

## Gastrokinetic and Gastroprotective Activity of Gasex

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### A B S T R A C T

Present study was aimed to evaluate the gastrokinetic and gastroprotective effect of Gasex a polyherbal formulation in experimental models of phenol red test meal method for gastrokinetic activity and acid-induced gastrointestinal lesions for gastroprotective activity. Gasex at a dose of 500 and 1000 mg/kg showed statistically significant gastrokinetic activity by increasing the percentage of gastric emptying and small intestinal transit, the higher dose of Gasex was comparable to the reference standard Domeperidone (10 mg/kg). The higher dose of Gasex (1000 mg/kg) showed gastroprotective activity by significantly decreasing the gastric volume and mean gastric lesion score and the same was reflected in histopathological findings. The present finding highlights few of the underlying modes of action of Gasex in the successful management of various gastrointestinal conditions.

**Keywords:** Gasex, Phenol red, HCl, gastrokinetic , gastroprotective, histopathology.

### Introduction

Indigestion or dyspepsia is a disorder characterized by upper abdominal pain or discomfort, with associated features that may include satiety, upper abdominal fullness, bloating, belching, nausea or heartburn in the absence of any proven structural abnormality. The treatment of dyspepsia is less systematic owing to the lack of its pathophysiological markers. Gastroparesis, or delayed gastric emptying, is another medical condition consisting of a paresis (partial paralysis) of the stomach, resulting in food remaining in the stomach for a longer period of time than normal. It is one of the troublesome complications of long-term diabetes and also numbers of commonly prescribed drugs are known to decrease gastric emptying [1, 2]

The common symptom of gastroparesis includes nausea, early satiety, heartburn, abdominal pain etc. In recent times, prokinetic drugs are used clinically in the management of dyspepsia and gastroparesis along

with proton pump inhibitors, but however the outcomes of such a treatment is far from satisfactory due to availability factors, cost and associated adverse effects. Indigenous or complementary medicines are widely used in the management of dyspepsia but their scientific evaluation is lacking [3]

Ayurveda, an Indian system of medicine has recommended number of drugs from plant sources for the management of indigestion and other gastric disorders [4]. Gasex, an Ayurvedic preparation of The Himalaya Drug Company has been used in the management of patients with dyspepsia and allied conditions for more than four decades. Gasex contains following indigenous herbal materials as a major ingredients: *Aconitum palmatum*, *Piper nigrum*, *Embelia ribes*, *Triphala*, *Zingiber officinale*, *Cowrie bhasma*, *Shankh bhasma* etc. The exact mode of action of Gasex is not evaluated, so the present study was aimed at evaluating its gastrokinetic and gastroprotective activity in experimental models.

## Materials and Methods:

**Drugs and Chemicals:** Gasex (The Himalaya Drug Company, Bangalore), Domeperidone (Torrent Pharmaceuticals Ltd., Ahmedabad, India), Phenol red sodium (SD fine chemicals limited) were used and all the other chemicals used in the experiments were of analytical grade and purchased from reputed suppliers.

### Experimental Animals

Inbred Wistar rats (250-300 g) were used and they were housed in standard conditions of temperature ( $22 \pm 3^\circ\text{C}$ ), relative humidity ( $55 \pm 5\%$ ) and light (12 h light/dark cycle) before and during the study. They were fed with standard pellet diet and water ad libitum. All the experimental protocols were approved by the Institutional Animal Ethics Committee (IAEC) of The Himalaya Drug Company, Bangalore, and the animals received humane care as per the guidelines prescribed by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), The Ministry of Environment & Forests, Government of India.

### Experimental protocol

#### Preparation of Phenol red test meal:

25 mg of Phenol red indicator was weighed and dissolved in 50 ml of distilled water and filtered. The filtrate was heated to  $70^\circ\text{C}$  and it was mixed with methylcellulose (0.75g) with continuous stirring. The mixture was then cooled to  $37^\circ\text{C}$ .

#### Gastrokinetic activity in rats administered with phenol red test meal:

Thirty two adult male Wistar rats, weighing between 250- 300 g were used for the study. The animals were segregated into 4 groups of 8 each. Group-I, served as Control and received DM water, while Group-II and III received Gasex granules 500 and 1000 mg/kg/p.o per day respectively for 7 days and Group-IV served as reference standard received single dose of domeperidone at 10 mg/kg/p.o. on day 8. After 7 days of treatment, all the animals were fasted for 18 hours prior to the experiment and water was provided ad libitum. On day 8, Two hours after the assigned treatment, phenol red meal (0.5 ml/animal) was orally administered to all the animals. Fifteen mins after the

administration of phenol red meal, the animals were euthanized by cervical dislocation and the abdomen was opened and stomach was isolated by ligating the cardiac and pyloric ends. The stomach was cut in to pieces and homogenised with 25 ml of 0.1 N NaOH. To this 5ml of 0.5ml of trichloroacetic acid (20 % w/v) was added and centrifuged at 3000 rpms for 20 mins. To 1 ml of supernatant 4 ml of the 0.5N NaOH was added. The absorbance of resultant pink colour liquid was measured using Synergy Biotek HT spectrophotometer at 560nm wavelength. The percentage of gastric emptying was calculated by the formula:

$$\text{Percentage Gastric Emptying} = 1 - \frac{X}{Y} \times 100$$

Where, X is the amount of phenol red present in the stomach homogenate from test animal and Y is amount of phenol red recovered from control animal.

Similarly, the intestine from duodenum to ileo-cecal junction was dissected out and the distance travelled by phenol red and total length of the intestine (from duodenum to ileo-cecal junction) was recorded. The small intestinal transit (SIT) was calculated by considering the total distance travelled by phenol red meal divided by total length of the small intestine multiplied by 100. [5,6,7]

#### Gastroprotective activity in pylorus ligated rats loaded with HCl:

Thirty two adult male wistar rats, weighing between 250-300 g were used for the study. The animals were segregated into 4 groups of 8 each. Group I and II, served as normal control and positive (pylorus ligated) control and received DM water 10 ml/kg/p.o., Group III and IV received Gasex granules 500 and 1000 mg/kg/p.o. per day respectively for 7 days. On day-8 overnight fasted animals were administered with assigned treatment, one hour after the respective treatment all the animals were subjected to pylorus ligation; In brief, Pylorus ligation was carried out through a midline abdominal incision under ether anaesthesia and the animals were loaded with 10ml/kg

b.wt. of 0.25M HCl and they were euthanized 3 hours after HCl administration by ether overdose. After removing the stomach, the gastric volume and gastric lesion scores were recorded. The degree of gastric mucosal damage was assigned and scaled 0 to 4. The score of 0 : no visible lesions; 1: a few erosions; 2: total lesion area 30 mm<sup>2</sup>; 3: total lesion area 30 mm<sup>2</sup>; 4 : perforation. After scoring, the gastric tissues were processed for histopathology. [8, 9]

**Statistical analysis:** The results of study were expressed as mean ± SEM and analyzed statistically using One Way ANOVA followed by Dunett's multiple comparison test to find out the level of significance. The minimum level of significance was fixed at 95% confidence limit. The analysis was performed using Graph pad Prism software package (Version 4.03).

**Results:**

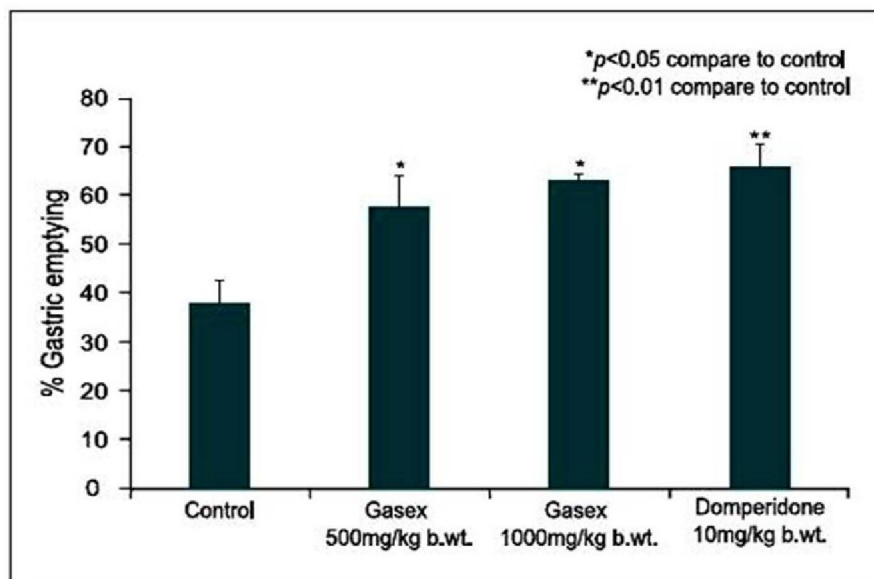


Figure 1: Effect of Gasex on percentage of gastric emptying in rats administered with phenol red test meal.

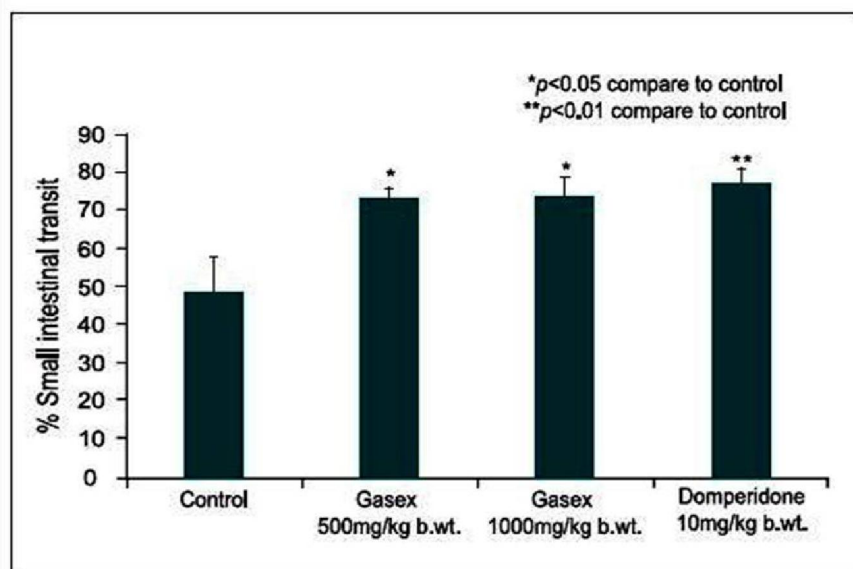


Figure 2: Effect of Gasex on percentage of small intestinal transit in rats administered with phenol red test meal.

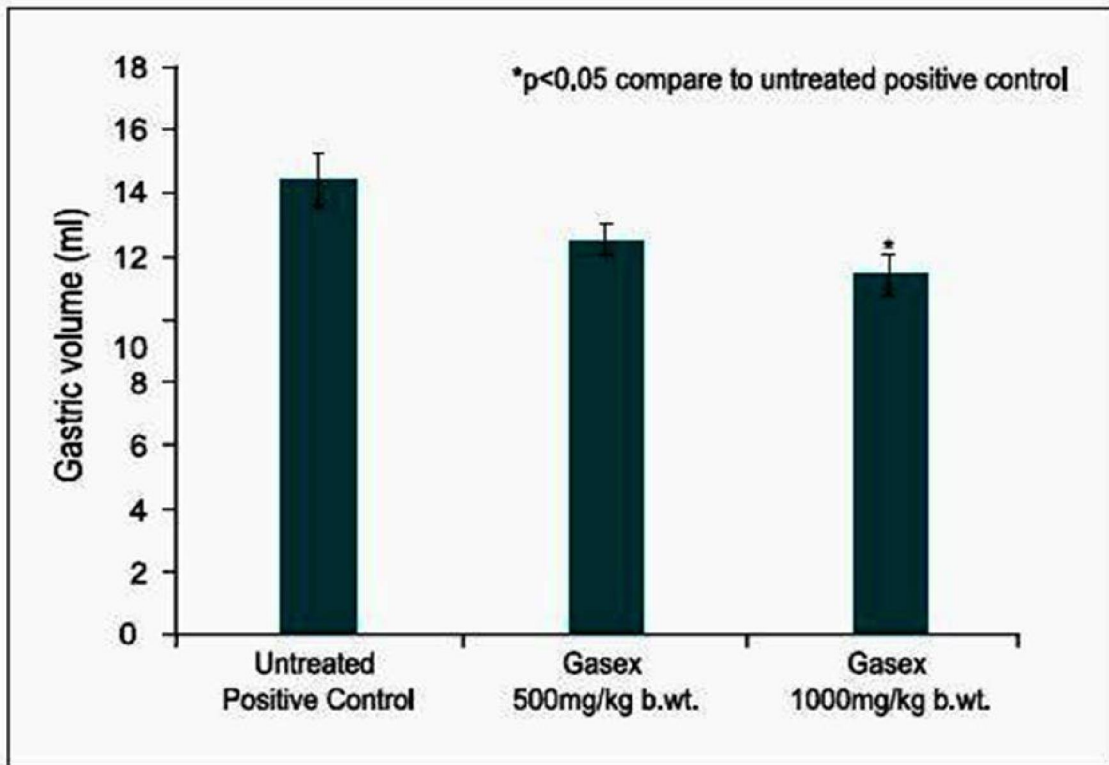


Figure 3: Effect of Gasex on gastric volume in pylorus ligated rats loaded with HCl.

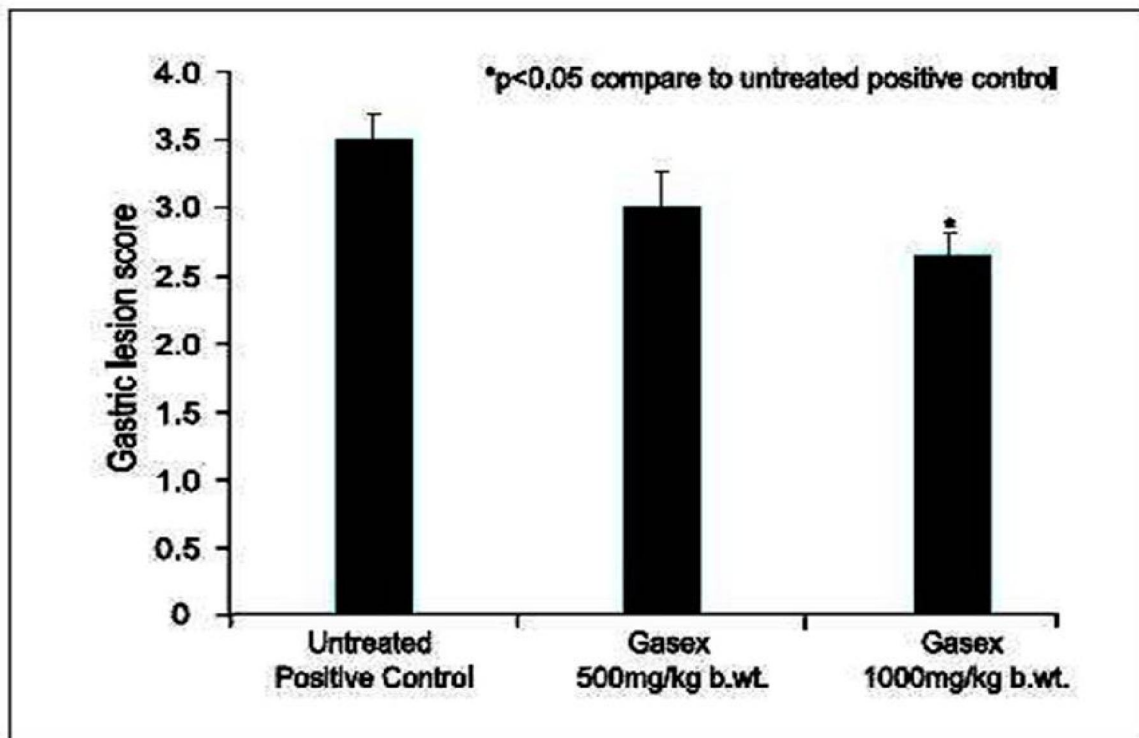
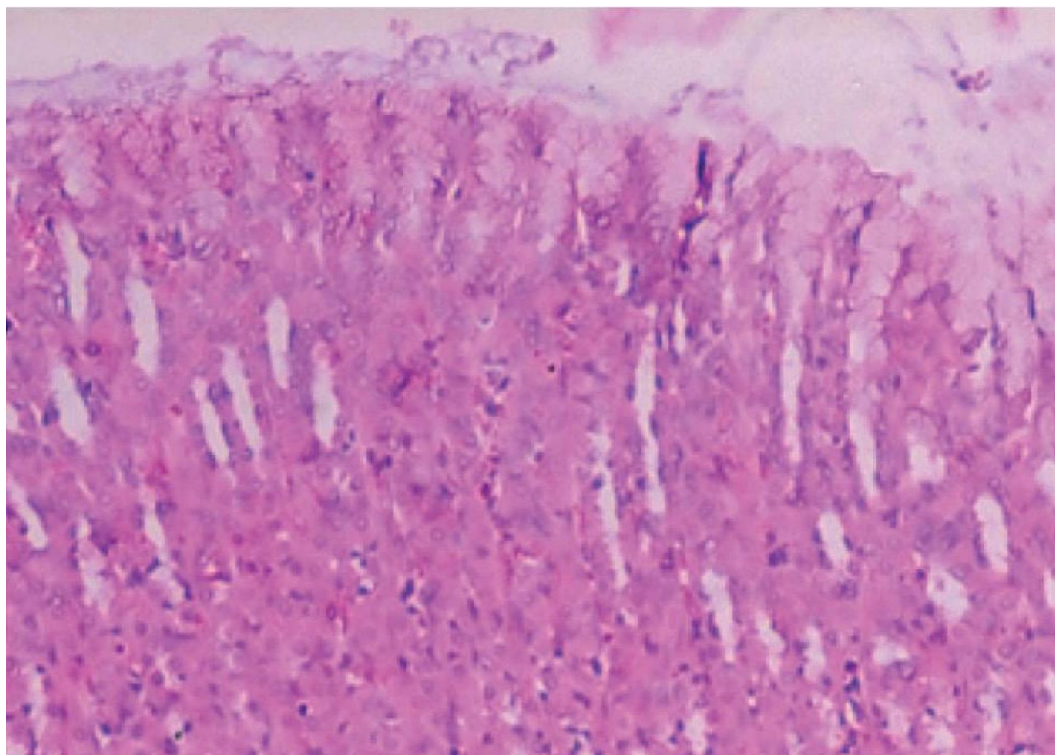
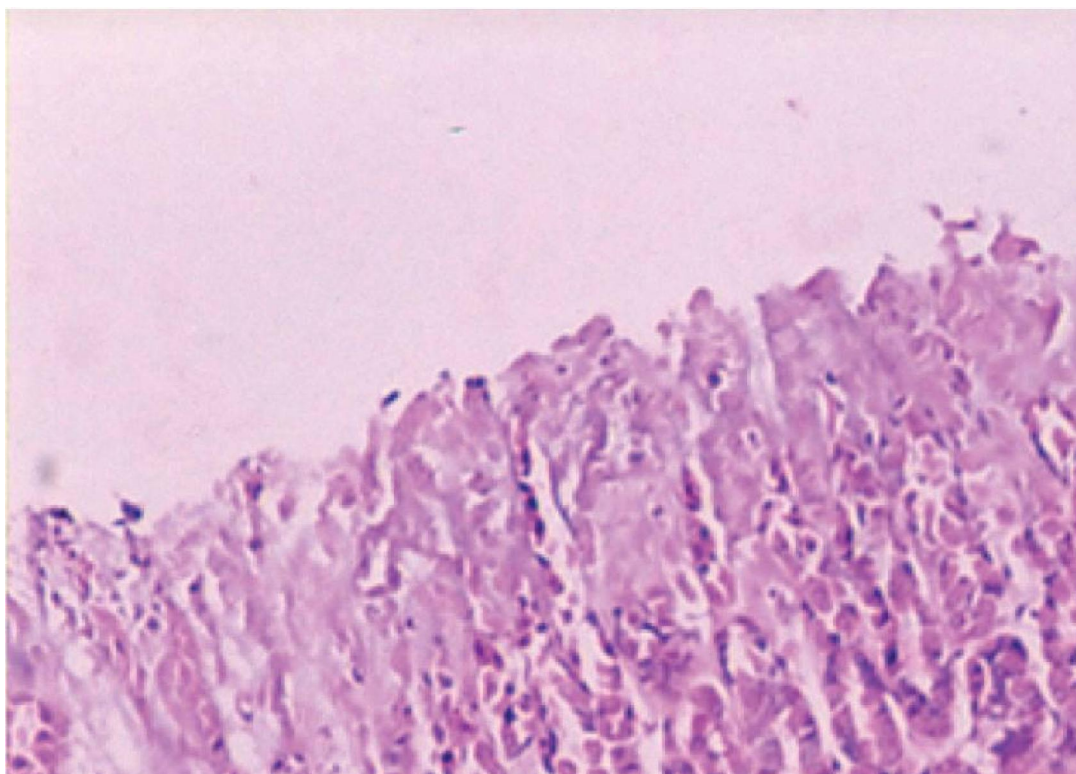


Figure 4: Effect of Gasex on mean gastric lesion score in pylorus ligated rats loaded with HCl.

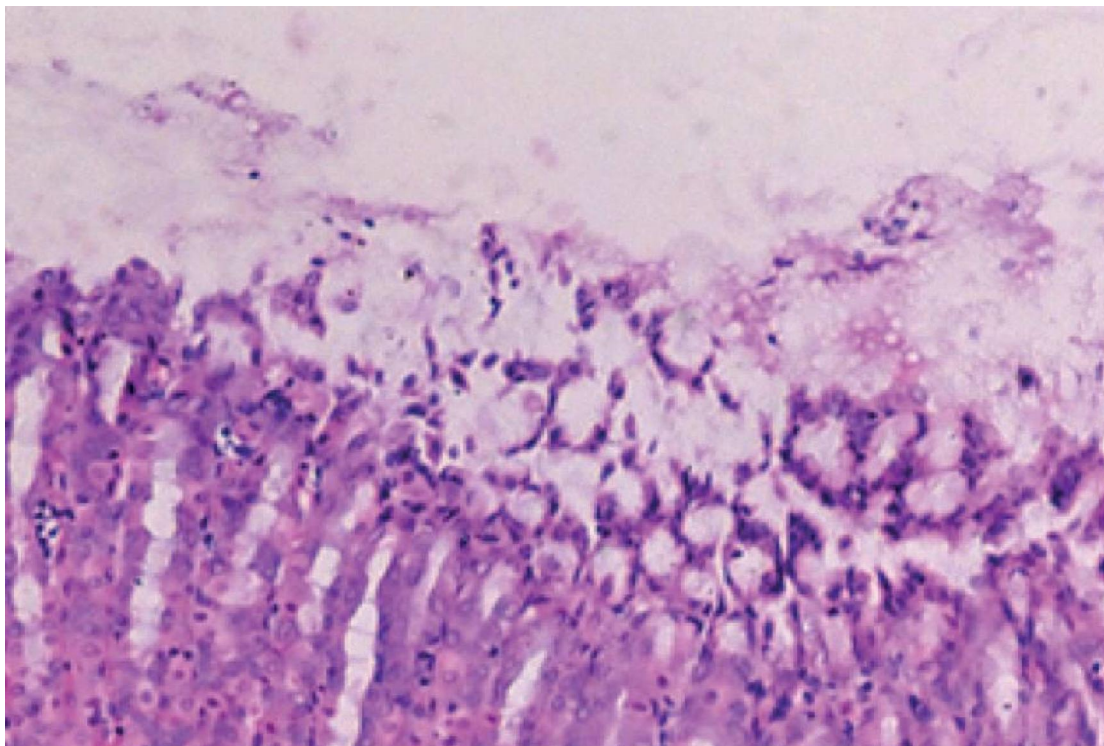




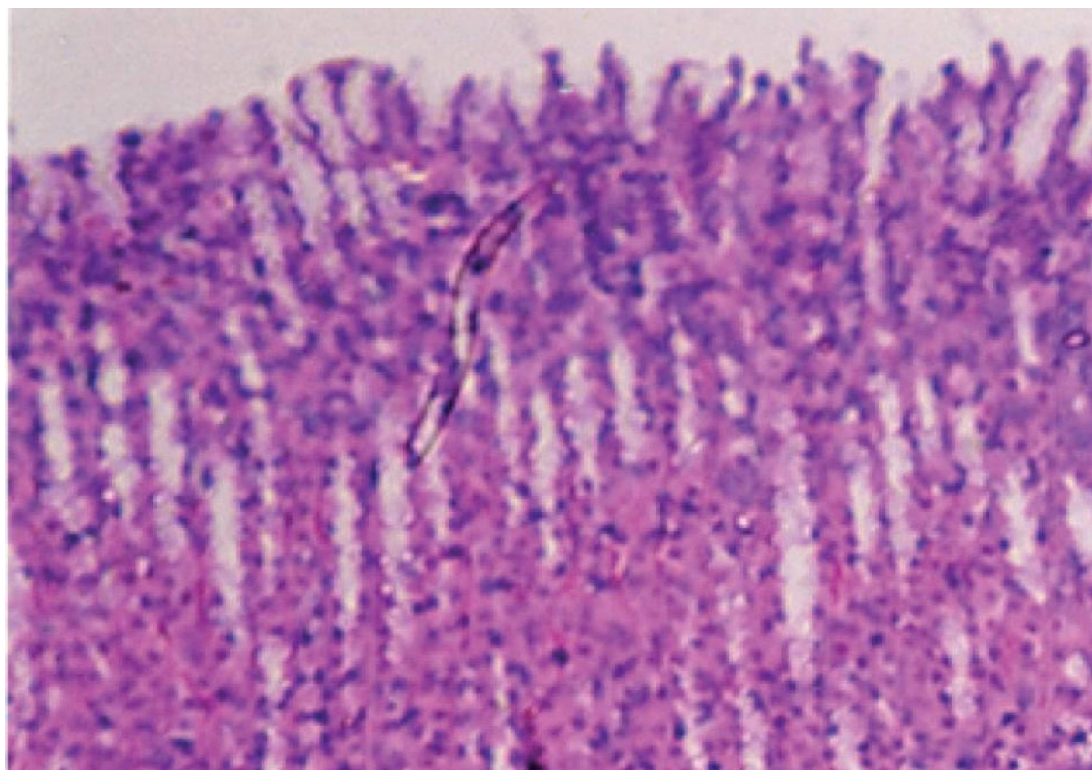
**Figure 5. Section of rat stomach showing normal appearance (H&E x 400).**



**Figure 6. Group II Untreated Positive Control: Section of stomach showing multifocal area of erosion/ulceration of mucosa with edema and leucocytic infiltration in lamina propria (H&E x 400).**



**Fig 7. Group III Animals Treated with Gasex 500mg/kg: Section of stomach showing minimal focal area of erosion/ulcer with surface epithelial damage ((H&E x 400).**



**Fig 8. Group IV Animals Treated with Gasex 1000mg/kg: Section of the stomach showing near normal structure and architectural intactness (H&E x 400)**



## Results and Discussion:

The present pre-clinical study was carried out to evaluate gastrokinetic and gastroprotective activity of Gasex granules in rats.

### Assessment of gastrokinetic activity using phenol red as an indicator:

It was found that Gasex, at both the selected doses exhibited gastrokinetic effect in rats when tested by phenol red meal method. Fifteen minutes after the administration of phenol red meal, gastric emptying in normal rats was found to be 38.18 %, whereas in Gasex (500 and 1000 mg/kg/p.o.) treated groups showed significant increase (57.69 % and 62.81 %) in gastric emptying compared to control untreated group. Further, animals treated with single dose of Domperidone (10 mg/kg/p.o.) showed 65.78 % gastric emptying and which was found to be statistically significant compared to control group (Fig.1).

Similarly, small intestinal transit (SIT) of normal control rats were found to be 48.74 %, whereas in Gasex at a dose of 500 & 1000 mg/kg/p.o (72.97% & 73.40%) and single dose of Domperidone at a dose of 10 mg/kg/po (76.92%) showed a significant increase in SIT percentage compared to control group (Fig.2).The effect observed in groups of animals treated with Gasex was comparable to that of those treated with standard prokinetic drug domperidone at selected dose, method employed and mode of administration.

### Gastroprotective activity in pylorus ligated rats:

Gastric volume was measured in the pylorus ligated rats loaded with 10ml/kg/p.o. of 0.25M HCl. In untreated positive control group the gastric volume was 14.75ml and in the animals treated with Gasex at a dose of 500 and 1000 mg/kg/p.o. it was 12.50 and 11.63ml respectively (Fig.3 & 4). Gasex at a dose of 1000 mg/kg/p.o significantly decrease the gastric volume and mean gastric lesion score compared to untreated positive control. Histopathological evaluation also indicates, Gasex appreciably reversed the acid-induced damage of gastric mucosa in pylorus ligated rats (Fig 5 to 8).The above observation indicates Gasex has gastroprotective activity against acid-induced changes.

Gastric motility disorders can be idiopathic or it can be due to postsurgical states like vagotomy or due to diseases like functional dyspepsia, type 1 diabetes, chronic renal failure, etc. [10], gastric motility disorders are relatively common. In Finnish primary care patients, about 43% of all dyspepsia is functional [11].Patients with functional dyspepsia, 30% have delayed gastric emptying, 40% impaired gastric accommodation and 37% hypersensitivity to gastric distention[12]. Diabetic gastroparesis with delayed gastric emptying occurs in 30 to 50% of both type 1 and type 2 diabetes at tertiary centers [13,14,15]. Delayed gastric emptying occurs in 36% of patients with chronic renal failure [16].Gastroparesis, functional dyspepsia, neuromuscular disorders of the stomach involving both motor and sensory dysfunctions are increasingly recognized as a cause of chronic abdominal symptoms in patients and thus represent significant health care burden [17].

Now a days, several prokinetic drugs like domperidone, metoclopramide and cisapride are used for the treatment of diseases associated with delayed gastric emptying, like gastroparesis, bloating, abdominal discomfort, nausea, vomiting, functional dyspepsia etc.. However their use is limited by an array of side effects, which occur as a result of their widespread actions [4].

Gasex, a well known herbomineral ayurvedic formulation of 'Himalaya Drug Company' is used for various gastrointestinal disorders. Its use in hyperacidity and abdominal discomfort is known, it has been reported to have an effective and safe role in the gastrointestinal complaints such as functional dyspepsia, flatulence, eructation, acid regurgitation, uneasiness with abdominal distension, and epigastric pain etc. It is also widely used prior to radiological investigation of abdomen. [18, 19, 20] but the prokinetic property of this formulation has not been evaluated.

In the present study, Domperidone a potent prokinetic drug has been taken as a reference standard. It is a peripheral dopamine<sub>2</sub>-receptor antagonist which regulates the motility of gastric and small intestinal

smooth muscle and has been shown to have some effects on the motor function of the esophagus. It acts as both an antiemetic and an upper gastrointestinal tract prokinetic agent [21]. It increases basal lower esophageal sphincter pressure, inhibit relaxation of the gastric fundus, enhance antral contractility and relax the pyloric sphincter and also stimulate and coordinate gastroduodenal motility [22,23]. Domperidone has been approved for the symptomatic management of upper gastrointestinal tract motility disorders associated with chronic and subacute gastritis and diabetic gastroparesis[24]. It may also be used to prevent gastrointestinal symptoms associated with the use of dopamine agonist agents in Parkinson's disease. Studies in animals and humans have shown the efficacy of the agent in promoting gastric emptying of several types of liquid and solid meals [25,26]

Most of the herbs used in this formulation have been reported for its effect on gastrointestinal disorders. *Aconitum palmatum* is found to be effective in dyspepsia, stomach irritability and nausea. Cowrie, a naturally processed calcium carbonate, is used in dyspepsia, indigestion, sprue, duodenal and gastric ulcers, and hyperacidity. *Shankha bhasma* which is mainly a silicate of magnesia is derived from conch shell is used in the treatment of ulcers. The fruits of *Piper nigrum* contain piperine, which is reported to have antioxidant activity and may contribute to the prevention of gastric ulcerations. It is known to protect the stomach against ulceration by decreasing the volume of gastric juice, gastric acidity and pepsin. *Embelia ribes* has been found to be effective against helminthes and is also reported to have analgesic and antibacterial activities, which may help in preventing gastric ulcerations. *Triphala*, a homogenous mixture of three fruits— *Emblica officinalis*, *Terminalia chebula* and *Terminalia bellerica* is a rich source of vitamin C, ellagic acid, gallic acid, and chebulinic acid, the phenolic compounds present in these extracts are mostly responsible for their free radical scavenging activity and may be helpful in various gastric problems. *Zingiber officinale*, used to treat various gastrointestinal tract disorders and is known to possess anti-emetic, stomachic and carminative properties [27]. The gastrokinetic and gastroprotective

effect of *Gasex* granules may be due to the synergistic effect of the various herbs used in this formulation.

### Conclusion:

The results of the present set of experiments indicates *Gasex* has gastrokinetic activity when tested by phenol red test meal method and it also has a gastroprotective activity against acid-induced gastrointestinal changes, which may highlight, few of the underlying mode of action of *Gasex* in the successful management of various gastrointestinal conditions.

### Authors contributions:

Mohammed Azeemuddin carried out the major research work, which was helped by Suryakant DA, and Rafiq Mohamed was the chief-investigator of the project. Patki PS and Rangesh P constituted management.

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