The Pharmacology of Myristicin and Nutmeg

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The long history of observations concerning the pronounced psychotropic effect of Myristica fragrans (nutmeg) has not gone unnoticed by many distinguished investigators, including some famous pharmacologists. A central problem in the pharmacology of nutmeg has been identification of the active component of the crude drug. As early as 1676, van Leeuwenhoek, the original microscopist noted that a volatile component which evolved from pieces of nutmeg in a glass tube repelled or killed mites. (*1*) Although Warburg, as late as 1897, still expressed doubt (*2*) it was clear by then that the volatile fraction, the oil of nutmeg, was more toxic than the crude drug. The well-known English pharmacologist, Cushny, stated that the residue from which the volatile oil has been removed has no effect upon animals. (*3*) In our early studies at Maryland, we confirmed this observation by human testing of a steam-distilled residue and noted only gastrointestinal effects. (*4*)

Another pharmacologist, George Wallace, used the highest distillate fraction (149°C, 14 mm), which he found to be the most active and easily administered component, and observed that the cat was the most susceptible species among the mammalia to the toxic action of the drug. (*5*) Both Wallace and, a year later, Jurss (*6*) correctly attributed the high toxicity to hepatic fatty degeneration, but the cat is also most sensitive to the central excitation, tremor, salivation, and stupor produced by oil of nutmeg. Sir Henry Dale in 1907 most clearly differentiated the primary psychotropic effect from the secondary hepatic coma causing death in cats. (*7*) Although he noted, as others had, that the oil required a higher myristicin amount than the crude drug in order to produce symptoms, Dale attributed this to absorption difficulties with the purified product. Power and Salway, re-examining the question in 1908, concurred that myristicin was probably responsible for the central effect, but was unfavorable for absorption in the pure state. (*8*)

Pharmacologic interest in nutmeg then subsided for more than 50 years, until renewed by the curiosity of Dr. John C. Krantz at the University of Maryland who was consulted by several former students encountering cases of nutmeg intoxication. (*4*) This study was conducted with a myristicin-containing fraction distilled from oil of nutmeg at 145–155°C and 15 mm Hg pressure. Subsequent gas-chromatographic studies by Shulgin have shown this to be a mixture of myristicin with elemicin and perhaps a small amount of methylisoeugenol. (*9*)

Initial studies on the pharmacologic action of myristicin and nutmeg which were conducted at the University of Maryland sought to answer

a variety of questions. (*4*) Toxicity studies showed that the East Indian spice was more toxic than a West Indian product. Animal toxicity determinations before and after steam distillation also confirmed Cushny's original observation that the volatile fraction was more toxic than the residue (*3*) In planning for human administration of a dose of the myristicin-elemicin fraction amounting to 400 mg per subject, a chronic study in rats was conducted and showed no growth inhibition at a daily dose of 10 mg/kg.

A stimulant effect of myristicin was demonstrated by a shortening effect of the oil fraction on barbiburate sleeping time. These data are shown in Table 1.

TABLE 1.—*The effect of myristicin on the sleeping time induced by phenobarbital in the rat*

Group	Mean sleeping time	Standard error	p value
Phenobarbital 120 mg/kg I. P.	162 min	±5. 31	
Phenobarbital 120 mg/kg I. P. plus 100 mg/kg myristicin I. P.	144 min	±2. 27	<0. 01

The intravenous injection of large doses in the order 50–76 mg/kg to dogs, monkeys, and cats confirmed the feline species toxicity and showed clearly that tranquilization of wildness is not produced in the jungle-bred monkey. It is of interest that the product was hypotensive in the dog as are other monamine oxidase inhibitors. These intravenous injections were suspensions of the oily substance in acacia solution. More recently a stable emulsion has been achieved having the following composition:

	Percent
Myristicin	1.0
Pluronic F-68	0.3
Dextrose	4.2
Ethyl alcohol	1.0
Distilled water qs	100.0

Using this formula, mice were injected into the dorsal tail vein with doses of 100 mg/kg. Within 1 to 2 minutes, loss of righting reflex and apparent sedation appeared.

One contribution to the metabolism of myristicin has recently evolved from interest in its synergistic effect upon other insecticides. Casida and his associates have shown that the methlyenedioxy bridge is the initial point of metabolic attack by hepatic microsomes and requires $NADPH_2$ (*10*). This reaction is shown in Figure 1. This metabolic transformation increases the chemical similarity of myristicin to the catecholamines.

The structural resemblences of myristicin to mescaline and epinephrine prompted studies directed at measuring competitive inhibition of myristicin to other monoamine oxidase substrates. The method of Tedeschi et al, (*11*) was employed for estimation of monoamine oxidase (MAO) inhibition by potentiation of the central convulsant action of tryptamine HCl. A 0.5%

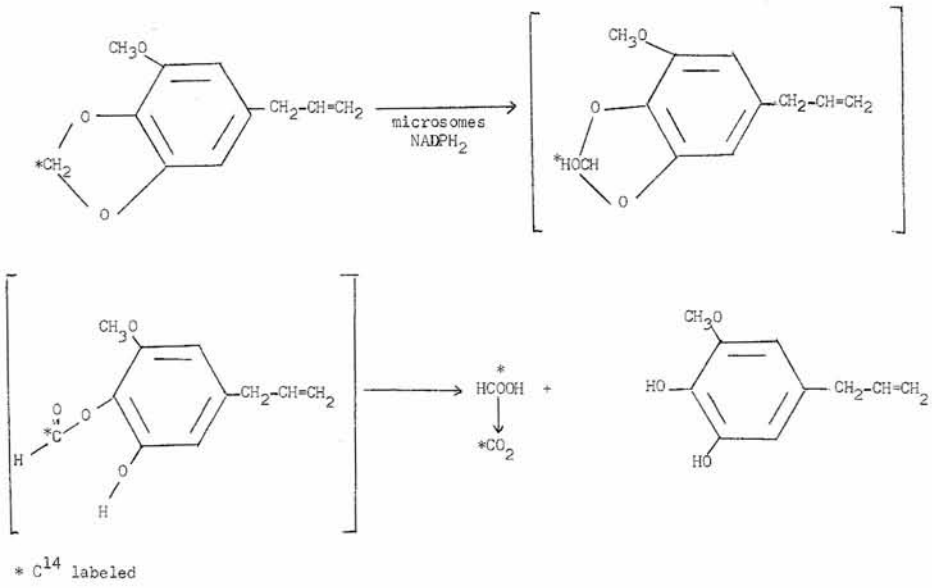

FIG. 1.—Major metabolic pathway for methylene C^{14} dioxyphenyl labeled myristicin in liver microsomal systems of the mouse. (Modified from Casida, et al. (10).)

solution was injected intravenously into 10 mice per dose level. Three seconds or more of clonic jerking, tremors, and/or side-to-side head movements were the endpoint criteria used to calculate the CD_{50} from dose-response lines by the method of Rubin et al. (*13*) in rats, scoring both eyes on a 5-point scale. Cerebral 5-hydroxytryptamine was measured by the Mead and Finger modification (*14*) of the method of Bogdanski et al. (*15*)

Results

No apparent effect was evident from the drug vehicles on the CD_{50} of tryptamine (Table 2). When given orally 18 hours in advance, East Indian ground nutmeg gave some evidence of tryptamine potentiation (Figure 2). The optimum dose was 500 mg/kg. However, a much larger dose, 1000 mg/kg showed reversal of the activity.

Several samples of synthetic myristicin [1] were tested by the tryptamine potentiation test 18 hours after their oral administration. These results are shown in Figure 3. Both of these preparations showed considerable activity when the sample was fresh and lemon yellow in color. Later tests (not shown) after the liquid had turned to a light amber color consistently showed a considerable decline in tryptamine potentiation. These deteriorated solutions when studied by gas chromatography showed the appearance of an unknown component in addition to the myristicin.

The distilled concentrate of oil of nutmeg was much less active than the synthetic myristicin and, like ground nutmeg, reversed its activity with a

[1] Synthetic myristicin was kindly made available by Dr. Carl D. Lunsford, A. H. Robins Company, Richmond, Virginia.

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TABLE 2.—*Tryptamine convulsion test for monoamine oxidase inhibition* in vivo. *Summary of control tests*

Species	No.	Vehicle-18 hr prior, cc/kg	CD_{50}, mg/kg	95% confidence limits, mg/kg
Mouse	40	None	25.0	15.4–40.5
"	21	"	17.3	12.1–24.7
"	28	Liq. pet.	24.5	19.9–30.1
"	38	" "	28.0	18.4–42.6
"	37	Acacia-2%	25.8	18.3–36.3
Avg	164		25.0	21.6–29.0
Rat	54	None	18.6	13.6–25.5

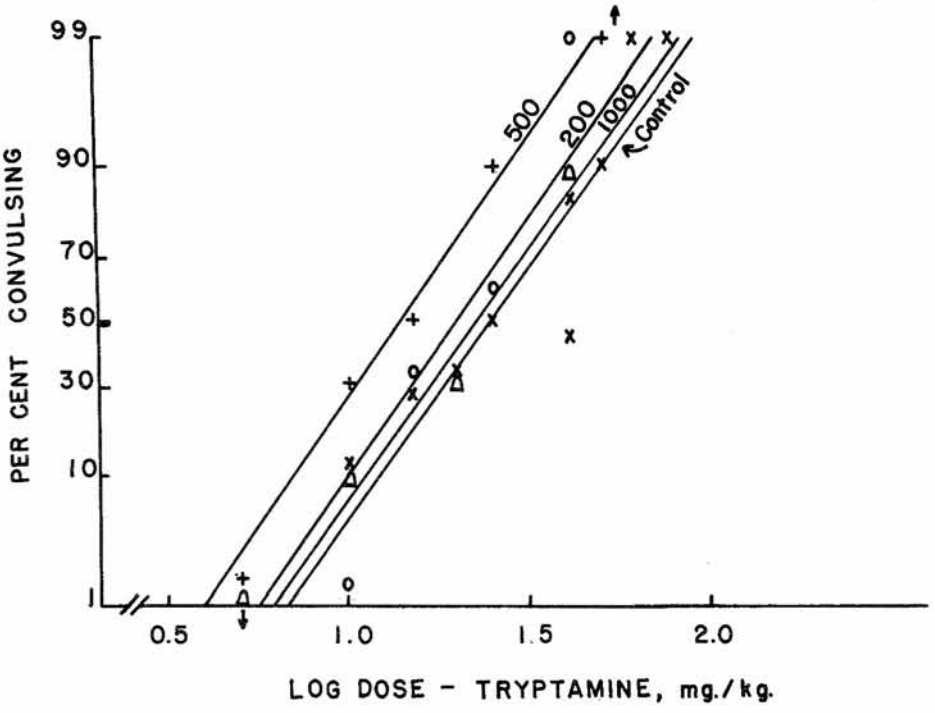

FIG. 2.—Effect of ground nutmeg on tryptamine convulsive threshold in mice when given orally in acacia suspension 18 hr before test: X——X Control, CD_{50} mg/kg (±95% confidence limits) 25.0 (15.2–41.0); ○——200——○ 200 mg/kg nutmeg, 20.0 (14.2–28.2); +—500—+ 500 mg/kg nutmeg, 14.0 (10.1–19.5); △——1000——△ 1000 mg/kg nutmeg, 23.0 (16.1–32.9).

large dose (Figure 3). Gas-chromatographic analysis of this oil showed the presence of volatile components similar to ground nutmeg, but no increased concentration of the myristicin, as expected from the selected distillation temperature.[2]

[2] These analyses and supplies of ground nutmeg were kindly furnished by Dr. William K. Stahl, McCormick and Company, Baltimore, Maryland.

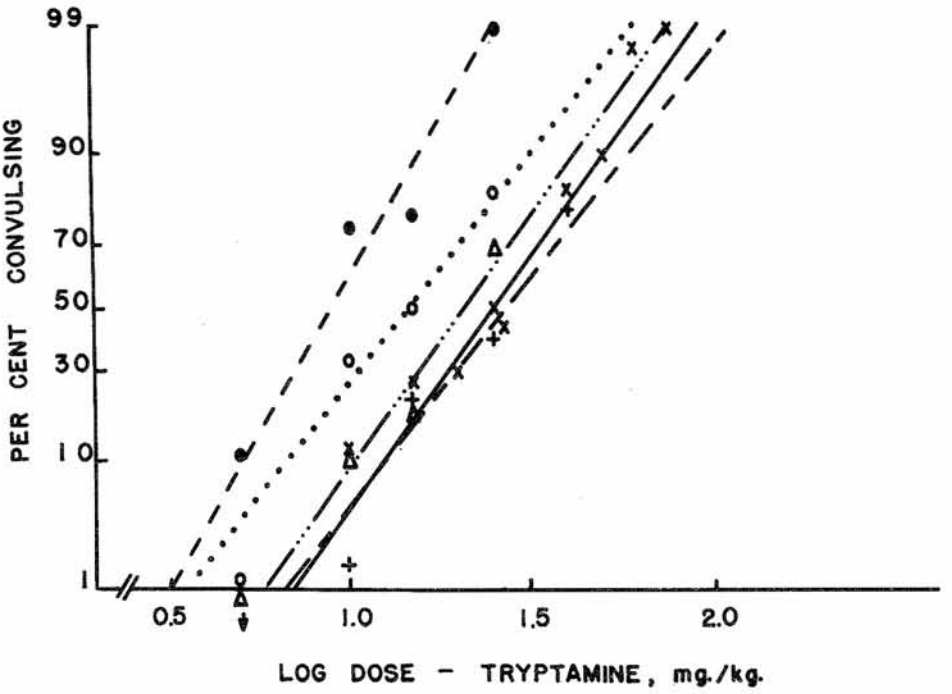

FIG. 3.—Effect of synthetic myristicin samples and oil of nutmeg concentrate on tryptamine convulsive threshold in mice when given orally in acacia suspension 18 hr before test: X— — —X Control, CD_{50} mg/kg (±95% confidence limits) 25.0 (15.2–41.0); ○——○ Myristicin sample 1 at 500 mg/kg, 8.7 (5.7–13.4); ○— . . . ○ myristicin sample 2 at 500 mg/kg, 14.0 (9.3–21.0); . . . . . oil of nutmeg concentrate 500 mg/kg, 20.5 (14.5–28.9); +— — —+ oil of nutmeg concentrate — 1000 mg/kg, 27.0 (19.9–36.7).

In Figure 4 the slope and activity of the best tryptamine assay for myoisticin is compared to tranylcypromine and iproniazid. All three drugs were administered orally 18 hours before the test. It may be seen that myristicin is less potent but parallel to the comparative drugs. Safrole, isoborneol, and geraniol, which are other volatile components of nutmeg, did not cause potentiation of tryptamine in doses up to 1 g/kg despite obvious signs of hyperactivity and excitement in the mice.

In Figure 5 the antagonism of reserpine ptosis in rats was used to study variations in dose and time for myristicin activity. Myristicin appears to be less active in the rat. Comparable activity to other MAO inhibitors was obtained only with the largest dose 17 hours after oral administration.

Myristicin treatment of six rats increased brain 5-hydroxytrptamine from control values averaging 0.48 (± 0.05) μg/g to 0.82 (± 0.03) μg/g when given in an oral dose of 1 g/kg; the difference was statistically significant ($p<0.001$). Lower doses were not significantly active.

A further test of an hypothesis of monoamine oxidase inhibition was conducted using the kynuramine disappearance rate in brain homogenates as

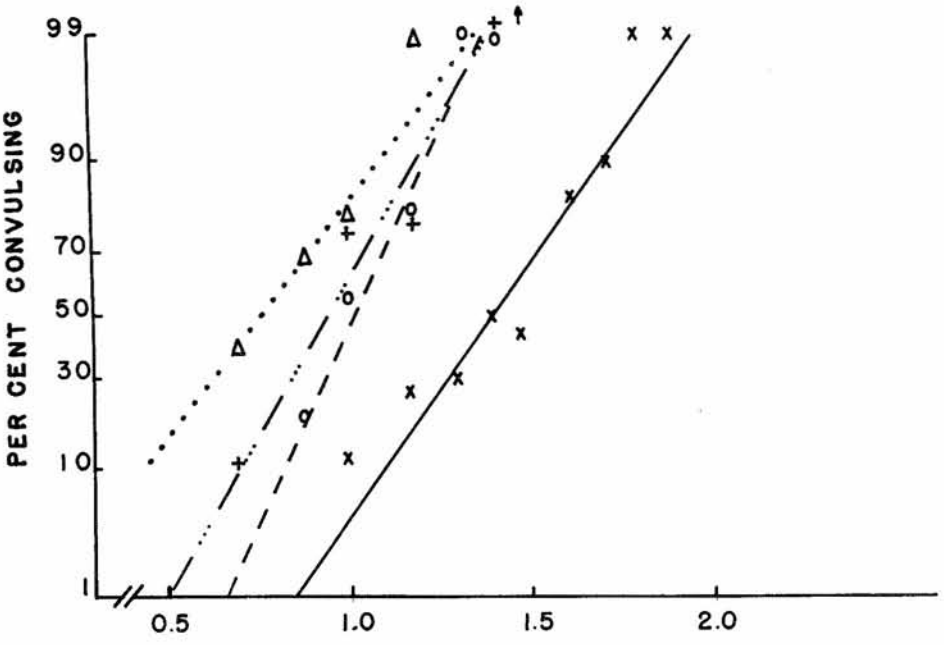

FIG. 4.—Effect of monoamine oxidase inhibitors and synthetic myristicin on tryptamine convulsive thresholds in mice when given orally in acacia suspension 18 hr before test: X———X Control, CD_{50} mg/kg (±95% confidence limits) 25.0 (15.2–41.0); ○——○ 150 mg/kg iproniazid, 10.4 (8.8–12.2); △. . . .△ 4 mg/kg tranyleypromine, 5.8 (4.4–7.7); +— . . . + 500 mg/kg, 8.7 (5.7–13.4).

described by Weissbach et al. (*16*) The results of this test are shown in Table 3. Slight inhibition was found in the mouse but not in the rat-brain preparation. One year after these data were obtained, the same ground-nutmeg source was completely inactive in the mouse as well, and the declining activity was attributed to a loss of volatile components owing to a nearby heater.

Discussion

Although the myristicin fraction from oil of nutmeg originally used in these experiments might not represent 100 percent myristicin, both this and elemicin most likely produce similar actions. The potency of myristicin is not adequate in most of these tests to account for the full action of nutmeg. The insufficiency is present with intravenous doses and therefore poor absorption is not a likely explanation. More rapid biodegradation of purified myristicin in contrast to its slow release from nutmeg might suggest a greater efficiency of the crude drug.

These data demonstrate a mild degree of monoamine oxidase inhibition by a variety of tests. The low potency of myristicin in comparison to tranylcypromine, a potent inhibitor, is in keeping with the large doses required for *in vivo* activity. The tryptamine potentiation test, although indirect, has been

shown to correlate with other *in vivo* assays. (*17*) It is quite likely that although myristicin displaces kynuramine from MAO with difficulty, it still may show inhibiting activity.

The main virtue of these data may be to reawaken interest in myristicin and its activity. Low activity of a prolonged nature, such as that shown by nutmeg, is sometimes a more useful drug attribute than high potency and rapid onset. An important question remains to determine if the myristicin stimulation is inevitably followed by depressed feelings, even upon continued intake. Work is indicated to improve absorption, and further pharmacologic studies are needed to define a proper course of treatment for nutmeg intoxication.

Summary

A myristicin-elemicin fraction of oil of nutmeg produces many of the characteristics of crude ground nutmeg, but lacks adequate potency to explain the nutmeg intoxication syndrome on a quantitative basis. Nutmeg and

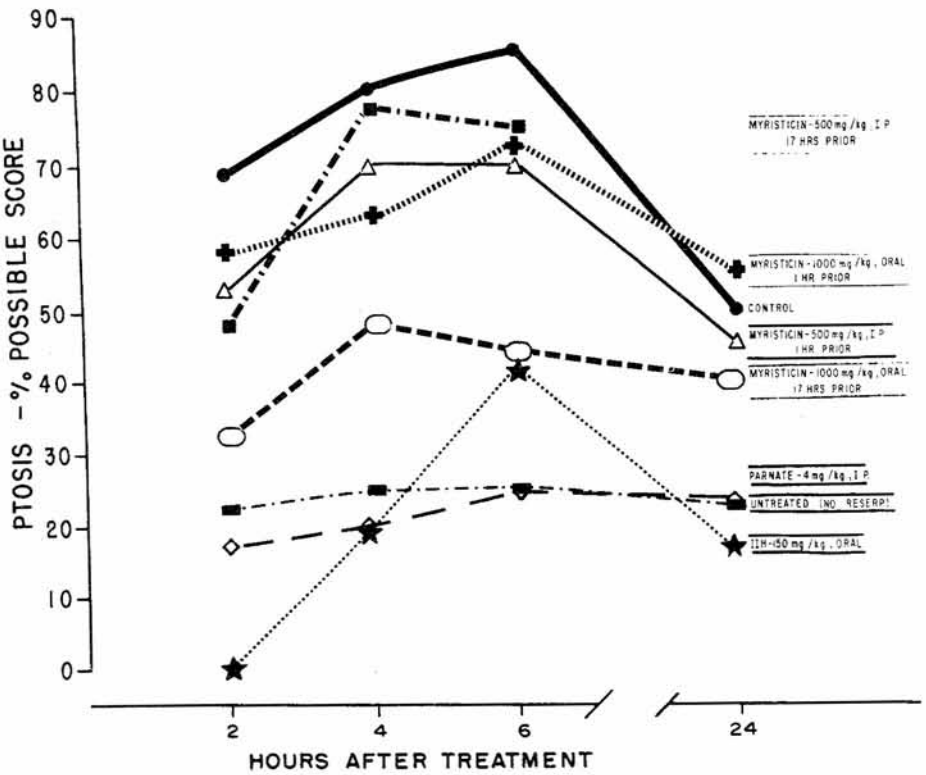

FIG. 5.—Effect of monoamine oxidase inhibitors and various schedules of myristicin on reserpine ptosis in rats. Ptosis score: 0=Eyelid fully open—5=Eyelid fully closed. Maximum score = 10/rat (both eyes). Group ptosis score (%)

$$= \frac{\text{No. rats/group X Max score/rat}}{\text{Sum of group eyelid scores}} \text{ X } 100.$$

TABLE 3.—*The effect of ground West Indian nutmeg on brain monoamine oxidase (MAO) activity in mice and rats measured by the kynuramine (Kyn) method of Weissbach, et al. (16)*

Species	No.	μM-ynK/mg/hr x 10^{-3} [a]	No.	Nutmeg treated [b] percent of control
Mouse	14	3.64±0.013	10	78.0±4.2%
Rat	6	4.74±0.18	5	104.0±5.5%

[a] Micromoles of kynuramine/mg of brain (wet weight)/hour x 10^{-3}.
[b] 18 hours after 500 mg/kg—mice or 1000 mg/kg—rat, P.O.

the synthetically made myristicin demonstrate a mild degree of monoamine oxidase inhibiting activity by *in vitro* and *in vivo* tests. Activity of this synthetic product declines with aging accompanied by color change. Monoamine oxidase inhibition and other actions of crude extracts depend upon the volatile component.

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