Arch. Pharm. Res. **1**(1), 13~19(1978)

A Survey of the Response of Korean Medicinal Plants on Drug Metabolism

Won Sick Woo, Kuk Hyun Shin, In Chull Kim and Chung Kyu Lee

Natural Products Research Institute, Seoul National University, Seoul 110, Korea

(Received 10 November 1978)

Abstract □ Alcohol extracts of plants widely used in the traditional medicine have been tested to establish if they affect the metabolism of drugs in mice.

Fourteen of the plants tested exhibited prolonging and/or inhibitory effect on hexobarbital sleeping time. Some of them also showed increasing effect on strychnine mortality, whereas *Piperis retrofracti Fructus* reduced the toxicity of strychnine.

Keyphrases □ —Korean medicinal plants–Hexobarbital hypnosis–Strychnine mortality–Inhibition and induction of drug metabolizing enzyme.

It is now almost universally recognized that most foreign compounds undergo a variety of metabolic changes by non-specific enzymes in mammals before they are excreted in the urine, bile or air. At birth, many of the hepatic enzymes that metabolize foreign compounds are relatively inactive, but their enzymatic activities rapidly reach normal adult levels in a few weeks after birth[1]. These enzyme activities may be induced by the treatment of the animals with a wide variety of environmental factors, such as drugs, insecticides, polycyclic hydrocarbons and food additives[2].

*Part 1 in the series, Studies on crude drugs acting on drug metabolizing enzymes.

It has been shown that the activities of drug metabolizing enzymes could be affected by nutritional and dietary factors[3,4] as well as naturally occurring compounds[5-21]. However, the response of various microsomal reactions to different inducers is not the same[22]. It is known that the compounds which induce a microsomal enzyme system for metabolizing one substrate vary in their abilities to induce those enzyme systems for metabolizing other substrates. Moreover, it was demonstrated that a variety of drugs caused biphasic responses on the liver microsomal enzymes: they blocked the oxidation of drugs in the first phase and stimulated the oxidation in the second phase.[23] For example, many inhibitors of the drug metabolism enhanced the activity of the microsomal drug metabolizing enzymes 48 hours after the administration; on the other hand, many inducers of these enzymes such as glutethimide inhibited their activity if they were administered to animals 30 minutes before the assay of the enzymes. Therefore, inducers and inhibitors of drug metabolizing enzymes may be expected to cause marked changes in the pharmacological and toxicological action of drugs[24,25].

In oriental countries such as Japan, China and Korea, crude plant materials have been prescribed alone or in combination as drugs according to ancient therapies, sometimes in combination with modern synthetic drugs.

The present survey was initiated to establish whether the constituents of widely employed medicinal plants affect the drug metabolizing enzymes, consequently modifying the intensity of the therapeutic or toxicologic reponses of drugs.

MATERIALS AND METHODS

Freshly collected plant materials were botanically identified and dried. The dried materials were coarsely crushed and extracted three times with 70~80% methanol at room temperature. The combined filtrate was evaporated under reduced pressure on a water bath of 40° to dryness. The dried residue was used for the test.

Male albino mice weighing 17~22g were used throughout the experiments. They were kept in a constant temperature environment (20 ± 2°) and were fed on laboratory chows and water *ad lib*. Hexobarbital sodium was prepared from hexobarbital base by reacting with equimolar quantities of metal sodium in anhydrous methanol. Hexobarbital sodium solution was prepared by dissolving in 0.9% NaCl to give a final concentration of 2.5 mg/ml or 5 mg/ml. Strychnine nitrate solution was prepared by dissolving in 0.9% NaCl to give a final concentration of 0.06 mg/ml. The materials were suspended in 0.5% carboxymethylcellulose solution.

Measurement of Hexobarbital Sleeping Time

Two sets of experiments were performed. In the first set, mice were pretreated with a single i.p. administration of the materials to be tested. Thirty minutes after the administration of the materials, mice were injected i.p. with hexobarbital sodium (50 mg/kg). Mice were observed for sleep as evidenced by the loss of the righting reflex. The duration of sleeping time was measured from the time of injection to the time the mice regained the righting reflex.

In the second set of experiments, mice were pretreated with three consecutive daily administrations of the materials to be tested. Forty eight hours after the last dose of the materials, hexobarbital sleeping time was measured after the administration of hexobarbital sodium (100 mg/kg) intraperitoneally.

Measurement of Strychnine Lethality

The materials were injected i.p. 30 min prior to the administration of strychnine nitrate (1.2 mg/kg). This dose of strychnine nitrate caused tonic convulsion and 50% mortality within 30 min in untreated mice. The mice were observed for 30 min and mortality was recorded.

RESULTS AND DISCUSSION

The screening results of the plant materials of 69 species, belonging to 64 genera and 36 families are tabulated in Table I.

It is generally recognized that barbiturates are useful reference drugs since their duration of action in the body is regulated largely by the

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

Plant names	Date coll.	Plant[a] part	Potentiation Dose (mg/kg)	Potentiation Percent of control	Potentiation Signif.	Inhibition Dose (mg/kg)	Inhibition Percent of control	Inhibition Signif.	Strychnine mortality (%)
Apocynaceae									
Nerium indicum	5/75	lf	60	121.6	N.S.	60	124.0	N.S.	
Araceae									
Pinellia ternata	3/72	tb	500	88.0	N.S.	50	101.9	N.S.	
Araliaceae									
Panax ginseng	4/72	rt	500	106.8	N.S.	500	81.8	N.S.	
Tetrapanax papyriferum	3/72	sm	500	114.0	N.S.	500	114.5	N.S.	
Asclepiadaceae									
Cynanchum willfordi	4/72	rt	500	94.8	N.S.	500	94.6	N.S.	
Aspidaceae									
Dryopteris crassirhizoma	7/75	rz	250	162.3	$P<0.02$	250	90.3	N.S.	80.0
	7/77			158.3	$P<0.01$[b]				
Campanulaceae									
Adenophora remotiflora	5/72	rt	500	116.1	N.S.	500	115.0	N.S.	
Platycodon grandiflorum	10/72	rt	125	118.1	N.S.	125	81.3	N.S.	
Caprifoliaceae									
Lonicera japonica	10/72	fl	500	93.0	N.S.	500	110.1	N.S.	
Compositae									
Arctium lappa	3/72	sd	500	99.3	N.S.	500	117.6	N.S.	
Chrysanthemum indicum	10/69	fl	500	120.6	N.S.	500	99.1	N.S.	
Echinops setifer	10/72	wp	250	122.3	N.S.	250	111.5	N.S.	
Inula helenium	10/72	rt	500	120.0	N.S.	500	87.2	N.S.	
Taraxacum platycarpum	10/72	wp	500	100.8	N.S.	500	83.8	N.S.	
Cornaceae									
Cornus officinalis	10/72	fr	500	153.9	$P<0.01$	500	116.4	N.S.	40.0
	10/77			213.1	$P<0.001$				
Cruciferae									
Raphanus sativus	4/72	sd	500	98.4	N.S.	500	101.9	N.S.	
Cupressaceae									
Biota orientalis	10/69	sd	500	82.9	N.S.	500	96.4	N.S.	
Cyperaceae									
Cyperus rotundus	10/69	rz	500	84.7	N.S.	500	83.2	N.S.	
Ephedraceae									
Ephedra sinica	7/75	wp	250	119.4	N.S.	250	110.0	N.S.	
Flacourtiaceae									
Hydnocarpus sp.	10/72	sd	500	140.4	$P<0.05$	500	107.6	N.S.	90.0
	10/77			215.9	$P<0.001$				
Gentianaceae									
Gentiana scabra	7/75	rt	250	120.0	N.S.	250	103.3	N.S.	
Gramineae									
Phyllostachys reticulata	10/72	wd	500	122.3	N.S.	500	111.5	N.S.	

Plant names	Date coll.	Plant part	Potentiation Dose (mg/kg)	Potentiation Percent of control	Potentiation Signif.	Inhibition Dose (mg/kg)	Inhibition Percent of control	Inhibition Signif.	Strychnine mortality (%)
Labiatae									
Elscholtzia splendeus	7/72	wp	500	123.4	N.S.	500	117.2	N.S.	
Elscholtzia patrini	7/72	wp	500	113.5	N.S.	500	107.4	N.S.	
Leonurus sibiricus	5/72	wp	500	122.2	N.S.	500	121.8	N.S.	
Nepeta japonica	5/72	wp	500	220.8	$P<0.01$	500	122.6	N.S.	90.0
	4/72			188.2	$P<0.01$				
Phlomis umbrosa	10/72	rt	500	117.1	N.S.	500	116.8	N.S.	
Prunella vulgaris	5/72	wp	500	103.6	N.S.	500	120.2	N.S.	
Scutellaria baicalensis	5/72	rt	500	144.0	$P<0.02$	500	115.5	N.S.	100.0
	4/77			174.8	$P<0.01$				
Lauraceae									
Cinnamomum cassia	5/72	bk	500	122.3	N.S.	500	120.4	N.S.	
Lindera strychnifolia	5/72	rt	500	407.3	$P<0.01$	500	93.9	N.S.	100.0
	4/77			423.3	$P<0.001$				
Leguminosae									
Astragalus membranaceus	5/72	rt	500	107.8	N.S.	500	116.1	N.S.	
Glycyrrhiza uralensis	4/72	rt	500	247.4	$P<0.001$	500	73.9	$P<0.05$	80.0
	4/77			166.7	$P<0.01$	500	75.0	$P<0.05$	
Pueraria Thunbergii	10/69	fr	500	95.0	N.S.	125	78.2	N.S.	
Liliaceae									
Anemarrhena asphodeloides	5/72	rz	125	117.9	N.S.	125	90.5	N.S.	
Asparagus lucidus	5/72	rt	500	88.9	N.S.	500	107.3	N.S.	
Polygonatum japonicum	5/72	rt	500	84.3	N.S.	500	117.7	N.S.	
Magnoliaceae									
Schizandra chinensis	8/75	fr	1000	175.7	$P<0.05$	500	101.3	N.S.	40.0
	9/77			222.7	$P<0.001$				
Oleaceae									
Forsythia viridissima	8/75	fr	500	88.7	N.S.	500	114.6	N.S.	
Orchidaceae									
Gastrodia elata	8/69	rz	500	108.3	N.S.	125	109.7	N.S.	
Piperaceae									
Piper retrofractum	10/75	fr	125	287.2	$P<0.01$	125	55.2	$P<0.01$	10.0
	9/77			302.5	$P<0.01$		46.2	$P<0.01$	
Polygonaceae									
Polygonum cuspidatum	10/72	rz	500	110.5	N.S.	500	113.7	N.S.	
Ranunculaceae									
Cimicifuga heracleifolia	4/72	rz	500	154.5	$P<0.02$	500	108.1	N.S.	90.0
	5/77			217.7	$P<0.01$				
Lycoctonum pseudolaeve	8/75	rt	125	95.6	N.S.	100	116.7	N.S.	
Paeonia ovata	8/75	rt	500	102.5	N.S.	500	104.6	N.S.	
Rhamnaceae									
Zizyphus vulgaris var. spinosus	8/75	sd	500	116.5	N.S.	500	116.4	N.S.	

Plant names	Date coll.	Plant part	Potentiation Dose (mg/kg)	Potentiation Percent of control	Potentiation Signif.	Inhibition Dose (mg/kg)	Inhibition Percent of control	Inhibition Signif.	Strychnine mortality (%)
Rosaceae									
Chaenomeles sinensis	4/75	fr	500	111.3	N.S.	500	101.4	N.S.	
Crataegus pinatifida	4/72	fr	500	110.6	N.S.	500	120.2	N.S.	
Prunus ansu	4/75	sd	250	113.1	N.S.	250	110.2	N.S.	
Prunus persica	4/75	sd	500	93.8	N.S.	500	110.6	N.S.	
Rubus coreanus	4/75	fr	500	119.2	N.S.	500	97.0	N.S.	
Rubiaceae									
Gardenia jasminoides	4/75	fr	500	109.9	N.S.	500	96.5	N.S.	
Rutaceae									
Citrus aurantium	4/72	pc	500	119.4	N.S.	500	99.6	N.S.	
Citrus unshiu	4/72	pc	500	104.5	N.S.	500	106.9	N.S.	
Evodia rutaecarpa	4/75	fl	500	86.8	N.S.	500	114.7	N.S.	
Poncirus trifoliata	4/75	fr	500	562.9	$P<0.001$	500	75.9	$P<0.05$	100.0
	9/77			418.0	$P<0.01$	500	70.9	$P<0.02$	
Scrophulariaceae									
Picrorrhiza kurroa	4/75	rz	500	107.3	N.S.	500	90.7	N.S.	
Rehmannia glutinosa	4/75	rt	500	84.9	N.S.	500	82.1	N.S.	
Sapindaceae									
Euphoria longana	4/75	al	500	120.8	N.S.	500	112.8	N.S.	
Stemonaceae									
Stemona japonica	4/75	rt	250	124.7	N.S.	250	115.5	N.S.	
Typhaceae									
Typha orientalis	4/72	fl	500	102.5	N.S.	500	115.3	N.S.	
Umbelliferae									
Angelica davurica	5/72	rt	500	514.9	$P<0.0001$	500	48.3	$P<0.001$	100.0
	7/77			487.6	$P<0.001$		55.9	$P<0.001$	
Angelica gigas	5/72	rt	500	516.7	$P<0.0001$	500	58.4	$P<0.05$	100.0
	7/77			517.9	$P<0.0001$		59.8	$P<0.05$	
Angelica koreana	5/75	rt	500	649.4	$P<0.0001$	500	53.4	$P<0.001$	100.0
	7/77			518.0	$P<0.0001$	500	63.0	$P<0.01$	
Anthriscus sylvestris	7/75	rt	500	119.3	N.S.	500	119.1	N.S.	
Bupleurum falcatum	8/75	rt	500	122.9	N.S.	250	120.2	N.S.	
Cnidium officinale	5/72	rz	500	117.2	N.S.	500	91.2	N.S.	
Siler divaricatum	5/72	rt	500	104.8	N.S.	500	88.7	N.S.	
Zingiberaceae									
Zingiber officinale	7/75	rz	500	96.8	N.S.	500	103.2	N.S.	

a) fl, flower; fr, fruit; lf, leaf; wp, whole plant; rt, root; rz, rhizome; sd, seed; al, aril; pc, pericarpium; tb, tuber; sm, stem; bk, bark; wd, wood

b) Retested value

c) Mortality in untreated control mice was 50%.

levels of liver microsomal enzymes[2]. The present results showed that several plant extracts possessed prolonging and/or inhibitory effects on barbiturate hypnosis which were

suggestive of inhibitory and/or inductive activities of drug metabolizing enzyme systems in the liver.

In order to establish initial results as valid, the extracts of all plants which gave positive results were newly recollected and retested. The effects were apparent especially in the extracts of three *Angelica* species, *Ponciri Fructus* and *Piperis retrofracti Fructus.*

Eight extracts gave only a prolonging effect on hexobarbital hypnosis (single administration), but did not show any inhibitory effect on hexobarbital hypnosis (repeated treatments). These results appear to indicate that the components of these extracts have a property of enzyme inhibitor rather than that of enzyme inducer. It was demonstrated that strychnine was metabolized enzymatically in the liver and typical enzyme inhibitors such as SKF-525A markedly increased the toxicity of strychnine[25]. Thus the significant increase in strychnine mortality by the plant extracts which have shown potentiating effects on hexobarbital hypnosis in the present experiment strongly suggests the involvement of the drug metabolizing enzyme system in the liver. As expected, most extracts possessing prolongation activity on hexobarbital-induced sleeping time were found to increase the strychnine mortality. The action of the two extracts *Corni Fructus* and *Schizandrae Fructus* which were ineffective in strychnine mortality seemed to be independent to the drug metabolizing enzyme system, though the precise mechanism is not known yet. In case of the extract of *Piperis retrofracti Fructus,* on the other hand, the strychnine mortality was markedly reduced. This phenomenon might be considered partly due to a CNS-depressant action of some components of the extract. From the present experimental results, it can be postulated that various plant drugs, when administered alone or in combination with other drugs, may influence not only their own metabolism but also those of other drugs, consequently changeing intensively other drug action.

ACKNOWLEDGMENT

This work was generously supported by a research grant from the Asan Foundation.

LITERATURE CITED

1) Eriksson, M., and Yagge, S. F., Drug metabolism in the newborn. *Ann. Rev. Med.* **24,** 29(1973).
2) Conney, A. H., Pharmacological implications of microsomal enzyme induction. *Pharmacol. Rev.* **19,** 317(1967).
3) Wattenberg, L. W., Dietary modification of intestinal and pulmonary aryl hydrocarbon hydroxylase activity. *Toxicol. Appl. Pharmacol.* **23,** 741(1972).
4) Campbell, T. C., and Hayes, J.R., Role of nutrition in the drug-metabolizing enzyme system. *Pharmacol. Rev.* **26,** 171(1974).
5) Boulos, B. M., Short, C. R., and Davis, L. E., Quinine and quinidine as inhibitors of hepatic microsomal enzymes in the mouse and rat. *Fed. Proc.* **28,** 418(1969).
6) Wattenberg, L. W., Page, M. A., and Leong, J. L., Induction of increased benzpyrene hydroxylase activity by flavones and related compounds. *Cancer Res.* **28,** 934(1968).
7) Jondorf, W. R., Johnson, R. K., and Donahue, J. D., Studies on drug-metabolizing enzyme activity in rats pretreated with phenobarbitone and compounds related to emetine. *Biochem. J.* **113,** 10p (1969).

8) Jondorf, W. R., Johnson, R. K., and Drassner, J. D., The inhibiting influence of emetine and 2,3-dehydroemetine on liver microsomal drug metabolism in the rat. *Fed. Proc.* **28,** 418(1969).

9) Jori, A., Bianchetti, A., and Prestini, P. E., Effect of essential oils on drug metabolism. *Biochem. Pharmacol.* **18,** 2081(1969).

10) Parke, D.V., and Rahman, H., The effects of some terpenoids and other dietary anutrients on hepatic drug-metabolizing enzymes. *Biochem. J.* **113,** 12p (1969).

11) Ruddon, R. W., and Cohen, A. M., Alteration of enzyme activity in rat liver after nicotine administration. *Fed. Proc.* **28,** 418(1969).

12) Graham, P.S., Hellyer, R. O., and Ryan, A. J., The inhibition of drug metabolism enzymes by some naturally occurring compounds. *Biochem. Pharmacol.* **19,** 759(1970).

13) Graham, P. S. Hellyer, R. O., and Ryan, A. J., The kinetics of inhibition of drug metabolism *in vitro* by some naturally occurring compounds. *Biochem. Pharmacol.* **19,** 769(1970).

14) Parke, D. V., and Rahman, H., Induction of hepatic microsomal enzymes by safrole. *Biochem. J.* **119,** 53p (1970).

15) Wattenberg, L. W., and Leong, J. L., Inhibition of the carcinogenic action of benzo(a)pyrene by flavones. *Cancer Res.* **30,** 1922(1970).

16) Leibman, K. C., Studies on modifiers of microsomal drug oxidation. *Chem. Biol. Interactions* **3,** 289(1971).

17) Parke, D. V., and Rahman, H., Induction of a new hepatic microsomal hemoprotein by safrole and isosafrole. *Biochem. J.* **123,** 9p (1971).

18) Lake, B. G., and Parke, D. V., Interaction of safrole and isosafrole with hepatic microsomal hemoproteins. *Biochem. J.* **127,** 23p (1972).

19) Witschi, H., and Saint-Francois, B., Enhanced activity of benzpyrene hydroxylase in rat liver and lung after acute cannabis administration. *Toxicol. Appl. Pharmacol.* **23,** 165(1972).

20) Berlin, C. M., Stackman, J. M., and Vesell, E. S., Quinine-induced alterations in drug disposition, *Clin. Pharmacol. Ther.* **18,** 670(1975).

21) Ariyoshi, T., Arakaki, M., Ideguchi, K., Ishizuka, Y., Nada, K., and Ide, H., Studies on the metabolism of α-limonene (*p*-mentha-1,8-diene). III. Effects of α-limonene on the lipids and drug-metabolizing enzymes in rat livers. *Xenobiotica* **5,** 33(1975).

22) Conney, A. H., Davidson, C., Gastel, R., and Burns, J. J., Adaptive increases in drug-metabolizing enzymes induced by phenobarbital and other drugs. *J. Pharmacol. Exptl. Therap.* **130,** 1(1960).

23) Kato, R., Chiesara, E., and Vassanelli, P., Further studies on the inhibition and stimulation of microsomal drug-metabolizing enzymes of rat liver by various compounds. *Biochem. Pharmacol.* **13,** 69(1964).

24) Gilette, J.R., and Mitchell, J. R., Drug actions and interactions. Theoretical considerations. *Handb. Exp. Pharmacol.* **28,** 359(1975).

25) Adamson, R. H., and Fouts, J. R., Enzymatic metabolism of strychnine. *J. Pharm. Exp. Ther.* **127,** 87(1959).