

MYRISTICA FRAGRANS: A COMPREHENSIVE REVIEW

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ABSTRACT

Myristica fragrans is a spreading tree, growing 9-12 m high, chiefly cultivated in Maluku region of Indonesia, known as the Spice Islands in earlier times. Caribbean islands of Grenada and Trinidad are also influential in growing this aromatic tree commercially. It belongs to Myristicaceae family and is the source of two spices, nutmeg (Jaiphal) and mace (Javitri). Nutmeg is the seed kernel inside the fruit and mace is the fleshy red, net-like skin covering (aril) on the kernel. Further, studies divulge the occurrence of different chemical constituents like Myristicin, Macelignan and Eugenol (4-allyl-2-methoxyphenol). Nutmeg possesses various pharmacological activities like hepato protective activity, anti-oxidant activity, memory enhancing activity, cytotoxicity, aphrodisiac activity, anti-diabetic activity, anti-depressant activity, hypolipidemic and hypocholesterolemic effect, anti-microbial activity, antibacterial, anti-inflammatory, anti-carcinogenic activity, flavouring properties and pesticidal activity. This article reviews various pharmacological properties of this medicinal plant.

Keywords: *Myristica fragrans*, Nutmeg, Myristicin.

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INTRODUCTION

Myristica fragrans, which is commonly known as Nutmeg, belongs to the family Myristicaceae and is a medium sized, evergreen aromatic tree [1]. It is distributed in India, South East Asia, North Australia and Pacific islands. The Nutmeg tree is indigenous to Banda islands in the Moluccas in east Indonesia [2]. The seed (Nutmeg) and its fleshy aril (mace) are used as spices. It contains 4% myristicin. The Nutmeg spice has been recognized in Europe since 12 century when it was used as condiment and fumigant [3]. Nutmeg butter, a fat derived from the seed is used in perfumery, tobacco and toothpaste. Medicinally, it is used to support digestion and to treat rheumatism. *Myristica fragrans* seed is also used for diarrhoea, mouth sore and insomnia. It has been proved that Malabaricon C, obtained from *Myristica fragrans*, has inhibitory activity against several kinds of anaerobic and aerobic microorganisms [4].

Oil obtained from seeds of nutmeg significantly reduced the production of listeriolysin O which is a bacterial extracellular protein responsible for successful infection by *Listeria monocytogenes* [5]. There were no hallucinogenic or other psychoactive properties except mild sedation [6]. Myristicin is the principal aromatic constituent of the volatile oil of the nutmeg. Nutmeg as a spice has persisted to the present day. Various nutmeg (*Myristica fragrans*) preparations are still used as analgesics, stomachics, digestives, hypnotics, aphrodisiacs and amenorrhoeal agents [7]. The aim of this review is to emphasize on the various pharmacological activities of *Myristica fragrans*.

Morphology

Myristica fragrans tree have brown-red bark which is soft, smooth and flakes off in thin layers or large plates. The branching pattern is such that horizontal branches radiate in whorls from the trunk. Leaves (5 to 15 cm × 2 to 7 cm) are simple, entire, 2 ranked and alternately arranged on branches. Leaf veins are pinnate and free or anastomosing or brochidodromous. Leaf blades may be densely pubescent or totally glabrous. *Myristica fragrans* plants are usually dioecious, with the exception of a few monoecious. Flowers are unisexual, inconspicuous, small in size (<4 mm), composed of three sepals (rarely 4) that are fused to varying degrees and exude a strong fragrance [8-9]. Female flowers (up to 1 cm long) are unicarpellate and uniovulate, and they show very little morphological differentiation within the family. Male flowers (5 to 7 mm long) are composed of 2-60 anthers which are fused to various degrees to a central column. Flowers are borne on racemose or thyrsoidal

paniculate inflorescences, which themselves originate within leaf axils. Once fertilized, the uni carpellate ovary develops into an elliptical fruit called a follicle. The fruit is comprised of a single seed, typically with a ruminant endosperm, covered to various degrees by a fatty white-reddish aril [10].

Ethnobotany

The nutmeg tree bears fruits that dehisce when ripe to reveal a single seed covered by a bright red aril, which are commercially known as nutmeg and mace respectively. The primary use of *Myristica fragrans* is, as a flavouring agent in cooking, but many cultures around the world have found it useful for a myriad of purposes. In its native range, the pericarps of nutmeg are made into a sweet snack called 'pala manis' or 'pala gulu' by repeated soaking in a sugar solution [6]. Indigenous Malukans topically apply nutmeg oil, which gives a warm strengthening feeling, to relieve headaches, stomach aches, diarrhoea and flu symptoms [6]. Both nutmeg and mace have been used as an aphrodisiac, anti-rheumatoid, anti-malarial, stimulant, and post childbirth tonic [11].

Chemical composition

The major chemical constituents of *Myristica fragrans* are alkyl benzene derivatives (myristicin, elemicin, safrole) myristic acid, alpha-pinene, terpenes, beta-pinene and trimyristin [12-13]. Nutmeg contains about 10% essential oil, chiefly composed of terpene hydrocarbons (sabinene and pinene), myrcene, phellandrene, camphene, limonene, terpinene, myrcene, pycmene and other terpene derivatives [14]. Nutmeg also yields nutmeg butter which contains 25 to 40 % fixed oil and is a semi-solid reddish brown fat having the aroma of nutmeg. Nutmeg butter contains trimyristin, oleic acid, linoleic acid and resinous material. The fixed oil of nutmeg butter is used in perfumes and for external application in sprains and rheumatism. [2]. Trimyristin is the major glycoside bearing anxiogenic activity [15].

Pharmacology

Anti-bacterial, Anti-microbial and Anti-fungal property

The antibacterial activity of the volatile oil obtained from the seeds of *Myristica fragrans* was tested in a study which included 25 different bacterial strains and it was observed that it was equally effective against the majority of gram positive and gram negative microbes [16]. Essential oil obtained from *Myristica fragrans* seeds has growth inhibition capability of bacterial spores and can be used

as food preservatives [17]. It has been observed experimentally that extract from the dried seed cover of Nutmeg has strong antifungal and antibacterial activity. The dried seed cover of *Myristica fragrans* contains two compounds and both exhibit strong antifungal and antibacterial activities [18]. It has been experimentally proved that nutmeg has potent antimicrobial activity. It also acts as a food preservative, antiseptic and disinfectant [19].

In another study, it was found that ethyl acetate extract of the flesh of *Myristica fragrans* had strong bactericidal activity against some cariogenic Gram positive and Gram negative bacteria [20]. In one study, several commonly used spices were evaluated for antifungal activity and turmeric and nutmeg were found to be most active. Antifungal compounds were isolated from Nutmeg, which were derivatives of neolignans and eugenol [21].

Hypoglycemic and antidiabetic activities

It was observed, that when rats were given pre-treatment with petroleum ether (60-80° C) extract of *Myristica fragrans*, at dose of 200 mg/kg, a significant decrease in blood glucose level, ($P < 0.05$), was obtained, i.e. blood glucose level reduced from 145.75 ± 9.65 to 81.5 ± 4.03 mg% in oral glucose tolerance test (OGTT) after 30 min compared to control group of glucose-fed rats. In alloxan induced diabetic rats, when petroleum ether extract of *Myristica fragrans* was given daily for two weeks, the blood sugar level reduced significantly from 326.25 ± 7.05 to 268.0 ± 9.6 mg % [22]. The nutmeg extract has significant peroxisome proliferator-activated receptor (PPAR) α/γ dual agonist activity, but its potency is less than PPAR α and PPAR γ full agonist. Therefore, nutmeg (*Myristica fragrans*) extract being a natural dual agonist PPAR α/γ can be developed as a potential anti-diabetic agent for the treatment of type 2 diabetes [23].

Hypolipidaemic and platelets anti-aggregatory activity

The hypolipidaemic and platelets anti-aggregatory activities of the extract of seeds of *Myristica fragrans* were studied in albino rabbits. It was observed that ethanolic extract of Nutmeg, at an oral dose of 500 mg/kg for 60 d, in albino rats, significantly reduced the total cholesterol in heart and liver. Low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) levels were also significantly reduced. The high-density lipoprotein (HDL) cholesterol was increased, but it was not significant. The total cholesterol: HDL ratio and LDL: HDL ratios were significantly lower in the treated animals compared to control group. The toxicity study showed that there was no adverse effect on various hematological and biochemical parameters. It also showed platelets anti-aggregatory activity [24]. The seed extract of *Myristica fragrans* when administered to hypercholesterolemic rabbits, significantly reduced serum cholesterol & LDL cholesterol and elevated the decreased LDL: HDL ratio. It also prevented the accumulation of phospholipids, triglyceride and cholesterol in heart, aorta and liver and aided in the dissolution of atheromatous plaque in the aorta. The excretion of cholesterol and phospholipids through faecal matter was increased significantly; in rabbits fed with seed extract [25].

Hepatoprotective activity

Myristicin, the foremost compound, in *Myristica fragrans* has ability to inhibit the lipopolysaccharide plus d-galactosamine induced enhancement of serum TNF- α concentrations in mice. Therefore, it was recommended that the hepatoprotective activity of Myristicin could be due to the inhibition of tumour necrosis factor (TNF)- α release from macrophages [26]. Mace is recognized to encompass hepatic detoxification system inducing activities. A study to determine modulatory effects of areca nut was carried out by determining the levels of enzymes of the hepatic detoxification system, such as cytochrome P-450, cytochrome b5, glutathione S-transferase (GST) and it was concluded that areca nut decreased the mace-induced increase in hepatic sulfhydryl (-SH) and GST levels and elevated levels of cytochrome P-450 and cytochrome b5 [27]. Another modern study revealed that mace lignan isolated from *Myristica fragrans* had a hepatoprotective effect on cisplatin-induced hepatotoxicity in mice. [28]. In another study, it was found that nutmeg aqueous extract had significant hepatoprotective and antioxidant activity against isoproterenol induced hepatotoxicity and oxidative stress [29].

Anti-inflammatory activity

The anti-inflammatory activity of *Myristica fragrans* was evaluated in carrageenan-induced edema in rats and acetic acid induced vascular permeability in mice. It was observed that the anti-inflammatory effect was approximately the same as that of Indomethacin. The results propose that myristicin present in mace is responsible for anti-inflammatory action [30]. The anti-inflammatory property of myristicin might be due to inhibition of chemokines, cytokines, nitrous oxide and growth factors in double-stranded RNA (dsRNA) stimulated macrophages via the calcium pathway [31]. The methanol extract from seeds of *Myristica fragrans* used for the treatment of inflammatory diseases also had inhibitory effects on nitric oxide (NO) production [32]. In another study, ethanolic extract of nutmeg seed showed high anti-inflammatory activity by inhibiting the inflammatory cytokines and Nitric oxide production. Quercetin was found to be the active compound responsible for the anti-inflammatory activity [33].

Anticancer activity

In one study, it was observed that, on adding essential oil of *Myristica fragrans* in various concentrations to the Michigan Cancer Foundation-7 (MCF-7) breast cancer cell line and A-357 epidermal skin cancer cell line, there was cytotoxic effect [34]. The essential oil of nutmeg showed significant inhibition on the expansion of a colon cancer cell line (undifferentiated Caco-2 cells) in an *in vitro* study [35]. The methanol extract of *Myristica fragrans* Hoult caused cell death of Jurkat leukemia T cell line by a mechanism involving SIRT1 mRNA downregulation [36]. It has been proved that *Myristica fragrans* inhibits the challenge growth microorganism using 20% v/v of the extract [37]. The covering of the seeds of Nutmeg has chemopreventive property. It significantly reduced the incidence of a skin papilloma in Swiss albino mice [38]. The preventive action of Nutmeg was studied on methylcholanthrene-induced carcinogenesis in the uterine cervix in Swiss albino mice. After a dose of 10 mg/mouse/day for 90 d there was a significant decrease in the extent of carcinoma. [39]. Ethanolic extract of *Myristica fragrans* was used to test anti-cancer activity against human cancer cell lines and it showed more than 70% growth inhibition at a concentration of 100 μ g/ml [40].

Memory enhancing activity

The effect of *Myristica fragrans* extracts, on recovery capability of learning and memory, were studied on aged and young mice against their impairment induced by scopolamine (0.4 mg/kg intraperitoneal) and diazepam (1 mg/kg intraperitoneal). N-hexane extract of *Myristica fragrans* was given orally for 3 successive days in three doses (5, 10, & 20 mg/kg) and found that the dose of 5 mg/kg p. o. significantly improved the memory and learning of young and aged mice. The mechanism of action was not elicited in these studies, but the authors believed that it is a mechanism based on the proven pro-cholinergic activities, anti-inflammatory and anti-oxidant properties of this plant [41]. Alzheimer's disease is treated on the basis of anticholinesterase inhibition by dropping the cognitive decline caused by reducing cholinergic deficits. In one study, it was found that a hydroalcoholic extract of Nutmeg did show significant (50%) inhibition of acetylcholinesterase for the treatment of Alzheimer's disease [42].

Aphrodisiac activity

50% ethanolic extract of Nutmeg and clove (500 mg/kg, p. o.) was given to various groups of male Swiss mice to study their mating activity, mounting behaviour and short-term toxicity against those being given 50% sildenafil citrate. The 50% ethanolic extract of the seeds of *Myristica fragrans* and clove showed an increase in the mating performance and the mounting performance of mice without showing any short-term toxicity [43].

Anti-diarrhoeal activity

Crude suspension and petroleum ether extract of Nutmeg were evaluated for anti-diarrhoeal activity and it showed a decrease in the mean number of loose stools and increased in the latency period. The crude suspension of nutmeg showed a good anti-diarrhoeal

effect [44]. In another study, hexane soluble fraction of ethanol extract of the dried fruits and flowers of *Myristica fragrans* showed anti-secretory properties in the ileum of rabbit and guinea pig against *Escherichia coli* enterotoxins [45].

Osteoblast proliferation stimulation activity

M. fragrans compounds have proven ability to stimulate osteoblastic differentiation. Machilin A from *Myristica fragrans* stimulated osteoblast differentiation by activating p38 mitogen-activated protein (MAP) kinase. Other lignans like safrole, myristargenol, mace lignan, nectandrin B, mesodihydroguaiaretic acid, machilin F, licarin B and licarin A from *M. fragrans* also showed similar action and have anabolic activity in bone metabolism [46].

Antidepressant activity

The n-hexane extract of *M. fragrans* seeds was studied in mice for its antidepressant effect by using the forced swim test (FST) and the tail suspension test (TST) at three different oral doses of 5, 10, and 20 mg/kg body weight. The highly potent dose was found to be 10 mg/kg dose, as it showed a maximum decrease in the immobility of mice when compared to control. Additionally, this dose also showed equivalent strength to Imipramine (15 mg/kg) and Fluoxetine (20 mg/kg). Thus, the extract of Nutmeg was competent to give significant antidepressant effect in mice, when evaluated by TST and FST. The antidepressant effect of the Nutmeg seed extract could be due to interaction with the dopaminergic, adrenergic and serotonergic systems [47].

Anti-oxidant activity

Antioxidant activity of some spices was compared with some food antioxidants like Propyl gallate, butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). Anise, Liquorice and Nutmeg showed good activity in the deoxyribose assay. Propyl gallate, Liquorice, Ginger and Nutmeg increased the stability of some fixed oils like olive, sunflower and corn oil and fats like margarine and butter and prevented oxidation at 110 °C. The antioxidant activity of nutmeg was found to be higher than BHT in the Trolox equivalent antioxidant capacity (TEAC) assay [48].

In another study, it was reported that methanolic extract of Nutmeg seed showed good antioxidant activity by methods of 1,1-diphenyl-2-picrylhydrazyl (DPPH) and ferric reducing antioxidant power (FRAP) due to high content of tannin, flavonoid and terpenoids. [49]. Acetone extract showed good antioxidant activity by the DPPH radical scavenging assay due to the presence of several terpenoids like sabinene, myristicin and eugenol [50].

Anti-cariogenic activity

In one study, it was found that mace lignan, isolated from a methanolic extract of Nutmeg, had anti-bacterial property and strong inhibitory activity against *Streptococcus mutans* which is an oral pathogen causing dental caries. Macelignan, at a concentration of 20 µg/ml, completely inactivated *S. mutans* in 1 min. The minimum inhibitory concentration (MIC) of mace lignan was found to be very lower than that of other natural anti-cariogenic agents [51].

Nutmeg can also be used for the treatment of periodontitis, which is an inflammation of supporting structures of teeth, due to its anti-inflammatory and anti-bacterial properties [52].

Pesticide activity: insecticidal

The insecticidal activity of a hexane-soluble fraction of a methanolic extract of Nutmeg seed compound against adult female *Blattella germanica* was compared with some commonly used insecticides like propoxur, permethrin, deltamethrin and dichlorvos. It was concluded that insecticidal activity of these compounds was mainly in the vapour phase [53]. The aqueous decoctions of Nutmeg seed were toxic to cockroaches [2]. The essential oil of Nutmeg seed showed insecticidal effects against larvae of *Lycoriella ingénue*, a mushroom infesting fly [54] and *Callosobruchus chinensis*, a pulse beetle. [55]

Anti-obesity activity

In one study, it was found that tetrahydrofuran (THF) type lignans isolated from *Myristica fragrans* showed an anti-obesity effect in

high fed diet (HFD) induced mice due to Adenosine Monophosphate (AMP)-activated protein kinase activation mechanism. The THF prevented the increase in adipose tissue mass, body weight, LDL levels and glucose in THF treated mice as compared to HFD group of mice [56].

CONCLUSION

Myristica fragrans is used for various medicinal properties. The fruit and seed extracts show various activities like hepatoprotective activity, anti-oxidant activity, memory enhancing activity, anti-cancer activity, aphrodisiac activity, anti-diabetic activity, anti-depressant activity, hypolipidaemic and hypocholesterolemic effect, anti-microbial activity, anti-bacterial, anti-inflammatory and anti-carcinogenic activity. More efforts are needed to study the traditional uses of the plant and for subsequent validation of activity and the mechanism of action. *Myristica fragrans* is a resource of medicinally active compounds and has diverse pharmacological effects; hence, this drug encourages researchers to explore its various novel therapeutic uses for the benefit of mankind.

CONFLICT OF INTERESTS

Declared none

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