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A Further Survey of the Action of Some Medicinal Plants on Drug Metabolism

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Abstract□ Tabulated results are presented of a test for an activity affecting on drug metabolism of 75 plant samples frequently used in the traditional medicine in Korea.

Keywords□ Medicinal plants—Hexobarbital hypnosis—Strychnine mortality—Inhibition and induction of drug metabolizing enzymes.

In the previous paper[1], the results were given of a survey of 69 medicinal plants for the activity affecting the drug metabolizing enzyme systems by using experimental models of the barbiturate-induced hypnosis and the strychnine mortality in mice. In continuation of this program of survey we now present results for an additional 75 plant materials.

EXPERIMENTAL

The experimental procedure for preparation of the extracts and the biological test was utilized as described previously[1].

RESULTS AND DISCUSSION

Table I shows the screening results of 75 plants belonging to 46 genera. The plants which gave significant changes in barbiturate-induced hypnosis were newly recollected and retested to confirm the initial positive results.

Among the plant extracts tested, 18 plant samples gave a significant prolongation in barbiturate-induced hypnosis on a single administration 30 minutes before hexobarbital injection (in inhibition test), whereas they did not give any shortening effect when repeatedly administered 48 hours before hexobarbital injection (in induction test).

The activity was found to be conspicuous especially in the extracts of *Acori graminei rhizoma, Perillae folium* and *Viticis rotundifoliae fructus.* This result suggested that these plants contained a strong enzyme inhibitor (s). Their enzyme inhibitory action was confirmed by the strychnine mortality test, in which a significant increase in mortality was observed by a single administration.

The extracts of *Piperis nigri fructus* and *Zedoariae rhizoma* prolonged barbiturate-induced hypnosis in inhibition test and shortend it in induction test, suggesting that the extracts possess both inhibitory and inductive activities on the drug metabolizing enzymes in the liver. It is not surprising because a variety of drugs was known to cause biphasic responses on the liver microsomal

* Part 2 in the series: Studies on Crude Drugs Acting on Drug Metabolizing Enzymes.

Table I: Effects of botanical drugs on hexobarbital sleeping time and strychnine mortality in mice.

Plant Names	Date Coll.	Plant[a)] Part	Prolongation Dose (mg/kg)	Prolongation Percent of Control	Prolongation Signif.	Shortening Dose (mg/kg)	Shortening Percent of Control	Shortening Signif.	Strychnine[c)] Mortality (%)
Alismataceae									
Alisma plantago var. parviforum	5/72	rz	500	108.6	N.S.	500	116.0	N.S.	
Amaranthaceae									
Achyranthes japonica	3/72	rt	500	213.5 161.0	$P<0.001$ $P<0.05$[b)]	500	86.4	N.S.	90.0
Anacardiaceae									
Rhus javanica	7/75	ga	15	168.4 141.4	$P<0.01$ $P<0.01$	15	119.7	N.S.	100.0
Araceae									
Acorus gramineus	12/72	rz	500 250	455.5 255.8	$P<0.01$ $P<0.001$	500	107.0	N.S.	100.0
Arisaema amurense var. serratum.	8/69	rz	500	123.8	N.S.	500	84.9	N.S.	
Araliaceae									
Acanthopanax spinosus	12/72	rt-bk	50	113.6	N.S.	50	124.0	N.S.	
Aralia continentalis	10/70	rt	500	100.0	N.S.	500	121.6	N.S.	
Kalopanax pictum	10/75	bk	125	101.0	N.S.	125.	113.7	N.S.	
Aristolochiaceae									
Asiasarum heterotropoides var. seoulensis	5/72	wp	500	133.1	N.S.	500	94.5	N.S.	
Campanulaceae									
Adenophora remotiflora	5/75	rt	125	95.2	N.S.	60	124.5	N.S.	
Caryophyllaceae									
Dianthus chinensis	3/72	wp	250	83.6	N.S.	250	179.9 139.0	$P<0.01$ $P<0.01$	
Gypsophyla oldhamiana	10/72	rt	25	139.3	N.S.	25	101.6	N.S.	
Melandrium firmum	3/72	wp	125	112.4	N.S.	125	169.6 164.9	$P<0.05$ $P<0.01$	
Combretaceae									
Terminalia chebula	2/75	fr	62.5	89.1	N.S.	62.5	120.2	N.S.	
Compositae									
Artemisia vulgaris var. indica	3/72	lf	125	125.6	N.S.	125	96.2	N.S.	
Aster tartaricus	2/72	rt	125	92.0	N.S.	62.5	103.0	N.S.	
Atractylodes japonica	10/75	rz	500	169.9 169.0	$P<0.01$ $P<0.001$	500	116.3	N.S.	70.0
Carthamus tinctorius	10/70	fl	500	107.1	N.S.	500	98.6	N.S.	
Chrysanthemum indicum	6/72	fl	500	104.1	N.S.	500	101.6	N.S.	
Echinops latifolius	6/75	rt	500	121.5	N.S.	500	163.2 155.0	$P<0.02$ $P<0.01$	
Siegesbeckia pubescens	10/69	wp	125	115.0	N.S.	125	186.4 129.4	$P<0.02$ $P<0.05$	
Convolvulaceae									
Cuscuta japonica	12/72	sd	125	87.5	N.S.	125	121.2	N.S.	
Pharbitis Nil	7/75	sd	5	103.0	N.S.	1	130.3	N.S.	
Cruciferae									
Brassica alba	10/72	sd	500	117.5	N.S.	500	89.4	N.S.	
Cucurbitaceae									
Tricosanthes kirilowii	12/72	sd	250	112.8	N.S.	250	118.3	N.S.	
Cyperaceae									
Scripus maritimus	5/72	tb	250	114.3	N.S.	250	127.5	N.S.	
Equisetaceae									
Equisetum hiemale var. japonicum	12/72	wp	500	126.8	N.S.	500	93.0	N.S.	

Eucommiaceae									
Eucommia ulmoides	10/75	bk	500	96.1	N.S.	500	91.4	N.S.	
Euphorbiaceae									
Croton tiglium	2/75	sd	1	118.0	N.S.	1	107.0	N.S.	
Graminiae									
Coix Lachryma-jobi	2/75	sd	250	102.1	N.S.	125	120.5	N.S.	
Iridaceae									
Belamcanda chinensis	12/72	rz	500	184.9 233.0	P<0.001 P<0.01	500	121.6	N.S.	100.0
Labiatae									
Anisomeles indica	10/69	lf	500	117.5	N.S.	250	79.8	N.S.	
Mentha arvensis var. piperasens	10/72	lf	500	107.4	N.S.	500	103.9	N.S.	
Perrila nankinensis	4/73	lf	125	459.1 278.7	P<0.001 P<0.01	125	120.0	N.S.	100.0
Lardizabalaceae									
Akebia quinata	10/69	lg	500	102.0	N.S.	250	119.2	N.S.	
Leguminosae									
Albizzia julibrissin	3/72	bk	250	124.7	N.S.	250	115.3	N.S.	
Cassia occidentalis	3/72	sd	500	218.2 230.1	P<0.01 P<0.01	125	115.1	N.S.	90.0
Dolichos Lablab	10/72	sd	500	113.3	N.S.	500	83.7	N.S.	
Sophora japonica	10/72	fl	250	93.0	N.S.	250	103.3	N.S.	
Liliaceae									
Fritillaria verticillata var. thunbergii	10/75	rz	500	120.8	N.S.	125	82.8	N.S.	
Liriope platyphylla	5/72	rz	500	91.5	N.S.	500	124.1	N.S.	
Smilax china	5/72	rz	500	118.5	N.S.	50	192.9 165.0	P<0.001 P<0.05	
Loganiaceae									
Strychnos ignatii	2/75	sd	500	164.4 151.0	P<0.001 P<0.05	500	103.0	N.S.	90.0
Magnoliaceae									
Magnolia obovata	3/75	bk	250	102.3	N.S.	250	209.8 164.3	P<0.01 P<0.001	
Menispermaceae									
Sinomenium acutum	10/72	rt	60	88.0	N.S.	60	99.3	N.S.	
Moraceae									
Morus bombycis	10/75	rt-bk	500	104.8	N.S.	500	89.8	N.S.	
Myristicaceae									
Myristica fragrans	5/72	sd	125	208.9 265.4	P<0.01 P<0.001	125	81.2	N.S.	80.0
Myrtaceae									
Eugenia caryophyllata	5/72	fl	125	96.0	N.S.	125	119.5	N.S.	
Nymphaceae									
Euryale ferox	7/75	sd	500	107.8	N.S.	500	128.3	N.S.	
Orchidaceae									
Dendrobium officinale	5/75	wp	500	168.2 221.9	P<0.05 P<0.02	250	77.5	N.S.	70.0
Palmae									
Areca catechu	10/72	sd	500	101.6	N.S.	250	116.1	N.S.	
Papaveraceae									
Corydalis ternata	12/72	tb	500	101.1	N.S.	250	80.2	N.S.	
Piperaceae									
Piper nigrum	11/77	fr	50	235.1 253.0	P<0.001 P<0.001	125	69.1 52.0	P<0.05 P<0.01	0.0
Poligonaceae									
Polygala tenuifolia	12/72	rt	25	156.6 168.1	P<0.05 P<0.05	5	77.0	N.S.	80.0

Rheum undulatum	2/73 rz	500	92.0	N.S.	500	85.0	N.S.	
Ranunculaceae								
Aconitum ciliare	10/72 rt	125	168.7 168.0	P<0.001 P<0.02	125	92.7	N.S.	80.0
Clematis manshurica	10/'72 rt	500	121.6	N.S.	500	112.9	N.S.	
Paeonia albiflora	2/72 rt	500	100.2	N.S.	500	116.5	N.S.	
Paeonia moutan	10/72 bk	500	103.6	N.S.	250	119.8	N.S.	
Rosaceae								
Prunus mume	5/75 fr	500	192.3 130.6	P<0.001 P<0.01	500	86.4	N.S.	80.0
Sanguisorba officinalis	10/69 rt	500	108.3	N.S.	125	127.5	N.S.	
Rubiaceae								
Rubia akane	12/72 rt	500	190.1 216.2	P<0.01 P<0.001	500	129.5	N.S.	100.0
Rutaceae								
Citrus aurantum	10/72 pc	500	288.6 143.6	P<0.001 P<0.01	250	108.3	N.S.	90.0
Phellodendron amurense	10/72 bk	125	98.0	N.S.	125	123.0	N.S.	
Solanaceae								
Lycium chinense	10/69 fr	500	107.4	N.S.	500	99.0	N.S.	
Lycium chinense	5/72 rt-bk	500	121.6	N.S.	500	91.4	N.S.	
Taxaceae								
Torreya nucifera	12/72 sd	250	131.5	N.S.	250	122.2	N.S.	
Umbelliferae								
Angelica tenuissima	10/72 rz	500	135.6	N.S.	500	117.2	N.S.	
Valerianaceae								
Patrinia scabiosifolia	2/72 rt	125	159.0 186.0	P<0.01 P<0.01	125	344.2 230.9	P<0.001 P<0.001	80.0
Verbenaceae								
Vitex rotundifolia	3/72 fr	500	311.0 227.9	P<0.001 P<0.01	500	108.5	N.S.	90.0
Zingiberaceae								
Amomum xanthioides	10/72 sd	500	184.5 218.5	P<0.001 P<0.01	250	118.8	N.S.	100.0
Curcuma aromatica	2/75 rz	500	226.8 211.8	P<0.001 P<0.02	500	100.0	N.S.	100.0
Curcuma zedoaria	7/75 rz	250	370.6 308.8	P<0.001 P<0.01	250	80.5 61.7	P<0.05 P<0.05	60.0
Zingiber nigrum	10/72 sd	500	119.2	N.S.	500	119.5	N.S.	
Zygophyllaceae								
Tribulus terrestis	7/75 fr	500	117.8	N.S.	250	112.6	N.S.	

a) fl, flower; fr, fruit; lf, leaf; wp, whole plant; rt, root; rz, rhizome; sd, seed; pc, pericarpium; tb, tuber; bk, bark wd, wood; lg, lignum; ga, gall and rt-bk, root-bark

b) retested value

c) Mortality in untreated control mice was 50%.

enzymes[2].

The extract of *Zedoariae rhizoma* did not show an increasing effect in the strychnine mortality test, implying that hexobarbital metabolizing enzyme system differs from the system for strychnine. In case of the extract of *Piperis nigri fructus*, on the other hand, the strychnine mortality was markedly reduced. This phenomenon might be partly due to a CNS-depressant action of some components of the extract.

It is worth noting that the plant extracts of

Dianthi herba, Melandrii herba, Echinopii radix, Siegesbeckiae herba, Smilax rhizoma, Magnoliae cortex, and *Patriniae radix* caused a significant prolongation of the barbiturate-induced hypnosis in induction test, in which shortening of the duration of the barbiturate-induced hypnosis had been expected.

This phenomenon is probably due to non-specific toxic effects of the constituents of the plant materials on the liver, though a precise mechanism of it is not known and remains to be elucidated. Crude plant materials have been prescribed alone or in combination as drugs without regard to their effects on drug metabolizing enzyme systems in the liver. The present results therefore strongly suggest a need for much investigation on the constituents of the medicinal plants acting on the drug metabolism, which may contribute to the modernization of the ancient therapies and in addition, to the development of new safe drugs from natural resources. On the basis of these results, some plants have been selected for deitailed chemical and biological studies. In the following paper we present the isolation and identification of substances which have been responsible for acting on the drug metabolism.

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