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Protective action of piperine against experimental gastric ulcer

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KEY WORDS *Piper longum*；peptic ulcer；gastric acid；pepsin A；stress；indomethacin；hydrochloric acid；pyloric stenosis；gastric juice；ranitidine

AIM：To study the effects of piperine (Pip) on several experimental gastric ulcers in rats and mice. **METHODS**：The gastric mucosa damage was induced by stress, indometacin, HCl, and pyloric ligation in rats or mice. The number of gastric ulcers, the volume and acidity of gastric juices, and pepsin A activity were detected. **RESULTS**：Pip 25, 50, 100 mg/kg ig protected animals from gastric ulceration in a dose-dependent manner. The inhibitory rates were 16.9 %, 36.0 %, and 48.3 % in stress ulcers；4.4 %, 51.1 %, and 64.4 % in indometacin ulcers；19.2 %, 41.5 %, and 59.6 % in HCl ulcers；4.8 %, 11.9 %, and 26.2 % in pyloric ligation ulcers, respectively；Pip inhibited the volume of gastric juice, gastric acidity, and pepsin A activity. **CONCLUSION**：Pip has the protective effects against gastric ulceration.

INTRODUCTION

Piperine (Pip) is one of the ingredients isolated from *Piper longum* L, a traditional herb for treating peptic ulcers[1]. Its sedative effect was found in previous works[2]. Our current work was to study the effects of Pip on several experimental gastric ulcers in rats and mice.

MATERIALS AND METHODS

Pip (Sigma；mp 131－135 ℃；purity 97 %；white, obligue columnar crystalline) was dissolved in ethanol, and emulsified with distilled water to 20 % (vol/vol) ethanol. Control was given 20 % ethanol. Ranitidine (Ran) was purchased from Shanghai Sixth Pharmaceutical Factory and prepared with the same process as above. Indomethacin (Ind) was from Inner Mongol Salaqi Pharmaceutical Factory and distilled water was added.

Wistar rats and Kunming mice of either sex (weighing 218 g ± 14 g and 24.5 g ± *s* 1.5 g, respectively) were purchased from Experimental Animal Center, Inner Mongol University, Grade Ⅱ, Certificate № 8806R011 and 8806M35, respectively).

Experimental gastric ulcer[3] Rats or mice were randomly divided into control, Ran, and Pip groups. Pip 25, 50, 100 mg/kg was given ig once. The control groups were treated similarily but 20 % ethanol. The rats or mice were fasted for 36 h and 24 h before the induction of ulcer, but allowed free access to water.

1 Stress Rats (n = 40 in 5 groups) were given ig Pip, Ran, or 20 % ethanol. After 30 min, rats were put in a stress cage that kept rat upside down in vertical position for 8 h. The rats were stunned and the stomachs were examined for mucosal damage.

2 Ind Mice (n = 40 in 5 groups) were given ig Pip, Ran, or 20 % ethanol. After 30 min, Ind 50 mg/kg, was injected sc and the stomach was examined after 8 h.

3 HCl Rats (n = 40 in 5 groups) were given ig Pip, Ran, or 20 % ethanol. After 30 min, HCl 0.6 mol/L, 3 mL/kg was given ig and the stomachs were examined after 8 h.

4 Pyloric ligation (PL) Rats (n = 30 in 5 groups were given ig Pip, Ran, or solvent (20 % ethanol). After 30 min, under ether anesthesia the abdomen was incised and the pylori were ligated. The stomachs were examined after 8 h.

Measurement of gastric lesions[4] Stomachs of rats and mice were filled with respectively 10 mL and 1 mL of 1 % formalin solution for 30 min. The stomach was incised along the greater curvature and spread on a glass plate. The lesion were measured as follows：No lesion = 0；for lesion ≤1 mm：1 point = 0.2, 2 points = 0.4, 3 points = 0.6；for lesion ≤2 mm：1 point = 0.4,

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2 points = 0.8, 3 points = 1.2, and so on. One stripe = 1, 2 stripes = 2, 3 stripes = 3. HCl lesion width ≤ 1.0 mm = 1, 1.0 mm < HCl lesion < 2.0 mm = 2, and so on. The inhibitory rates were calculated as follows:

$$R_i = (U_c - U_t)/U_c \cdot 100\ \%$$

where U_c and U_t were the $\bar{x}$ of ulcers in control rats and mice, respectively.

Gastric juice Gastrc acid was titrated with NaOH 10 μmol/L using phenolphthalein as indicator.

$$R_s(\mu mol/h) = T_a/P_t$$

where T_a was the total acid output, and P_t was the tested period.

Pepsin assay[5] The pepsin activity was determined by Anson's method and expressed as μg/min.

Statistical analysis Data were expressed as $\bar{x} \pm s$ and assessed by t test.

RESULTS

In the rats or mice treated with Pip 25, 50, and 100 mg/kg, the number of ulcers decreased dose-dependently. The inhibitory rates were 16.9 %, 36.0 %, and 48.3 % in stress ulcer; 4.4 %, 51.1 %, and 64.4 % in Ind ulcer; 19.2 %, 41.5 %, and 59.6 % in HCl ulcer; 4.8 %, 11.9 %, and 26.2 % in PL ulcer, respectively (Tab 1).

In rats with PL ulcer, the volume of gastric juice was decreased *vs* control by 0, 11.1 %, 44.4 %; juice acidity by 4 %, 25.6 %, 29.3 %; and the activity of pepsin by 14.7 %, 48.4 %, 46.3 %, respectively (Tab 2).

Tab 1. Effect of ig piperine on experimental gastric ulcer in rats or mice. $n = 8 - 10$ rats. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

Group/mg·kg^{-1}		Number of ulcers	n	Inhibitory rates/%
Stress				
Control		8.9 ± 2.3	8	
Ranitidine	50	3.2 ± 1.4^c	8	64.0
Piperine	25	7.4 ± 2.4^b	8	16.9
	50	5.7 ± 1.4^b	8	36.0
	100	4.6 ± 0.9^c	8	48.3
Indomethacin				
Control		4.5 ± 1.4	10	
Ranitidine	50	1.1 ± 0.4^c	10	75.5
Piprerine	25	4.3 ± 2.0^a	10	4.4
	50	2.2 ± 0.9^c	10	51.1
	100	1.6 ± 0.9^c	10	64.4
HCl				
Control		9.4 ± 2.7	8	
Ranitidine	50	2.9 ± 1.1^c	8	69.1
Piperine	25	7.6 ± 2.6^a	8	19.2
	50	5.5 ± 2.1^b	8	41.5
	100	3.8 ± 1.2^c	8	59.6

DISCUSSION

The gastric ulcer formation in rats or mice is complex and multifactorial. The pepsin and hydrochloric acid in the gastric juice are the aggressive factors inducing ulcers. The present study clearly demonstrates that treatment of rats or mice with Pip before stress, Ind sc, HCl ig, pyloric ligation decreased the number of gastric ulcers, dose-dependently inhibited the gastric acid and pepsin secretion. These results show that the improvement of the gastric lesions by Pip might be due to its inhibitory effect on peptic activity and gastric acid secretion. The anti-ulcer effect of Pip 100 mg/kg was nearly equal to Ran 50 mg/kg. The stress increased gastric acid and pepsin that damaged gastric mucosa and formed ulcers. Ind inhibited and reduced synthesis of prostaglandins (PG), which, protect gastric mucosa

Tab 2. Effect of ig piperine on experimental gastric ulcer and juice in rats. $n = 6$ rats. $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$ *vs* control.

Drug/ mg·kg^{-1}	Number of ulcer	Inhibitory rates/%	Gastric juice/ mL·h^{-1}	Gastric acid/ μmol·h^{-1}	Tyrosine/ μg·min^{-1}
Pyloric ligation					
Control	4.2 ± 2.1		0.9 ± 0.5	35.1 ± 20.5	9.5 ± 5.2
Ranitidine 50	2.3 ± 1.3^b	45.2	0.4 ± 0.2^b	20.2 ± 10.1^b	5.2 ± 3.2^b
Piperine 25	4.0 ± 1.9^a	4.8	0.9 ± 0.4^a	33.7 ± 23.2^a	8.1 ± 4.5^a
Piperine 50	3.7 ± 1.5^a	11.9	0.8 ± 0.4^a	26.1 ± 11.5^a	4.9 ± 2.8^b
Piperine 100	3.1 ± 1.4^b	26.2	0.5 ± 0.3^b	24.8 ± 9.5^b	5.1 ± 3.8^b

against gastric acid and pepsin. The gastric mucosa is easily damaged when PG are lowered. HCl destroys the gastric mucosa so that H^+ diffuses invertly into the cells and changes the balance of H^+ and HCO^- hence induces ulcers. Pyloric ligation can also cause rodent ulcers. In these models, the increase in gastric acid and the attenuation of gastric mucosal barrier were major factors leading to formation of peptic ulcers[6,7].

Ran is a H-receptor blocker which reduces the gastric acid secretion and keeps gastric mucosa intact against H^+ penetration[8,9]. In this study, Pip showed the same anti-ulcer action as that of Ran. Pip might be a new gastric mucosal protectant. It is not clearl whether Pip's sedative effects are involved in its anti-ulcer effect or not[2]. The detailed mechanisms need to be further studied.

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胡椒碱抗实验性胃溃疡的作用

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关键词　荜茇；消化性溃疡；胃酸；胃蛋白酶 A；应激；吲哚美辛；盐酸；幽门狭窄；胃液；雷尼替丁

目的：研究胡椒碱抗大鼠或小鼠实验性胃溃疡的作用. **方法**：实验性胃溃疡是由应激、吲哚美辛、盐酸和幽门结扎引起，实验前 5 h ig 胡椒碱. **结果**：胡椒碱 25、50、100 mg/kg 能抑制大鼠或小鼠胃粘膜损伤，对应激性型胃粘膜损伤，抑制率分别为 16.9 %，36.0 %，48.3 %；吲哚美辛型胃粘膜损伤为 4.4 %，51.1 %，64.4 %；盐酸型胃粘膜损伤为 19.2 %，41.5 %，59.6 %；对幽门结扎型胃粘膜损伤为 4.8 %，11.9 %，26.2 %；胃液分泌减少；胃酸、胃蛋白酶活性降低. **结论**：胡椒碱具有抗实验性胃溃疡作用.

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