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ANTI-HISTAMINIC AND ANTI-ALLERGIC PRINCIPLES OF *PETASITES JAPONICUS* MAXIM.

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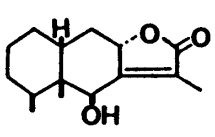
It was found that the eremophilenolides (1) and (2), the constituents of the rhizomes of *Petasites japonicus* Maxim., have moderate anti-histaminic and anti-allergic activities.

KEYWORDS —— eremophilenolide; *Petasites japonicus*; anti-histaminic; anti-allergic

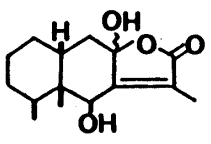
The flower buds and roots of *Petasites japonicus* Maxim. have been used since Edo times as a folk medicine for the treatment of cough and phlegm. In particular, the rhizomes have been utilized from ancient times as the most common agent for the purgation of embryonic poison (taidoku kudashi), as reported in a historical and folk survey.[1] We investigated the chemical constituents of the rhizomes and their pharmacological activities in connection with its folk usage as a medicine and found that the sesquiterpene constituents, 6β-hydroxyeremophilenolide (1), dose dependently inhibited histamine induced contraction. Also, (1) and 6β,8-dihydroxyeremophilenolide (2) significantly inhibited guinea pig PCA reactions.

The eremophilenolides (1),[2] mp 212-213° C, and (2),[3] mp 206-207° C, were isolated from hot water extracts of the roots of *Petasites japonicus* Maxim. var. *giganteus* Hort. (collected in the Akan district of Hokkaido), followed by incubation with yeast to remove large amounts of the sugar components. Pharmacological tests of these two sesquiterpenes were focused only on their anti-histaminic and anti-allergic activities in line with the folk usage of this plant, although it was reported that the sesquiterpenes, which have an α,β-unsaturated lactone moiety like (1) and (2), also have anti-inflammatory, cyctotoxic, anti-fungal[4], and plant growth inhibition[5] activities.

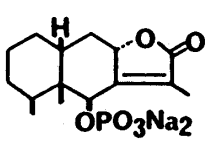
Anti-histaminic effects of (1) and (2) on male Hartley guinea pig trachea and ileum were examined as follows. A preparation of trachea or ileum was suspended in a 10 ml organ bath filled with Tyrode's solution, kept at 37° C (trachea) or



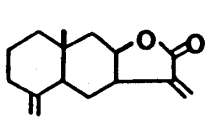
(1)



(2)



(3)



(4)

26° C (ileum) and bubbled with air. Contraction activity was recorded isotonically. A fixed dose of histamine 10^{-5} g/ml was used to stimulate the trachea. The dose-response curve for histamine was obtained by cummulative applications in the ileum. The sesquiterpenes (1) and (2) were dissolved in 18 to 50% ethyl alcohol and presented at 5 min before the addition of the agonist. The vehicle preparations were treated with ethyl alcohol (final c of 0.3 and 0.5%) instead of the antagonist. Results of these experiments are shown in Table I and Fig. 1 in which (1) produced a dose dependent inhibition of the histamine induced contraction in trachea. Also, (1) produced a parallel shift to the right of the dose-response curve for histamine in ileum and this potency was about 1/500 to 1/100 as great as diphenhydramine. However, the histamine induced contraction and the dose-response curve in trachea and ileum were unaffected by the treatment with (2). The vehicle did not influence the dose-response curve for histamine.

The anti-allergic effects of (1) and (2) on male Hartley guinea pig 3 h heterologous passive cutaneous anaphylaxis (3 h PCA),[6] and of (3) on guinea pigs and male Wister rats 3 h PCA and 48 h homologous PCA (48 h PCA)[7] were examined. The sodium phosphate (3) was prepared by treating (1) with $POCl_3$ in pyridine followed by NH_4OH to give the ammonium salt of phosphate, mp 200-201° C, and then further treatment with alcoholic NaOH of the ammonium salt. Heterologous and homologous PCA reactions were carried out as follows. The titer of domestic white male rabbit anti-egg albumin (EA) antiserum including IgG (rabbit antiserum) was 1:20,000 as estimated by guinea pig 3 h PCA. The titer of male BALB/C mouse anti-EA antiserum including IgE (mouse antiserum) was 1:500 by rat 48 h PCA. The diluted samples of rabbit antiserum or mouse antiserum (0.1 ml) were given intradermally on the shaved backs of normal guinea pigs or rats. After 3 or 48 h, the animals were challenged with an i.v. injection of 5.0 ml/kg saline containing 25 mg of EA and Evans Blue; they were sacrificed after 30 min. The skin was removed and the wheals were measured. The mean wheal size for each group was calculated and the percentage of inhibition was calculated by the following equation:

$$100 \times \frac{A - B}{A}$$

A: wheal size of control group
B: wheal size of drug treatment group

Table I.
Effects of the Eremophilenolides (1) and (2) and Diphenhydramine on Histamine induced Contraction in Isolated Guinea Pig Trachea

Drug	(g/ml)	Inhibition (%) (Histamine=10^{-5} g/ml)
(1)	10^{-5}	2.3
	10^{-4}	78.7
(2)	10^{-5}	0
	10^{-4}	0
Diphenhydramine	10^{-8}	3.3
	10^{-7}	52.9
	5×10^{-7}	94.8

Table II.

Effects of the Eremophilenolides (1), (2) and Isoproterenol on 3 h Heterologous PCA in Guinea Pigs provoked by Anti-egg Albumin Rabbit Serum

Drug	(mg/kg)	Number of animals	Inhibition (%) Antibody concentration* 1:5,000	1:10,000	1:20,000
Control		5	–	–	–
(1)	10	5	14.9**	19.1***	36.5***
	30	5	35.5***	54.5***	52.5***
(2)	10	5	9.7	16.0**	28.6***
	30	4	32.7***	42.0***	54.2***
Isoproterenol	0.1	5	24.8***	28.7***	46.0***

*: Serum dilution. **: Indicates significance $p<0.05$.
***: Indicates significance $p<0.01$.

Table III.

Effects of Sodium Phosphate of 6β-Hydroxyeremophilenolide (3) and Isoproterenol on 3 h Heterologous PCA (a) and 48 h Homologous PCA (b) in Guinea Pigs and Rats

(a)

Drug	(mg/kg)	Number of animals	Inhibition (%) Antibody concentration* 1:1,000	1:5,000	1:10,000
Control		5	–	–	–
(3)	40	5	8.4	19.2**	28.7***
	80	5	17.1**	36.4***	39.6***
Isoproterenol	0.1	5	25.4**	28.7***	50.0***

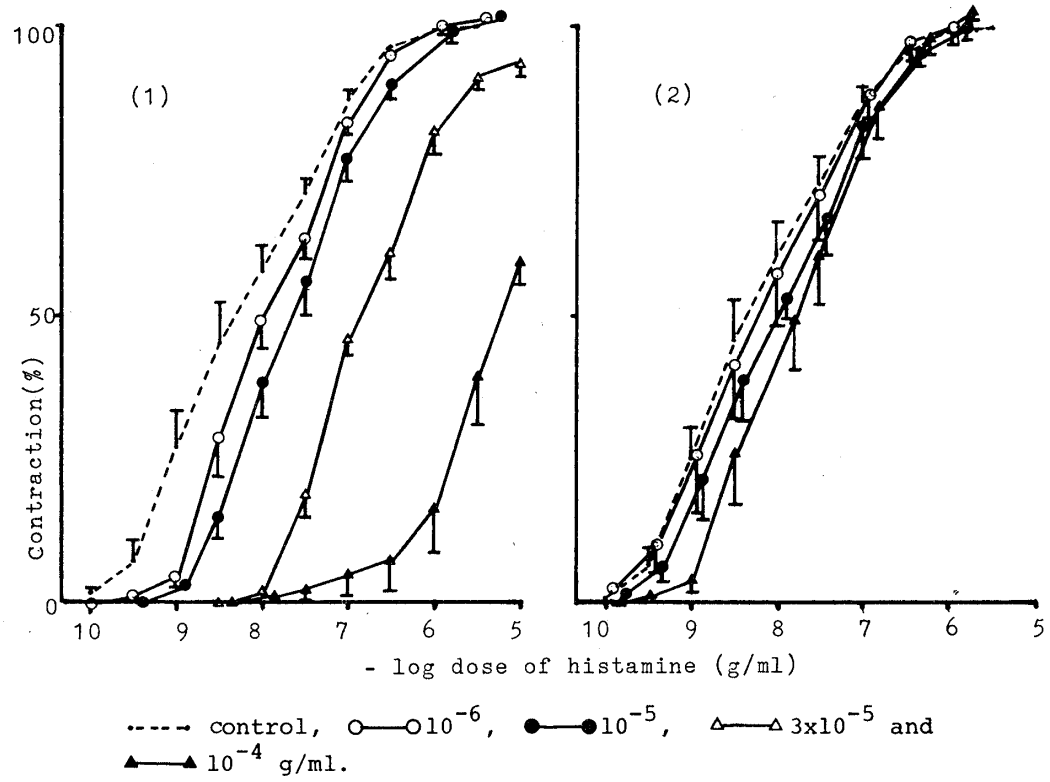
(b)

Drug	(mg/kg)	Number of animals	Inhibition (%) Antibody concentration* 1:100	1:250	1:500
Control		5	–	–	–
(3)	40	5	7.5	5.3	6.6
	80	5	2.3	2.0	3.0
Isoproterenol	0.1	5	20.6***	40.1***	72.7***

*: Serum dilution. **: Indicates significance $p<0.05$.
***: Indicates significance $p<0.01$.

The drugs were intravenously injected at 1 min before the injection of the antigen. Results on 3 h PCA of (1) and (2), and on 3 h and 48 h PCA of (3) are shown in Tables II and III, respectively. Significant inhibitory effects, which are more potent in (1) than in (2), are observed in the pretreatment of 10 and 30 mg/kg of (1) and (2) as shown in Table II. Significant effects also occur in the injections of 40 and 80 mg/kg of (3), but are rather weaker in activity than (1) as shown in Table III. (3) had no effect on the rat 48 h PCA.

Fig. 1.
Effects of the Eremophilenolides (1) and (2) on Histamine induced Contraction in Isolated Guinea Pig Ileum



These anti-histaminic and anti-allergic activities of (1) and (2) become of interest in connection with the allergic contact dermatitis activity of isoalantolactone (4) and related compounds which have α-methylene-γ-butyrolactone moiety[8] and raise an interesting question about the structure-activity relationship of these sesquiterpene lactones. Why are some compounds which have an α,β-unsaturated-γ-butyrolactone moiety anti-allergic while other compounds which have an α-methylene-γ-butyrolactone moiety are allergic?

REFERENCES AND NOTES

1) S. Tobinaga, N. Takeuchi, T. Kasama, J. Yamashita, Y. Aida, and Y. Akiba, 4th Symposium on the Development and Application of Naturally Occurring Drug Materials (Osaka, Japan), 1982, Abstracts p 22-24, refs. cited therein.
2) L. Novotný, V. Herout, and F. Šorm, Coll. Czech. Chem. Commun., 29, 2189 (1964).
3) K. Naya, R. Kanazawa, and M. Sawada, Bull. Chem. Soc. Japan, 48, 3220 (1975).
4) M. Uchida, Y. Koike, G. Kusano, Y. Kondo, S. Nozoe, C. Kabuto, and T. Takemoto, Chem. Pharm. Bull., 28, 92 (1980), refs. cited therein.
5) M. R. Garciduenas, X. A. Dominguez, J. Fernandez, and G. Alaniz, Rev. Latinoam. Quim., 3, 52 (1972).
6) Z. Ovary, J. Immunol., 71, 6 (1953).
7) Z. Ovary, S. S. Caiagza, and S. Kojima, Int. Archs. appl. Immun., 48, 16 (1975).
8) G. Schlewer, J-L. Stampf, and C. Benezra, J. Med. Chem., 23, 1031 (1980), refs. cited therein.

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