Himalayan Journal of Applied Medical Sciences and Research
ISSN Print : 2709-3506 | ISSN Online : 2709-3514
OPEN ACCESS

Anti-Ulcer Activity of Methanolic Extract of *Alpinia Nigra Rhizome* on Experimentallys Induced Gastric Ulceration in Albino Rats

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Article History

Received:	2021-04-08
Revised:	2021-05-22
Accepted:	2021-06-13
Published:	2021-06-30

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DOI: 10.47310/hjcmph.2021.v02i01.007

How to Cite the Article:
Borah, Naba Jyoti *et al*. "Anti-ulcer activity of methanolic extract of *Alpinia Nigra Rhizome* on experimentally induced gastric ulceration in albino rats." *Himalayan Journal of Applied Medical Sciences and Research*, vol. 02, no. 01, 2021, pp. 1-6.

Abstract: Peptic ulcer is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice or upper small intestinal secretions. Since NSAID abuse is the main exogenous cause of refractory peptic ulcer the present model was chosen. In the present study gastric ulceration was induced by single dose of Aspirin 400 mg/kg on 7th day of the experiment. The experiment consists of treatment with the test herb and standard drug for seven days and on seventh day inducing the ulcer with aspirin. On 8th day pyloric ligation was performed on all the rats under light ether anesthesia on fasted animals over night from 7th day after pyloric ligation. The stomach was replaced and abdomen was then sutured. After 4 hours the rats were sacrificed with proper doses of ether and stomach was dissected out. After that stomach was opened along the greater curvature and the contents were collected in test tubes for analysis. The mucosa of the stomach was examined for ulcers and subjected for gastric mucus estimation. In all the parameters estimated it was found that the Methanolic Extract of Rhizomes of Alpinia Nigra (MERAN) showed similar results as of the standard drug Omeprazole which was significantly better than the aspirin control group. The findings of the present study put forward Alpinia Nigra as a promising new anti-ulcerogenic agent, which can be further evaluated with more refined techniques and innovate formulations with least adverse for the treatment of gastric ulcers.

Keywords: Methanolic extract, Alpinia Nigra rhizome, MERAN, Anti-ulcerogenic, Ulcer, Gastric, Peptic Ulcer

INTRODUCTION

Peptic ulcer is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice or upper small intestinal secretion [8]. At least 98% of peptic ulcers are either in the first portion of the duodenum or in the stomach, in a ratio of about4:1 [14]. Development of ulcer disease and death from it has been associated with the birth of urbanisation and was interpreted as a birth-cohort event with the peak of disease in those born during the late 19th century [28]. Peptic ulcer is the most common gastrointestinal tract disorder, affecting approximately 10% of the people during their life time. Peptic ulcers are very common in United States, with 4 million individuals (new cases and recurrences) affected per year. An estimated 15,000 deaths per year occur as a consequence of complicated peptic ulcer disease in United States [13]. Although there is poor statistical data on peptic ulcers in India, a report by Tovey showed a marked regional differences in India, ulcer being more prevalent in southern than in northern India. High-prevalence areas stretch from the south up the west coast to Bombay, all the way up the east coast, and into the plains of Assam and Kashmir [6]. A study showed 11% lifetime prevalence of peptic ulcer in Kashmir region alone [11] A recent study in Chandigarh region showed the peptic ulcer lifetime prevalence of 8.8% with the point prevalence of active peptic ulcer of 3.4%. Gastric ulcers occur most frequently in the older age group and in the lower socio-economic class. Duodenal ulcers, on the other hand, occurs commonly in younger individuals and are evenly distributed among various socio-economic groups [25]. The male-female ratio for duodenal ulcers is about 3:1 and for gastric ulcers is about 1.5 to 2:1 [34].

Peptic ulcers are produced due to imbalance between the gastro-duodenal mucosal defenses (gastric mucus and bicarbonate secretion, cellular resistance, epithelial regenerative capacity, growth factors, prostaglandins, nitric oxide, mucosal blood flow) and damaging forces (gastric acidity and peptic enzymes) due to injurious agents (Helicobacter pylori infection, NSAIDS, smoking,

alcohol, caffeine, corticosteroids, chemotherapy, radiotherapy etc.) or environments (head injury, burn, shock, ischemia, delayed gastric emptying, psychological stress, gastric hyperacidity etc.) [34].

Treatment approaches for peptic ulcer include reducing gastric acid secretion or neutralizing the acid after it is secreted, providing agents that protect the gastric mucosa from damage and eradicating Helicobacter pylori infection [9].

The drugs currently used in the treatment of gastric ulcers are proton pump inhibitors, H2-receptor antagonists, prostaglandin analogues, antacids, anti-cholinergics, sucralfate and anti H. pylori agents. However, the majority of these drugs produce adverse reactions, such as headache, diarrhea (both sometimes severe), rashes, Dizziness, somnolence, mental confusion, impotence, gynaecomastia, and pain in muscles and joints, drug interactions etc [20].

Herbal medicines as the major remedy in traditional system of medicine have been used in medical practices since antiquity [33]. According to WHO, still more than 80% of the world's population relies on traditional herbal medicine for their primary healthcare [29]. It is well known that traditional herbal medicines existed before the application of the modern scientific methods to health care. Exploring traditional herbal medicines in the context of modern science is the need for optimum and proper utilization of traditional plant drugs (A, 2001).

A search for ulcer treatment that is affordable, effective and devoid of side effects seen in currently available drugs, has turn to natural resources [32]. Alpinia Nigra (synonyms Alpinia allughas Retz. and Zingiber nigrum Gaertn.) is a medium-sized herb belonging to the ginger family. The rhizome of the plant is well known in many Asian cultures as a medicinal and culinary item. In many Asian tribal communities it is a part of the diet along with rice. It is endemic to south-east Asia including Bhutan, China, India, Thailand, Bangladesh, Burma and Sri Lanka. In India it is found mainly in the hillocks and riversides of northeastern states such as Assam, Mizoram and Tripura [31].

The aqueous extract of rhizome of Alpinia Nigra (assamese name "Tora") has been traditionally used in Assam for curing health problems like bone weakness, irregular menstruation, jaundice and gastric ulcers (Tushar BS, 2010). Though Alpinia Nigra has been used in the treatment of gastric ulcer traditionally, there is no scientific evidence available on its anti-ulcer potential. Hence, the present work is designed to investigate the antiulcer potential of methanolic extract of rhizome of Alpinia Nigra on experimentally induced gastric ulcer in albino rats.

Aspirin induced gastric ulcer model was chosen because NSAID abuse is the main exogenous cause of refractory peptic ulcer constituting 39% of the cases of peptic ulcer. NSAIDs produce a spectrum of injury to the gastrointestinal mucosa, from haemorrhages and petechiae to erosions and ulcers. Aspirin is known to inhibit PG cycloxygenase, leading to reduced production of PGE and endothelial PGI. This causes vasoconstriction, inhibition of platelet aggregation (enhanced bleeding) and contributes to the enhanced acid secretion. It can also cause mast cell degranulation resulting in the release of histamine. Tissue damaging free radicals which are produced from the conversion of hydroperoxy to hydroxy fatty acids by aspirin further contribute to cell destruction. In our study gastric ulceration was induced by single dose of Aspirin 400 mg/kg on 7th day of the experiment.

Experimental Section

Collection and extraction of plant material: The plants of the Alpinia Nigra was collected from Lahoal, Dibrugarh district in the month of April 2015, and plant material was identified by Dr .L.R Saikia, Professor Department of life science Dibrugarh university, Dibrugarh .A voucher specimen no (DULsc) was deposited at the Department of Life Sciences, Dibrugarh University. Then Fresh Rhizomes of Alpinia Nigra were washed thoroughly with tape water, and dried in shade at room temperature. The methanolic extracts of Rhizomes of Alpinia Nigra were prepared as per the procedure of (Organization for Economic Cooperation and Development guidelines for testing of Chemicals, 2008).

Phytochemical Analysis of Meran

Qualitative phytochemical analysis were carried out for MERAN as per standard methods
described by P Tiwari (Table-2).

Grouping of Animals

Study was carried out on healthy Albino rats of Wistar strain (Rattus norvegicus) of either sex weighing 150-200 grams each. Five groups each containing six animals were used in the study making a total of 30 animals. The animals were kept in Central Animal House, Assam Medical College, Dibrugarh with Bengal gram,wheat, maize, carrot in diet and distilled water sufficiently when required for the entire period of the experiment. Care of the animal was taken under ethical consideration after permission from Institutional Animal Ethics Committee for the laboratory use of animals (Registration No. 634/02/a/CPCSEA; dated 19/05/02).

Acute oral toxicity test for selection of dose

Acute oral toxicity tests for the Methanolic extract of the rhizome of Alpinia Nigra (MERAN)was carried out as per Organization for Economic Cooperation and Development, (OECD) Guidelines 425.The limit test at 2000 mg/kg which required a total of 5 Non-pregnant, nulliparous, healthy adult female albino rats weighing 150-200 gms was used. No sign of toxicity and mortality was recorded in the rats upto the dose of 2000mg/kg (for the extract); hence 1/10th and 1/5th of the 2000 mg/ kg dose, i.e 200mg/kg and 400mg/kg respectively was selected for the study. Two doses were taken to see the dose dependent effect [30].

Table 1: Represents the Grouping of Animals used for the study

GROUP A (Vehicle Control)	Distilled water (5ml/kg) for 7 days
GROUP B (Aspirin Control)	Distilled water (5ml /kg) for 7 days plus Aspirin (400mg /kg as single dose) on 7th day
GROUP C (MERAN 200mg/kg)	MERAN 200mg/kg for 7 days plus Aspirin (400mg/kg as single dose) on 7th day
GROUP D (MERAN 400mg/kg)	MERAN 400mg/kg for 7 days plus Aspirin (400mg /kg as single dose)on 7th day
GROUP E (Standard Control)	Omeprazole(8mg/kg/day) for 7 days plus Aspirin (400mg/kg as single dose) on 7th day

Experimental design

Thirty numbers of healthy albino rats of either sex weighing 150-200 gms was divided and grouped as given in Table-1. All drugs were administered orally with the help of a gavage needle as given in Table-1.

MATERIALS AND METHODS

After administration of aspirin on 7th day of the experiment, the animals were kept fasted overnight and water was given as required. On 8th day pyloric ligation was performed on all the rats under light ether anesthesia as described by (Shay H, 1945). The stomach was replaced and abdomen was then sutured. After 4 hrs the rats were sacrificed with proper doses of ether and stomach was dissected out. After that stomach was opened along the greater curvature and the contents were collected in test tubes for analysis. The mucosa of the stomach was examined for ulcers and subjected for gastric mucus estimation.

The anti-ulcer activity of rhizome of Alpinia Nigra in comparison to omeprazole was tested by estimation of

- Volume of gastric juice by the method of [24].
- Ulcer index by the method of [2]
- Pepsin activity by the method of [19] and [15].
- Free acidity and total acidity by the method of [12].
- Gastric mucus estimation by the method of [3].

Volume of Gastric Juice

The contents of the resected stomachs of the rats were taken in graduated test tubes were allowed to centrifuge at 2000 rpm for 10 minutes. The supernatant fluid was measured for volume of gastric juice and expressed as ml/ 100gm body weight.

Ulcer Index

The resected stomachs of the rats were opened along the greater curvature and were given a gentle wash with running stream of water. The stomachs were then placed on the card board with luminal surface facing up. The ulcer index was then calculated from the glandular portion of the stomach, with the aid of a magnifying glass and measuring tape. The ulcer index was calculated as

$$\text{Ulcer index} = 10/X$$

$$\text{Where } X = \frac{\text{Total mucosal surface}}{\text{Total ulcerated area}}$$

Measurements Rules

- Each lesion was measured along the greatest length.
- In case of petechie, five of these were considered to be equivalent to 1 mm^2 of ulcer area.

Pepsin Activity

1ml of the supernatant gastric juice was diluted with 0.01M HCl (1:250).Then 1ml of the diluted gastric juice ws mixed with 2.5ml of 2% haemoglobin solution in 0.06M HCl. The mixture was allowed to incubate at 370C for 20 minutes and immediately thereafter,0.06 M ice cold trichloroacetic acid was added in equal volume. The tube containing this mixture was allowed to stand in an ice bath for 15 minutes. The mixture was then centrifuged for 10 minutes at 2000 rpm to separate the precipitated proteins. 0.6 ml of the clear supernatant thus obtained was used to determine the liberated amino acids by the methods of [15].

In a 6 ml test tube, 0.6ml supernatant was taken. Then 3ml of reagent C was added to the supernatant and allowed to stand for 10 minutes at room temperature. Then 0.3 ml of reagent E was added with constant stirring. The mixture was allowed to stand for 30 minutes.. Thereafter the sample was read for optical density in a colorimeter at 610 nm, against a blank similarly prepared with distilled water. The pepsin activity is expressed in terms of µmole tyrosine/ml gastric juice.

Free Acidity and Total Acidity

As described by [12], after centrifuging the gastric contents 1ml of the supernatant was taken in a conical flask and diluted with distilled water to make a volume of 10ml. 2 drops of Topfer's reagent was added to it.0.01 N NaOH was taken in a burette and allowed to titrate into the conical flask until the solution in conical flask changed to yellow or the methyl yellow end point. Then 2 drops of phenolphthalein was added and titration was continued till orange colour or phenolphthalein end point was reached. The amount of 0.01N NaOH required to titrate to the methyl yellow end point is the measure of the free acid present. The amount of 0.01 N NaOH required to titrate from the beginning to the phenolphthalein end point is a measure of the total acid present in the sample. The acidity is calculated by the following formula and expressed in mEq/l.

$$\text{Acidity (mEq/l)} = \frac{\text{Volume of NaOH} \times \text{Normality} \times 100}{0.01}$$

Gastric Mucus Estimation

The quantitative estimation of gastric mucus was carried out according to Corne SJ The glandular portions of the previously resected stomachs of the albino rats were excised and weighed. Then they were allowed to soak for 2 hours in 0.1% alcian blue 8GX dissolved in 0.16M sucrose buffered with 0.05 M sodium acetate adjusted to pH 5.8 with HCl. The stomachs were taken out after 2 hours and the uncomplexed dye was removed by 2

successive washes of 15 and 45 minutes in 0.25 M sucrose. The stomachs were then allowed to soak for 2 hrs in 10 ml aliquots of 0.5 M MgCl2 to extract the dye. The resulting blue solutions were shaken briefly with equal volumes of ether and the optical density of the aqueous phase was measured at 605nm against a blank of 0.5 M MgCl2.

The gastric mucus estimation is expressed as mg of alcian blue/gm of glandular tissue of stomach.

RESULTS

The qualitative phytochemical analysis of Meran revealed the phytochemicals as depicted. Phytochemical screening was also done as described by [17] to correlate the phytochemicals with their ulcer protective action. The phytochemical analysis showed the presence of flavonoids, alkaloids, saponins, gum, glycosides and tannins.

Ulcer Index

In the present study ulcer index was reduced significantly by both the treatment groups of Meran. The Aspirin induced group [F (4, 24) = 19.78, P<0.001] expressed significantly elevated Ulcer index in comparison to the vehicle control treated group. Meran 400 mg/kg [F (4, 24) = 14.43, P< 0.001] reduced the ulcer index similar to that of standard Omeprazole 8 mg/kg [F (4, 24) = 17.37, P<0.01] treated group significantly in comparison to the Aspirin induced group. From the above findings of ulcer index it can be concluded that the plant extract prevented the ulcer formation by Aspirin similar to the standard drug Omeprazole. So the Plant Extract (Meran) has ulcer protective effect (Table 3).

Volume of Gastric Juice

In the present study the volume of gastric juice (ml/gm body weight) in Aspirin induced group [F (4, 24) = 55.36, P<0.001] was found significantly elevated in comparison to the vehicle control group. The treatment MERAN 200 mg/kg [F (4, 24) = 16.90, P<0.001] and MERAN 400 mg/kg [F (4, 24) = 46.27, P<0.001] significantly reduced the volume of Gastric juice in comparison to the aspirin induced group. MERAN 400 mg/kg showed similar reduction to standard Omeprazole treated group [F (4, 24) = 46.27, P<0.001] in comparison to the Aspirin Induced group. From the above findings of it can be concluded that the plant extract reduced the gastric juice secretion similar to that of standard drug Omeprazole (Table 3).

DISCUSSION

The present study was conducted to evaluate the anti-ulcerogenic activity of MERAN in experimentally induced gastric ulcer in albino rats. The animals selected for the study were the Swiss albino rats. The rat stomach shows an obvious division into two parts. The upper two fifth non-secretory portion (rumen) is translucent and thinner than the lower three- fifth glandular secretory portion, which is analogous to the body of the stomach in man both anatomically and functionally. The rat being, resembles man nutritionally [18].

For comparison of ulcer protective effect, a standard anti-ulcer agent Omeprazole was taken. Omeprazole the proton pump inhibitor play an important role in the reduction of gastric volume and total acidity and thus perform a cytoproective effect. Omeprazole was found to be most effective drug among different anti-secretory and cytoprotective agents on healing of ulcers induced by aspirin. Omeprazole produced highest protection of 89.74% followed by misoprostol, ranitidine and sucralfate. These inducing methods of gastric lesions are rapid and convenient way of screening plant extracts for antiulcer potency and cytoprotection in macroscopically visible lesions. Omeprazole was given at a dose of 8mg/kg for 7days [18].

The phytochemical analysis of MERAN showed the presence of flavonoids, alkaloids, saponins, gum, glycosides and tannins correlating the extracts with their ulcer protective action. From the above findings of ulcer index it can be concluded that the plant extract prevented the ulcer formation by Aspirin similar to the standard drug Omeprazole. So, the Plant Extract (MERAN) have ulcer protective effect.

Peptic ulceration usually occurs in the presence of high acid levels, such as those found in patients with a gastrinoma (Zollinger–Ellison syndrome), and as all ulcers can be healed in the absence of acid, it is clear that acid is an important etiological factor for peptic ulceration [21]. So, in the present study we evaluated the volume and

Table 2: Phytochemical screening of Meran

Phytochemicals	Meran
Alkaloids	Present
Flavonoids	Present
Tannins	Present
Saponins	Present
Terpenoids	Absent
Gum	Present
Glycosides	Present

Table 3: The effects of methanolic extracts of *Alpinia Nigra* on aspirin induced gastric ulcers in albino rats

GROUP	ULCER INDEX	VOLUME OF GASTRIC JUICE ml/100gm	PEPSIN ACTIVITY µmol tyrosine/4hrs	FREE ACIDITY meq/l	TOTAL ACIDITY meq/l	GASTRIC MUCUS µg alcian blue/gm wet glandular tissue
A. Distilled Water	0.02±0.01	3.49±0.03	349.6±3.59	34.45±0.77	63.94±1.14	68.36±1.39
B. Aspirin Induced (400 mg/kg)	0.76± 0.02^{c}	6.11±0.05^{c}	730.9±8.36^{c}	66.35±1.28^{c}	121.2±1.95^{c}	31.33±0.84^{c}
C. MERAN 200mg/kg	0.60±0.05 ^{c,y,f}	5.31±0.03 ^{c,z,f}	621.7±6.81^{c,z,f}	58.28±0.91^{c,z,f}	106.1±1.24^{c,z,f}	39.91±1.07^{c,z,f}
D. MERAN 400mg/kg	0.22± 0.02^{c,z}	3.92±0.03^{c,z,e}	421.6±5.26^{c,z,e}	46.51±0.76 ^{c,z,e}	75.21±1.24^{c,z}	60.79±1.32^{b,z}
E. Omeprazole 8 mg/kg	0.11±0.01^{z}	3.71±0.02^{c,z}	387.1±2.94^{b,z}	41.34±0.88^{c,z}	70.24±1.15^{a,z}	65.41±1.16^{z}

acidity of gastric juice. From the above findings for the gastric juice estimation it can be concluded that the plant extract reduced the gastric juice secretion similar to that of standard drug Omeprazole suggesting its enhanced potential to heal ulcers and hence its anti-ulcer activity.

The Free acidity and total acidity (mEq/l) of the MERAN 200mg/kg and 400mg/kg treated groups are significantly lower when compared to Aspirin 400 mg/kg treated group. Omeprazole (8mg/kg) treated group also showed significantly lower($p<0.05$) free acidity and total acidity when compared to Aspirin treated group. Similar results were found in the studies by (Das S, 2008) and (K Prasad, 2014). From the above findings it can be interpreted that the plant extract (MERAN) have acid reducing property, which may be the reason for its ulcer protective effect.

Mucin, a highly glycosylated glycoprotein, which is secreted from both gastric surface mucous cells and mucous neck cells, forms a viscous gel which is adherent to the mucosal surface. This adherent mucus gel layer exerts a protective role against (i) acid, by acting as a stable mixing barrier with the epithelium-secreted bicarbonate, (ii) luminal pepsin, by forming a diffusion barrier, and (iii) gastric motility-induced mechanical damage, by acting as a lubricant. The viscous and gel-forming properties of the mucus depend on the polymeric structure of the native high molecular weight glycoprotein. Degraded and lower molecular weight gastric mucins lose both their viscosity and their barrier function. Various noxious factors such as NSAIDs, bile acids and Helicobacter pylori-derived protease and urease reduce the integrity of the gastric mucus gel layer. Maintenance of the polymeric structure of gastric mucus glycoproteins and gastric mucus secretion is therefore essential for gastroprotection [23].

In the present study the gastric mucus estimation (µg alcian blue/gm glandular tissue) was done by the method of [3]. From the above findings it was observed that the plant extract increased the gastric mucus production.

Prostaglandins are also known to stimulate the synthesis of mucus and inhibit gastric acid secretion (W Domschke, 1978) In the present study the plant extract (MERAN 200mg/kg and 400mg/kg) also showed significant increase in mucus secretion and decrease in acid production. Hence it assumed that the ulcer protective effect may be mediated through prostaglandins.

Acid and pepsin are the major aggressive factors believed to play a role in the pathogenesis of peptic ulcer disease. Hydrochloric acid alone in the absence of pepsin does not produce ulceration of the stomach [35]. In the present study the pepsin activity of MERAN 200mg/kg and MERAN 400mg/kg was found to significantly lower when compared to Aspirin 400mg/kg treated group which shows that the plant extract (MERAN) reduces pepsin activity, which may be attributable for its antiulcer effect.

From all the above analysis it can be concluded that the methanolic extract of rhizome of Alpinia Nigra (MERAN) has significant dose dependant anti- ulcer activity in aspirin induced gastric ulcer. The Phytoconstituents Flavonoids, tannins, terpenoids, and saponin are cytoprotective active materials for which anti ulcerogenic efficacy has been extensively confirmed (Table 2). It is suggested that these compounds stimulate mucus, bicarbonate and prostaglandin secretion in gastrointestinal lumen. Tannins prevent ulcer development due to their protein precipitating and vasoconstriction effects. Their astringent action help precipitating micro proteins on the ulcer site, thereby forming an impervious layer over the lining that hinders gut secretions and protects the underlying mucosa from toxins and other irritants. Alkaloids and terpenoids prevent ulcers induced by stress [5].

Gum and Mucilaginous drugs have the property of covering and protecting the mucosa of the stomach and are used in the treatment of gastric ulcer [22].

The methanol extract of Alpinia Nigra showed the presence of flavonoids, tannins, alkaloids, gum and Saponin. These phytoconstituents present in the extract could be the possible mechanism involved in the prevention of gastric lesion in rats.

One of the major underlying factor of peptic ulcer is the generation of free radicals. There is substantial evidence that oxygen derived free radicals play an important role in the pathogenesis of the injury of various tissues, including the digestive system, involvement of oxygen derived free radicals such as the superoxide anion, hydrogen peroxide, and hydroxyl radical are well established in the pathogenesis of ischemic injury of gastrointestinal mucosa and in other models of mucosal damage induced by non-steroidal anti-inflammatory drugs and ethanol [7].

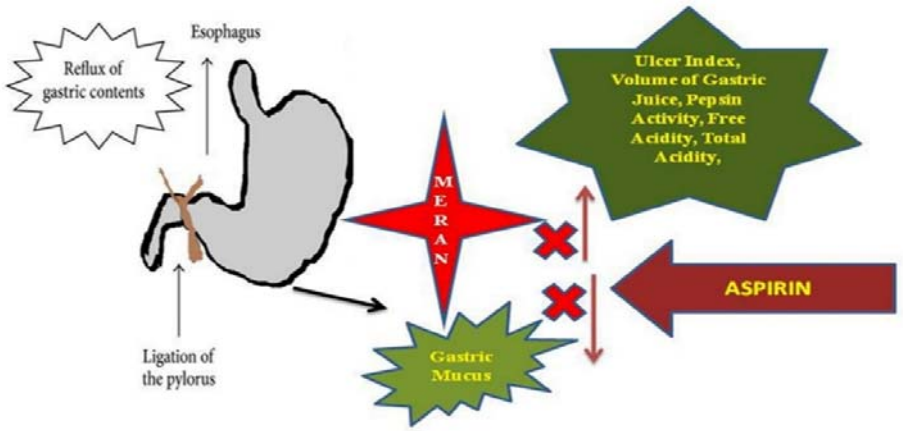


Figure 1: Representing mechanism of action of meran in aspirin induced gastric ulcer in pyloric ligated rats

Flavonoids and tannins are phenolic compounds that act as primary antioxidants for free radical scavengers. As the plant extract (MERAN) also contains flavonoids and tannins which have anti-oxidant property, may be a possible mechanism of gastro-protective activity [7].

CONCLUSION

In the present study the plant extract produces significant reduction of ulcer index, volume of gastric juice, free acidity, total acidity along with increased production of gastric mucus in aspirin induced gastric ulcer.

The anti-ulcerogenic activity of Alpinia Nigra may be due to the presence of bioactive phytochemical compounds like flavonoids, alkaloids, tannins, gum and saponin in the plant. The findings of the present study put forward Alpinia Nigra as a promising new anti-ulcerogenic agent, which can be further confirmed with more refined techniques on animal and human and innovate formulations with lesser adverse and side effects for the treatment of Gastric Ulcers. subjects are required to establish the true potential in terms of therapeutic and economic and economic viability of this herbal plant

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