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# A REVIEW ON BIOACTIVE COMPOUNDS AND PHARMACOLOGICAL ACTIVITIES OF *Myristica fragrans* AS A MEDICINAL PLANT

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**ABSTRACT**

*Myristicafragrans* which is commonly known as nutmeg produces two spices called nutmeg and mace. From very ancient time *M.fragrans* fruit has been used as a folk medicine. Apart from that due to the chemical composition of nutmeg and mace, it can be used in many other industries like microbial industry, bakery industry, beverage industry and cosmetic industry. Research works have done to elucidate ant diabetic, antibacterial, anti-fungal, memory enhancing, hypolipidaemic and hypocholesterolemic, anticonvulsant, anti-inflammatory and analgesic properties of the plant. Due to the valuable chemical composition, wide spreading and easy collection of the fruit, it is beneficial to carryout extensive investigation of this plant in human as well since most of the experiments have done only to rats and rabbit models. From this review it clearly emphasizes that *M.fragrans* deserve more attention to develop new products which can be used by human with low cost and minimum adverse effects.

***Keywords:*** *Myristicafragrans*, Bioactive compounds, Medicinal herbs.

## INTRODUCTION

*Myristica fragrans* is a widely spread evergreen plant with several pharmacological and phytochemical properties. Genus *Myristica* comprises of 72 different species spread throughout Asian and Australian continent. (Mabberly,1987). This plant can be found in Grenada, Sri Lanka, India, Singapore, Mauritius, South Africa, Unites States of America and Indigenous to Moluccas. (Gomathi et al., 2016). *Myristica fragrans* produce two spices, nutmeg which is the seed kernel inside the fruit and mace which is the red color net like covering on the kernel. Tree grows approximate 5 to 13m height. Dark green pointed leaves (5 to 15cm cm × 2 to 7 cm) are arranged alternately. Bark contain pink or red sap. Flowers are single sexed, male and female flowers found on the same tree. Both male and female flowers can be seen in groups. Female flowers are of 1 to 3 groups and male flowers are in 1 to 10 groups. Fruits are yellow in color, smooth and fleshy. When ripe, fruit coat splits into halves.(Puraseglove et al., 1968) Trees usually do not flower till 9 years but once it starts flowering, it will continue till 75 years. Nutmeg is a known spice with a characteristic fragrance and it has many therapeutic properties. It uses in bakery industry to flavor cakes, to flavor puddings, vegetables, beverages, meats, sauces and etc. Apart from that it is used as an ingredient of curry powder, soft drinks, milk, teas and alcohol (Olaleye et al., 2006). To treat diseases like mouth sores, diarrhea and insomnia nutmeg has used as a folk medicine. For rheumatism nutmeg essential oil is used and it possesses anti-inflammatory and analgesic properties as well. (Santos et al., 1997; Olajide et al., 1999). Also some isolated compounds of nutmeg have reported anti aggregatory properties. (Venton et al., 1991). Atherosclerosis and hypercholesterolemia can be preventing from nutmeg (Sharma et al., 1996). Though safrole which is present in nutmeg has suspected as carcinogenic, myristicin and elemicin is related to hallucinogenic action and intoxication activity of nutmeg.

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Chemopreventive and anti-Helicobacter pylori activities of crude extract of nutmeg was reported in several research work. (Bhamarapravati et al., 2006) Apart from that acetylcholine esterase inhibitory activities, tyrosine phosphate inhibitory activity and hepatoprotective activities were shown. (Min et al., 2011). Due to the inhibition of prostaglandin synthesis in the colon mucosa nutmeg extract is used as an anti-diarrheal agent for patients with medullar carcinoma of the thyroid. (Olaleye et al., 2006)In this review photochemistry, medicinal values, biological effects and uses of *M.fragrans* has summarized since there is systematic analysis or review of all these areas are not available. The main intention of this review is to put forward the traditional knowledge and uses of *M.fragrans* and improve the current usage of *M.fragrance* as a potent plant in different industries in the world like pharmacological, bakery, cosmetic and in microbial industry.

## METHODOLOGY

PubMed and PMC Academic Quest Completed were used to perform literature searches using the keywords "Myristicafragrans". These terms have also been entered into common search engines like Google and Google Scholar to look up secondary information about this herb. All content was reviewed, regardless of source, and a review structure was produced to represent the information available. The "MedChem designer" program was used to draw all of the phytochemicals' chemical structures.

## RESULTS AND DISCUSSION

### Pharmacologically useful parts of the plant

Dried seed kernel, nutmeg is the well-known most important part of the plant. Apart from that mace, endosperm of the fruit has been used in different purposes from ancient times. There are some reports regarding the intoxication from use of mace, but it is very rare. Mace widely used in food industry as a flavoring agent. Apart from that it is used as a hair dye and according to folk medicine, mace has been

used as an anti-carcinogenic, anti-papillomagnetic, (Hussain & Rao, 1991) and possess anti-inflammatory properties. (Ozaki et al., 1989). Nutmeg is used as a component of tea, milk, alcohol and as a spice for various dishes. Nutmeg oil is used as a stimulant of appetite, to control flatulence, as a stomachic, carminative, intestinal catarrh and colic, as an abortifacient and as an emmenagogue. (Nadkarni, 1988).

**Chemical composition M.fragrans fruit**

Most of the important chemicals of *M.fragrans* are from the seed which are volatile phenolics, terpenoids, proteins, starch, lignin compounds and multifunctional bioactive compounds including Trimyristine, Myristicin and Dihydrogualaretic acid (Figure 1) (El-Alfy et al., 2009). According to Olaleye et alaqueous extract of *M. fragrans* contain flavonoids, saponins, alkaloids, cardiac glycosides and anthraquinones. 10% of essential oils are contain in the fruit (Maya et al. 2004).In the essential oil 60-90% contain camphene, sabinene, limonene, mycene,a-pinene and p-cymene. 5-15% contain terpene derivatives, 2-20% contain phenylpropanes including elemicin, myristicin and safrole. Myristicin and elemicin present in the seed cause for the intoxicating effects. (Sonavane et al., 2001). 80% of alkenylbenzene derivatives consists of myristicin and elimicin. (Janssen and Lackman, 1990). Myristic, palmitic, lauric, oleic, stearic and linoleic are the fixed oils present in the seed. (Gopalakrishnan et al., 1992). According to Pal et al, 2011, essential oil of nutmeg collected from Andaman Nicobar Island consists of β-pinene (7.3%), terpine-4-ol (5.8%), sabinene (41.7%), α-pinene (9.4%), limonene (3.7%), safrole (1.4%) and myristicin (2.7%). As major constituents in the M.fragrans leaves, α-pines (18.04%), sabinene (19.07%), β-pinene (7.92%), limonene (8.32%), 4-terpineol (11.83%) were identified. (Zachariah et al., 2008). Lignin compounds such as meso-monomethyl dihydroguaiaretic acid, (+) guaiacin, including (8R,8'S)-7'-(3',4'-methyl enedioxyphenyl)-8,8'-dimethyl - 7-(3, 4 - dihydroxy - phenyl)-butane, 9-epoxylignan and many more lignins were isolated from M. fragrans seeds. (Min et al., 2011). Novel compounds (−)-1-(2,6-dihydroxyphenyl)-9-[4-hydroxy-3-(p-menth-1-en-8-oxy) - phenyl]-1-nonanone and (7R,8R)-7,8-dihydro-7-(3,4-dihydroxyphenyl)-3'-methoxy-8-methyl-1'-(E-propenyl)- benzofuran were characterized in the fruits of M.fragrans (Duan et al., 2009).Due to the presence of terpenes, Mace, dried seed covers of M.fragrans are aromatic. Mace has same aromatic compounds as nutmeg but in different proportions. Mace has 30% fixed oils and 7-14% essential oils depending on their origin. Monoterpenes (87.5%), monoterpene alcohols (5.5%) and other aromatic compounds(7%) can be found in mace. (Pooja et al., 2012) Resorcinol malabaricone B and malabaricone C were also have been isolated from mace. (Orabi et al., 1991)

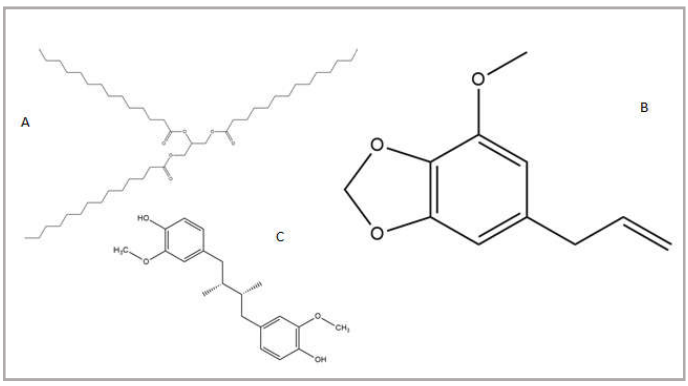


Figure 1: Major bioactive compounds in *M.fragrans* (A).Trimyristine, (B). Myristicin, (C) Dihydrogualaretic acid.

**Anti-diabetic properties**

Macelignan isolated from M.fragrans have the ability to suppress lipid metabolic disorders by activating peroxisome proliferator receptor, enhance the sensitivity of insulin, attenuating endoplasmic reticulum (ER) stress which it can be used as a type 2 diabetic treatment. (Han et al., 2008). According to the research by Somani and Singhai, 2008 petrolium ether extract of M.fragrans were fed to normal, glucose fed and alloxan-induced diabetic rats and according to the results blood glucose level of all categories of rats were decreased. Induced insulin release from the beta –cells can be the reason for this hypoglycaemic effect. Rats who orally administered extract were shown suppressionin blood glucose level. There was an increasement in the body weight of diabetic rats who have given the extract orally. That can be due to the better glycemic control and enhancement of insulin secretion. (Somani and Singhai, 2008). Suppression of glucose level during external glucose loading might be due to increase glucose uptake or glucose absorption reduction or potentiation of secretion of pancreatic juices. Moderate reduction of blood glucose level in streptozotocin induced diabetic rats, which administered the ethanolic extract of M.fragrans fruits were observed after 3-7 hours post treatment. Maximum reduction was seen after 7 hours of post treatment. (Ahmad et al., 2008). These results exhibit the anti-diabetic properties of M.fragrans extracts and further experimental studies needed to carryout for its action and to used it as a commercially available product.

**Neuropharmacologic properties**

Anxiogenic activity of trimyristin in hexane extract of *M.fragrans* have shown in mice administrated with 10-100 and 30-300 mg/kg body weight intraperitonellay, when tested in elevated hole-board paradigms and plus maze. (Sonavane et al., 2002). Apart from that there are reports which listed nutmeg as a recreational drug commonly used as a substitute for marijuana. Historically *M.fragrans* extract has been used as a pain reliever as a substitute for morphine narcotic drugs. (Rudgley, 1998). In a related study, neuro-pharmacological activity of different nutmeg extracts was compared with commonly abused drugs morphine, tetrahydrocannabinol and amphetamine (El-Alfy et al., 2009). This comparison has been associated with the hypothesis of activation of metabolismby nutmeg extract constituents to amphetamine like compounds. Forced swim test and tail suspension test were conducted by Dhingra and Sharma (2006) at dose levels of 5, 10 and 20 mg/kg of body weight of mice to determine the n-hexane extract of *M.fragrans* antidepressant activity. When compared with the control, 10mg/kg of body weight dose exhibit the highest reduction of immobility period. And also 10 mg/kg dose has the potency to fluoxetine and imipramine. From these two tests, extract of *M.fragrans* have shown the capability to elicit antidepressant like effect in mice. This property might be due to interaction of extract with dopaminergic, adrenergic and serotonergic systems.

**Hypolipidaemic and Hypocholesterolemic property**

In hyperlipidaemic albino rabbits, ethanolic extract of *M.fragrans* were orally administered at a dose of 500mg/kg body weight for 60 days and it significantly reduced the lipoprotein lipids level.(Ram et al.,1996). According to another research administration of *M.fragrans* seed extract to hypercholesterolemic rabbits, has reduced the serum cholesterol by 69.1%, LDL cholesterol by 76.3%, significantly elevate the reduced HDL-ratio and reduced the ratio of cholesterol to phospholipid by 31.3% (Sharma et al.,1995). And also this research depicts that cholesterol and phospholipids in fecal matter in rabbits were significantly reduced when seed extract of *M.fragrans* were fed

to the rabbits. Also accumulation of phospholipids, cholesterol and triglycerides in heart, liver and aorta prevented by the *M.fragrans* extract. These properties show that *M.fragrans* has the hypolipidaemic and hypocholesterolemic properties.

**Memory enhancing activity**

By using elevated plus- maze and passive avoidance apparatus Parle et al. (2004) was conducted a research to investigate the memory level and learning capabilities of mice who have fed *M. fragrans* seed extract. In young and aged rats' administration of n-hexane extract of *M.fragrans* 5mg/kg of body weight of rats for 3 successive days significantly increased the learning and memory level. In young mice scopolamine and diazepam-induces impairment in learning and memory has reversed by the extract. This memory and learning capability enhancement of *M.fragrans* extract might be due to anti-inflammatory, procholinergic or antioxidant activities or combinations of these properties.

**Anticonvulsant activity**

Anticonvulsant activity of *M.fragrans* extract can be due to the decreased dopaminergic transmission. This property has been tested in animal models of Petit mal, Grand mal and status epilepticus. (Sonavan et al., 2002). Anticonvulsant activity of nutmeg essential oil was found against electro shock induced hind limb tonic extension. It exhibits a dose dependent activity against pentylenetetrazole induced tonic seizures. Strychnine induced the hind limb tonic extensor jerks and onset of the jerk delayed by the nutmeg essential oil. It is also weak proconvulsant at higher does against bicuculline induced clonic seizures and pentylenetetrazole and it is anticonvulsant at lower doses(Wahab et al., 2009).

**Anti-inflammatory and analgesic property**

Nowadays there are several anti-inflammatory drugs developed but still scientists and health sectors focus more towards the natural sources which have the anti-inflammatory properties, due to various adverse effects of chemical drugs(Hyun and Kim, 2009; Shokrzadeh and Saeedi, 2009).Traditionally essential oils of mace and nutmeg were used to relief sprains, paralysis and rheumatism (Chatterjee and Pakrashi, 1992). Petrolium ether extract of *M.frangrance*, display the similar properties as non-steroidal anti-inflammatory drugs. (Olajide et al., 2000). Carrageenan induced edema in rats can be inhibit by the chloroform extract of nutmeg. Apart from that methanol extract of mace and nutmeg exhibit long lasting anti-inflammatory activity. These properties can be due to the presence of myristicin in the essential oils of nutmeg (Naikod et al.,2011).

**Antibacterial and Antifungal properties**

According to Ibrahim et al (2011) extract of *M.fragrans* exhibit antibacterial activity against *Proteus vulgaris, Staphylococcus aureus* and *Klebsiella pneumoniaand* not effective against *Salmonella typhirium, Bacillus subtilis* and *Pseudomonas aeruginosa*. According to the radial growth determination, 0.1% nutmeg essential oil inhibit *Aspergillus glaucus, Aspergillus niger, Collectotrichum gloeosporoides, Colletotrichummusae, Fusariumoxysporum and Fusariumsemitectum*. This growth inhibition can have increased up to 100% when the *M. fragrans* concentration increased up to 0.3% (Valente et al., 2011). Apart from that nutmeg and mace exhibit strong antimicrobial activities against animal and plant pathogens like Escherichia coli, Saccharomyces cerevisiae and *Helicobacter pyroli*. (De et al., 1999; Dorman & Deans, 2000; Rani & Khullar, 2004). Also alcoholic extract of nutmeg shows anti-bacterial activity against *Micrococcus pyogens*. (Anonymous, 1995). Yersinia enterocolitica and Listeria monocytogenes in broth culture and Iranian barbecued chicken, shows inhibition in growth in the presence of alcoholic extract of nutmeg. (Firouzi et al., 2007). Antifungal properties of methanol extract of *M. fragrans* showed in isolated lignans such as meso-dihydroguaiaretic acid, erythro-austrobailignan-6 and nectandrin- B against fungal strains such as Colletotrichum gloeosporioides, *Agrobacterium tumefaciens, Magnaporthegrisea, Acidovoraxkonjaci*, *Alternaria alternate* and *Colletotrichumcoccodes* (Cho et al., 2007).

**Aphrodisiac activity**

*M.fragrans* extract has been used in Unani medicine to treat sexual disorders. According to an experiment carryout by Tajuddin et al. (2005) it was found that, the oral administration of ethanolic extract of nutmeg at a dose of 500mg/kg of body weight has the ability to increase the sexual ability of male rats significantly and in a sustained way without any adverse effects that might be related to its nerve stimulation property.

**Hepatoprotective activity**

Myristicin present in *M.fragrans* extract has the hepatoprotective activity against the liver damage caused by lip polysaccharides plus D-galactosamine in rats (Morita et al. (2003). And also it is reported that myristicinn have the possibility to suppress the hepatic DNA fragmentation and lip polysaccharides plus D-galactosamine induced enhancement of serum TNF-alpha concentrations in mice. This can be due to the inhibition of TNF-alpha release from macrophages. Another research reveals that macelignan isolated from M.fragrans have the ability to activate the JNK and c-Jun in mitogen activated protein kinase signaling pathway (Sohn et al.,2008).

## CONCLUSION

Accordingly *M.fragrans* extract have many useful properties like antibacterial, antifungal, hepatoprotective activity, anti-inflammatory and analgesic property, memory enhancing activity, anticonvulsant activity, anti-diabetic properties, neuropharmacologic properties, hypolipidaemic and hypocholesterolemic property due to its valuable bioactive compounds and they may have potentials for development of drugs against pathogenic microorganisms as well as cure for different non-communicable diseases. Since *M.fragrans* is natural source, adverse effects after consumption is less and can be developed to use in many areas like drug industry, bakery industry, cosmetics industry. Many research works have been done in animal models but very few reported regarding human trials. Further experiments needed to be done to determine the efficacy of *M.fragrans* against pathogenic microorganisms as well as for develop other natural and modern drugs in human use. Attention should be drawn towards this plant by scientists and health community to carryout extensive research to get the maximum benefits from this plant.

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