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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Myristica fragrans (Nutmeg): Phytochemistry, Pharmacological Properties, and Therapeutic Potential – A Comprehensive Review

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ABSTRACT:

Myristicin, a substance found in nutmeg, has been connected to hallucinogenic effects when taken in excess. Despite being widely used as a spice, excessive consumption can result in toxic reactions. Symptoms like agitation, confusion, and other neurological issues can appear within 3–6 hours and occasionally last up to 72 hours. The majority of reported exposures to nutmeg, particularly among teenagers, were deliberate attempts to experience its psychoactive effects, according to poison control data from Texas and California. Nutmeg, especially *Myristica fragrans* and the less researched *M. argentea*, has long been used in traditional medicine to treat infections, pain, and digestive problems, though such misuse is dangerous. Bioactive substances with antioxidant, anti-inflammatory, antidiabetic, anticancer, and neuroprotective properties can be found in both species. Hepatoprotective, antioxidant, memory-boosting, cytotoxic, aphrodisiac, antidiabetic, antidepressant, hypolipidemic, antimicrobial, antibacterial, anti- inflammatory, anticancer, flavouring, and pesticidal qualities are just a few of the many pharmacological activities that nutmeg demonstrates. The many pharmacological characteristics of this useful medicinal plant are thoroughly reviewed in this article.

INTRODUCTION:

Nutmeg, or Myristica fragrans, is a medium-sized, fragrant evergreen tree in the Myristicaceae family.[1] It can be found in northern Australia, South-east Asia, India, and a number of Pacific islands. The Banda Islands in the Moluccas region of eastern Indonesia are the original home of the nutmeg tree.[2] Tobacco, toothpaste, and perfumes all contain nutmeg butter. Nutmeg contains Malabaricon C, which inhibits a variety of microorganisms, helps with digestion, relieves rheumatism, and treats minor illnesses.[3] The production of listeriolysin O, an extracellular protein that Listeria monocytogenes uses to successfully infect host cells, has been demonstrated to be considerably reduced by the oil extracted from nutmeg seeds.[4] The predominant fragrant element in nutmeg's essential oil is myristicin. People have used nutmeg as a spice for hundreds of years, and it is still highly appreciated today. Various formulations of Myristica fragrans are traditionally used as pain relievers, stomach and digestive aides, sleep supports, aphrodisiacs, and to assist regulate menstrual flow.[5,6] Lignans from nutmeg seeds and their extracts exhibit potent antibiotic activity against Bacillus, Staphylococcus, and Shigella.[7] The antioxidant qualities of nutmeg oil formulations are well acknowledged. Piaru et al. showed that nutmeg oil has strong antioxidant activity using the DPPH free radical scavenging assay.[8] Another study found that when human neutrophils were stimulated by PMA (phorbol 12- myristate 13-acetate), nutmeg oil decreased the generation of reactive oxygen species (ROS).[9] Myristicin, elemicin, safrole, and sabenene combined account for approximately 80% of the essential oil of nutmeg.[10] Like safrole, myristicin is produced both naturally and artificially. It alters perception, emotion, and cognitive processes through hallucinogenic effects.[11] Numerous health advantages, such as anti-diarrheal, anti-diabetic, stimulant, antifungal, carminative, and anti-inflammatory qualities, have been claimed for nutmeg.[12,13]

Fig.1: Nutmeg (Myristica fragrans)

MYRISTICIN

As previously mentioned, nutmeg intoxication is believed to be primarily caused by myristicin. Large doses, however, have the potential to be toxic and result in fatty liver degeneration.[14] Besides nutmeg, myristicin is also found in carrots, parsley, celery, dill, parsnip, and black pepper.[15] Figure 1Depicts the chemical properties and structure of myristicin.

Chemical name:

1- allyl-5-methoxy-3,4 methylene-Dioxy-benzene

- CAS No: 607-910-0
- Empirical formula: C11H12O3
- Molecular weight: 192.22 [15]

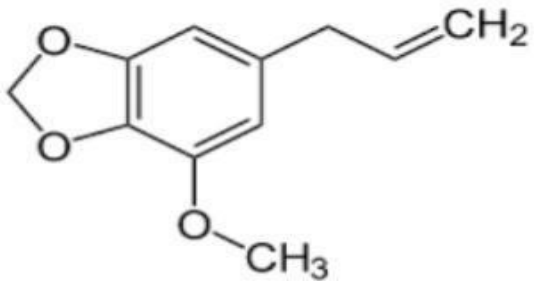

Fig.2: Properties and chemical structure of myristicin.

Metabolism of Myristicin

Both humans and rats undergo substantial metabolism of myristicin.[16] The psychoactive effects of nutmeg may result from the conversion of myristicin and elemicin into molecules that resemble amphetamines. While other components imitate serotonin and have an impact on the cardiovascular system, myristicin produces MMDA and slightly inhibits monoamine oxidase.[17,18] Figure 3 represent chemical structure of myristicin before and after metabolisation

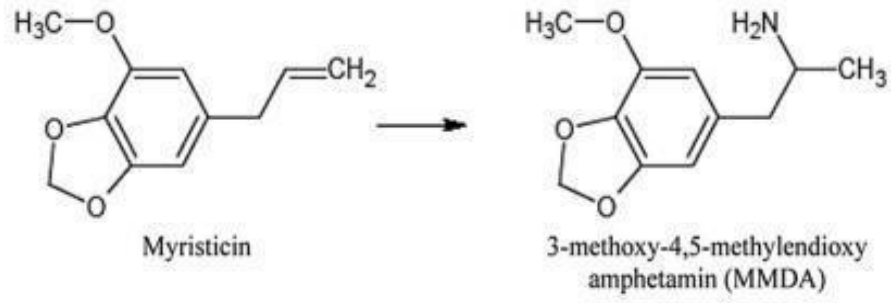

Fig.3: Metabolism of myristicin into 3-methoxy-4,5-methylendioxyamphetamine (MMDA) after ingestion. MMDA are major compounds that are responsible for hallucinogenic Effects[17]

PHARMACOLOGY

Antioxidant activity

Compounds like β-caryophyllene and eugenol, whose allylic or benzylic hydrogens are readily taken by peroxy radicals, are responsible for nutmeg's antioxidant activity. Eugenol also boosts important antioxidant enzymes in the body.[19] Because they readily give electrons or hydrogen, compounds with catechol-like structures, including caffeic acid, are effective antioxidants. Nutmeg seeds' lignan derivatives also contribute to this antioxidant potential.[20]

Immuno-modulatory and radio-protective activities

Fresh nutmeg and mace contain lignans that lower reactive oxygen species, modify immunological responses by controlling splenocyte proliferation and apoptosis, shield cells from radiation-induced DNA damage, and have dose-dependent, non-toxic effects on lymphocytes.[21]

Antimicrobial activity

Strong antibacterial action is demonstrated by essential oils and different extracts from aromatic plants, which successfully stop the growth of a variety of bacteria and fungi.[22] While substances like carvacrol, γ-cymene, α-pinene, β-pinene, and β-caryophyllene in nutmeg seed essential oil also show antibacterial activity, these three lignans helped prevent wheat leaf rust and rice blast.[23] While other plant phenolics are known to have antimicrobial activities, β-caryophyllene is primarily responsible for the antifungal and anti- inflammatory qualities of plant essential oils.[24] By compromising the integrity of microbial cell membranes, α-pinene and β-pinene, two monoterpene hydrocarbons, function as antimicrobial agents.[25] While its precursor γ-cymene amplifies this effect synergistically, carvacrol alone shows only modest antibacterial activity. Carvacrol is a crucial antimicrobial molecule that affects microbial membranes, increasing permeability, disrupting proton-motive force, and depleting ATP.[26]

Anti-carcinogenic and hepatoprotective activity

Nutmeg exhibits anti-carcinogenic properties. Oral mace treatment reduced 3-methylcholanthrene-induced cervical cancer in Swiss albino mice, according to Hussain and Rao (1991).[27] Hepatoprotective properties of nutmeg have been demonstrated in liver-damaged rats. According to studies, its essential oil supports liver health by influencing hepatic enzymes including glutathione-S-transferase, arylhydrocarbon hydroxylase, and cytochrome P450.[28]

Anti-inflammatory activity

Nutmeg and its essential oil have been shown in numerous tests to have strong anti- inflammatory qualities.[29] The pharmacological actions of nutmeg oil are comparable to those of non-steroidal anti-inflammatory medications.[30] Nutmeg petroleum ether extracts activate AMPK, an important enzyme for the treatment of metabolic diseases such as obesity and type-2 diabetes. Tetrahydrofuroguaiacin B and nectandrin A are two isolated substances that significantly activate AMPK in cells.[31,32] Leukaemia inhibitory factor (LIF), IFN-γ, oncostatin M, CNTF, TGF-β, IL-8, IL-11, IL-12, IL-17, IL-18, and other chemokines that attract inflammatory cells are additional pro-inflammatory mediators.[41,42]

Cognitive benefits

Bioactive substances found in Myristica fragrans, such as myristicin and eugenol, have potent neuroprotective properties that protect neurones from oxidative damage and enhance motor performance in animal models of Parkinson's disease.[33] Myristica fragrans extract has been demonstrated to affect the gut microbiome and its metabolic activities in addition to its direct effects on the central nervous system.[34]

Pharmaceutical applications

In Indonesian traditional medicine, Myristica argentea has long been used to cure a variety of conditions, such as headaches, rheumatism, and digestive problems.[35] In addition to its conventional applications, Myristica argentea has the potential to cure neurodegenerative illnesses; in animal models of Parkinson's disease, chemicals such myristicin improve motor function.[33] The development of Myristica argentea into standardised phytopharmaceuticals is supported by scientific data. For safe, efficient treatments, standardisation should take into account regional and seasonal changes, maximise the bioavailability of substances like myristicin, and combine conventional wisdom with cutting-edge technology.

Clinical Effects and Reactions

The majority of nutmeg exposures come orally, although they can also occur by inhalation, unintentional skin contact, or ocular contact.[36] Facial flushing, a fast heartbeat, elevated blood pressure, dry mouth, impaired vision, hallucinations, euphoria, and delirium might result from consuming a lot of nutmeg seeds. Usually, symptoms start to show up 3–6 hours after consumption and go away in 24–36 hours.[17] Nutmeg has little to no effect at low dosages, but it can be psychotropic at high quantities. These effects are caused by myristicin, a monoamine oxidase inhibitor found in freshly ground nutmeg.[37] Convulsions, a fast heartbeat, nausea, thirst, and severe bodily pain can all be symptoms of myristicin poisoning.[18] Consuming 6–7 mg of nutmeg per kilogramme of body weight can have psychopharmacological effects on people. Intoxication may result with consuming about 5 grammes of nutmeg, which is equal to 1-2 mg of myristicin per kilogramme.[38] Although tiny culinary doses of nutmeg are usually regarded as safe during pregnancy, it was once believed to trigger abortion. However, the foetus may be impacted by large amounts of prostaglandin inhibition and hallucinogenic substances.[39] When given as a 50% ethanolic extract, nutmeg has been shown to have aphrodisiac effects on male mice.[40]

Fig.4: Nutmeg fruit (top), dried mace (bottom left), nutmeg Seed (bottom right)

Conclusion

Nutmeg, or *Myristica fragrans*, is a plant with significant botanical, pharmacological, and commercial value. Its extensive phytochemical profile, which includes lignans, flavonoids, essential oils, and other bioactive substances that support a variety of medicinal qualities, is highlighted in this thorough analysis. Its traditional medical usage are supported by experimental investigations that show its antibacterial, antioxidant, anti-inflammatory, neuroprotective, and gastroprotective properties. Nutmeg is a versatile resource that has significant value in the commercial, industrial, and culinary domains in addition to its medicinal potential.

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