PHYTOTHERAPY RESEARCH
Phytother. Res. **15**, 625–627 (2001)
DOI: 10.1002/ptr.831

SHORT COMMUNICATION

Antiulcerogenic Effect of *Hippophae rhamnoides* L.

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The antiulcerogenic effect of a hexane extract (HRe-1) from *Hippophae rhamnoides* (Eleagnaceae) was tested on indomethacin- and stress-induced ulcer models. As a result HRe-1 was found to be active in preventing gastric injury.

Keywords: Hippophae rhamnoides; Eleagnaceae; gastric ulcer; misoprostol; omeprazole.

INTRODUCTION

Hippophae rhamnoides L. is a member of the Eleagnaceae family. It is a thorny small tree which is widely distributed throughout north and east Anatolia (Davis, 1982). This plant contains carotenoids (α, β, γ), vitamins B, C, E, riboflavin, folic acid and tannins. The roots of *Hippophae rhamnoides* have been used extensively in traditional medicine in east Turkey to treat ulcers (Baytop, 1984). Peptic ulcers are poly-aetiologic, frequently recurrent and a widespread chronic disease. Although there are many antiulcerogenic drugs, it is not always possible to obtain effective treatment of the ulcer with these drugs. Therefore, the treatment of ulcers is still an important problem and the development of new drugs for stomach ulcers is required. There are a number of medicinal plants that are alleged to be effective against ulcer diseases in traditional medicines. Because the folkloric uses are supported by a long history of human experience, these medicinal plants may be a good source for the isolation of potential drugs. The aim of this study was to identify new compounds with more potency against ulcers and few side effects. In addition we wished to investigate the potential effects of the new drugs on ulcer aetiology models and to compare them with classic antiulcerogenic drugs. Therefore the antiulcerogenic effect of a hexane extract (HRe-1) obtained from the ripe fruit of *Hippophae rhamnoides* was investigated on ulcer models produced by stress and indomethacin.

MATERIALS AND METHODS

Plant material. The ripe fruits of *Hippophae rhamnoides* were collected from Tortum (east Anatolia alt. 750 m) in January 1996. The plant was identified by the Botanical Institutes, Atatürk University, Erzurum, Turkey, where a voucher specimen is kept.

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Extraction. 1 kg of *Hippophae rhamnoides* fruits was percolated in hexane and the hexane evaporated to obtain an oily orange residue.

Stress induced ulcers. Obligatory immobilization was performed to investigate the effect of HRe-1 in rats in which a stress ulcer had been produced. Experiments were carried out on 32 Wistar albino male rats weighing 250–270 g. The rats were separated in four groups of 8 rats each and placed in cages. The rats were fasted and allowed to drink only water for 18 h. One group was administered with 1 mL/kg of HRe-1, and the other groups were administered with 20 mg/kg of omeprazole, 30 mg/kg of famotidine or the same volume of isotonic saline solution per oral (gavage) respectively. After 1 h of drug administration, the animals were kept for 24 h in a prone position, at room temperature. Finally, the animals were killed with 70 mg/kg i.p. of thiopental sodium and their stomachs were removed. The ulcerative zones were macroscopically evaluated and their number and area were examined.

The antiulcerogenic effects of HRe-1 were compared with omeprazole, famotidine and the control group.

Indomethacin induced ulcers. The antiulcerogenic effects of HRe-1 were also investigated on ulcer models produced by indomethacin (Anichkov *et al.*, 1969; Sturdevant and Wals, 1978). For this purpose, male albino Wistar rats weighing 220–230 g were used. They were grouped and placed in cages and deprived of food for 24 h but given free access to water. At the end of this period, one group was administered with HRe-1 (1 mL/kg) and the other group with misoprostol (200 mg/kg) orally. The same volume of saline solution was given to the control group. Five minutes after the administration of the drugs, 20 mg/kg of indomethacin was given orally to all animals. Six hours later, the animals were killed with 70 mg/kg i.p. of thiopental sodium. The stomachs were removed and the number and areas of ulcerative zones were determined. The antiulcerogenic effect of HRe-1 was determined by comparison with those obtained from the misoprostol and control groups. The results were statistically evaluated with

Received 24 June 1999
Accepted 12 April 2000

Table 1. The effects of HRe-1 and omeprazole on stress-induced gastric ulcers

	Dose	Ulcerated animals	Mean number of ulcerations	Ulcerative areas (mm^2)
Control ($n = 8$)	—	8	15.6 ± 1.89	33.6 ± 1.45
HRe-1 ($n = 8$)	1 mL/kg	8	7.2 ± 1.43^b	10.1 ± 1.30^c
Omeprazole ($n = 8$)	20 mg/kg	8	12.0 ± 1.89	22.0 ± 1.84^b
Famotidine ($n = 8$)	30 mg/kg	8	9.0 ± 1.91^a	19.1 ± 1.91^c

p value (vs control) by Student's t-test:
[a] $p < 0.05$;
[b] $p < 0.01$;
[c] $p < 0.001$.

Student's t-test and $p < 0.05$ was accepted as statistically meaningful.

RESULTS AND DISCUSSION

Stress ulcers were produced in rats using the obligatory immobilization method. Hyperemia on the gastric mucosa of the control group was seen more than those in the HRe-1, famotidine and omeprazole groups. Ulcers were distributed homogenously throughout the gastric surface of various sizes and depths, rounded, oval and irregular mucosal defects. The surrounding tissues of the ulcer areas were oedematous. As seen from Table 1, the mean number of ulceration areas were 7.2 ± 1.43, 12 ± 1.89, 9.0 ± 0.88, 15.6 ± 1.89 in HRe-1, omeprazole, famotidine and control groups, respectively. It was observed that the number of ulceration areas was prominently decreased in the HRe-1 group. While the mean area of the zones was $10.1 \pm 1.33\ mm^2$ in the HRe-1 group, this value was $22.0 \pm 1.84\ mm^2$, $19.0 \pm 1.91\ mm^2$ and $33.6 \pm 1.45\ mm^2$ in the omeprazole, famotidine and control groups, respectively. It is evident from the data that the number and areas of ulcerative zones of the HRe-1 group was lower than that from rats treated with the other drugs. However, it is difficult to compare potency as HRe-1 was dosed at 1 mL/kg whereas the controls were dosed at 20 or 30 mg/kg. Stress has an important role in the induction of gastroduodenal injury (Aydin *et al.*, 1997). In some studies, it was reported that oxygen free radicals have a role in the pathogenesis of this injury (Freeman and Crapo, 1981; Pieri *et al.*, 1994). β-carotenes, being antioxidants, were shown to scavenge superoxide radicals and to suppress singlet oxygen. It was also determined that vitamin E by reducing lipid peroxidation and vitamin C by scavenging superoxide and hydroxyl radicals showed antioxidant effects (Seis, 1991). As mentioned above, HRe-1 contains α, β, γ carotenoids, vitamins B, C, E, riboflavin, folic acid and tannins. The cumulative effects of these vitamins on the prevention of mucosal injury and the fact that some vitamins are needed for metabolic events to occur in a normal manner may explain why HRe-1 is active in preventing gastric injury. Detailed studies are required to investigate this subject. The seed oil of *Hippophae rhamnoides* at doses of 2.5 mL/kg and betasitosterol beta-D-glucoside at relatively small doses of 12 mg/kg had a significant protective effect on acetic acid-induced chronic gastric ulcers in rats and mice (Jiang *et al.*, 1988). Xiao reported the antiulcerogenic effect of betasitosterol and daucosterol from the oil of *Hippophae rhamnoides* (Xiao and Wen, 1996). In addition, the activities of a hexane extract of *H. rhamnoides* seeds on gastric ulcers in rats and rabbits were reported (Mironov *et al.*, 1989). On the other hand, while ulcers were detected in all animals of the control and misoprostol groups, only four animals given HRe-1 had ulcers. Ulcerative lesions were widely distributed all over the gastric mucosal surface with different sizes and shapes. The gastric mucosa was hyperemic and the margin of ulcers was sharply demarcated and the surrounding tissues were oedematous. In two animals of the HRe-1 group in which no ulceration was detected only hyperemia was observed in the gastric mucosa. As seen from Table 2, the number of ulcer areas induced by indomethacin was significantly decreased by HRe-1 (number of ulcers 1.3 ± 0.49/animal). On the other hand, the mean number of areas was 10.6 ± 1.59/animal in the misoprostol group and 14.3 ± 1.15/animal in the control group. Additionally while the area of the ulceration zone was $1.66 \pm 0.62\ mm^2$ in the HRe-1 group; it was $26.33 \pm 1.87\ mm^2$ in the misoprostol group and $31.0 \pm 3.4\ mm^2$ in the control group. Although it has been proven that misoprostol is an effective drug in preventing gastric mucosal injury caused by NSAIDs (Griffin *et al.*, 1991),

Table 2. The effects of HRe-1 and misoprostol on indomethacin-induced gastric ulcers

	Dose	Ulcerated animals	Mean number of ulcerations	Ulcerative areas (mm^2)
Control ($n = 6$)	—	6	14.3 ± 1.15	31.0 ± 3.4
HRe-1 ($n = 6$)	1 mL/kg	4	1.3 ± 0.49^b	1.66 ± 0.62^a
Misoprostol ($n = 6$)	200 mg/kg	6	10.6 ± 1.59	26.33 ± 1.87

p value (vs control) by Student's t-test:
[a] $p < 0.01$;
[b] $p < 0.0001$.

it may not be as potent as HRe-1 in the prevention of the indomethacin-induced ulcer model. Nevertheless, it was reported that misoprostol was more effective than both omeprazole and sucralfate in terms of preventing gastroduodenal injury induced by NSAIDs (Hawkey and Walt, 1986). In conclusion HRe-1 obtained from *H. rhamnoides* has a reliable usage in folk medicine and should be investigated further for its potential as an antiulcerogenic drug.

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