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Effect of Spices on Hepatic Microsomal Enzyme Function in Mice

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Abstract ☐ The effect of twenty two spices on liver microsomal monooxygense activity was tested as measured by alteration of hexobarbital (HB) narcosis and strychnine mortality in mice. Oral administration of seven spices for 7 consecutive days caused a significant shortening of the duration of HB-induced sleeping time. The treatment of mice with a single *i.p.* injection of 9 spices resulted in a significant prolongation of the sleeping time. White pepper, dill and fennel reduced the toxicity of strychnine. These results strongly indicated that some spices might affect the activity of liver microsomal drug metabolizing enzyme (DME) function.

Keywords ☐ Spices, Hexobarbital hypnosis, Strychnine mortality, Liver microsomal monooxygenase.

Various environmental factors such as drugs, pesticides, carcinogens and food additives have been known to influence hepatic oxidative metabolism of other drugs and chemicals in man and animal, changing markedly the intensity of the therapeutic or toxic action of many drugs.[1] Shin and Woo[2], Wattenberg[3], and Whang, *et al.*,[4] demonstrated that a number of medicinal plants and edible plants stimulated the drug metabolism. There is a possibility that various spices commonly used not only for food additives but also for condiments may influence liver monooxygenase activity, from the fact that a certain essential oil increases the drug metabolism.[5]

In this paper, screening results for 22 spices, belonging to 10 species are presented, by using experimental models of hexobarbital-induced hypnosis and strychnine mortality in mice.

EXPERIMENTAL METHODS

Male albino mice (dd strain) weighing 17-25g were used and maintained on purina lab chows in a constant temperature environments throughout the experiments. The mice were given free access to tap water.

Dried spice materials purchased from market were crushed coarsely and extracted five times with ether at room temperature.

The combined extracts were concentrated to dryness. Phenobarbital was U.S.P. grade. Other chemicals were reagent grade commercially available. SKF-525A was a gift from Smith, Kline and French Lab., Philadelphia, U.S.A.

Measurement of HB-induced Sleeping Time

In the first phase experiment, mice were administered i.p. with a single dose of the extracts suspended in 0.5% CMC solution. Thirty min. later, the animals were injected *i.p.* with HB-Na (50mg/kg) and the duration of sleeping time was measured.

In the second phase experiment, mice were pretreated with 7 daily consecutive oral administrations of the extracts. Forty eight hr. after the last treatment of the extracts, hexobarbital sleeping time was measured by *i.p.* administration of HB-Na (100mg/kg).

When there was a toxic symptom at a given

dose, the dosage was reduced and retested. In order to establish the initial positive result as valid, all extracts in question were retested. Phenobarbital and SKF-525A, were used as reference compounds for an enzyme inducer and an inhibitor, respectively.

Measurement of Strychnine Mortality

The extracts in 0.5% CMC were injected *i.p.* 30 min prior to the administration of strychnine nitrate (1.2mg/kg). The mice were observed and number of animals died within 30 min was recorded.

RESULTS AND DISCUSSION

The effect of twenty two kinds of spices belonging to 10 families on hexobarbital-induced sleeping time and strychnine mortality in mice is summarized in Table I.

On daily oral administration for 7 days, seven spices such as fennel, dill, nutmeg, mace, white pepper, sage and paprika caused a significant shortening effect on HB-induced sleeping time, suggesting induction of hepatic monooxygenase activity.[1)]

The spices which caused a significant prolongation of HB-induced sleeping time in the phase I experiment were thyme, fennel, dill, nutmeg, mace, white pepper, celery, tarragon, rosemary, and paprika.

White pepper caused 395% and 490.1% increases in duration of HB-hypnosis at a relatively low dose of 50mg/kg whereas others prolonged weakly at 200mg/kg dose level.

Among them, tarragon, nutmeg and mace also gave a significant increase in strychnine mortality. This result strongly indicates the inhibition of DME function in the liver by these plant extracts.[9)]

Nutmeg and mace exhibited biphasic response on DME, that is, inhibitory effect in the early stage and inducing effect in the late stage.

The others either markedly reduced the strychnine mortality or did not affect on it, which might be considered partly due to antagonistic effect against strychnine action. As a matter of fact, piperine was recently isolated as a CNS-depressant principle from the *Piper* species.[6,7)] *Foeniculum vulgare* and *Anethum graveolens*, which not only strongly reduced the strychnine mortality, but prolonged HB-induced sleeping time, might be suggested to be dormant resources for CNS depressants.

Remmer, *et al.*[8)] demonstrated that induction of hepatic microsomal monooxygenase activity by phenobarbital was associated with a massive proliferation of smooth endothelial reticulum in the hepatic parenchymal cell and consequent increase in liver weight.

As shown in Table II, the liver weight expressed relative to body weight (RLW) in animals that elicited reduction in sleeping time by repeated treatments of spices such as sage, fennel, dill, paprika and mace was significantly increased as compared with that of the control.

This result strongly suggests a significant increase in hepatic microsomal protein and/or hypertrophy of the smooth endothelial reticulum as could be observable in phenobarbital type inducers.[8)]

From the present experimental results, it can be postulated that some spices may influence the activity of hepatic microsomal monooxygenase systems, consequently changing the intensity of the therapeutic or toxicologic responses of drugs.

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Table I: Effect of spices on hexobarbital induced sleeping time and strychnine mortality in mice.

Plant name (Common name, part)	Hexobarbital hypnosis[a]						Strychnine mortality (No. dead/ No. treated)
	phase Ⅱ (Induction)			phase Ⅰ (Inhibition)			
	Daily Dose (mg/kg, *p.o.*)	Min±S.E.	% of control	Dose (mg/kg, *i.p.*)	Min±S.E.	% of control	
Control	—	58.3± 7.0	100	—	22.3±2.4	100	5/10
Phenobarbital	50	15.7± 0.9[f]	26.9	—	—	—	—
SKF-525A	—	—	—	30	156.0±8.8[f]	699.5	9/10
Compositae							
Artemisia dracunculus	200	50.5± 9.5	86.6	100	41.2± 1.7[e]	185.0	7/10
(Tarragon, leaves)					49.3± 5.2[e]	221.1	
Cruciferae							
Brassica spp. (Mustard, seeds)	200	46.6± 4.4	80.0	100	25.9± 2.9	116.3	—
Labiatae							
Majorana hortensis (Majoram, leaves)	200	42.1± 6.5	72.3	200	20.6± 2.4	92.5	—
Mentha piperita (Mint, leaves)	200	47.9± 6.3	82.2	200	21.1± 2.4	94.6	—
Ocimum basilicum (Basil, leaves)	200	43.3±12.7	74.3	200	21.3± 1.9	95.5	—
Origanum vulgare (Origanum, leaves)	200	40.6± 9.9	69.7	100	27.8± 0.9	125.0	—
Rosmarinus officinalis	200	48.3± 7.0	82.9	100	43.1± 1.7[e]	193.4	6/10
(Rosemary, leaves)					35.6± 3.1[d]	159.6	
Salvia officinalis (Sage, leaves)	200	38.6± 2.2[e]	66.3	100	18.6± 2.9	83.6	—
		33.9± 3.2[e]	58.3				
Thymus vulgaris (Thyme, leaves)	200	53.9± 3.5	92.5	200	54.9± 1.8[e]	246.7	4/10
					38.0± 5.1[c]	170.4	
Lauraceae							
Laurus nobilis (Bay, leaves)	200	44.0± 5.5	75.5	200	26.1± 3.8	117.1	—
Myristicaceae							
Myristica fragrans	200	32.7± 6.6[d]	56.1	200	34.5± 1.2[e]	154.9	7/10
(Nutmeg, seeds)		33.4± 3.9[e]	57.4		53.8± 7.9[e]	241.3	
Myristica fragrans (Mace, aril)	200	32.5± 2.8[e]	55.7	100	43.4± 4.7[e]	195.0	7/10
		31.6± 1.4[e]	54.2		71.9± 0.6[f]	322.4	
Myrtaceae							
Pimenta officinalis (Allspice, fruit)	200	62.9± 5.8	107.9	100	16.4± 6.1	73.8	—
Papaveraceae							
Papaver somniferum (Poppy, seeds)	200	53.8± 3.7	92.4	200	26.7± 4.9	119.8	—
Piperaceae							
Piper nigrum[b]	200	28.9± 5.9[d]	49.7	50	110.2±14.0[f]	495.0	1/10
(White pepper, fruit)		13.1± 1.1[f]	22.4		131.6± 0.2[f]	590.1	
Solanaceae							
Capsicum frutescens	200	34.8± 1.6[e]	59.8	200	33.7± 1.9[e]	151.2	5/10
(Paprika, fruit)		43.8± 2.6[c]	75.1		34.3± 1.0[e]	153.8	

Umbelliferae							
Anethum graveolens(Dill, weeds)	200	34.8± 1.3[e]	59.8	200	35.1± 2.5[e]	157.5	2/10
		37.7± 5.4[c]	64.7		71.1± 9.1[e]	318.8	
Apium graveolens(Celery, seeds)	200	57.9± 3.1	99.3	200	44.6± 0.3[f]	200.4	6/10
					57.0± 4.6[f]	255.6	
Carum cervi(Caraway, seeds)	200	44.3± 8.6	79.0	200	23.4± 0.9	105.2	—
Cuminum cyminum(Cumin, seeds)	200	48.5± 6.3	83.2	100	26.7± 3.5	120.0	—
Foeniculum vulgare(Fennel, seeds)	200	28.2± 6.1[e]	48.4	200	37.1± 1.1[f]	167.7	2/10
		36.2± 8.3[c]	62.1		38.2± 1.7[e]	171.3	
Pimpinella anisum(Anise, seeds)	200	48.9± 2.7	83.9	100	34.3± 6.3	154.0	—

All experimental conditions are described in Experimental Methods.

a) Five or six mice were used.

b) Positive effects for black pepper have been previously reported. (Woo, W.S., Shin, K.H. and Kim, I.C. Kor. J. Pharmacog., 8, 115(1977)).

Significantly different from the control; c: $p<0.05$, d: $p<0.02$ e: $p<0.01$, f: $p<0.001$

Table II: Effect of repeated administration of spices on liver weight of mice.

Treatments	No. of Mice	Body Weight(g)	Wet Weight of Liver(g)	R.L.W	% of Control
Control	7	17.80±0.76	0.77±0.047	0.044±0.0027	100
Sage	5	19.10±0.68	1.00±0.115	0.052±0.0017*	118.2
Nutmeg	5	16.86±1.85	0.84±0.075	0.050±0.0022	113.6
White pepper	5	18.98±1.65	0.80±0.114	0.042±0.0022	95.5
Fennel	5	23.80±1.68	1.44±0.051	0.061±0.0022***	138.6
Dill	5	20.20±1.43	1.16±0.103	0.057±0.0022***	129.5
Paprika	6	20.70±0.79	1.25±0.076	0.060±0.0025***	136.4
Mace	6	19.58±0.53	1.08±0.048	0.055±0.0025**	125.0

Significantly different from the control group as *$p<0.05$, **$p<0.02$ and ***$p<0.01$

R.L.W.=Liver weight expressed relative to body weight.

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