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Analgesic and antipyretic activities of *Rumex patientia* extract on mice and rabbits

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The aqueous extract from the roots of *Rumex patientia* L. (Polygonaceae) was investigated for its analgesic and antipyretic effects on mice and rabbits. When the activities of the extract were evaluated in comparison with acetylsalicylic acid (ASA), indomethacin and morphin, it was found to possess significant analgesic and antipyretic activities.

1. Introduction

Several *Rumex* species are ethnomedically used for the treatment of inflammation and fever [1]. In our previous study, an antiinflammatory effect of *R. patientia* roots was reported [2]. It is known that antiinflammatory drugs (NSAI) have analgesic and antipyretic activities [3]. The present study examines possible analgesic and antipyretic effects of *R. patientia* suggested by its traditional use.

2. Investigations, results and discussion

In this study, analgesic and antipyretic activities of D-1 (aqueous extract from the roots of *R. patientia*) were investigated and its effects were compared with classical analgesic and antipyretic drugs. In our previous studies [2, 4], an antiinflammatory activity of D-1 in carrageenan-, histamine-, serotonine-, dextrane-, formaldehyde- induced arthritis models was reported.

At the injection site of dextrane, formaldehyde and carrageenan, it was found that release of inflammation mediators (histamine, serotonine, bradykinin, prostaglandine, substance-P), is increased [5–8]. These mediators cause pain, fever, increased vascular permeability and consequently oedema develops. The synthesis of these mediators are inhibited by various antiinflammatory drugs [9–11].

As shown in Table 1, after formaldehyde injection, the paw licking period of animals in the early phase (0–5 min) was 78.2 s in the control group. This period was 39.2 ($p < 0.001$), 31.0 ($p < 0.001$), 49.5 ($p < 0.001$) and 28.7 ($p < 0.01$) s in D-1 (150 mg/kg), indomethacin (10 mg/kg), ASA (300 mg/kg) and morphin (10 mg/kg) treated animals, respectively (Fig. 1). The corresponding values for the late phase (15–30 min) were 15.2 ($p < 0.01$), 20.7 ($p < 0.001$), 2.0 ($p < 0.001$) and 21.0 ($p < 0.001$) s in D-1, indomethacin, ASA and morphin treated groups, respectively whereas it was 81.3 s in the control group (Fig. 2).

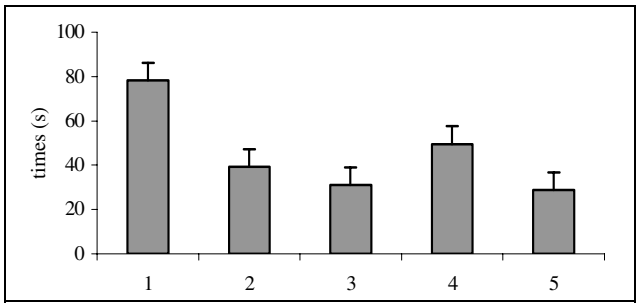

Fig. 1: Analgesic effects of D-1, indomethacin, acetylsalicylic acid and morphin on formaldehyde induced pain in rats at 0–5th minute. (1-control, 2-D-1, 3- indomethacin, 4- acetylsalicylic acid, 5-morphin)

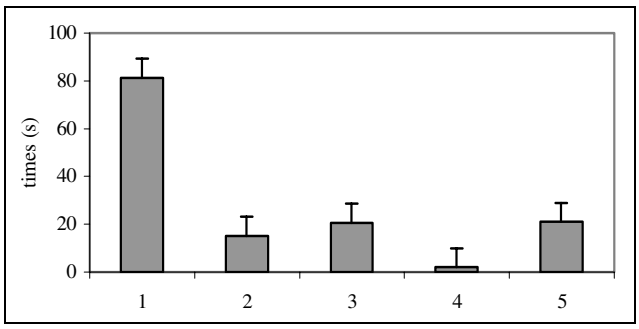

Fig. 2: Analgesic effects of D-1, indomethacin, acetylsalicylic acid and morphin on formaldehyde induced pain in rats at 15–30th minute. (1-control, 2-D-1, 3- indomethacin, 4- acetylsalicylic acid, 5-morphin)

In the early phase, D-1 (150 mg/kg) caused a significant decrease (1.9 times) in pain induced by formaldehyde in comparison with the control group. Morphin had a significant analgesic effect in this time. Morphin, ASA and indomethacin reduced the pain 2.7, 1.6 and 2.5 times more than the control group, respectively.

It was suggested that 6–10 mg/kg of morphin and 100–400 mg/kg of ASA inhibit the formaldehyde-induced

Table 1: Analgesic effects of D-1, indomethacin, acetylsalicylic acid and morphin on formaldehyde induced pain in rats

Compound	Dose (mg/kg)	Paw-licking times at 0–5th min ± SEM (s)[a, b]	Paw-licking times at 15–30th min ± SEM (s)[a, b]
D-1	150	39.2 ± 2.98	15.2 ± 2.12
Indomethacin	10	31.0 ± 2.35	20.7 ± 2.65
Acetylsalicylic acid	300	49.5 ± 4.08	2.0 ± 0.89
Morphin	10	28.7 ± 1.62	21.0 ± 2.35
Control	–	78.2 ± 3.29	81.3 ± 5.0

[a] Values were expressed as mean ± SEM ($n = 6$)
[b] Significantly different from control: $p < 0.001$

Table 2: Antipyretic effects of D-1, indomethacin and acetylsalicylic acid on pirogen induced hyperthermia in rabbits

Compound	Dose (mg/kg)	Rectal temperature (°C)[a]					
		Initial	3 h after pirogen injection	Time after drug administration			
				1 h	2 h	3 h	4 h
D-1	150	38.6	40.8 ± 0.20	40.5 ± 0.19 p < 0.008	40.0 ± 0.17 p < 0.001	39.3 ± 0.21 p < 0.0001	39.0 ± 0.20 p < 0.0006
Acetylsalicylic acid	300	38.7	40.8 ± 0.20	40.5 ± 0.17 p < 0.006	39.8 ± 0.18 p < 0.0001	39.2 ± 0.14 p < 0.0005	38.9 ± 0.17 p < 0.001
Indomethacin	10	38.8	40.8 ± 0.23	40.7 ± 0.23 p < 0.02	40.5 ± 0.32 p < 0.006	40.0 ± 0.17 p < 0.001	39.7 ± 0.25 p < 0.008
Control	–	38.6	40.73 ± 0.24	40.86 ± 0.23 p < 0.05	40.86 ± 0.18 p < 0.05	40.6 ± 0.14 p < 0.05	40.1 ± 0.24 p < 0.05

[a] Values were expressed as mean ± SEM (n = 6)

pain [12]. It was also shown that enhancement of ASA doses does not cause any analgesic effect [13]. Cyclooxygenase (Cox) does not possess major activity in the early phase of the formaldehyde test indicating that pain directly depends on stimulation of nerve ends with formaldehyde [14]. Morphin has central analgesic activity, therefore, it has a stronger effect than the other drugs [9]. D-1 inhibited the pain which occured in the late phase (15–30 min) of the formaldehyde test, 5.3 times more than control. In this phase, the effect of indomethacin (3.92 times) was similar to the effect of morphin (3.87 times). ASA showed the strongest analgesic activity and decreased the pain 40.6 times more than control. The effect of ASA was found to be 7.6 times stronger than that of D-1, 10.3 times more than that of indomethacin, 10.5 times more than that of morphin. Analgesic effects of D-1, indomethacin and ASA increased in the late phase of the formaldehyde test. It is reported that release of the inflammation mediators increases in the late phase of formaldehyde test [14, 15]. However, prostaglandins play an important role in inflammation, pain and fever [9]. ASA inhibits the synthesis of prostaglandins irreversibly while indomethacin and other antiinflammatory drugs inhibits them reversibly [11]. Therefore, it is reasonable that ASA can possess stronger activity than D-1, indomethacin and morphin.

Rumex extract showed significant antipyretic activity. The results are given in Table 2. According to these results, 150 mg/kg D-1 reduced hyperthermia. The maximal inhibitory effect of *Rumex* extract was obtained at different times after treatment, the average temperature was reduced by 0.3 °C ($p < 0.008$ after 1 h), 0.8 °C ($p < 0.001$ after 2 h), 1.5 °C ($p < 0.0001$ after 3 h) and 1.8 °C ($p < 0.0006$ after 4 h) as compared to hyperthermic rabbits. The inhibitory effect remained significant for 3 h after treatment. ASA and indomethacin exerted activity profiles similar to those obtained with *Rumex* extract.

However, in comparison to the *Rumex* extract, their inhibitory effects were more sizeable, since the dose of 300 mg/kg ASA reduced the hyperthermia by 0.3 °C ($p < 0.006$ after 1 h), 1 °C (after 2 h $p < 0.0001$), 1.6 °C (after 3 h $p < 0.001$) and 1.9 °C (after 4 h $p < 0.008$), that of 10 mg/kg indomethacin by 0.1 °C ($p < 0.02$ after 1 h), 0.3 °C ($p < 0.006$ after 2 h), 0.8 °C ($p < 0.001$ after 3 h) and 1.1 °C ($p < 0.008$ after 4 h). The mean body temperature of control group increased by 0.13 °C ± 0.12 at the 1st and 2nd hours and reduced by 0.13 °C and 0.6 °C at the 3rd and 4th hours, respectively. The 150 mg/kg dose of D-1 showed a similar effect to that obtained with 300 mg/kg dose of ASA. The body temperature of the animals were found to be normal 4 h after D-1 and ASA administrations. D-1 had no significant effect on normal body temperature similar to that of ASA [16].

Together, all these findings confirmed the ethnomedical data concerning the analgesic, antipyretic effects of the herbal remedies prepared from this plant species.

3. Experimental

3.1. Plant material

Plant materials were collected from Niğde-Bor (1050 m) and authenticated. Voucher specimens are deposited in the Herbarium of the Faculty of Pharmacy (HUEF-94102), Hacettepe University, Ankara, Turkey.

3.2. Animals

Adult male Swiss albino mice (40–45 g) and adult male albino rabbits (3–3.5 kg) were used in this study and fed on a standard laboratory diet with free access to drinking water and kept under a 12/12 hours light/dark cycle.

3.3. Sample preparation

Roots (5 g) were exhaustively extracted in a soxhlet apparatus with water at 40 °C and the extract was concentrated and then liyophilized to yield a residue (1.2 g, D-1).

3.4. Analgesic effect

Male albino mice weighing 40–45 g were used for these studies and divided into five groups of six animals each. 150 mg/kg D-1, 300 mg/kg acetylsalicylic acid (ASA), 10 mg/kg indomethacin, 10 mg/kg morphin were given by oral route separately for four groups. Control group animals consumed water only. One hour after drug administration, 0.1 ml of 5% formaldehyde solution was injected into the hind paw of mice [17] and the time period of paw licking (0–5 min: early phase and 15–30 min: late phase) was measured [15]. A positive correlation was found between the paw licking period and amplitude of pain.

3.5. Antipyretic effect

Male albino rabbits weighing 3–3.5 kg were divided into four groups of six animals each. Rectal temperature was recorded three times at 30 min intervals using an electric thermometer [16]. All animals received an lipopolysaccaride pyrogen from *Salmonella typhi* 20% suspension in saline into the venousus of ear. When the temperature made a peak (3 h after pyrogen injection), body temperature was recorded again. D-1 150 mg/kg, ASA 300 mg/kg and indomethacin 10 mg/kg were administered orally. Body temperature was recorded at every hour for four hours following the administration of test drugs.

3.6. Acute toxicity

In our previous study acute toxicity of D-1 was tested. From 500 to 3000 mg/kg doses of D-1 were orally administered to rats. None of the rats died [2].

3.7. Statistical method

All tabulated results were expressed as means ± SEM, and were compared using Student's t test. A p value of less than 0.05 was considered significant.

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