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Gastroprotective and antiulcerogenic effects of *Rumex patientia* L. extract

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Gastroprotective and antiulcerogenic effects of the aqueous extract of *Rumex patientia* L. roots (D-1) were investigated in rats and compared to non-steroidal antiinflammatory drugs (NSAIDs). Whereas oral administration of high doses of NSAIDs caused stomach damage, D-1 (aqueous extract of *Rumex patientia* roots, 150 and 500 mg/kg) and nimesulid (100 and 300 mg/kg) did not cause any damage. In rats, the number of stress ulcers induced by the administration of 150 mg/kg of D-1 were identical to that of the control group. However, compared to the control group, the number of stress ulcers decreased 1.9 times and the size of ulceration areas decreased 1.1 times in the group treated with 500 mg/kg of D-1.

1. Introduction

The genus *Rumex* (Polygonaceae) is represented by 25 species in the flora of Turkey [1, 2]. Chemical constituents of *Rumex patientia* were reported in our previous studies [3, 4]. We also reported that the aqueous extract of the roots of *R. patientia* (D-1) exhibited a potent antiinflammatory effect on histamine-, formaldehyde-, dextrane-, seratonine- and carrageenan-induced inflammation models. D-1 also decreased inflammation in adrenalectomized rats [5]. Additionally, capillary permeability which was induced by xylol and hyaluronidase, was significantly decreased by D-1 [6]. The antipyretic and analgesic activities of D-1 were shown as well [7]. All findings show that D-1 has an effect similar to that of NSAIDs. It is known that NSAIDs cause some damages in the stomach [8, 9].

The aim of this study was to investigate the effect of D-1 on normal stomach tissue and in a stress-induced ulcer model in rats with a comparison to NSAIDs such as nimesulide, indomethacin, diclofenac, naproxen and ibuprofen.

2. Investigations, results and discussion

In the first part of our study, the effects of D-1 and some NSAIDs on stomach tissue at the doses of antiinflammatory effect (Table 1) were studied.

150 and 500 mg/kg of D-1 did not cause any damage on the stomach, macroscopically only light hyperemia of the gastric mucosa was observed. The same results were seen with nimesulid (100 and 300 mg/kg).

Various numbers and sizes of ulcers were established with indomethacin (10 and 25 mg/kg), diclofenac (25 mg/kg), naproxen (250 mg/kg) and ibuprofen (400 mg/kg). Ulcers distributed homogenously at various size and depth, rounded, oval shaped and as irregular mucosal defect on the gastric surface. Surrounding tissues of ulcer areas were manifested.

Table 1: Ulcerative effects of D-1 and some of NSAIDs on stomach tissue*

Samples	Dose (mg/kg)	No. of rats	Mean number of ulcerations	Mean of ulceration areas (mm^2)
D-1	150	6	–	–
D-1	500	6	–	–
Indomethacin	10	6	14.8 ± 5.19	26.7 ± 4.14
Indomethacin	25	6	19 ± 5.58	38.6 ± 7.11
Diclofenac	25	6	1.6 ± 0.51	1.6 ± 0.51
Ibuprofen	400	6	10 ± 2.52	20.8 ± 5.52
Naproxen	250	6	6.3 ± 1.36	19 ± 2.36
Nimesulide	100	6	–	–
Nimesulide	300	6	–	–

* $p < 0.05$

Data in Table 1 show the mean number of ulcerations and the mean area of ulcerations in the stomachs of animals treated with different NSAIDs.

150 mg/kg of D-1 and 100 mg/kg of nimesulide did, however, not show any damage in the stomach. Therefore, the effects of higher doses of D-1 (500 mg/kg) and nimesulide (300 mg/kg) on stomach tissues were investigated. In our previous study, D-1 which was orally administered at the 500–3000 mg/kg dose intervals, none of the rats died [5]. Even when higher doses were administered, no damage was detected and none of the rats died.

In this study, it was shown that the damage of diclofenac on the stomach was less than those caused by indomethacin, ibuprofen and naproxen.

Many of therapeutic NSAIDs inhibit both COX-1 and COX-2 [10]. COX-1 and COX-2 play a role in biosynthesis of cytoprotective prostaglandins in gastric mucosa and kidneys, and proinflammatory prostaglandins in various tissues [10, 11]. Cytoprotective prostaglandins increase mucous and bicarbonate fluid in the stomach and facilitates blood flow. Thus they increase the resistance of gastric mucosa against aggressive factors [11, 12].

In our study, high doses of D-1 and nimesulide did not cause any damage on the stomach of rats which may be explained by the hypothesis that COX-1 products are not inhibited by these preparations.

10 mg/kg dose of indomethacin significantly increased both the ulceration numbers and ulceration areas in animals more than diclofenac, ibuprofen and naproxen ($p < 0.05$). In the ibuprofen treated animals, ulceration numbers were 1.6 times greater than naproxen. Increase in ulceration areas were similar under ibuprofen and naproxen. Moreover, the ulceration increased after a higher dose of indomethacin (25 mg/kg). Compared to indomethacin, ibuprofen and naproxen, the less ulcerogenic activity of diclofenac (25 mg/kg) may be explained by its less inhibition of COX-1.

Mitchell et al. showed that the ulcerogenic effects of diclofenac and naproxen were less than those of indomethacin. In the same study, it was shown that indomethacin and ibuprofen inhibited COX-1 more than COX-2, however,

Table 2: Effects of D-1, diclofenac and nimesulide on the stress ulcers

Samples	Dose (mg/kg)	No. of rats	Mean number of ulcerations	p	Mean of ulceration areas (mm^2)	p
D-1	150	6	7.0 ± 3.03	>0.93	14.6 ± 6.15	>0.18
D-1	500	6	3.5 ± 2.16	<0.026	9.0 ± 3.22	>0.58
Diclofenac	25	6	13.3 ± 2.58	<0.002	13.6 ± 3.32	<0.026
Diclofenac	75	6	27.8 ± 2.22	<0.002	46.3 ± 5.57	<0.002
Nimesulide	100	6	31.5 ± 1.87	<0.002	46.0 ± 1.26	<0.002
Nimesulide	200	6	16.6 ± 2.42	<0.002	31.1 ± 3.31	<0.002
Nimesulide	300	6	3.5 ± 1.51	<0.009	4.1 ± 0.75	<0.002
Control	–	6	6.8 ± 1.60	–	10.0 ± 2.09	–

diclofenac and naproxen inhibited COX-2 more than COX-1 [13].

In the second part of our study, the effects of D-1, nimesulide and diclofenac, which have less ulcerogenic effects than the other NSAIDs, were investigated on stress-ulcers of rats (Table 2).

Although the number of stress ulcers at the 150 mg/kg dose of D-1 administered animals were almost the same as in the control group, ulceration areas increased 1.5 times more than the control group. However, 500 mg/kg D-1 reduced the number of stress ulceration 1.9 times and the size of ulceration areas 1.1 times than the control group.

Diclofenac (25 mg/kg) increased the number of stress ulceration twice and ulceration areas 1.4 times more in comparison with the control group. The corresponding results for the high dose diclofenac (75 mg/kg) were 4.1 and 4.6 times more than the control group.

Whereas nimesulide, when administered with a dose of 100 mg/kg, showed the most stress ulcers, at a higher dose it caused a decrease in stress ulcers. In the group treated with a higher dose of nimesulide (300 mg/kg), the number of stress ulcers and ulceration areas were 1.9 and 2.4 times less than in the control group.

It was shown that COX-2 selectivity of nimesulide dissappears in therapeutic doses [11]. But in our study we found that it did not cause any ulceration and prevented stress ulcers at higher doses.

The increase in stress ulcers at 150 mg/kg dose of D-1 (antiinflammatory dose) and the decrease in stress ulcers at 500 mg/kg dose of D-1 indicates that both D-1 and nimesulide inhibit COX-2 at the same scale. In addition, their selectivities to COX-2 increased with higher doses.

It was shown that free oxygen radicals are present in the pathogenesis of stress ulcers [14]. However, it is known that NSAIDs prevent damage in inflammation areas by the inhibition of the production of free oxygen radicals [15].

In this study, it is interesting that D-1 and nimesulide did not cause any damage on stomach tissue and prevented stress ulcers even at the high doses. In conclusion, the main differences of D-1 and nimesulide compared to the other tested NSAIDs are that COX-2 selectivities and antioxidant effects of D-1 and nimesulide are dose dependent. Further studies are needed to elucidate their exact mechanisms of action.

3. Experimental

3.1. Plant material

The roots of *R. patientia* were collected from Niğde-Bor, Turkey (1050 m) in September 1996. A voucher specimen is deposited in the Herbarium of the Faculty of Pharmacy (HUEF-96003), Hacettepe University, Ankara, Turkey.

3.2. Animals

Adult male Wistar albino rats, weighing between 210–220 g and 230–240 g from the Experimental Animal Laboratory of Atatürk University, were used for the testing the effects of test materials on normal stomach tissue (n = 54) and stress-induced ulcer (n = 42). Animals were nourished under standard conditions. The rats were seperated in groups and placed in cages. 24 hours prior to the assays, no food and drinks were allowed, except water.

3.3. Preparation of the test sample

Five grams of material was extracted in a soxhlet apparatus with 100 ml water at 40 °C and the extract was lyophilized. The yield of extract (D-1) was 1.2 g and it was kept in a dessicator.

3.4. Gastroprotective effect

D-1 (150 and 500 mg/kg), indomethacin (10 and 25 mg/kg), diclofenac (25 mg/kg), naproxen (250 mg/kg), ibuprofen (400 mg/kg) and nimesulide (100 and 300 mg/kg) were administered orally. Six hours after drug administration, the animals were killed by administration of intraperitoneal (i.p.) thiopental sodium and their stomachs were removed. The ulcerative zones were macroscopically evaluated to examine their numbers and areas.

3.5. Antiulcerogenic effect in stress-induced ulcers

Obligatory immobilization method was performed to investigate the effect of D-1, diclofenac and nimesulide in rats in which a stress ulcer is produced. 150 and 500 mg/kg doses of D-1, 75 mg/kg dose of diclofenac, 100, 200 and 300 mg/kg doses of nimesulide were administered orally with the same volume of water. One hour after the drug administrations, the animals were kept 24 hours at a prone position at room temperature. Finally, the animals were killed by administration of i.p. thiopental sodium and their stomachs were removed. The ulcerative zones were macroscopically evaluated to examine their numbers and areas. The antiulcerogenic effects of drugs were compared with those of the control group [14].

3.6. Statistical evaluation

The results were statistically evaluated with one-way analysis of variance by Mann Whitney-U test. A p value of less than 0.05 was considered significant.

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