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Pharmacological Effects of *Myristica dactyloides*-A Review

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Abstract:

Myristica dactyloides is an evergreen tree that produces two spices, nutmeg and mace. Its medicinal uses in the aurvedic system of treatment are based on traditional experience inherited from one generation to other. Scientists from various disciplines are now directing their research towards investigat- ing the effects of *M. dactyloides* on human health. The chemical constituents of *M. dactyloides* have been investigated for hypolipidaemic and hypocholesterolemic effects, antimicrobial, antidepressant, aphrodi- siac, memory enhancing, antioxidant and hepatoprotective properties. Recent studies have revealed strong insecticidal and molluscicidal activities of *M. dactyloides*. Despite some laboratory studies on the insecti- cidal / molluscicidal activity of *M. dactyloides*, more field studies are recommended for effective control of pests. It is clearly evident from the literature review that *M. dactyloides* deserves more attention by scientific community and public health specialists to explore its full range of benefits in the welfare of the society.

Keywords: *Myristica dactyloides,* nutmeg, mace, antimicrobial, antioxidant, pesticidal.

INTRODUCTION

Myristica *dactyloides* Gaertn., or Javitri and Jaiphal as it is called in India, is a member of the Myristicaceae family. Spices produced by it are mace and nutmeg. The fleshy crimson, net-like covering (aril) on the seed kernel within the fruit is called mace. Usually reaching a height of 5 to 13 metres, but sometimes reaching 20 metres, it is a spreading scented evergreen tree. Carrying on leaf stalks of 1 cm long, the pointed dark green leaves are placed alternately along the branches. Surfaces of upper leaves are glossy. Although they are sometimes seen on the same tree, blooms are typically single sexed. Male flowers grow in groups of 1 to 10; female flowers in groups of 1 to 3. Waxy, squishy, light yellow flowers fashioned like bells. The fruits are 6–9 cm long, smooth, golden, drooping, and longitudinally ridged. Ripe yellow fruit coat separates into two valves to expose a lustrous, purplish-brown nutmeg seed encircled by crimson aril (mace). The firm, meaty, white, broadly oval (2 to 3 cm long) seeds are crossed by red-brown veins. Aril (mace) is brilliant crimson while fresh, becoming sticky, brittle, and yellowish-brown when dried (Purseglove, 1968). The trees grow two to three crops year, but they do not bloom until they are around nine

years old. Once they do, they bloom for an additional seventy-five years. Nutmeg seeds need three to six weeks to dry before they can be used.

Distribution

Usually seen in its natural habitat, this South Pacific island species is native to the Moluccas and Banda islands. Tropical areas, such as Sri Lanka, Indonesia, and the West Indian island of Grenada, are now its primary growing grounds (Purseglove, 1968; Bown, 1995).

Pharmacologically active parts of the plant

The dried kernel (seed), more often known as nutmeg, is the most valuable component of the plant both medicinally and commercially. There have been very rare reports of intoxication caused by mace, which is the common name for the fruit's aril (seed case). Nutmeg oil, a portion of the spice that includes the pharmacologically active components, has a history of therapeutic usage as well. Use it as a seasoning in a variety of foods, add it to tea and soda, or combine it with milk and booze for a cocktail. Among nutmeg's traditional medical uses are as an emmenagogue, an abortifacient, a stimulant for the stomach and intestines, a carminative, a stimulant for the appetite, and a remedy for intestinal catarrh and colic (Nadkarni, 1988). Mace has several traditional and modern uses, including as a spice, a hair colour, and a medicinal herb. In addition to its anti-inflammatory and anticarcinogenic properties, it has antipapillomagenic and anticarcinogenic actions (Hussain & Rao, 1991; Ozaki *et al.,*, 1989).

Chemical Composition

Alkyl benzene derivatives (such as myristicin, elemicin, and safrole), terpenes, alpha-pinene, beta-pinene, myristic acid, and trimyristin are the primary components of Myristica *dactyloides*, according to research conducted by Qiu *et al.,* (2004), Wang *et al.,* (2004), Forrester (2005), and Yang *et al.,* (2008). The majority of the essential oil in nutmeg, which makes up around 10% of the total, consists of terpene hydrocarbons (sabinene and pinenes, plus camphene, p-cymene, phellandrene, terpinene, limonene, myrcene, 60 to 80% of the total), terpene derivatives (5 to 15% of the total), and phenylpropanoids (15 to 20% of the total). Is responsible for nutmeg's hallucinogenic effect is myristicin (methoxy-safrole, generally 4%). The scent components are the same in oil of mace (which makes up up to 12% of the spice), but the overall proportion of terpenoids is about 90% higher. About 2% of the essential oils in nutmeg and mace are phenylpropanoid components, such as dehydrodiisoeugenol, while the remaining 99% are lignans, also known as diarylpropanoids (Anonymous, 1995). According to Sonavane *et al.,* (2002), the primary glycoside with anxiogenic action is trimyristin.

Biological Effects

According to De *et al.,* (1999), spices in India have antibacterial and disinfecting characteristics, hence they have been utilised for food preservation from ancient times. Nutmeg is said to have antidiarrheal properties according to Ayurveda, the old Indian medical discipline. Nadkarni (1988) notes that nutmeg and mace both have medicinal and condimental uses. It is employed in tonics and electuaries and is a component of medicines given for dysentery, stomach discomfort, flatulence, nausea, vomiting, malaria, rheumatism, sciatica, and early stages of leprosy. Nutmeg is a stimulant, carminative, astringent, and aphrodisiac. After 1–6 hours, delirium and epileptic convulsions signs manifest; these dosages provide a narcotic effect (Anonymous, 1995; Hang & Yang, 2007).

Most people think that myristicin is the main ingredient that makes people drunk (Hallstrom & Thuvander, 1997). According to Anonymous (1995) and Beyer *et al.,* (2006), myristicin may induce fatty degeneration of the liver and is dangerous when consumed in high quantities. A naturally occurring allylbenzene in nutmeg, myristicin (1- allyl-3,4-methylenedioxy-5-methoxybenzene) promotes cytotoxicity in human neuroblastoma SK-N-SH cells via an apoptotic mechanism, according to Lee *et al.,* (2005). Sonavane *et al.,* (2002) found that trimyristin had anxiogenic action. Antibacterial efficacy against both Gram-positive and Gram-negative bacteria is shown by trimyristin and myristicin, which are extracted from seeds of M. *dactyloides* (Narasimhan & Dhake, 2006).

Researchers Grover *et al.,* (2002) discovered that nutmeg extracts had a strong sedative impact in addition to a positive antidiarrheal effect. Additionally, the extracts have a mild analgesic effect and do not negatively impact blood pressure or electrocardiogram readings. The effects of verapamil and M. *dactyloides* extract on the amount and acidity of carbachol-induced gastric discharge in fasting rabbits were studied by Jan *et al.,* (2005). Researchers have discovered that M. *dactyloides* extract, which includes a natural calcium channel blocker, lowers gastric secretion volume, free acidity, and total acidity. The effects of verapamil are same as well. Since M. *dactyloides* has an effect that is comparable to verapamil, it may be useful in the treatment of peptic ulcers and other ailments that call for calcium channel blockers.

Antimicrobial activity

Orabi *et al.,* (1991), De *et al.,* (1999), Dorman & Deans (2000), Rani & Khullar (2004), Mahady *et al.,* (2005), and O'Mahony *et al.,* (2005) all found that M. *dactyloides* (nutmeg and mace) has potent antimicrobial action against a variety of bacteria, including those that cause food poisoning and spoilage, as well as plant and animal diseases. According to a 1995 anonymous study, nutmeg alcoholic extracts inhibited the growth of Micrococcus pyogens var. aureus bacteria. According to a study by Firouzi *et al.,* (2007), the growth and survival of Yersinia enterocolitica and Listeria monocytogenes were significantly inhibited by essential nutmeg oil in both broth culture and Iranian grilled chicken.

The antibacterial efficacy of nutmeg extract (from M. *dactyloides* seeds) against Escherichia coli O157 was shown by Takikawa *et al.,* (2002). O157 and non-pathogenic E. coli bacteria vary significantly in their tolerance to nutmeg when incubated with spice extract at doses of 0.01% and 0.1%, respectively. Though the numbers of harmless strains cannot be decreased, the numbers of O157 strains have been drastically cut down. However, nutmeg extract did not exhibit antibacterial action against enterotoxigenic (O6 and O148), enteroinvasive (O29 and O124), or enteropathogenic (O111) Escherichia coli. All of the O157 strains of E. coli were found to be more susceptible to beta-pinene than the non-pathogenic E. coli strains when the antibacterial action of volatile nutmeg oils was tested on them. The bactericidal efficacy of nutmeg aqueous extract against Helicobacter pylori was shown by O'Mahony *et al.,* (2005). Dyspepsia, gastritis, gastric cancer, primary gastric B-cell lymphoma, peptic ulcer disease, and gastritis are all linked to H. pylori infections. The in vitro susceptibility of fifteen different H. pylori strains to botanical extracts was investigated by Mahady *et al.,* (2005). A methanol extract from M. *dactyloides* seeds, which has a minimum inhibitory concentration (MIC) of 12.5 µg/ml against some strains of H. pylori, has shown remarkable efficacy in the management of

gastrointestinal problems. M. *dactyloides* methanol extract showed significant antibacterial action against M. typhi, a strain of Salmonella that is resistant to many drugs, according to research by Rani and Khullar (2004). De *et al.,* (1999) found that nutmeg effectively inhibits the growth of Escherichia coli (ATCC 10536), Bacillus subtilis (ATCC 6633), and Saccharomyces cerevisiae (ATCC 9763). Dorman and Deans (2000) found that the volatile oils of M. *dactyloides* had a strong inhibitory impact on several species of bacteria, including those that cause food poisoning, plant and animal diseases, and spoilage (Dorman & Deans, 2000). According to Smith-Palmer *et al.,* (1998), the oil of nutmeg is very effective against the food-borne pathogen Listeria monocytogenes at 35°C. Orabi *et al.,* (1991) found that the antimicrobial resorcinols malabaricone B [1] and malabaricone C [2] contained in mace showed potent antifungal and antibacterial effects. At a concentration of 0.7 µg/ml, Malabaricone C, which is extracted from M. *dactyloides* (nutmeg), permanently reduces the activity of Arg-gingipain by 50% and inhibits the development of Porphyromomas gingivalis (Shinohara *et al.,*, 1999). Natural anti-biofilm agent macelignan obtained from Mycobacterium *dactyloides* is effective against Streptococcus sanguis and Actinomyces viscosus, the two main oral colonisers. The colonisers originally formed a biofilm by attaching to the surface of the tooth that was covered with pellicle. Yanti *et al.,* (2008) found that after 5 minutes of treatment with 10µg/ml of macelignan, the development of these colonies was reduced by 30%. The lignans erythro-austrobailignan-6, meso-dihydroguaiaretic acid, and nectandrin-B were extracted from the seeds of M. *dactyloides* by Cho *et al.,* (2007). Both in vitro and in vivo tests showed that these lignans were effective against the following bacteria: Agrobacterium tumefaciens, Magnaporthe grisea, Colletotrichum coccodes, C. gloeosporioides, Acidovorax konjaci, and Burkholderia glumae.

Both developed and developing nations have acknowledged rotaviruses as the leading cause of diarrhoea in newborns and young children. Some Brazilian medicinal plants used to treat diarrhoea have been investigated for their in vitro anti-rotavirus activity by Goncalves *et al.,* (2005). A dose of 160 µg/ml was determined to be effective in inhibiting human rotavirus by the extracts from M. *dactyloides* seeds (90% inhibition). In cases when rotavirus is the causative agent of diarrhoea in humans, M. *dactyloides* may therefore prove to be an effective therapy.

Hypolipidaemic and hypocholesterolemic effect

Nutmeg, or Melisium *dactyloides*, has a hypolipidaemic impact on albino rabbits who were given hyperlipidaemia in an experimental setting. Researchers Ram *et al.,* (1996) found that hyperlipidaemic albino rabbits had a significant decrease in lipoprotein lipid levels after 60 days of oral treatment of nutmeg extract at a dosage of 500 mg/kg body weight. Hypercholesterolemic rabbits given M. *dactyloides* seed extract had a 69.1% reduction in serum cholesterol and a 76.3% reduction in LDL cholesterol, a 31.2% reduction in the cholesterol/phospholipid ratio, and a significant increase in the decreased HDL-ratio, according to research by Sharma *et al.,* (1995). Aortic atheromatous plaques may be dissolved by 70.9% to 76.5% of the time, and it also prevents the buildup of triglycerides, cholesterol, and phospholipids in the liver, heart, and aorta. Rabbits given M. *dactyloides* seed extract had far better faecal cholesterol and phospholipid removal rates.

Antidepressant activity

By administering n-hexane extract from M. *dactyloides* seeds to mice at doses of 5, 10, and 20 mg/kg body weight, Dhingra and Sharma (2006) assessed its antidepressant effectiveness using the forced swim test (FST) and the tail suspension test (TST). Based on the largest reduction in the immobility duration compared to the control, it was determined that the 10 mg/kg dosage was the most powerful. Additionally, the effectiveness of this extract dosage was determined to be on par with that of imipramine (15 mg/kg) and fluoxetine (20 mg/kg). This means that when tested with both TST and FST, the M. *dactyloides* extract may have a strong antidepressant effect in mice. The combination between the adrenergic, dopaminergic, and serotonergic systems seems to produce the extract's antidepressant-like effect.

Antidiabetic activity

Macelignan is an organic substance that is derived from M. *dactyloides* by isolation. The activation of peroxisome proliferator receptor (PPAR, á/ã) and the reduction of endoplasmic reticulum stress increased insulin sensitivity and lipid metabolic abnormalities. This suggests that it may be used as an antidiabetic drug for treating type 2 diabetes (Han *et al.,*, 2008).

Aphrodisiac activity

M. *dactyloides*, often known as nutmeg, has been recognised in Unani medicine for its therapeutic potential in treating male sexual issues. Tajuddin *et al.,* (2005) conducted an experiment where they discovered that when normal male rats were given an oral dose of 500 mg/kg body weight of a 50% ethanolic extract of nutmeg, it resulted in a notable and lasting increase in their sexual activity. This effect was observed without any noticeable negative effects and is likely due to the extract's ability to stimulate the nerves.Betes (Han *et al.,*, 2008).

Cytotoxicity

In their study, Lee *et al.,* (2005) revealed that myristicin, a naturally occurring alkyl benzene derivative present in nutmeg, causes cytotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism. A decrease in cell viability that depended on the dosage was seen when the myristicin concentration reached or exceeded 0.5 mM in SK-N-SH cells. The myristicin-induced apoptosis was characterised by an increase in cytochrome-c levels and the activation of caspase-3. Chirathaworn *et al.,* (2007) discovered that the methanolic extract of M. *dactyloides*, even at a concentration of 10 µg/ml, triggers apoptosis in the Jurkat leukaemia T cell line via reducing the expression of SIRT1 mRNA.

Memory enhancing activity

The impact of M. *dactyloides* seeds on the learning capacity and memory level in mice was studied by Parle *et al.,* (2004). The elevated plus-maze and passive-avoidance apparatus were used to evaluate the learning and memory characteristics. Both young and old mice showed considerable improvements in their learning and memory after being given the n-hexane extract of M. *dactyloides* for three days in a row at a dosage of 5 mg/kg body weight. Additionally, the extract restored the learning and memory impairments caused by diazepam and scopolamine in young mice. Multiple characteristics, including antioxidant, anti-inflammatory, and procholinergic action, may contribute to the memory-enhancing impact of Mycoplasma *dactyloides*.

Antioxidant activity

Using the typical food antioxidants butylated hydroxyanisole (BHA) (E-320), butylated hydroxytoluene (BHT) (E-321), and propyl

gallate (E-310), Murcia *et al.,* (2004) investigated the antioxidant capabilities of several spices. Based on the results of the deoxyribose test, licorice, nutmeg, and anise were the most protective. Sunflower, maize, and olive oils, as well as butter and margarine, were made more resistant to oxidation at 110°C when spiced with nutmeg, ginger, propyl gallate, and licorice. According to the Trolox equivalent antioxidant capacity (TEAC) test, which ranks antioxidant activity, nutmeg has a greater antioxidant capacity than BHT. The antioxidant activity of nutmeg extracts derived from phenylpropanoid compounds was shown by Murcia *et al.,* (2004). Chequer *et al.,* (2008) found that lignans in fresh nutmeg mace aqueous extract had effects on mammalian cells that are antioxidant, radioprotective, and immunomodulatory. According to Maeda *et al.,* (2008), nutmeg seed extracts rich in monoterpenes, such as terpinene-4-ol, alpha-terpineol, and 4-allyl-2,6-dimethoxyphenol, have high antioxidant activity.

The capacity of the aril of M. *dactyloides* to reduce lipid peroxidation and scavenge superoxide radicals in rats gave it high antioxidant activity, according to Yadav and Bhatnagar (2007). Reduced lipid peroxidation and acid phosphatase activity, together with increased hepatic glutathione and alkaline phosphatase activity, show that pretreatment with M. *dactyloides* protects mice against radiation-induced biochemical changes (Sharma & Kumar, 2007).

Hepatoprotective activity

In rats exposed to lipopolysaccharide (LPS) and D-galactosamine (D-GalN)-induced liver injury, Morita *et al.,* (2003) found that myristicin from Myristica *dactyloides* (nutmeg) had the most hepatoprotective effects. Myristicin considerably reduced the elevation of blood TNF-alpha concentrations and hepatic DNA fragmentation in mice that was produced by LPS/D-GalN. These results point to the possibility that myristicin's hepatoprotective effects are related, in part, to its ability to block macrophage TNF-alpha production. The mitogen-activated protein kinase (MAPK) signalling system, particularly JNK and c-Jun, is associated with the hepatoprotective properties of macelignan, which was isolated from Magnaporthe *dactyloides*, according to Sohn *et al.,* (2008).

Pesticidal activity

Insecticidal

The insecticidal activities of chemicals found in M. *dactyloides* seeds were documented by Jung *et al.,* (2007) in their study of Blattella germanica adult females (Dictyoptera: Blattellidae). Despite being ineffective on its own, the myristicin found in the kernel may be used to increase the toxicity of pyrethrum, making it more effective against houseflies (Anonymous, 1995). According to Anonymous (1995), cockroaches can't handle the water-based M. *dactyloides* decoctions. Research has shown that the essential oil of M. *dactyloides* may kill the larvae of two pests: Callosobruchus chinensis and Lycoriella ingenua (Park *et al.,*, 2008; Chaubey, 2008).

Molluscicidal

The seeds and petals of Melisandria *dactyloides*, often known as mace and nutmeg, may contain molluscicides that may kill Lymnaea acuminata, according to research by Jaiswal and Singh (2009). The liver fluke, which affects 94% of the buffalo population in northern India, is caused by Fasciola hepatica and F. gigantica, which are intermediate hosts for these snails (Singh & Agarwal, 1981; Singh & Agarwal, 1983). Mace and nutmeg both have potent molluscicidal components that dissolve in ethanol, chloroform, and acetone, while nutmeg's molluscicidal components are

insoluble in ether and carbon tetrachloride. Mace powder often has a greater toxicity level than nutmeg powder against L. acuminata. According to Jaiswal and Singh (2009), the primary components of nutmeg and mace that are known to be molluscicidal are trimyristin and myristicin. After 96 hours, the toxicity of myristicin was shown to be 43.81 times more than that of trimyristin.

The LC50 (96h) values of synthetic molluscicides such as carbaryl (4.40 mg/l), phorate (15.0 mg/l), formothion (8.56 mg/l) (Singh & Agarwal, 1983) and aldicarb (11.50 mg/l) (Singh & Agarwal, 1981) are higher than the LC50 (96h) values of the column purified fraction of nutmeg (3.98 mg/l) and mace (2.77 mg/l) against L. acuminata. 96h LC50 of crude powder of nutmeg (36.95 mg/l) and mace (28.61 mg/l) against L. acuminata are lower than the crude powder of common spices, Allium sativum bulb (271.06 mg/l), Zingiber officinale rhizome (273.80 mg/l), Trachyspermum ammi (97.59 mg/l), Allium cepa bulb (253.27 mg/l), Cinnamomum tamala leaf (830.90 mg/l), Ferula asafoetida dried latex powder (82.71 mg/l) and Syzygium aromaticum flower bud (51.98 mg/l) (Singh & Singh, 1995; Singh *et al.,*, 1997; Srivastava & Singh, 2005; Kumar & Singh, 2006).

Researchers Dhingra *et al.,* (2006) found that Swiss albino mouse brains had dramatically reduced AChE activity when exposed to an n-hexane extract from M. *dactyloides* seeds. Using AChE derived from bovine erythrocytes, Mukherjee *et al.,* (2007) found that hydroalcoholic extracts of M. *dactyloides* inhibited 50% of AChE activity in vitro at concentrations of 100-150 µg/ml. In their 2009 study, Jaiswal *et al.,* showed that the nervous tissue of Lymnaea acuminata was significantly inhibited in AChE (acetylcholinesterase), ACP (acid phosphatase), and ALP (alkaline phosphatase) activity when snails were treated in vivo with sublethal concentrations of trimyristin and myristicin (40% and 80% of the 24h and 96h LC50, respectively). The primary mechanism by which Myristica *dactyloides* kills molluscs is by blocking certain enzymes in the nervous system of L. acuminata.

Clinical effects

The symptoms of nutmeg intoxication in humans are similar to those of overconsumption of anticholinergic drugs, such as increased heart rate, flushing of the face, confusion, dry throat, and profuse perspiration. Constantly present is a distorted mental state characterised by things like hallucinations, disorientation, and a feeling of imminent disaster. The duration that has passed after the poison was consumed determines the consistency or lack thereof of the clinical symptoms. Dosage and variation among nutmeg samples can influence the onset of symptoms.

Conclusion

Extensive literature research has shown that M. *dactyloides* has a wide range of pharmacological effects. It is possible that a single spice might alleviate symptoms of several illnesses. Mace and nutmeg made from Myroxylon *dactyloides* are powerful deterrents to a wide range of pests, including fungus, insects, snails, and bacteria. There is a lot of evidence in the scientific literature that M. *dactyloides* has antidepressant, aphrodisiac, antioxidant, and hepatoprotective properties. So far, M. *dactyloides* has only been tested on rats and rabbits; it has not been applied to humans. Its effectiveness against many human ailments, in comparison to other natural items and contemporary medications, warrants more investigation. Thus, the scientific community and public health

experts should pay more attention to M. *dactyloides* in order to uncover all of its societal advantages.

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