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Antitumor Activity of *Leguminosae* Plants Constituents. I. Antitumor Activity of Constituents of *Sophora subprostrata*

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The antitumor activity of several constituents of *Sophora subprostrata* and related compounds were tested against Sarcoma-180 in mice, and also against Ehrlich ascites tumor of mice as well *in vivo* as *in vitro*.

Matrine, one of its alkaloids demonstrated antitumor activity against Ehrlich ascites tumor of mice, *in vitro* as well as *in vivo*. No anti-Ehrlich ascites tumor activity was observed with oxymatrine. Both alkaloids showed remarkable antitumor activity against solid Sarcoma-180 in mice. Anti-Sarcoma-180 activity of one new base was also demonstrated. The chemotherapeutic index of oxymatrine for Sarcoma-180 was about 7.8 times larger than that of Mitomycin C.

Pterocarpoids also had definitive antitumor activity. Parent compound, chromanocoumarane, itself showed slight antitumor activity against solid Sarcoma-180 in mice. In general, the glucoside had greater antitumor activity than its aglycone, and the *d*-isomer showed relative greater antitumor activity than the *l*-isomer.

The root of *Sophora subprostrata* Chun et T. Chen. (Chinese drug: Shan-Dou-Gen (山豆根), Leguminosae) was reported to have antitumor activity both in animal[2] and clinical experiments.[3] Also, crude extracts of *Sophora formosa*,[4] *Sophora angustifolia* (=*Sophora flavescens* Aiton),[5] *Sophora japonica*,[6] *Sophora nuttalliana*,[7] and *Sophora tetraptera*[8] were reported to be moderately effective against Sarcoma-180, lymphoid leukemia 1210 and melanotic melanoma with intraperitoneal doses of 250—400 mg/kg. Therefore, it was of interest for us to determine what kinds of constituents of these *Sophora* plants are responsible for the antitumor effect.

Shibata and Nishikawa[9,10] demonstrated that the crude drug contained nearly the same alkaloids as those found in the root of *Sophora flavescens* Aiton (Chinese drug Ku-Shen (苦参)) and a few pterocarpoids. So the alkaloids and pterocarpoids in *Sophora subprostrata* and related compounds were tested for antitumor activity in mice.

The purpose of the present paper is to present and discuss the results obtained in this series of experiments.

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1) Location: *a) 3-6-6 Asahimachi, Machidashi, Tokyo; b) 2-2-1 Oshika, Shizuoka.*
2) G. Nitta, *Nihontoyoigakukaishi*, **10**, 1 (1959).
3) M. Osawa, G. Nitta, Y. Nagahama, Y. Uehara, and M. Wakabayashi, *Nihontoyoigakukaishi*, **11**, 1 (1960).
4) B. J. Abbott, J. Leiter, J. L. Hartwell, M. E. Caltwell, and S. A. Schepartz, *Cancer Research, Cancer Chemotherapy Screening Data*, **26**, 666 (1966).
5) B. J. Abbott, J. L. Hartwell, J. Leiter, R. E. Terdue, Jr., and S. A. Schepartz, *Cancer Resareh, Cancer Chemotherapy Screening Data*, **26**, 1499 (1966).
6) B. J. Abbott, J. Leiter, J. L. Hartwell, J.R. Price, R. E. Terdue, Jr., and S. A. Schepartz, *Cancer Resareh, Cancer Chemotherapy Screening Data*, **26**,349, (1966); B. J. Abbott, J. Leiter, J. L. Hartwell, M. E. Caltwell, and S. A. Schepartz, *ibid.*, **26**, 716, (1966); B. J. Abbott, J.L. Hartwell, J. Leiter, R.E. Terdue, Jr., and S.A. Schepartz, *ibid.*, **26**, 1365 (1966).
7) B.J. Abbott, J.L. Hartwell, H.H. Iltis, S.M. Kutchan, J. Leiter, R.E. Terbue, Jr., and S.A. Schepartz, *Cancer Resareh, Cancer Chemotherapy Screening Data*, **26**, 1254 (1966).
8) B. J. Abbott, J.L. Hartwell, J. Leiter, R.E. Terdue, Jr., and S.A. Schepartz, *Cancer Resareh Cancer Chemotherapy Screening Data*, **26**, 1517 (1966).
9) S. Shibata and Y. Nishikawa, *Yakugaku Zasshi*, **81**, 1635 (1961).
10) S. Shibata and Y. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **11**, 167 (1963).

Materials and Methods

Compounds tested——Matrine (I): $C_{15}H_{24}ON_2$, mp 77°, easily soluble in water, was isolated from the root of *Sophora flavescens* Aiton.

Oxymatrine (II): $C_{15}H_{24}O_2N_2$, mp 164°, easily soluble in water, was isolated from the same root.

A New Base not identified (III): $C_{15}H_{24}ON_2$, mp 133—134°, $[\alpha]_D^{21}=+44°$, easily soluble in water, was isolated from the same root.

Sophojaponicin (IV) (*d*-Maackiain-*d*-Glucoside): $C_{22}H_{22}O_{10}\cdot CH_3OH$, mp 202—203°, slightly soluble in water, was isolated from the root of *Sophora japonica* L.

Trifolirhizin (V) (*l*-Maackiain-*d*-Glucoside): $C_{22}H_{22}O_{10}\cdot CH_3OH$, mp 142—144°, slightly soluble in water, was isolated from *Sophora flavescens* Aiton.

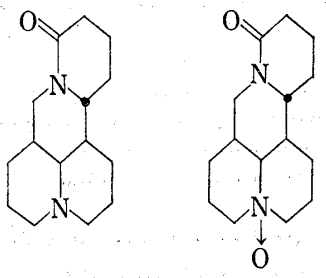
d-Maackiain (VI): $C_{16}H_{12}O_5\cdot \frac{1}{2}H_2O$, mp 180—181°, $[\alpha]_D$ (in acetone) $=+251°$, practically insoluble in water, was prepared from sophojaponicin (IV) according to the method of T. Kubota and H. Hinoh[11] used in the preparation of unstable genuine sapogenin from saponin of the root of *Bupleurum falcatum* L.

l-Maackiain (VII): $C_{16}H_{12}O_5\cdot \frac{1}{2}H_2O$, mp 180—181°, $[\alpha]_D$ (in acetone) $=-257°$, practically insoluble in water, was isolated from *Sophora flavescens* Aiton.

Chromanocoumarane (VIII): $C_{15}H_{12}O_2$, mp 126—127°, practically insoluble in water, was synthesized according to the method of H. Suginome.[12]

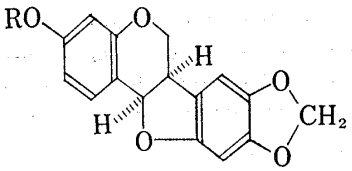
These compounds were dissolved or finely suspended in saline shortly before use.

Details of isolation, identification and structure elucidation of these compounds will be reported elsewhere.

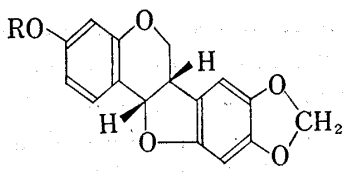


matrine (I)

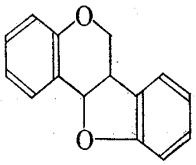
oxymatrine (II)



trifolirhizin (V) : R = *d*—glucose
l—maackiain (VII) : R = H



sophojaponicin (IV) : R = *d*—glucose
d—maackiain (VI) : R = H



chromanocoumarane (VIII)

Chart 1

Methods——*In vivo* and *in vitro* tests

Experiment 1: Antitumor Activity of I, II and IV against Ehrlich Ascites Carcinoma in Mice: Male dd strain mice weighing 26±2 g were used. The control group consisted of 4 mice, and each of the test groups consisted of 5 mice. Ascites carcinoma was inoculated intraperitoneally at a dose of 2×10^6 tumor cells per animal. Intraperitoneal injection of each dose of compounds in 0.5 ml saline (or 0.5 ml saline; control group) per mouse was started 24 hours after inoculation, and continued once daily for 5 days. After the end of the treatment, the body weight of each animal was measured every other day in order to estimate the extent of ascites, and observation was made of the survival time.

Experiment 2: Antitumor Activity of II and IV against Solid Sarcoma-180, Bulgaria Strain, in Mice: Male dd strain mice weighing 21±1 g were used. The control group consisted of 2 mice, and each of the test groups consisted of 5 mice. Each mouse was implanted subcutaneously in the dorsal area with an 8 mm^3 fragment of solid Sarcoma-180 Bulgaria strain. Intraperitoneal injection of each dose of compounds in 0.5 ml saline (or 0.5 ml saline; control group) per mouse was started 24 hours after tumor implantation, and continued once daily for 5 days. 5 days after the end of the treatment, all of the mice were killed and

11) T. Kubota and H. Hinoh, *Tetrahedron*, **24**, 675 (1968).
12) H. Suginome and T. Iwadare, *Bull. Chem. Soc., Japan*, **39**, 1535 (1966).

the tumors were removed and weighed. The mean value of the tumor weight of each treated group was compared with that of the control group in order to evaluate the antitumor effect.

Experiment 3: Antitumor Activity of II, IV and Mitomycin C against Solid Sarcoma-180 Bulgaria Strain in Mice: A group of 5 mice treated with 25 μg Mitomycin C in 0.5 ml saline was added, and the other experimental conditions were the same as those described under experiment 2.

Experiment 4 and 5: Antitumor Activity of VIII against Solid Sarcoma-180 Bulgaria Strain in Mice: Each of the control and test groups consisted of 5 mice weighing about 20 g, and the other experimental conditions were essentially the same as those described under experiment 2.

Experiment 6 and 7: Antitumor Activity of I, II, III, IV, V, VI and VII against Solid Sarcoma-180 Hokken Strain in Mice: Male ddy strain mice weighing about 20 g were used. Each of the control and test groups consisted of 5 mice. Each mouse was implanted in the axillary region subcutaneously with an 8 mm^3 fragment of solid Sarcoma-180, Hokken strain. Intraperitoneal injection of each dose of compound in 0.2 ml saline (or 0.2 ml saline; control group) per mouse was started 24 hours after tumor implantation, and continued once daily for 7 days. 3 days after the end of treatment, all the mice were weighed and killed, and the tumors were removed and weighed.

Experiment 8: Antitumor Activity of I, II and 5-Fluorouracil against Ehrlich Ascites Carcinoma Cells *in Vitro*: 2—3 weeks after inoculation of Ehrlich ascites tumor cells (2×10^6), ascites was aspirated from the abdominal cavity and mixed with saline buffer of pH 7 (1:2). Aliquots of the ascites suspension (0.4 ml) were added to small test tubes (ϕ 0.8 cm, 10 cm length) containing 0.1 ml of test compounds solution in various concentrations. To the control test tubes was added only 0.1 ml saline buffer of pH 7. All the test tubes were first shaken and then incubated at 37° for 30 minutes. During incubation they were shaken every 15 minutes. At this time, various amounts (0.1—0.3 ml) of 2,6-dichlorphenolindophenol solution (5 mg/10 ml) were added to the control test tubes. The tubes were shaken and allowed to stand for an additional 10 minutes at 37°. The maximum amount of the pigment solution which would become clear was then determined. Immediately, the determined amount of the pigment solution was added to each of the tubes containing test compounds. The tubes were shaken and allowed to stand for an additional 15 minutes at 37°. The remaining degree of pigment was then observed for each test tube. The evaluation of antitumor activity was based on the following criteria: complete fading was regarded as — effect marked fading as + effect, moderate fading as ++ effect, slight fading as +++ effect and no fading as +++ effect.

Experiment 9: Acute Toxicity of I, II and IV: LD_{50} values of I, II and IV for male dd strain mice and female Wister strain rats were estimated by the usual method.[13]

Result

Experiment 1

As indicated in Fig. 1, matrine (I) yielded a 40 and 20% survival rate, when it was administrated at 500 μg and 250 μg per mouse respectively. The body weights of 2 surviving mice, as shown in Fig. 4, were increased until the 20th day, showing a decrease thereafter. On the contrary, neither oxymatrine (II) (Fig. 2) nor sophojaponicin (IV) (Fig. 3) showed an antitumor effect against Ehrlich ascites carcinoma in mice.

Experiment 2

The effect of oxymatrine (II) and sophojaponicin (IV) against solid Sarcoma-180 Bulgaria strain are summarized in Table I. As shown in this table, oxymatrine (II) and sophojaponicin (IV) showed appreciable antitumor activity, though there was considerable variation in the susceptibility of individual animals. There was not, however, a distinct parallel relationship between dose and response.

Experiment 3

The results of this experiment, which was performed to determine reproducibility, are summarized in Table II. In this case oxymatrine (II) and sophojaponicin (IV) again showed marked antitumor activity. Sophojaponicin, administered at 1000 μg per mouse, exhibited as extensive effect as Mitamycin C. As in the case of experiment 2, dose-response parallelism was not seen.

Experiment 4 and 5

These experiments were carried out to see whether chromanocoumarane (VIII), which is the parent compound of sophojaponicin (IV), also has antitumor activity. The results

13) J.T. Litchfield, Jr, and F. Wilcoxon, *J. Pharmacol. Exptl. Therp.*, **96**, 99 (1949).

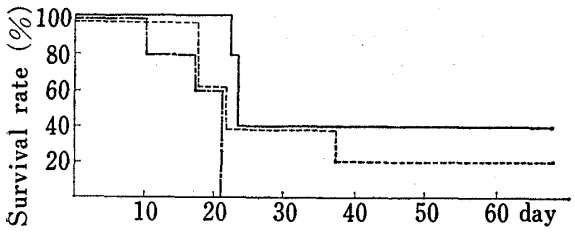


Fig. 1. Prolongation Effect of Matrine (I) on the Survival Time of Mice inoculated with Ehrlich Ascites Carcinoma

———: matrine 500 μg/0.5 ml/mouse×5
----------: matrine 250 μg/0.5 ml/mouse×5
—·—·—: saline 0.5 ml/mouse×5

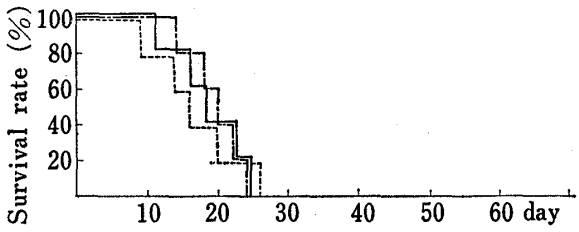


Fig. 2. Prolongation Effect of Oxymatrine (II) on the Survival Time of the Mice inoculated with Ehrlich Ascites Carcinoma

———: oxymatrine 500 μg/0.5 ml/mouse×5
----------: oxymatrine 250 μg/0.5 ml/mouse×5
—·—·—: saline 0.5 ml/mouse×5

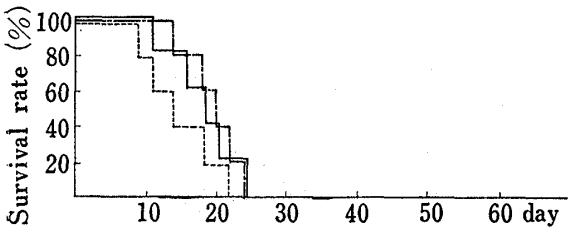


Fig. 3. Prolongation Effect of Sophojaponicin (IV) on the Survival Time of the Mice inoculated with Ehrlich Ascites Carcinoma

———: sophojaponicin 500 μg/0.5 ml/mouse×5
----------: sophojaponicin 250 μg/0.5 ml/mouse×5
—·—·—: saline 0.5 ml/mouse×5

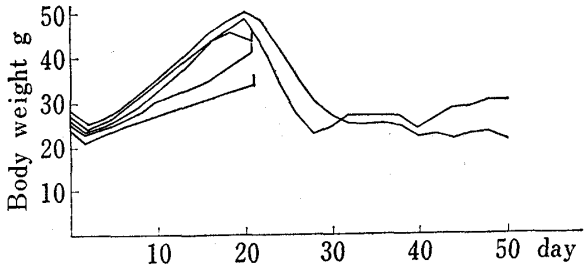


Fig. 4. The Change of Body Weight of Mice inoculated with Ehrlich Ascites Carcinoma after Receiving Matrine (500 g×5)

Table I. Antitumor Activity of II and IV against Solid Sarcoma-180 Bulgaria Strain in Mice

Compounds	Dose (μg/mouse)	Weight of tumor mg	Mean weight mg	Percent (T/C)[a]
Oxymatrine (II)	500×5	51.4		
		84.3		
		236.6	81.9	26.1
		21.0		
		16.3		
	250×5	350.3		
		99.5		
		95.2	181.7	57.9
		95.5		
		268.2		
Sophojaponicin (IV)	500×5	39.7		
		497.8		
		150.5	237.6	75.8
		328.9		
		171.4		
	250×5	22.0		
		107.5		
		11.8	79.9	25.5
		214.7		
		43.6		
Saline	0.5 ml×5	439.0	313.3	100
		187.5		

a) T/C: mean weight (mg) of tumor of test group/mean weight (mg) of tumor of control group

Table II. Antitumor Activity of II, IV and Mitomycin C against Solid Sarcoma-180 Bulgaria Strain in Mice

Compounds	Dose (μg/mouse)	Weight of tumor mg	Mean weight mg	Percent (T/C)
Oxymatrine (II)	1000×5	27.1		
		227.0		
		320.8	115.0	31.2
		0		
		0		
	500×5	0		
		0	31.6	8.6
		117.2		
		9.0		
Sophojaponicin (IV)	1000×5	0		
		11.0		
		0.6	4.0	1.1
		8.3		
		0		
Mitomycin-C	25×5	7.8		
		32.1		
		1.7	10.0	2.7
		5.9		
		2.4		
Saline	0.5 ml×5	201.8		
		585.7	368.1	100
		25.0		
		660.2		

are summarized in Table III and IV. In experiment 4, chromanocoumarane (VIII) seemed to show slight antitumor effect, but in experiment 5 showed no significant activity.

Experiment 6 and 7

These experiments were carried out to confirm whether there was any correlation between antitumor activity and the configuration of the aglycon. Another objective of these experiments was to confirm the antitumor activity of the new base of *Sophora flavescens* (III). The results are shown in Table V and VI. The antitumor activity of the new base (III) was extensive in both experiments. In general, dextrorotatory isomers showed superior activity to levorotatory isomers, but the difference in activity was not great. The change in body weight of the mice in experiment 6 and 7 is illustrated graphically in Fig. 5 and 6 respectively. As can be seen in these figures, all of the compounds tested, except Mitomycin C, permitted an increase in the body weight of the mice.

Experiment 8

The results are summarized in Table VII. The antitumor activity of matrine (I) on Ehrlich ascites carcinoma cells *in vitro* was not strong, and was equivalent to about 1/20 of that of 5-fluorouracil (Kyowa). Oxymatrine (II) was ineffective as in the case of experiment 1.

Experiment 9

LD_{50} values of matrine (I), oxymatrine (II) and sophojaponicin (IV) are listed in Table VIII.

Discussion

In these experiments, several constituents of *Sophora subprostrata* Chun et T. Chen, *Sophora flavescens* Aiton and *Sophora japonica* L. were found to be more or less effective against the solid type experimental tumor in mice.

TABLE III. Antitumor Activity of Chromanocoumarane (VIII) and Oxymatrine (II) against Solid Sarcoma-180 Bulgaria Strain in Mice

Compounds and dose (μg/mouse)	Initial weight of body (g)	Weight of 10th day (g)	Weight of tumor (mg)	Percent (T/C)
Chromanocoumarane 500/0.2 ml×5	21.8	22.9	1137	
	20.5	21.6	865	
	18.9	19.7	514	79.4
	21.5	23.1	1214	
	20.5	22.2	424	
	20.6	21.9	830	
Chromanocoumarane 250/0.2 ml×5	21.2	22.4	1290	
	19.2	20.3	406	
	21.2	22.6	677	67.1
	21.0	22.2	592	
	20.7	19.9	588	
	20.6	21.5	710	
Chromanocoumarane 125/0.2 ml×5	19.8	20.5	500	
	22.5	23.8	476	
	19.5	20.0	499	58.0
	20.5	22.6	930	
	22.7	23.5	610	
	21.0	22.1	603	
Oxymatrine 125/0.5 ml×5	19.5	19.7	706	
	23.0	24.6	1176	
	20.3	21.8	1043	77.5
	19.3	20.5	691	
	19.4	16.2	436	
	20.3	20.5	810	
Control saline 0.2 ml×5	22.4	23.3	866	
	18.9	20.0	1163	
	21.5	23.2	1500	100
	20.3	20.9	570	
	19.7	20.9	1187	
	20.5	21.6	1057	

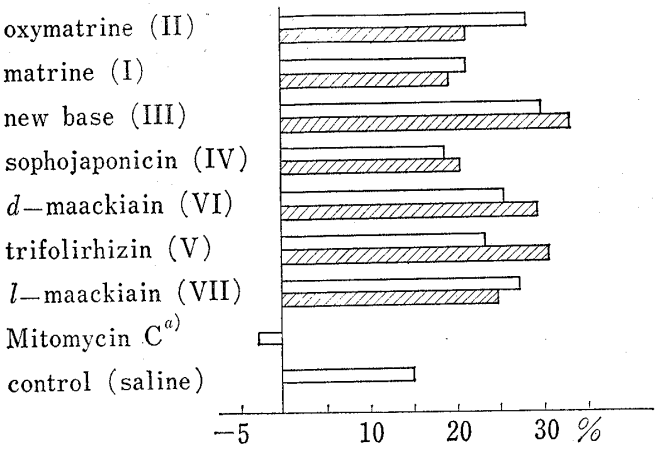


Fig. 5. Change of the Body Weight of Mice during Experiment 6

□: 500 μg/mouse×7 ▨: 250 μg/mouse×7
a) 11.6 μg/mouse×7, tumor weight T/C: 25.9%

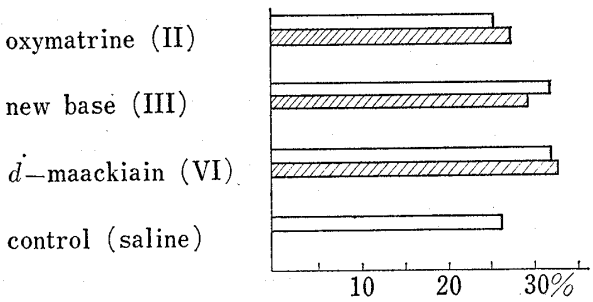


Fig. 6. The Change of the Body Weight of Mice during Experiment 7

□: 500 μg/mouse×7
▨: 250 μg/mouse×7

The results of experiment 1 and 8 demonstrate that matrine (I) showed antitumor activity against Ehrlich ascites carcinoma in mice, *in vivo* as well as *in vitro*, but oxymatrine (II) did not. It is of interest that N-oxidation of matrine results in disapperance of the antitumor activity against ascites carcinoma in mice.

Table IV. Antitumor Activity of Chromanocoumarane (VIII) against Solid Sarcoma-180 Bulgaria Strain in Mice

Compounds and dose (μg/mouse)	Initial weight of body (g)	Weight of 10th day (g)	Weight of tumor (mg)	Percent (T/C)
Chromanocoumarane 125/0.2 ml×5	19.3	20.9	862	
	20.6	22.6	958	
	20.6	19.5	502	89.4
	20.8	22.3	490	
	19.9	19.8	884	
	20.2	21.0	739	
Chromanocoumarane 62.5/0.2 ml×5	20.8	22.1	554	
	20.2	21.8	398	
	19.6	21.7	727	77.9
	20.5	22.6	350	
	20.4	22.5	1190	
	20.3	22.1	644	
Chromanocoumarane 31.25/0.2 ml×5	19.4	21.7	694	
	20.9	22.2	424	
	20.8	19.2	394	94.3
	20.5	22.5	1306	
	19.4	21.7	1078	
	20.1	21.4	779	
Control saline 0.2 ml×5	20.4	21.8	970	
	19.2	21.6	676	
	20.3	22.4	960	100
	20.2	22.2	698	
	19.8	19.0	827	
	20.0	21.4	826	

Table V. Antitumor Activity of I, II, III, IV, V, VI and VII against Solid Sarcoma-180 Hokken Strain in Mice

Compounds	Dose μg/mouse	Mean initial weight of mice g	Mean weight of mice at 10th day g	Mean weight of tumor mg	Percent (T/C)
Oxymatrine (II)	500×7	19.6	25.4	248.3	19.8
	250×7	20.1	24.6	221.1	17.7
Matrine (I)	500×7	19.8	24.4	439.1	35.1
	250×7	19.8	24.3	670.1	53.5
New base (III)	500×7	20.1	26.4	318.6	25.4
	250×7	20.0	26.9	295.5	23.6
Sophojaponicin (IV)	500×7	20.0	24.1	320.9	25.4
	250×7	20.2	25.1	762.8	60.9
d-Maackiain (VI)	500×7	19.7	25.3	602.1	48.1
	250×7	19.7	25.8	366.2	29.3
Trifolirhizin (V)	500×7	20.1	25.5	737.7	58.9
	250×7	19.7	26.6	909.1	72.6
l-Maackiain (VII)	500×7	20.3	26.5	696.5	55.6
	250×7	20.0	25.5	730.6	58.4
Saline	0.5 ml×7	20.2	24.5	1251.9	100

Table VI. Antitumor Activity of II, III and VI against Solid Sarcoma-180 Hokken Strain in Mice

Compounds	Dose μg/mouse	Mean initial weight of mice g	Mean weight of mice at 10th day g	Mean weight of tumor mg	Percent (T/C)
Oxymatrine (II)	500×7	20.0	25.2	102.8	9.3
	250×7	20.0	25.9	353.0	32.0
New base (III)	500×7	19.4	25.8	298.0	27.1
	250×7	19.4	25.2	180.2	16.3
d-Maackiain (VI)	500×7	19.6	26.2	335.4	30.4
	250×7	19.4	26.2	500.8	45.4
Saline	0.5 ml×7	20.2	26.7	1101.4	100

Table VII. Antitumor Activity of I, II and 5-Fluorouracil (KYOWA) against Ehrlich Ascites Carcinoma Cell *in Vitro*

Compounds	Concentration (μg/ml)								
	10000	4000	2000	1000	400	200	100	50	25
Matrine (I)	##	##	##	+	+				
Oxymatrine (II)	−	−	−	−	−				
5-Fluorouracil (KYOWA)					##	##	##	±	±(−)

Table VIII. LD_{50} Values of Matrine (I), Oxymatrine (II) and Sophojaponicin (IV)

Experimental animal	Mouse		Rat
Route of administration	Intravenous	Intraperitoneal	Intraperitoneal
Compounds			
Matrine (I)		150 mg/kg	~125 mg/kg
Oxymatrine (II)	150 mg/kg	~750 mg/kg	
Sophojaponicin (IV)		200—250 mg/kg	~300 mg/kg

The results of experiment 2 and 3 demonstrate that both oxymatrine (II) and sophojaponicin (IV) have an extensive antitumor effect against solid Sarcoma-180 Bulgaria strain in male dd strain mice.

Chromanocoumarane (VIII), which is the parent compound of the pterocarpoids, showed slight antitumor activity against solid sarcoma in mice. This suggests that the antitumor activity of pterocarpoid derivatives is based, at least partially, on the structure of the parent compound.

Based on the results of experiment 6 and 7, oxymatrine (II) would appear to be the most effective componnd among those tested against solid Sarcoma-180 Hokken strain in ddy strain mice. The new base obtained from *Sophora flavescens* (III) was found to be the second most effective compound.

Among the pterocarpoid derivatives tested, dextrorotatory isomers; sophojaponicin (=*d*-maackiain-*d*-glucoside) (IV) and *d*-maackiain (V), were found to be more effective than levorotatory isomers; trifolirhizin (=*l*-maackiain-*d*-glucoside) (VI) and *l*-maackiain (VII) respectively.

The change in body weight of mice in the cource of the treatment (Fig. 5 and 6) revealed that all of the compounds tested permitted an increase in body weight. On the contrary,

Mitomycin C, administered at a dose eliciting the same degree of effect, resulted in a decrease of body weight.

However, for almost all the compounds tested, a linear relation between dose and response was not observed. Instead, reverse relationship between dose and response was observed in several cases. The basis for the tumor inhibition has not been elucidated as yet, but these alkaloids and pterocarpoids might possibly react indirectly on the tumor cell through a host reaction.

The acute toxity of matrine (I), oxymatrine (II) and sophojaponicin (IV) (Table VII) was not great as compared with the effective doses of these compounds. For example, intraperitoneal doses of 500 μg/mouse and 250 μg/mouse correspond approximately to 1/30 and 1/60 of the LD_{50} doses respectively. On the other hand, the tumor index of Mitomycin C was about 30%, when it was administered by the same route with 7.8/30 of the LD_{50} dose. Thus, the chemotherapeutic index of oxymatrine is about 7.8 times as high as that of Mitomycin C.

Considering from the data mentioned above, oxymatrine (II) may be regarded as the antitumor agent worthy of further studies with other kinds of experimental tumors. Matrine (I) itself is also of interest on the grounds that it showed antitumor activity both against experimental ascites carcinoma and solid carcinoma.

Almost all of the pterocarpoids tested in this study were practically insoluble, and only sophojaponicin (IV) was slightly soluble in water. If these pterocarpoids can be solubilized, it might results in an improvement of their effectiveness.

In any case, it is of considerable interest that two different kinds of constituents; alkaloids and pterocarpoids, in the same plant, were both found to be effective against experimental tumors in mice. And it is of great interest for us that the phytoallexine, the antifungal substance of plant, like pterocarpoid has a marked antitumor activity.

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