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PHARMACOLOGICAL EVALUATION OF HYDROXYOMEPRAZOLE FOR ANTIULCER ACTIVITY USING ANIMAL MODELS

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ABSTRACT
Novel compounds are tried for its antiulcer properties on ethanol and aspirin-induced ulcers in a time and dose subordinate ulcer inquire about. The utilize of new juice as a treatment diminished the stomach's by and large corrosiveness. Compound has antioxidant and anti-ulcer properties. Glutathione (g-glutamylcysteinylglycine, GSH) levels were appeared to be lower in tissues from patients with stomach ulcers. A single dose of COMPOUND in a single plan and 0.5ml/100gm for 15 and 30 days of treatment diminished ulcer file.

KEYWORDS: Compound, GSH, Antiulcer.

INTRODUCTION
Peptic ulcers are wounds in the lesions that most often afflict younger to elderly people. adulthood, however it is possible that this will be detected in adolescence. After a period of days to months of the disease's active phase, it may manifest as an evident sign and symptom.

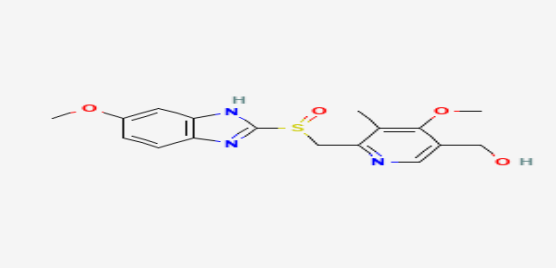
Heal with or without medication. It may also be caused by H. Pylori bacterial infections.

Compounds for the study

- **Compound**

Hydroxyomeprazole
Molecular formula $C_{17}H_{19}N_3O_4S$
Molecular weight 361.4

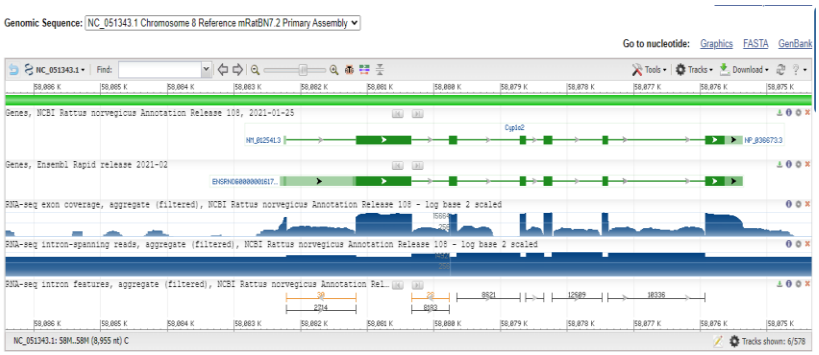
Chemical structure



IUPAC Name
[4-methoxy-6-[(6-methoxy-1H-benzimidazol-2-yl)sulfinylmethyl]-5-methylpyridin-3-yl]methanol

CAS
92340-57-3

Gene
Cyp1a2 cytochrome P450, family 1, subfamily a, polypeptide 2 [Rattus norvegicus (Norway rat)]
Gene ID: 24297



MATERIALS AND METHODS

Chemicals

All the chemicals and reagents used in the study were of analytical grade and procured from reputed Indian manufacturers.

Collection and Characterization of chemical derivatives

Chemical Derivatives will be procured from the GMPL, Hyderabad.

Pharmacological screening animals

The albino rat (average body weight 200-300g), used from in house laboratory. The animals were maintained under standardized environmental conditions (22-28°C, 60-70% relative humidity,12 hr dark/light cycle) in animal house, Department of pharmacology, Shadan Women's College of Pharmacy, Hyderabad. The animals were provided with standard mouse chow (and water *ad libitum*. All animal experiments will be conducted in the present study with prior permission from Institutional Animal Ethics Committee (IAEC approved) and following the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) constituted by the Animal Welfare Division, Government of India.

Pylorus ligation in rat

This model is a simple and convention method for induction of gastric ulceration in the rat through ligature in the pylorus region, the ulceration is affected by accumulation of acidic juice inside the stomach. Ulcer index & pH of gastric content of treated animals are compared with control groups. Different cumulative group administration followed by dose - response curves establishment for ulcer formation can be measured in this method.

Procedure: Rats weighing 150-170 g are starved for 48 hours having access to drinking water ad libitum. During this time, they are housed single in cages in prevent coprophagy. Six animals are used per dose and as control groups. Under mild ether anaesthesia an incision is made at the abdominal midline. The pylorus is closed by using small nylon the higher supervision is required to avoid the damage of blood vessels inside the pylorus region. Grasping the stomach with instruments is to be meticulously avoided; else ulceration will invariably develop at such points. The abdominal wall is sutured through surgical procedure. The test sample are administrated through oral ingestion or injected subcutaneous route. The animals are placed for 19 hours in a suitable plastic container. Afterwards, these animals are sacrificed in CO_2 anaesthesia. The abdomen is re ligated and a ligature is placed above the esophagus region and closer to the diaphragm area. The stomach is replaced to a watch glass and the materials are collected in to a centrifugal tube. Above the longer curvature the stomach fully opened and pinned between a cork plate. The mucosal layer is observed with the help of a stereomicroscope.

Evaluation parameters

- Determination of gastric p^{H}
- Free and total acidity determination
- Volume of gastric secretion
- Ulcer index, Ulcer scores, Size of ulcers, Number of gastric ulcers

Study design

Test animal – 6-8weeks old Adult Wistar rats of male and female, nulliparous and non- pregnant animals were obtained from centralized animal house and acclimatized to holding for 1 week prior dosing.

Housing conditions

Temperature – The experimental animal room temperature maintained at 22°C±3°C OECD guideline-425, 2001. These ranges are designed to allow homeotherms to maintain metabolic rate or to be within their thermo neutral zones. Because, temperature below the recommended range leads to increased food intake, increased energy expenditure but decrease in efficiency. In contrast, temperature above the recommended range leads to decreased food intake, decreased weight and decreased energy expenditure. Toxicity can vary with temperature might increase with linearity with temperature.

Humidity – The relative humidity maintained at 40%-60% preferably not exceeds 70% (OECD-425, 2001).The relative humidity below the recommended range can develop lesions such as ring tail and food consumption may be increased.

Light – 12-12 hours, Light/dark cycle. Appropriate lighting and light cycle play a key role in maintaining the physiology and the behavior rat. Light provided for adequate vision and for neuroendocrine regulation of diurnal and circadian cycles (CPCSEA guidelines for laboratory animal facility 2003).

Light intensity – The light intensity maintained at 325 lux approximately 1m above the floor. Consideration of variations in light intensity, for the arrangement of animals on cage rack for toxicology study is necessary.

Caging – Polypropylene cages with solid bottom and walls. Lids made up of stainless steel grill capable of holding of both feed and water.

Feeding condition – Sterile laboratory feed (*ad libitum*) and RO water bottles daily.

Feed – Brown colored chow diet

Drug administration – Animals were fasted for 12hour prior to dosing on day 0. Treatment rats were dosed by oral gavages, using a curved and ball tipped stainless steel feeding needle, with 20% gum acacia solution.

Clinical observations – All rats were monitored continuously for 4 hour after dosing for signs of toxicity. For the remainder of the 14 days study period, animals were monitored and any additional behavioral or clinical signs of toxicity. Animal's body weight was measured prior to dosing and on days 7 and 14.On all animals were killed and at the end of the study LD_{50} value was

established. Clinical observations and gross pathological examination was carried out.

Ethanol induced gastric ulcer

Albino Wistar rats of both sex having (150-200g) are divided in to 5 groups of 6 animals each. They are housed in individual cages and fasted for 24hrs allowing free access to drinking water. Care being taken to avoid coprophagy. Ulceration was induced in 36 hours without feeding the rats by the administration of 80% ethanol orally in a dose of 1ml for each rat. Test and Standard is given each dose level of rat, one hour before the ethanol administration. After two hours of ethanol administration, animals will be sacrificed by CO_2 poisoning. The stomach is dissected out, opened along the greater curvature and the contents are drained in a centrifuge tube and were centrifuged at 1000rpm for 10 minutes and the volume is noted. The p^H of the gastric juice is recorded by using a p^H meter. Then the contents are subjected to analysis for free and total acidity. The stomachs are then washed with running water to see for ulcers in the glandular portion of the stomach. The numbers of ulcers per stomach are noted and severity of the ulcers scored microscopically with the help of 10x lens.

Experimental design

24 rats are divided into 4 groups of six rats each (n=06) and treated orally as follows –

Group-1: (normal): it was used as a normal saline rats seven days.

Group-2: (Aspirin): rats received distilled water orally daily for seven days, on the fifth day rats received oral dose of Aspirin.

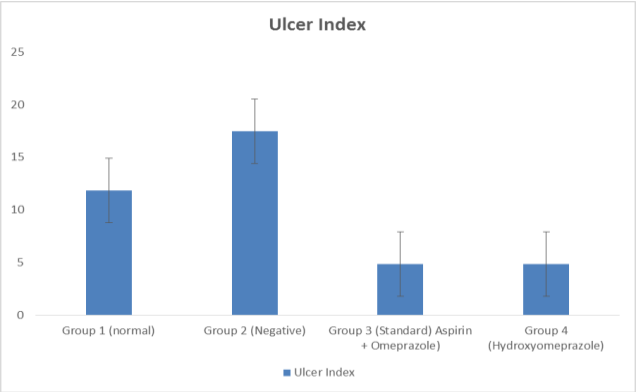
Group – 3: (Aspirin + Omeprazole): rats received Omeprazole orally daily for seven days, on the fifth day rats received oral dose of Aspirin.

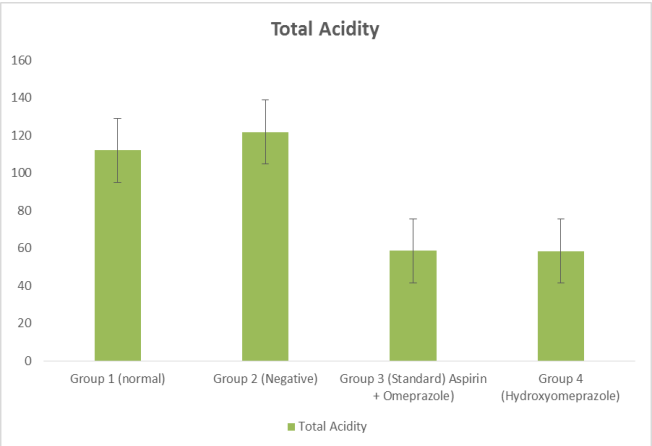
Group-4: (Aspirin + *Hydroxyomeprazole*): rats received extract orally for seven days; on the fifth day rats received oral dose of Aspirin

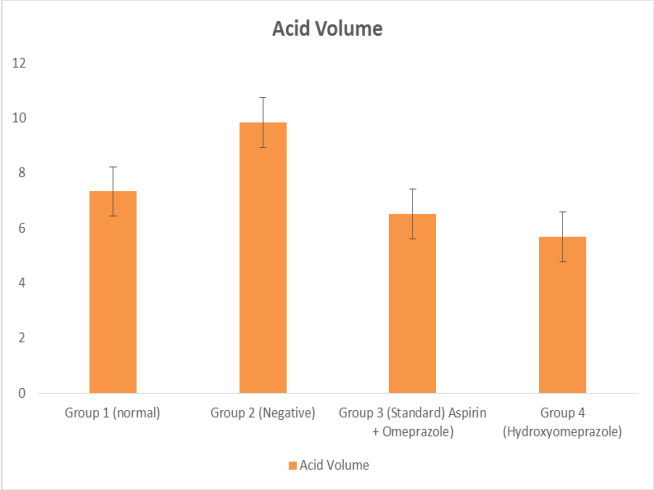
RESULTS

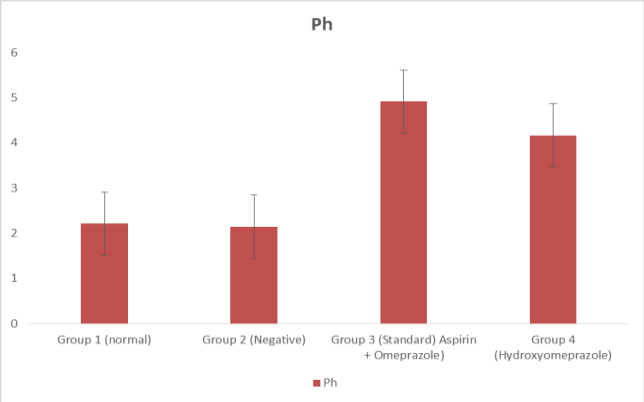
Dose dependent studies of COMPOUND using ethanol induced ulcer model rat model

Treatments	Ulcer Index	Total Acidity (m Eq/L)	Acid Volume (ml)	Ph
Group 1 (normal)	11.830 0.16	112.113 ± 0.12	7.332 ± 0.16	2.210 ± 0.13
Group 2 (Aspirin)	17.459 ± 0.24	121.868 ± 0.25	9.843 ± 0.08	2.141± 0.33
Group 3 (Standard) Aspirin + Omeprazole	4.821 ± 0.08	58.584 ± 0.34	6.511 ± 0.05	4.916 ± 0.04
Group 4 (Hydroxyomeprazole)	4.837 ± 0.07	58.386 ± 0.03	5.685 ± 0.12	4.164 ± 0.29



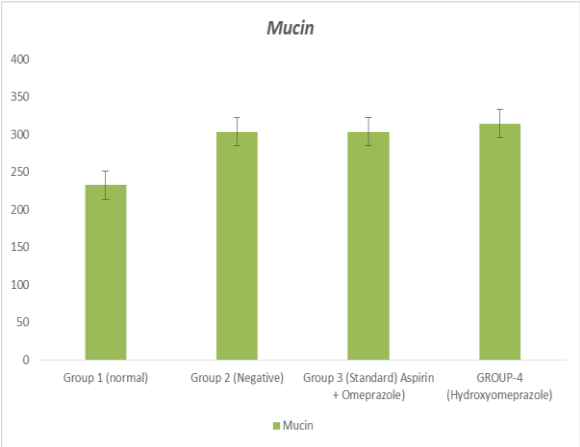


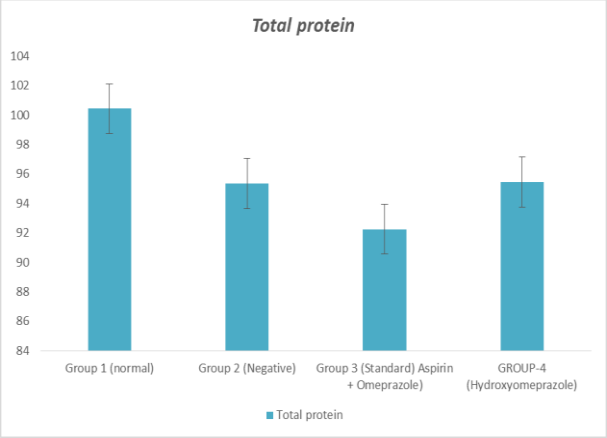


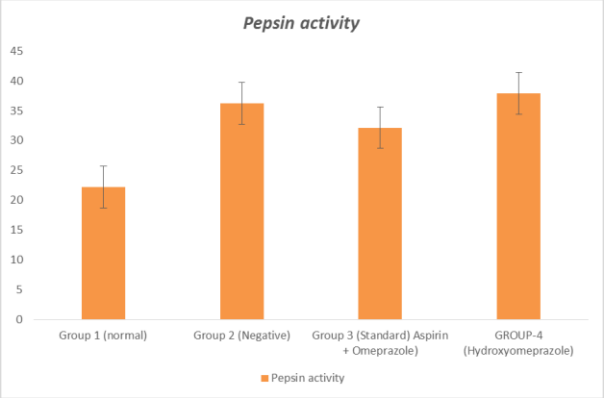


Estimation of mucin, total protein and pepsin activity

Grouping of animals	*Mucin*	*Total protein (µg/ml)*	*Pepsin activity (µmole/ml)*
GROUP-1	232.68 ± 0.38	100.43 ± 0.26	22.24 ± 0.28
GROUP-2	303.56 ± 0.26	95.35 ± 0.28	36.25 ± 0.25
GROUP-3	303.43 ± 0.31	92.24 ± 0.12	32.16 ± 0.19
GROUP-4 (Hydroxyomeprazole)	314.56 ± 0.16	95.45 ± 0.18	37.87 ± 0.19







DISCUSSION

The antiulcer activity was related with the decrease in the gastric ulcers, gastric acidity volume.

In Group 4, results not only a lower acid volume but also the maximum degree of antiulcer activity attributing to lowest ulcers. These findings are important.

The level of gastric juice inhibition in classes was found to be less moderate.

CONCLUSION

The above results can be inferred that the similar Compound against induced ulcer in the rat model can be called as an adjuvant in ulcer treatment that can greatly reduce the adverse effects caused by oral NSAIDS agents such as Aspirin.

The efficacy and feasibility of the long-term usage of this formulation as a potential antiulcer agent have been demonstrated in planned pre-clinical procedure in the form of low doses of the formulation Compound.

Aspirin treatment on rats caused increase in the frequency of gastric ulcerations.

The standard drug Omeprazole doesn't showed any significant difference in the results because of low dosage whereas the high dosages of medicine has an extra pain relief impact on Aspirin induced rats and is proved to be possessing anti ulcerative activity.

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