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Original Research Article

Gastroprotective effects of 1-Hydroxy-2-phenylbenzimidazole in Ethanol-induced Gastric Ulcers in Rats.

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Abstract

Introduction: Benzimidazole compounds are known for their reduction of gastric secretion by inhibition of H+/K+-ATPase enzyme.

Aim: The gastroprotective activity of the synthesized 1-hydroxy-2-phenylbenzimidazole (HPB) is examined on gastric lesions induced in rats by the oral ingestion of ethanol.

Methods: Gastroprotective activity was evaluated by estimation of the numbers and cumulative lengths of glandular gastric ulcers induce by ethanol. The effect of pretreatment with HPB given alone and in combination with ranitidine on the number and length of gastric ulcers; and as well as on gastric volume and total gastric acidity were investigated.

Results: Pre-treatment of rats with HPB at the doses of 25 and 50 mg/kg IP, significantly decreased the number and the length of ethanol induced gastric ulcers compared to control group. The highest curative ratio 53.89% and the most reduction of gastric acidity were obtained with the highest dose of HPB (50 mg/kg) in combination with ranitidine. Histopathological findings confirmed the protective effect of the HPB.

Conclusion: The synthesized benzimidazole derivative (HPB) provided a gastroprotective effects on ethanol-induced gastric lesions in rats. This protective activity may be partly due to its ability to attenuate acid secretion.

Key-words:

Peptic ulcer, 1-Hydroxy-2-phenylbenzimidazole, ranitidine, rats.

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INTRODUCTION

Peptic ulcer disease (PUD) is one of the most common diseases affecting the gastrointestinal tract. It causes inflammatory injuries in the gastric or duodenal mucosa. The etiology of the disease is multifactorial, the mechanisms normally operating to protect the mucosa from self-digestion by the acid and pepsin of gastric juice either failing or being overcome by a combination of injurious factors [1, 2, 3].

The pharmacological treatment of PUD is based on using drugs such as antacids, acid suppressive agents (antisecretory drugs) and cytoprotective agents. Antimicrobials are also used for eradication of *H. pylori*[4].

Ethanol induced peptic ulcer is one of the most common methods used to study effects of drugs and their mechanisms in peptic ulcer [5].

A series of benzimidazole derivatives have proven to possess antiulcer activity through inhibition of proton pump [6]. The current study is conducted to evaluate the gastroprotective effect of 1-hydroxy-2-phenylbenzimidazole (HPB) on gastric lesions induced by ethanol in rats.

MATERIAL & METHODS

Synthesis of 1-hydroxy-2-phenyl-benzimidazole:

The HPB was prepared according to the method described by Stacy[7], by refluxing a solution of 13.8 gms (0.10 mole) of *o*-nitroaniline and 21.2 gms (0.20 mole) of benzaldehyde in 20 ml of dry toluene for 3 days during which time 2.2 ml of water was collected in a Dean-Stark trap. After the reaction mixture had been cooled, 18.5 gms of product was obtained by filtration. This crude product was purified by treatment with boiling ethanol, yielding 18.0 gms (86%).

Animals:

Male Albino Wistar rats bred at the animal care unit, department of pharmacology and clinical pharmacy, faculty of pharmacy, weighing between 150-200 gms were used. The animals were housed at constant room temperature (20-25°C) under 12 hours light/dark cycles. Standard food pellet diet and water were available ad libitum. The animals were fasted for 24 hours prior to all experiments with free access to water only. The study was approved by the Faculty of Pharmacy and the experiments were done according to the ethics guidelines of the University.

Drugs& Chemicals:

Benzaldehyde and *o*-nitroaniline and were used as received from the chemical supplier. Solvents such as toluene and absolute ethanol 99% were used without further purification. Ranitidine hydrochloride (Sigma-Aldrich, Germany) was dissolved in distilled water. Carboxymethyl cellulose powder (CMC), sodium hydroxide (0.01 N NaOH), and normal saline (0.9% NaCl) are aqueous solutions prepared by dissolving the chemicals in distilled water. Phenolphthaline (pph) indicator is prepared by dissolving phenolphthaline in ethanol.

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Ethanol-induced gastric ulcer:

Rats were given an oral dose of absolute ethanol (1ml/200gms) and were killed 30 minutes after ingestion of ethanol by exposure to diethyl ether[8]. A midline abdominal incision was made and the stomach rapidly removed after legating both the oesophageal and pyloric ends. Each stomach was opened along the greater curvature; its content was drained and completely recovered by washing with 10 ml isotonic saline.

Each stomach was pinned flat on paraffin wax-filled Petri dish and examined for ulcers using a hand lens (X10). The sum of the total length long of ulcers and petechial lesions (each five petechial lesions were taken as 1 mm of ulcer) in each group of rats was divided by its number to calculate the ulcer index (mm). The curative ratio was determined according to the formula described by Khazaei and Salehi [9] as follows:

$$\text{Curative ratio} = \frac{\text{(Control ulcer index)} - \text{(test ulcer index)}}{\text{(Control ulcer index)}} \times 100$$

Experimental protocols:

Rats were randomly divided into 7 groups of six animals each. Group 1 was the sham operated control and was given 1 ml of 0.5%, CMC only. Group 2 was the control ulcer and was given 1 ml/200 gms absolute ethanol. Group 3 was given ranitidine 50 mg/kg + 1 ml/200 gms ethanol. Group 4 was given HPB 25 mg/kg + 1 ml/200 gms ethanol.Group 5 was given HPB 50 mg/kg + 1 ml/200 gms ethanol. Group 6was given ranitidine 50 mg/kg + HPB 25 mg/kg + Ethanol 1ml/200gms.Group 7 was givenranitidine 50 mg/kg + HPB 50 mg/kg + ethanol 1ml/200gms.

Ranitidine was given intraperitoneally (50 mg/kg, IP) to groups 3, 6 and 7, one hour before ethanol administration. Intraperitoneal injection of different doses of HPB to groups 4, 5, 6 and 7 was given one hour before administration of ethanol. All animals were killed one hour after ethanol administration. The stomachs removed and processed as explained above for evaluation of induced ulcer, gastric acidity and histopathological manifestation.

Determination of gastric content:

The recovered solution was centrifuged (Heraeuslabofuge 400, Heraeus, Germany) at 3500 rpm for 10 minutes to remove contaminating debris. The remaining supernatant was used for acid determination. One ml of the supernatant was completed to 50 ml with distilled water and titrated against 0.01N NaOH, using phenolphthalein as indicator. Acid content was expressed as µEq/100 g body weight[10].

Histopathological analysis:

After the evaluation of stomachs for induced ulcers, specimen from each rat stomach was fixed in 10% buffered formalin overnight and embedded in paraffin. Sections were cut at a thickness of 5 µm and stained with hematoxylin and eosin (H&E) as previously described[11]. Three slides were investigated from each specimen in a blind fashion for histological changes.

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Statistical analysis:

Data are expressed as mean ±S.E.M. Statistical calculations were done with SPSS 18.0 software package. Comparison between two groups was performed using Student's t-test and comparison between more than two groups was carried using one-way analysis of variance (ANOVA). Differences between groups were considered significant when the degree of confidence was 95% or better ($P< 0.05$).

RESULTS

Effect of HPB on gastric ulcers induced by ethanol

Pre-treatment of rats with HPB at the doses of 25 and 50 mg/kg IP, significantly decreased the number of gastric ulcers compared to control group. The mean number of ulcers were 4.00±0.79, 3.33±0.84 and 7.65±1.04, respectively($P<0.01$). The standard antiulcer drug ranitidine given in a dose of 50 mg/kg IP, significantly reduced the number of gastric lesions compared to control group (5.11±0.36 vs 7.65±1.04, respectively) (Figure 1). The macroscopic appearance of stomachs from different treatment groups are shown in Figure 4 a-g. The higher dose of HPB (50 mg/kg) combined with ranitidine resulted in a significant reduction in the number of gastric ulcers compared to control ulcer group (2.42±0.33 and 7.65±1.04 respectively). The dose of HPB (25 mg/kg) combined with ranitidine failed to provide such reduction in the number of ulcers (Figure 1).

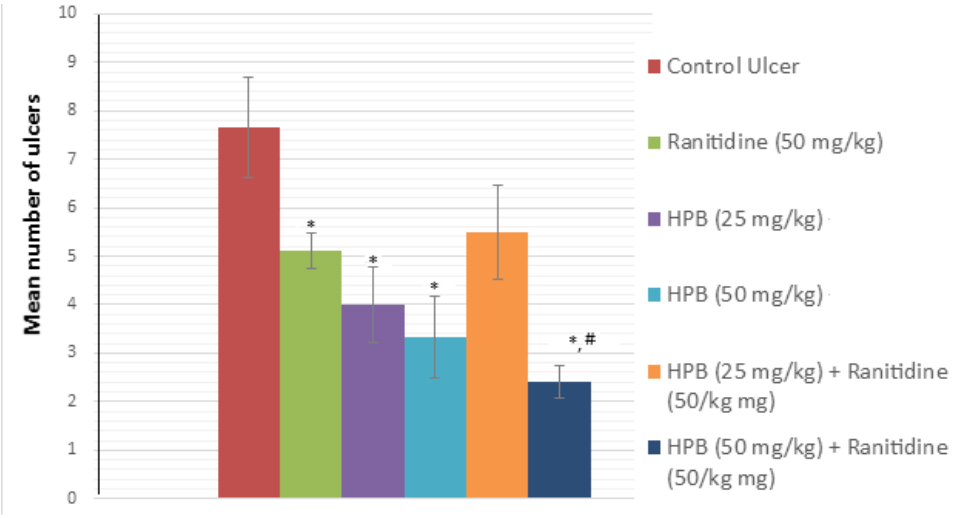

Figure 1: Effect of compound HPB and ranitidine on the number of ethanol-induced gastric ulcers in rats. Data are expressed as mean ± SEM (n=6). *$P<0.05$, significantly less than control ulcer group. #$P<0.05$, significantly less than ranitidine group.

Treatment of rats with ranitidine and HPB (25 and 50 mg/kg) alone resulted in a significant reduction in ulcer length compared to ethanol control group (5.77±0.17, 6.12±0.21, 4.40±0.21 mm vs 9.50±0.36 mm respectively). The curative ratio of ranitidine, HPB (25 and 50 mg)

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compared to ulcer control group were 39.26%, 35.57%, and 53.68% respectively. In the combination groups, the most significant reduction in length of gastric lesions was obtained with ranitidine and HPB 50 mg/kg when given together compared to ulcer control group (4.38±0.20 mm vs 9.5±0.36 mm respectively). The curative ratio of HPB doses of 25 and 50 mg/kg plus ranitidine were 21.58% and 53.89% respectively compared to ulcer control group (Figure 2).

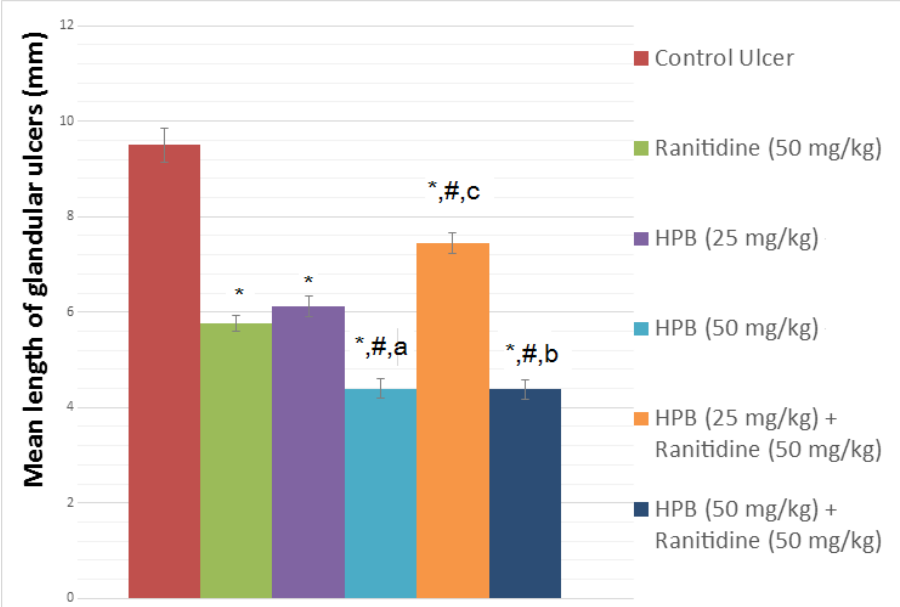

Figure 2: Effect of compound HPB and ranitidine on the length of ethanol-induced gastric ulcers in rats. Data are expressed as mean ± SEM(mm) (n=6). * *P*<0.05 significantly less than control ulcer group.# *P*<0.05 significantly different from ranitidine group. (a) *P*<0.05 significantly different from the group given 25 mg/kg HPB without ranitidine. (b) *P*<0.05 significantly different from the group given 50 mg/kg HPB without ranitidine. (c) *P*<0.05 significantly different from the group given the corresponding dose without ranitidine.

Effect of HPB on the volume of gastric juice and total gastric acidity in rats treated with absolute ethanol:

Animals treated with ethanol alone had the highest gastric volume. Pretreatment with HPB at 25 and 50 mg/kg either alone or combined with ranitidine 50 mg/kg, significantly and dose-dependently reduced the volume of gastric content compared to the ethanol control group (1.75±0.10, 1.60±0.11, 1.58±1.30, 0.88±0.09 ml vs 2.35±0.18 ml respectively). The higher dose of HPB (50 mg/kg) plus ranitidine produced a highly significant reduction in comparison to the positive control ranitidine given alone (0.88±0.09 ml vs 1.67±0.08 ml respectively) (Table 1).

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Table 1. Effect of treatment with compound HPB on the volume of gastric content in rats.

Treatment group	Volume of gastric content
Sham	1.30 ± 0.16*
Control ulcer	2.35 ± 0.18
Ranitidine (50 mg/kg)	1.67 ± 0.08*
HPB (25 mg) + ETOH	1.75 ± 0.10*
HPB (50 mg) + ETOH	1.60 ± 0.11*
HPB (25 mg) + Ranitidine (50	1.58 ± 0.13*
HPB (50 mg) + Ranitidine (50	0.88 ± 0.09*,#

***Data are expressed as mean ± SEM (n=6) *P<0.05, significantly different from the control ulcer group. # P<0.05 significantly less than the ranitidine group*.**

The total gastric acidity was significantly attenuated in the group treated with ranitidine and in groups treated with HPB (25 and 50 mg/kg) alone and in combination with ranitidine compared to the ulcer control group (224.3±8.41, 195.33±3.52, 178.00±3.5, 135.17±5.78 and 93.50±4.24 vs 264.50±8.27 respectively). The reduction in total acidity with the higher dose of HPB (50 mg/kg) was significantly higher than the standard antiulcer drug ranitidine (93.50±4.24 vs 224.3±8.41) (Figure 3).

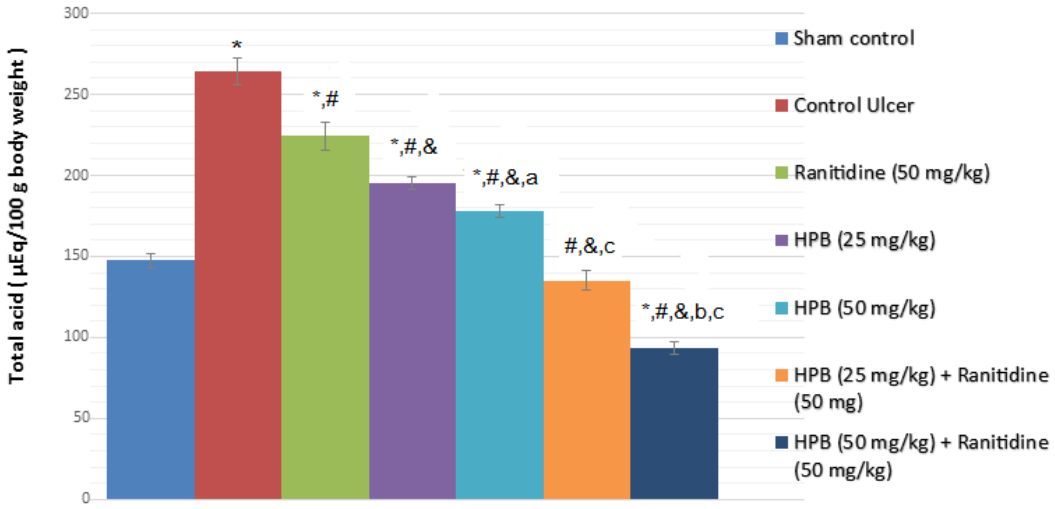

Figure 3: Effect of compound HPB on total gastric acidity in rats treated with absolute ethanol. ****P*<0.05 different from sham; # *P*<0.05 less compared to control ulcer; & *P*<0.05 significantly less compared to ranitidine group. (a) *P*<0.05 significantly less than small dose group without ranitidine, (b) *P*<0.05 significantly less than the group given small dose of HPB with ranitidine. (c) *P*<0.05 significantly less than the corresponding dose without ranitidine.

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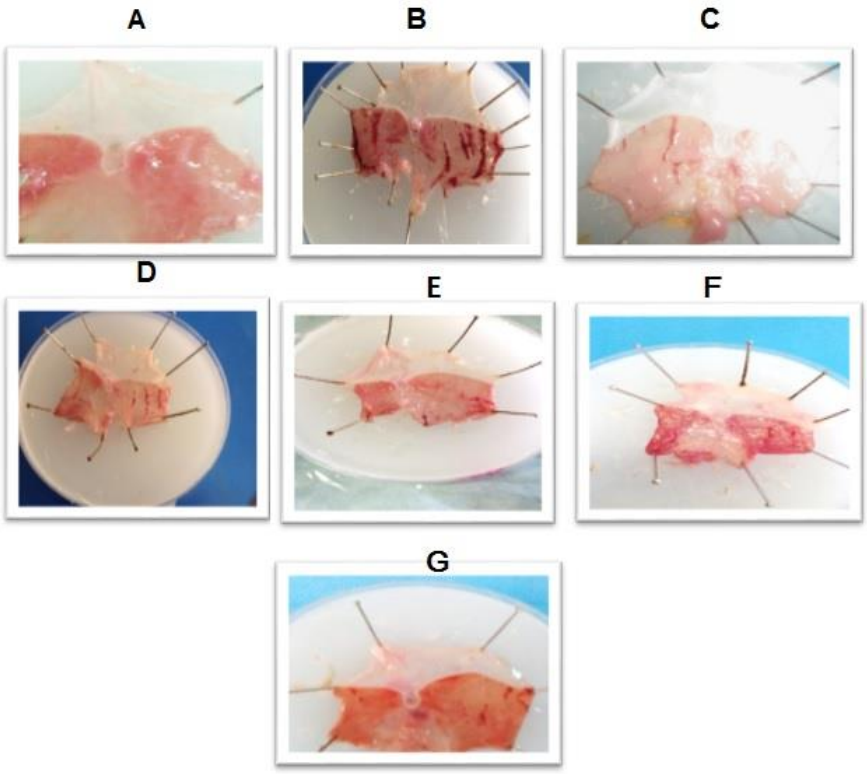

Figure 4: Representative stomachs of rats treated with CMC A: (0.5%), B: absolute ethanol, C: ranitidine (50 mg/kg), D&E: HPB (25 and 50 mg/kg), F&G: HPB (25 and 50 mg/kg) + ranitidine (50 mg/kg). Black arrows indicate longitudinal haemorrhagic lesions (characteristics of ethanol-induced ulcers).

Rats treated with absolute ethanol (control ulcer) demonstrated noticeable ulcerogenicity as indicated by the presence of longitudinal and petechial haemorrhagic lesions and hyperemia in the glandular part of the stomach. The lesions were located in the glandular portion of the stomach and were parallel to the axis (Figure 4 b). The macroscopic appearance of stomachs from different treatment groups are shown in figure 4 A-G.

Assessment of the histology of the gastric mucosa in ulcer control rats showed multiple areas of mucosal erosion, mucosal haemorrhage and acute inflammation mainly neutrophils (Figure 5 B). Pre-treatment with HPB at both doses (25 and 50 mg/kg) resulted in an improvement of mucosal architecture but with slight submucosal oedema (Figure 5 D & E). On the other hand, pre-treatment with ranitidine (50 mg/kg) showed acute inflammation mainly neutrophils and lymphoid aggregation, but with no mucosal erosion (Figure 5 C). Combination treatment with ranitidine and HPB resulted in a significant improvement of mucosal protection against ethanol-induced lesions with the higher dose of HPB (50 mg/kg) plus ranitidine

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producing the maximum protection. The histopathological micrograph showed moderate disruption to the epithelium surface although the gastric wall appears almost normally (Figure 5 F & G).

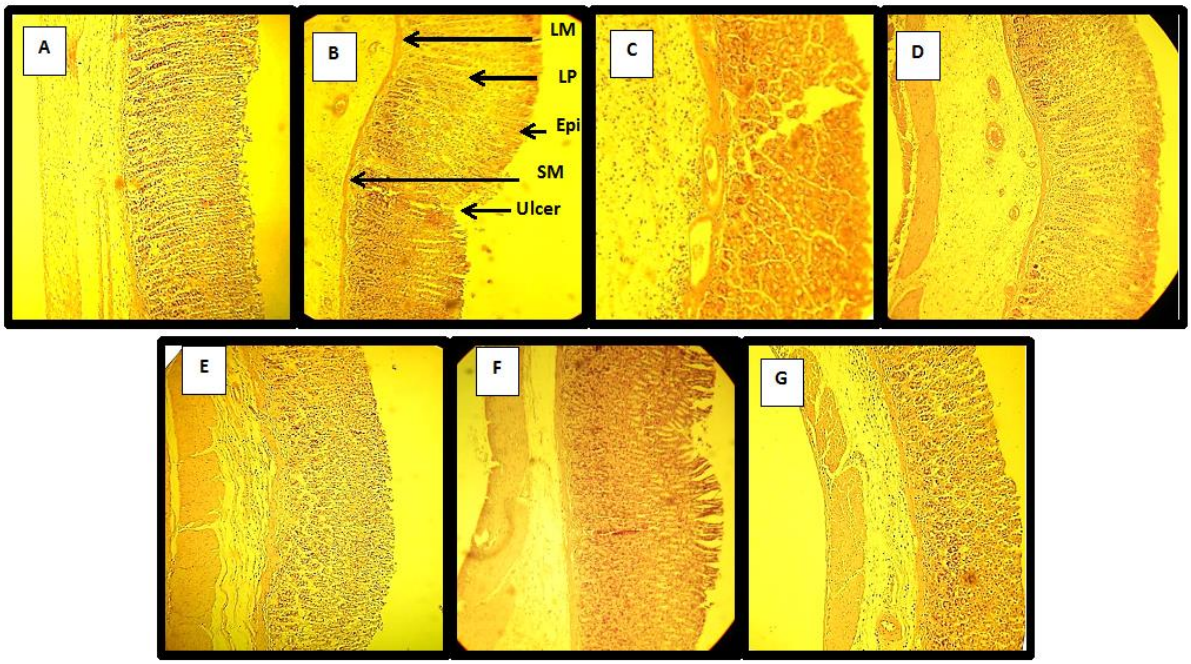

Figure 5: Histology of the rat gastric mucosa with different treatments. A: sham control; B:control ulcer (ethanol group); C:(50 mg/kg ranitidine); D: HPB(25mg/kg); E: HPB(50mglkg); F: HPB (25mg/kg) + ranitidine; G: HPB(50mg/kg) + ranitidine. H&E stain, magnification: X10.Epi= epithelium; LP=Lamina propria; LM=Lamina muscularis mucosa; SM=submucosa.

DISCUSSION

Despite the availability of many drugs for the treatment of PUD, the search for newer more effective treatment and strategies is continuous either through newly synthesized drugs or the use of herbal medicines. The present study demonstrated that the benzimidazole derivative, 1-hydroxy-2-phenylbenzimidazole (HPB) had a significant gastroprotective effect against ethanol-induced gastric ulcers in rats.

Benzimidazole derivatives play vital role in biological field such as antimicrobial, antiviral, antiulcer, antidiabetic, anticancer, inhibitors of type I DNA topoisomerases, antihelmintic and anti-allergic[12]. The benzimidazoles contain a benzene ring fused to an imidazole ring. The most prominent benzimidazole compound in nature is N-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12}[13].

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A series of benzimidazole derivatives have proven to possess antiulcer activity through inhibition of H^+/K^+ATPase (proton pump) [6], which is responsible for gastric acid production and is located in the secretary membranes of the parietal cell[14]. Various irreversible acting pyridinyl, methyl, sulfinylbenzimidazole derivatives have been synthesized, but only few of them are potent and are in current use as antiulcer agents[6].

HPB used in our study had a hydroxyl group added at position 1 of benzimidazole and a phenyl ring in position 2. This compound produced a significant and dose-dependent reduction in the number and length of ethanol-induced gastric lesions in rats. Moreover, our data demonstrated a significant reduction of gastric contents and total gastric acidity by HPB and a potentiation of these effects by pre-treatment with ranitidine. Therefore, one of the possibility is that the gastroprotective effect provided by HPB in this study may be related to its ability to reduced gastric acid production. On the other hand, It has been demonstrated that various benzimidazole derivatives showed marked anti-inflammatory[15] and a strong antioxidant properties[16], thus it tempting to speculate that the gastroprotective effect of HPB on ethanol-induced gastric ulcers may be in part due to inhibition of the release of free radicals and other inflammatory mediators known to play a role in pathogenesis of ethanol ulcers [17,18].

CONCLUSIONS

The present finding concluded that 1-Hydroxy-2-phenylbenzimidazole (HPB) had potential gastroprotective effect against ethanol-induced ulcers. However, further research is needed to explore functional mechanisms of HPB including its effects on gastric mucus content, local prostaglandins, oxidant and antioxidant parameters and on gastric blood flow.

FUNDING

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COMPETING INTERESTS

Authors declare that there are no competing interests with others.

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ملخص باللغة العربية

دراسة التأثير المضاد للمركب 1-هيدروكسي2-فينيل بينزيميدازول لقرحة المعدة المستحدثة في الفئران بتجريعها الكحول الايثيلي

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مقدمة:

من المعروف أن مشتقات البينزيميدازول لها فعالية في التقليل من افراز الحمض المعدي عن طريق تثبيط مضخة البروتون. الهدف من هذا البحث هو دراسة التأثير المضاد لقرحة المعدة المستحدثة في الفئران بتجريعها الكحول الايثيلي للمركب 1-هيدروكسي2-فينيل بينزيميدازول HPB.

الطرق:

تم تقييم النشاط المضاد لقرحة المعدة بحساب الأعداد والأطوال التراكمية لقرحة المعدة المستحدثة بواسطة الكحول الايثيلي (الإيثانول). كما تم دراسة تأثير المعالجة المشتركة لمركب HPB مع الرانيتيدين على عدد وطول قرحة المعدة وكذلك على محتوى الحامض المعدي.

النتائج:

المعالجة المسبقة للفئران بمركب HPB بجرعات 25 و50 ملغ/كجم، سبب انخفاض ملحوظ في عدد وطول قرحة المعدة الناجمة عن الإيثانول وذلك بالمقارنة بالمجموعة الضابطة. وقد تم الحصول على أعلى نسبة علاجية (53.9٪) والحد الأقصى في تقليل حموضة المعدة بواسطة أعلى جرعة من HPB (50 ملغ/كلغ) عند حقنه في نفس الوقت مع الرانيتيدين. التشريح المرضي لأمعاء الفئران أكدت هذه النتائج.

الخلاصة:

المركب المخلق (HPB) هو أحد مشتقات البينزيميدازول له خاصية مضادة لقرحة المعدة المستحدثة في الفئران بواسطة الكحول الايثيلي وهذه الخاصية قد تكون ناتجة عن تثبيط افراز الحمض المعدي.

الكلمات المفتاحية:

القرحة الهضمية، 1-هيدروكسي 2-فينيل بينزيميدازول، رانيتيدين، فئران.

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