 % Na CMC

Group-2: Ethanol + Pylorus ligation +1 % Na CMC

Group-3: Ethanol + Pylorus ligation + pantoprazole (20 mg/kg, p.o.)

Group-4: Ethanol + Pylorus ligation + alcohol extract (100 mg/kg, p.o.)

Group-5: Ethanol + Pylorus ligation + N-butanol extract (100 mg/kg, p.o.)

Animals of various groups were treated as above one hour before the alcohol administration (1 ml/rat, p.o.). Pylorus of anesthetized rat was ligated one hour after the alcohol administration. Two hours after pylorus ligation, rat was sacrificed by ether anesthesia, and esophagus was clamped. The stomach was removed, opened along the greater curvature and the ulcer index was determined [2]. The gastric content was centrifuged at 2500 rpm for 10 min. The volume of the supernatant was measured. The juice was subjected to biochemical analysis for total acidity, total acid output [7] and pepsin activity [8].

**RESULTS**

**Antiulcer activity**

**1. Effect of *H. isora* on gastric ulcers induced by ethanol in rats**

In this model, linear hemorrhagic gastric mucosal erosions in the glandular region of stomach were observed. Different extracts of *H. isora* were orally administered one hour before the alcohol administration. The parameters investigated included ulcer index and gastric wall mucus content.

**Ulcer index**

Pretreatment of rats with pentoprazole, alcoholic (AE), and N-butanol extracts (NB) significantly prevented the ethanol-induced gastric ulcers compared to vehicle treated rats (Table-1; Figure-1). The N-butanol extract was found to be effective in reducing the ulcer index more in ethanol induced gastric ulcer model in a dose dependent manner. (Table-3; Figure-3).

**Table-1: Effect of different extracts of *H. isora* on ulcer index in ethanol induced gastric ulcer model in rats**

| Treatment | Dose | Ulcer index |
|---|---|---|
| Control | - | 2.903 ± 0.318 |
| Pentoprazole | 20 mg/kg, p.o. | 0.176 ± 0.047 * |
| Alcohol extract | 100 mg/kg, p.o. | 0.560 ± 0.121 * |
| N-butanol extract | 100 mg/kg, p.o. | 0.236 ± 0.081 * |

N= 6 in each group, All values are mean ± S.E.M., * significant at p < 0.001, when compared with the control group.

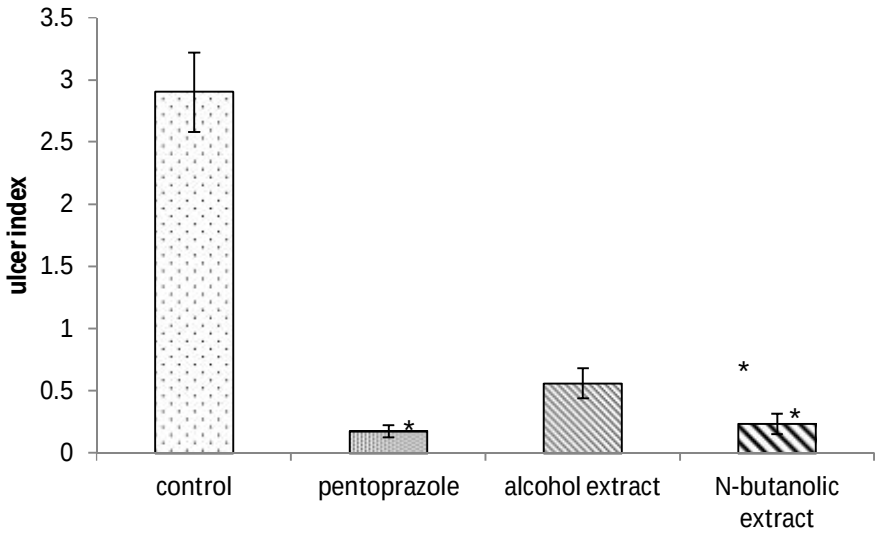


**Fig-1: Effect of *H. isora* on ulcer index in ethanol induced gastric ulcer model in rats.** Each bar represents Mean ± S.E.M., No. of animals in each group = 6. Control = Vehicle treated (1 ml/kg), Pentoprazole (20 mg/kg, p.o.), Alcoholic extract (100 mg/kg, p.o.), n-Buntanol extract (100 mg/kg, p.o.),

* Significantly different from control, P < 0.001.

**Gastric wall mucus content**

Pretreatment of rats with EA and NB significantly increased the gastric wall mucus content compared to vehicle treated rats (Table-2; Figure-2).

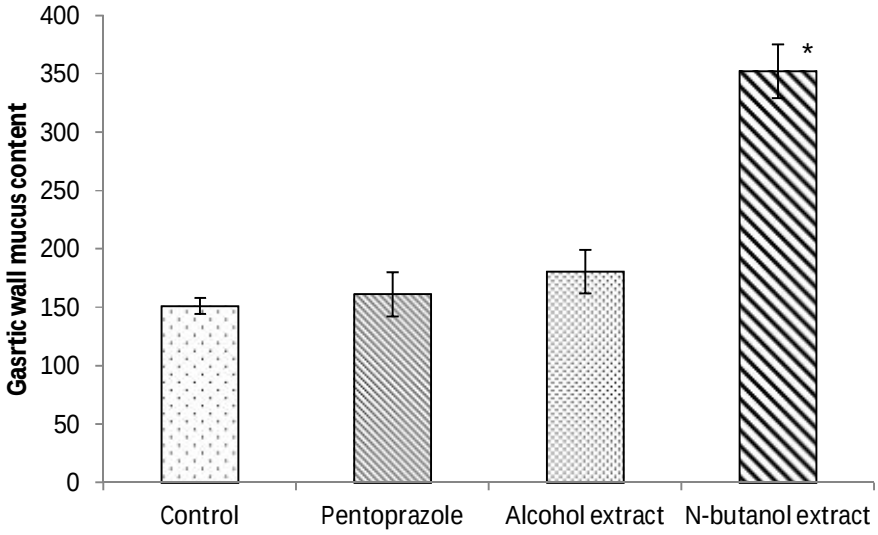


**Fig-2: Effect of *H. isora* on gastric wall mucus content in ethanol induced gastric ulcer model in rats.** Each bar represents Mean ± S.E.M., No. of animals in each group = 6. Control (vehicle, 1 ml/kg), Pentoprazole (20 mg/kg, p.o.), Alcoholic extract (100 mg/kg, p.o.), n-Buntanolic extract (100 mg/kg, p.o.),

* Significantly different from control, $p < 0.05$,

**Table-2: Effect of different extracts of *H. isora* on gastric wall mucus content in ethanol induced gastric ulcer model in rats**

| Treatment | Dose | Gastric wall mucus content (mg alcian blue/g wet tissue) |
|---|---|---|
| Control | - | 151.39 ± 6.82 |
| Pentoprazole | 20 mg/kg, p.o. | 161.57 ± 18.92 |
| Alcohol extract | 100 mg/kg, p.o. | 181.13 ± 18.59 |
| N-butanol extract | 100 mg/kg, p.o. | 352.72 ± 23.16[a] |

N=6 in each group, All values are mean ± S.E.M., [a] significant at $p < 0.05$, when compared with the control group

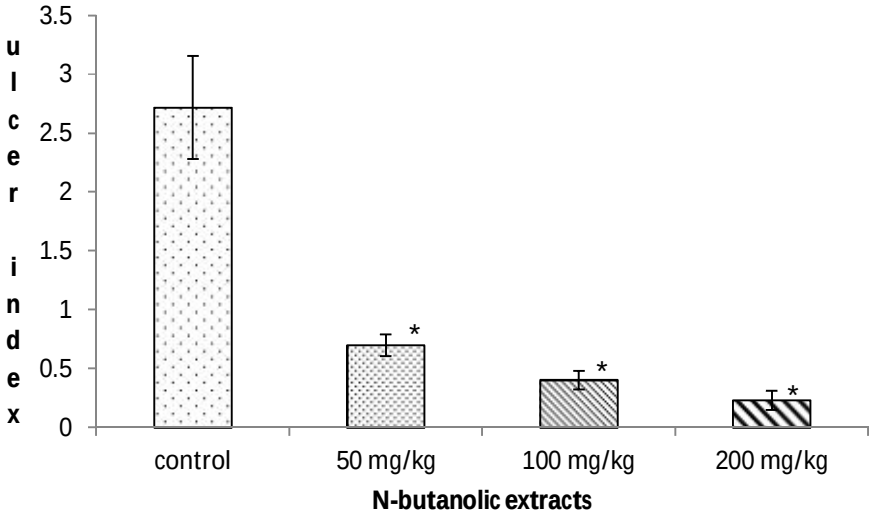


**Fig-3: Dose dependent effect of *H. isora* on ulcer index in ethanol induced gastric ulcer model in rats.** Each bar represents Mean ± S.E.M., No. of animals in each group = 6. Control (vehicle, 1 ml/kg), n-Buntanolic extract (50, 100 & 200 mg/kg, p.o.), * Significantly different from control, P < 0.05,

**Table-3: Dose dependent effect of N-butanolic extracts of *H. isora* on ulcer index in ethanol induced gastric ulcer model in rats**

| | Dose | Ulcer index |
|---|---|---|
| Control | - | 2.722 ± 0.4378 |
| N-butanolic extract | 50 mg/kg, p.o. | 0.701 ± 0.0919 * |
| N-butanolic extract | 100 mg/kg, p.o. | 0.405 ± 0.0790 * |
| N-butanolic extract | 200 mg/kg, p.o. | 0.234 ± 0.0811 * |

N=6 in each group, All values are mean ± S.E.M., * significant at p < 0.05, when compared with the control group

**2. Effect of *H. isora* on ethanol-induced gastric ulcers in indomethacin pretreated rats**

Pretreatment with indomethacin reversed the gastroprotective effect of AE and NB extracts in ethanol induced gastric ulcers in rats. No significant difference in ulcer index was observed in AE and NB treated rats when compared to controls (Table-4; Figure-4).

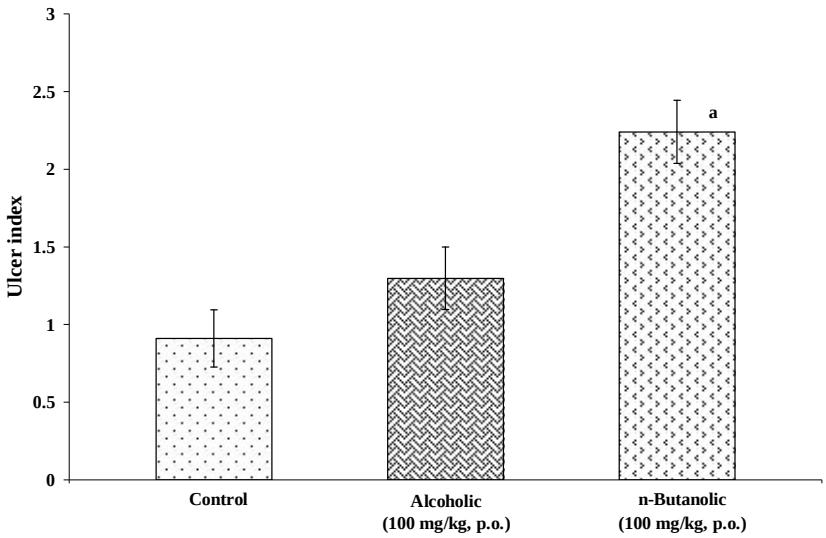


**Fig-4: Effect of *H. isora* on ethanol induced gastric ulcers in indomethacin pretreated rats.** Each bar represents Mean ± S.E.M., No. of animals in each group = 6. Control (vehicle, 1 ml/kg), Alcoholic extract (100 mg/kg, p.o.), n-Buntanolic extract (100 mg/kg, p.o.), [a] Significantly different from control, P < 0.05.

**Table-4: Effect of alcoholic and N-butanolic extracts of H. isora on ethanol induced gastric ulcers in indomethacin pretreated rats.**

| | Control | Alcoholic extract (100 mg/kg, p.o.) | N-butanolic extract (100 mg/kg, p.o.) |
|---|---|---|---|
| Ulcer index | 0.9114 ± 0.1842 | 1.297 ± 0.2010 | 2.24 ± 0.2034 [a] |

N= 6 in each group, All values are mean ± S.E.M., [a] significant at p < 0.05, when compared with the control group

**3. Effect of *H. isora* on gastric ulcers in alcohol pretreated and pylorus ligated rats**

Intragastric administration of ethanol caused circular and linear hemorrhagic lesions along with petechies in the mucosa of the glandular stomach. The parameters studied were ulcer index, total acid output and pepsin activity.

**Ulcer index**

Administration of alcohol increased the severity of gastric ulcers as evident from increase in ulcer index in pylorus ligated rats (Table-5; Figure-7). Pretreatment of rats with pentoprazole,

AE and NB significantly decreased the ulcer index in alcohol pretreated and pylorus ligated rats as compared to vehicle treated rats.

**Total acid out put**

Total gastric output was also found to be significantly higher in alcohol treated plus pylorus ligated rats compared to only pylorus ligated rats. Pentoprazole, AE and NB significantly decreased the total acid output as compared to ethanol treated and pylorus ligated rats (Table-5; Figure-6).

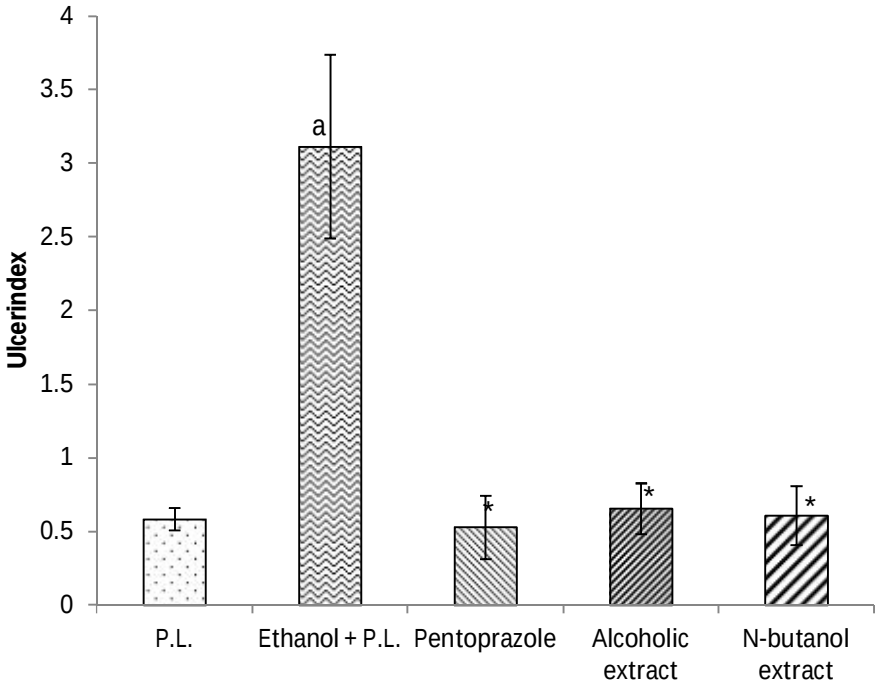


**Fig-5: Effect of alcohol and N-butanol extracts of *H. isora* on ethanol induced gastric ulcers in pylorus ligated rats.** Each bar represents Mean ± S.E.M., No. of animals in each group=6. PL (Vehicle, 1 ml/kg, p.o.), PL + Ethanol (Vehicle, 1 ml/kg,p.o.), Pentoprazole (20 mg/kg, p.o.), Alcoholic extract (100 mg/kg, p.o.), N-butanolic extract (100 mg/kg, p.o.), [a] Significantly different from pylorus ligated (PL) group, $P < 0.05$, [c] Significantly different from ethanol + pylorus ligated (PL) group, $P < 0.05$,

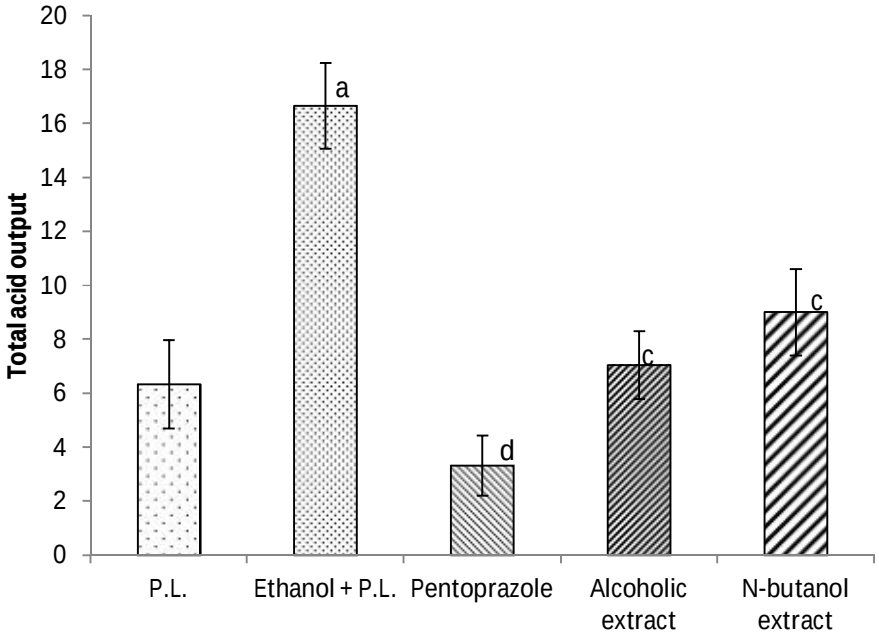


**Fig-6: Effect of alcohol and N-butanol extracts of *H. isora* on total acid out put in ethanol treated and pylorus ligated rats.** Each bar represents Mean ± S.E.M., No. of animals in each group=6. PL (Vehicle, 1 ml/kg, p.o.), PL + Ethanol (Vehicle, 1 ml/kg,p.o.), Pentoprazole (20 mg/kg, p.o.), Alcoholic extract (100 mg/kg, p.o.), N-butanolic extract (100 mg/kg, p.o.), [a] Significantly different from pylorus ligated (PL) group, $P < 0.05$, [b] Significantly different from pylorus ligated (PL) group, $P < 0.001$, [c] Significantly different from ethanol + pylorus ligated (PL) group, $P < 0.05$, [d] Significantly different from ethanol + pylorus ligated (PL) group, $P < 0.001$.

**Table-5: Effect of alcoholic and N-butanolic extracts of *H. isora* on ulcer index, total acid out put, pepsin activity in pylorus ligated rats**

| | Ulcer index | Total acid out put (µEq/100 g.b.w.) | Pepsin activity (µg/ml) |
|---|---|---|---|
| Pylorus ligation | 0.583 ± 0.0745 | 6.339 ± 1.644 | **12.25 ± 0.511** |
| Ethanol + Pylorus ligation | 3.113 ± 0.6238[a] | 16.67 ± 1.584[a] | **15.12 ± 0.182** |
| Pentoprazole (20 mg/kg, p.o.) | 0.528 ± 0.2152[c] | 3.339 ± 1.117[d] | **3.587 ± 0.636[d]** |
| Alcoholic extract (100 mg/kg, p.o.) | 0.654 ± 0.1728[c] | 7.057 ± 1.248[c] | **5.910 ± 0.813[d]** |
| N-butanol extract (100 mg/kg, p.o.) | **0.607 ± 0.2013[c]** | **9.014 ± 1.598[c]** | **5.957 ± 0.835[d]** |

N=6 in each group, All values are mean ± S.E.M., [a] significant at p < 0.05, when compared with the pylorus ligation group, [b] significant at p < 0.001, when compared with the pylorus ligation group, [c] significant at p < 0.05, when compared with the pylorus ligation group, [c] significant at p < 0.05, when compared with the ethanol + pylorus ligation group, [d] significant at p < 0.001, when compared with the ethanol + pylorus ligation group.

**Pepsin activity**

There was no significant change observed in the pepsin activity by ethanol in the pylorus ligated rats. However, pretreatment with pentoprazole, AE and NB showed significant decrease in the pepsin activity as compared to ethanol treated and pylorus ligated rats (Table-5; Figure-7).

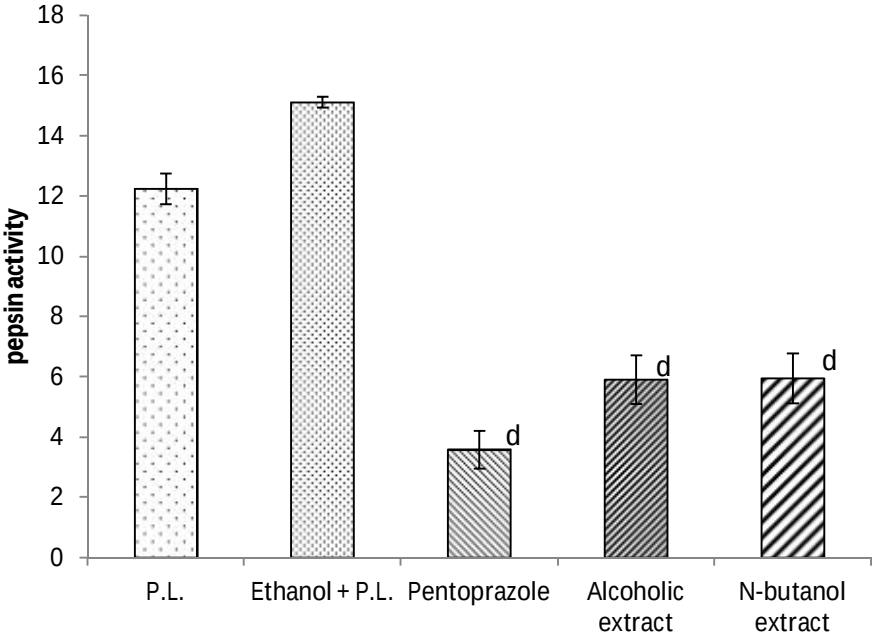


**Fig-7: Effect of alcohol and N-butanol extracts of *H. isora* on pepsin activity in ethanol treated and pylorus ligated rats.** Each bar represents Mean ± S.E.M., No.of animals in each group=6. PL (Vehicle, 1 ml/kg, p.o.), PL + Ethanol (Vehicle, 1 ml/kg,p.o.), Pentoprazole (20 mg/kg, p.o.), Alcoholic extract (100 mg/kg, p.o.), N-butanolic extract (100 mg/kg, p.o.), [a] Significantly different from pylorus ligated (PL) group, P < 0.05, [b] Significantly different from pylorus ligated (PL) group, P < 0.001, [c] Significantly different from ethanol + pylorus ligated (PL) group, P < 0.05, [d] Significantly different from ethanol + pylorus ligated (PL) group, P < 0.001.

**6.1. Antiulcer activity**

We studied the antiulcer activity of *Helicteres isora* fruit in ethanol-induced gastric ulcer model with reference to its traditional use. Both the extracts of *H. isora* were found to prevent the

ethanol-induced gastric lesions in rats. β-sitosterol and α-amyrin have been shown to possess antiulcer activity in ethanol-induced gastric ulcers [9]. N-butanol fraction was further studied for its antiulcer activity as it was found to be more effective in ethanol-induced gastric ulcer model. In the same model, N-butanol extract was found to prevent gastric lesions in a dose dependent manner. The gastroprotective effect of alcoholic and n-butanolic extracts was reversed by indomethacin (prostaglandin synthesis inhibitor). Further, alcoholic and n-butanolic extracts were found to have gastroprotective and antisecretory activity in ethanol-treated and pylorus-ligated rats.

Ethanol rapidly penetrates the gastric mucosa and apparently causes cell and plasma membrane damage that result in increased membrane permeability leading to intracellular accumulation of sodium and water. These changes produce cell death and exfoliation in gastric mucosa [10]. It has been shown that endogenous ulcerogenic mediators are released by stress and by noxious agents [11]. These mediators could participate in ethanol-induced mucosal injury either by causing vascular changes, which result in mucosal edema and increased mucosal permeability [12], or by nonvascular effects (e.g. mucus depletion and lysosomal enzyme release) in the stomach [13-15].

It has been suggested that ethanol-induced gastric mucosal injury is due to break down of mucous bicarbonate barrier, a fall in potential difference followed by an increase in back diffusion of hydrogen ions and stasis of blood flow in mucosa. It is also known that ethanol-induced gastric ulcers are prevented by agents enhancing the mucosal defensive factors [16] ,e.g. sucralfate [17] and cetraxate [18]. From the present study, it can be suggested that the antiulcer activity of *H. isora* may be attributed by its gastric mucosal strengthening effect as it was found to increase the gastric wall mucus content with significant protection against ethanol-induced gastric ulcers in the rats.

Intragastric instillation of excessive ethanol results in gastric mucosal injury characterized by mucosal edema, subepithelial hemorrhage, cellular exfoliation, and inflammatory cell infiltration [19, 20]. Studies focusing on the pathogenesis of ethanol-induced injury have suggested that several factors are implicated in such processes: products of arachidonate metabolism (eg. Leukotriene) [21], mast cell secretory products [22], and reactive oxygen species (ROS) [23-25]. It has been demonstrated that oxygen derived free radicals are involved in the pathogenesis of ethanol-induced gastric mucosal damage and cause neutrophil infiltration into the gastric mucosa [26]. Therefore, xanthine oxidase and neutrophils are considered main sources of free radicals in ethanol-induced damage. These oxygen derived free radicals are detrimental to the integrity of the duodenal mucosa. They are directly implicated in the mechanism of secretogogue induced acute and chronic duodenal ulceration and the agents capable removing these radicals protects the duodenum against ulceration [27]. In addition, it is

reported that oral administration of ethanol interrupts the mucosal defense and produces mucosal damage by necrosis or apoptosis of gastric mucosal cells [28, 29]. The mucosal injury due to ethanol administration consists mainly of separation of the surface epithelium from the underlying lamina propia with complete loss of epithelium. This is due to the hazardous effect of ethanol which rapidly penetrates gastro-duodenal mucosa causing membrane damage. The subsequent increase in mucosal permeability together with the release of vasoactive products from mast cells, macrophages and other blood cells may lead to vascular injury, necrosis and ulceration [30]. It is suggested that chronic ethanol administration induces oxidative stress, mainly increasing lipid peroxidation of the cell membrane and this leads to increased membrane fluidity, disturbances of calcium homeostasis and finally cell death [31] In the present study, *H. isora* inhibited the increase in lipid peroxidation in mucosa injured by ethanol, suggests it's protective effect due to the scavenging of free radicals produced in the injured mucosa.

The decrease in the level of lipid peroxidation and increase in the activities of free radical scavenging enzymes (SOD and catalase) in the *H. isora*-treated gastric mucosa when compared with the ulcerated group, suggests the ability of *H. isora* to protect the gastric mucosa against free radical mediated tissue injury.

The changes in the permeability of gastric mucosa, permitting a rapid back diffusion of gastric acid has two effects. First, release of histamine that produces changes in the vascularity of the mucosa and the second, the rupture of the histamine dilated capillaries resulting in the production of gastric lesions [32].

Leukotrienes were involved in pathophysiology of tissue injury and trauma [33], particularly in ethanol-induced damage [34] .Research suggest inhibition of leukotriene synthesis leads to decrease in gastric mucosal damage in different experimental models including ethanol-induced gastric ulcers [35,36]. Flavonoids can reduce the concentration of Leukotrienes in different biological systems [37-39]. The gastroprotection exerted by *H. isora* could be through regulation of release of leukotriene as flavonoids have been reported and isolated from *H. isora* during phytochemical analysis [40]. These flavonoids may prevent synthesis and release of leukotriene in the injured tissue. Further, *H. isora* has also been found to act through NO in the ethanol-induced gastric ulcer. In the present study, *H. isora* was found to prevent the ethanol-induced gastric ulcers in rats due to its free radical scavenging activity and gastric mucosal strengthening effect.

Endogenous prostaglandins (PGs) are important in the defense of the gastric mucosa. PGs are present in large quantity in the mucus membrane of fundus, body and pylorus of stomach and

duodenum. PGE1 and PGE2 inhibit basal histamine and pentagastrin stimulated acid secretion in human subjects and other species [41].

Although many chemical mediators participate in producing coordinated and effective mucosal responses to injury, prostaglandins and nitric oxide are important for mucosal defense: they inhibit acid secretion, stimulate mucus and bicarbonate secretion, elevate mucosal blood flow, and accelerate the healing of ulcers. In present study, *H. isora* significantly reduced the gastric ulcers and increased the amount of mucus. The *H. isora* induced gastroprotection is evident since the inhibition of prostaglandin biosynthesis by pretreatment with indomethacin reversed the protection afforded by *H. isora*.

In the present study, we have studied the role of gastric acid secretion, and its inhibition by *H. isora* as a part of mechanism in ethanol-induced gastric ulcer model. Gastric ulcer is a multifactorial disease, resulting from imbalance between mucosal defensive and aggressive factors. Gastric acidity plays an important role in ethanol-induced ulcerogenesis, as significant correlation has been observed between gastric acidity and the severity of gastric damage. Furthermore, antisecretory agents like famotidine, omeprazole, and lansoprazole prevents ethanol-induced gastric ulcers in pylorus ligated rats with significant antisecretory effect. Gastric acid secretion being under the vagal control, several anticholinergics have been reported to reduce the gastric acid secretion in pylorus ligated rats.

*H. isora* has been reported to inhibit effect of acetylcholine, histamine, and $BaCl_2$ in isolated guinea pig ileum [42]. In the present study, *H. isora* was observed to inhibit gastric ulcers as well as gastric acid secretion in pylorus ligated rats. Furthermore, pepsin activity was also found to be decreased in the drug treated animals which may also impart antiulcer activity.

Based on the present study, it can be concluded that the ability of *H. isora* in preventing ethanol-induced gastric mucosal barriers, antioxidant activity, antisecretory activity, and through increase/ release of gastroprotective mediators like nitric oxide, prostaglandins etc.

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