Nutmeg (*Myristica fragrans* Houtt.)

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**History**

Nutmeg probably was imported into Europe during the 12th century by Arab merchants. For many years, this spice has been used as an aromatic stimulant, abortifacient, antiflatulent, and as a means to induce menses.¹ The Portuguese discovered the nutmeg tree on the Banda Islands of Indonesia (Spice Islands) in 1512. In 1576, de Lobel reported the first case of nutmeg intoxication in a pregnant English woman, who ingested 10-12 nutmeg nuts.² Beginning in the 17th century, the Dutch controlled the Spice Islands, and they monopolized the spice trade until the British obtained nutmeg seedlings from the Banda Islands at the end of the 18th century. References to the central nervous system effects of nutmeg appeared in the first part of the 19th century when Purkinje developed lethargy after consuming three nutmeg nuts.¹ Because of the alleged hallucinogenic and euphoria-inducing properties of nutmeg, abuse of this spice has occurred for many years, particularly in persons with limited access to other drugs. The autobiography of Malcolm X contains accounts of his use of nutmeg while incarcerated.³

**Botanical Description**

- **Common Name:** Nutmeg
- **Scientific Name:** *Myristica fragrans* Houtt.
- **Botanical Family:** Myristicaceae (nutmeg)
- **Physical Description:** This aromatic evergreen tree grows 9-12 m (30-39 ft) high with spreading branches and a yellow fleshy fruit similar in appearance to an apricot or peach. The ripe fruit splits to expose a single glossy brown nut enclosed by a scarlet aril. The tree produces fruit year round, but the harvest usually occurs in April and November.


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**Distribution and Ecology:** The nutmeg tree is indigenous to the Maluku Province of Indonesia, formerly known as the Spice Islands. The nutmeg tree is grown commercially on the Caribbean islands of Grenada and Trinidad as well as in Central and East Java.

**Exposure**

Traditional uses of nutmeg include the treatment of rheumatism, cholera, psychosis, stomach cramps, nausea, diarrhea, flatulence, and anxiety in addition to use as an aphrodisiac and an abortifacient. Nutmeg is not used as a narcotic or hallucinogen in traditional Indonesian culture. Although a case report associated the resolution of diarrhea secondary to thyroid medullary carcinoma with the use of nutmeg, there are no approved medical indications for this spice. Nutmeg is a substitute psychotomimetic substance of abuse, particularly for adolescents, students, and prisoners with limited access to other psychotomimetic agents. The unpleasant taste, large doses required for effect, frequent adverse effects, and relative lack of potency as a hallucinogen limit the abuse of nutmeg.

The mature fruit from the nutmeg tree contains a 2.5 cm (1 in.) nut with a bright red, fleshy covering (scarlet aril). Nutmeg is the nut, whereas the dried scarlet aril is called mace. The nut and mace are dried and processed separately. Mace is also a spice, and this spice has been used as an aphrodisiac by physicians in the Near East. There are relatively few reports of poisoning following the ingestion of mace.

**Principal Toxins**

**Structure and Properties**

The concentration of active components depends on the botanical source, environmental conditions, storage, and analytical methods. The two oils of nutmeg are fixed oil (expressed oil, nutmeg butter) and essential oil. The fixed oil is an orange, butter-like material obtained by
applying heat and hydraulic pressure to nutmeg. This oil contains primarily trimyristin, and the product has no culinary value. Essential oil of nutmeg is a steam distillate that appears as a pale-yellow, nearly colorless liquid with the characteristic odor of spice. Table 1 lists some properties of myristicin, which is the main psychoactive constituent of nutmeg. This compound is structurally similar to kawain and related psychoactive constituents of kava (Piper methysticum Forst.). Myristicin is also the major component of the aromatic ether fraction of essential oil of mace. Fig 1 displays the chemical structure of myristicin.

**Poisonous Parts**

This essential oil contains from 5-15% volatile oils comprised of about 80% monoterpenes (α-pinene, sabinene, 1,8-p-methadiene, β-pinene, 1,4-p-menthadiene, camphene), 5% monoterpane alcohols, an aromatic ether fraction, and miscellaneous compounds. The aromatic fraction contains myristicin, elemicin, safrole, and minor constituents (methyleugenol, eugenol, isoeugenol, toluene). The essential oil of nutmeg contains variable amounts (0.1-18%) of methyleugenol, which is a potentially genotoxic compound with DNA-binding potency similar to safrole. Myristicin, elemicin, and safrole account for the majority (85-95%) of the compounds in the aromatic fraction, and myristicin represents about 4-12% of the compounds present in the essential oil. Myristicin is present in plants from the carrot (Umbelliferae) family including dill, celery, parsnip, parsley, and carrot. This compound is also a minor constituent of oil of black pepper (Piper nigrum). The estimated intake of myristicin from these sources by the general population is a few mg daily.

**Mechanism of Toxicity**

Structural similarities of myristicin to classical hallucinogenic compounds (eg, mescaline) suggest that myristicin may act as a serotonin receptor agonist and hallucinogenic compound. However, the acute
toxicity of myristicin is relatively low. Although myristicin comprises the largest fraction (ie, about 4-8%) of compounds in the aromatic fraction of nutmeg, human studies with myristicin have not duplicated the effects of nutmeg intoxication on the central nervous system. In rodent studies, myristicin and elemicin impair coordination and decreased motor activity. Safrole, eugenol, and isoeugenol do not have similar behavioral effects in these animal studies.

**Dose Response**

One grated nutmeg is approximately one tablespoon and weighs about 6-7 g with typical recreational doses ranging from 5-30 g. The administration of 6 g nutmeg to students did not significantly alter performance on neuropsychological tests. Symptoms do not usually develop following the ingestion of <10 g nutmeg. The ingestion of two whole nutmegs caused moderate toxicity; the ingestion of an estimated dose of 18 g of finely ground nutmeg powder resulted in prolonged periods of obtundation. The ingestion of 25-28 g of nutmeg powder produced tachycardia, anxiety, miosis, paresthesias, palpitations, anticholinergic signs (miosis, difficulty voiding, tachycardia), and paranoid behavior without hallucinations. The ingestion of an estimated dose of 37 g nutmeg blended in a milkshake was associated with tachycardia, palpitations, drowsiness, nausea, dry mouth, anxiety, restlessness, and agitation without hallucinations. Variation in toxicity may result from the loss of essential oils from the ground nutmeg.

The ingestion of a single dose 400 mg myristicin by 10 subjects was associated with alertness, a feeling of irresponsibility, and euphoria in 2 subjects as well as an unpleasant reaction (anxiety, fear, tremor, nausea, tachycardia) in 2 subjects. Onset of symptoms occurred about 1-2 hours after ingestion and resolved within 24 hours. This dose of myristicin is equivalent to the amount of myristicin present in 40 g of nutmeg.

**Toxicokinetics**

In the 1970s, an in vitro study suggested that psychoactive amphetamine derivatives (eg, 3-methoxy-4,5-methylenedioxyamphetamine, MMDA) are potential metabolites of myristicin. Although the alkenebenzene derivatives, myristicin, elemicin, safrole, are extensively metabolized following ingestion, subsequent studies have not confirmed the presence of amphetamine metabolites. Limited toxicokinetic studies indicate that these alkenebenzene undergo hydroxylation of the side chain, and elemicin undergoes O-demethylation prior to hydroxylation. Metabolites detected in the urine of rats fed these compounds include O-demethyl
elemicin, O-demethyl dihydroxy elemicin, demethylenyl myristicin, dihydroxy myristicin, and demethylenyl safrole. In vivo animal studies suggest that enzymatic hydrolysis of myristicin produces at least two metabolites (5-allyl-1-methoxy-2,3-dihydroxybenzene, 1’-hydroxymyristicin) that are conjugated and excreted in the urine. Amphetamine derivatives were not detected in these two studies.

Clinical Response

The clinical features of nutmeg intoxication resemble belladonna (anticholinergic) toxicity manifest by facial flushing, tachycardia, hypertension, dry mouth, blurred vision, and delirium. However, mydriasis is uncommon. Symptoms usually begin about 3-6 hours after ingestion and resolve by 24-36 hours. Initially, these symptoms include nausea, vomiting, abdominal pain, chest pain, restlessness, agitation, tremor, ataxia, nystagmus, vertigo, and a feeling of doom. These symptoms occur with alternating periods of lethargy and delirium. Other effects of nutmeg intoxication documented in case reports include the sensation of warmth and coldness of the extremities, distortion of space and colors, auditory and tactile hallucinations, headache, and generalized weakness. Patients usually recover without sequelae. The medical literature does not contain any fatalities solely related to nutmeg intoxication since the first decade of the 20th century. There are few data on the reproductive effects of nutmeg. A 29-year old woman, who developed signs of nutmeg intoxication at 30 weeks’ gestation, delivered a healthy infant at term.

The processing of nutmeg does not usually produce irritative symptoms in spice workers. However, allergic contact dermatitis may develop in workers sensitized to allergens (eg, isoprenyl myristate) in nutmeg. Occupational asthma may also occur in workers sensitized to spices including mace.

Diagnostic Testing

Chromatographic methods easily separate marijuana and the components of nutmeg and mace. Human metabolites of the constituents in nutmeg are detectable by the use of gas chromatography mass spectrometry after acid hydrolysis, liquid-liquid extraction of analytes, and microwave-assisted acetylation of extracted analytes. These metabolites include O-demethyl elemicin, O-demethyl dihydroxy elemicin, demethylenyl myristicin, dihydroxy myristicin, and demethylenyl safrole. Developing biomarkers for nutmeg intoxication is complicated by limited data on the toxic constituents of nutmeg. Six hours after ingestion 14-21
g nutmeg powder, a 16-year-old adolescent developed tachycardia, drowsiness, dry mouth, warm skin, and mydriasis.\textsuperscript{30} The myristicin concentration in a blood sample drawn 8 hours after ingestion was 2 $\mu$g/mL. The postmortem blood from a 55-year-old woman contained 4 $\mu$g/mL of myristicin and 0.072 $\mu$g/mL of flunitrazepam.\textsuperscript{30} Death was attributed to the combination of the two substances. However, myristicin does not necessarily account for the toxic effects of nutmeg, and the contribution of myristicin and nutmeg to this death remains speculative. Routine laboratory tests during nutmeg intoxication are usually normal.\textsuperscript{24} The ingestion of nutmeg does not produce positive urine drug screens.\textsuperscript{14}

**Treatment**

Management is usually supportive. The presence of hemodynamic instability suggests the presence of other toxins or illnesses. Decontamination measures are usually unnecessary because of the presence of vomiting or delayed contact (ie, \textsuperscript{1-2} hours after ingestion) with the health care facility. There are no clinical data to guide management of nutmeg intoxication. The use of standard antiemetics (prochlorperazine, trimethobenzamide, odansetron, metoclopramide) and intravenous fluids may be required to treat protracted nausea and vomiting. Sedatives (diazepam, haloperidol) should be used with caution because of alternating periods of delirium and obtundation during nutmeg intoxication.

**REFERENCES**