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Pharmacology and chemistry of *Myristica fragrans* Houtt. – a review

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Abstract

The information available on the pharmacology and chemistry of nutmeg (*Myristica fragrans*) has been reviewed and the areas of interest for further investigation have been suggested.

Key words: chemistry, *Myristica fragrans*, nutmeg, pharmacology.

Introduction

Nutmeg (*Myristica fragrans* Houtt.) (Family: Myristicaceae) is believed to be a native of Banda Islands of Eastern Indonesia, formerly called the 'Spice Islands'. In India it is mainly cultivated in South India particularly in certain pockets of Kerala, Tamil Nadu and Karnataka, having been introduced by the British during the 18th century (Krishnamoorthy *et al*. 2001). The name '*Myristica*' is derived from the Greek word 'Myron', a sweet liquid distilled from the plant (Everett 1981).

M. fragrans is a dioecious or monoecious tree, bushy and evergreen, 9–12 m tall. The fruit is a one-seeded fleshy drupe, succulent, pendulous, smooth, 6–9 cms long and nearly as broad. When the fruit ripens, the aromatic orange yellow pericarp, about 1.3 cm thick splits into two halves along the suture to expose the albuminous seed, the nutmeg and the red, fleshy, lobed net–like aril or mace. Nutmeg and mace are the two major primary products of *M. fragrans* and are commercially considered as spices (Krishnamoorthy & Rema 2001).

Pharmacological studies

Antimicrobial effects

The essential oils from *M. fragrans* seeds are used in tonics (Purseglove 1968). They showed inhibitory effects against *Bacillus anthracis*, *B. mycoides*, *B. pumilus*, *B. subtilis*, *Escherichia coli*, *Saccharomyces cerevisiae*, *Shigella* spp. I and II and pathogenic staphylococci (Bhat & Broker 1953; Pathak *et al*. 1979; Satyavathy *et al*. 1987; Minakshi *et al*. 1999). It inhibited the growth of *Listeria monocytogenes* by suppressing the production of the bacterial extracellular protein, listeriolysin and the bacterial enzyme phospholipase (Palmer *et al*. 2002). *M. fragrans* extract showed mild antibacterial activity against pathogenic staphylococci (Bhat & Broker 1953). The aqueous paste of *M. fragrans* seed had a marked inhibitory effect on the

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fluid accumulation capabilities of enterotoxigenic *E. coli,* in the ligated gut of rabbit. It had no effect, however, on bacterial growth and production of enterotoxin by the organism *in vitro* (Rasheed & Misra 1984). Strong antibacterial activity was shown by the methanol extract of *M. fragrans* seed against multi-drug resistant *Salmonella typhi* (Rani & Khullar 2004), with the minimum inhibitory concentration (MIC) of 12.5 μg ml^{-1}.

The mace of *M. fragrans* showed antimicrobial properties against *Staphylococcus aureus* and *Candida albicans* (Orabi & Mossa 1991) at MIC of 1 μg ml^{-1} and 4 μg ml^{-1}, respectively. Dehydro-di-isoeugenol and 5-methoxy eugenol from mace helped to prevent dental caries caused by *Streptococcus mutans* (Hattori & Hada 1986). Methanolic extract of *M. fragrans* mace was reported to inhibit the growth of the gram negative bacterium, *Helicobacter pylori,* which is a human carcinogen (Bhamarapravati *et al*. 2003).

Cytotoxic, anticancer and chemoprotective effects

Extracts of nutmeg suppressed the growth of human lymphoid leukaemic cells, Molt 4 B (Moteki *et al*. 2002). Myristicin, present in the volatile oil of *M. fragrans* is a potential cancer chemopreventive agent (Zheng *et al.* 1992). The essential oil is reported to modulate the formation of DNA adducts by aflatoxin *in vitro* (Hashim *et al.* 1994). The dihydroguaiaretic acid from *M. fragrans* mace suppressed leukaemic cells, colon cancer and lung cancer cells *in vitro* (Park *et al.* 1998). The mace of *M. fragrans* protected from bone marrow genotoxicity in male Swiss albino mice (Kumari 1992). It also significantly protected from methylcholanthrene-induced carcinogenesis in uterine cervix of mice (Hussain & Rao 1991) and had chemopreventive effects on dimethylbenz(a)anthracene (DMBA)-induced papillo-magenesis in the skin of mouse (Jannu *et al*. 1991).

Hepatoprotective effects

Myristicin from nutmeg exhibited significant hepatoprotective effects (Morita *et al.* 2003). The mace is reported to modulate glutathione–S-transferase activity in mouse liver (Kumari & Rao 1989; Singh & Rao 1993). Active principles present in the aqueous extract of mace were effective in transmammary modulation of hepatic xenobiotic metabolizing enzymes in the liver of mouse pups (Chhabra & Rao 1994). These active principles from mace also influenced the hepatic detoxification systems in adult mice (Shin & Kim 1988; Kumari & Rao 1989; Singh & Rao 1993).

Antioxidant effects

Nutmeg essential oils are powerful antioxidants (Dorman *et al.* 2000). *M. fragrans* seeds are reported to possess antilipid–peroxidant properties (Hattori *et al*. 1993).

Antiinflammatory effects

The nutmeg oil showed pharmacological properties, similar to those of non-steroidal anti-inflammatory drugs (Olajide *et al*. 2000). It inhibited prostaglandin synthesis in rat kidney (Misra *et al*. 1978). *M. fragrans* seeds as well as the mace showed anti-inflammatory effects, similar to indomethacin and this was due to the presence of myristicin (Ozaki *et al*. 1989).

Antithrombotic effects

M. fragrans seeds (chloroform extract), as well as nutmeg oil, are reported to inhibit platelet aggregation and hence showed antithrombotic effects (Janssens & Laekeman 1990; Olajide *et al*. 1999, 2000).

Hypolipidaemic and antiatherosclerotic effects

M. fragrans seeds showed significant hypolipidaemic, anticholesterolaemic and antiatherosclerotic effects in rabbits (Sharma & Mathur 1995; Ram *et al*. 1996; Capasso *et al.* 2000).

Behavioural effects

Nutmeg and mace are called pshychotropic spices (Forrest & Heacock 1972). The seed oil has a depressent effect on isolated frog rectus and direct relaxant effect on rat ileum. It also potentiated hexobarbital–induced hypnosis in rats (Bhagwat & Saifi 1980). *M.*

fragrans seeds exhibited anticonvulsant (Sonavane *et al*. 2004), anxiogenic, sedative and analgesic effects (Shidore & Majumdar 1985; Sonavane *et al*. 2001, 2002). Ligroin extract of nutmeg increased the duration of sleep in chicken (Sherry *et al*. 1982).

Miscellaneous effects

The aphrodisiac property of nutmeg has been reported (Tajuddin *et al.* 2003). Nutmeg oil showed antipyretic effects in rats and mice (Olajide *et al*. 2000). Insulin-like biological activity of *M. fragrans* aqueous extracts has been reported (Broadhurst *et al.* 2000). The antiulcer (Capasso *et al.* 2000) and antidiarrhoeal (Gupta & Yadava 1992) activities of *M. fragrans* seeds have been reported. *M. fragrans* seed suspension had no harmful effect on blood pressure (Grover *et al*. 2002). Sastre *et al*. (1996) reported the development of occupational asthma on inhalation of mace dust.

Toxicological effects

Toxicological effects including weak pulse, hypothermia, delirium, vertigo and nausea associated with ingestion of *M. fragrans* has been reported (Hallstrom & Thuvander 1997). Zaki & El (1987) reported teratogenic effects of nutmeg in foetus of rats. Randerath *et al*. (1993) reported the development of covalent DNA adducts in the liver of adult and foetal mice, treated with extracts of nutmeg or mace or myristicin, the major spice constituent of nutmeg. Safrole, a minor constituent of nutmeg also produced DNA adducts in the liver of mice.

Pesticidal properties

The aqueous decoction of *M. fragrans* seed is toxic to cockroaches (Krishnamoorthy *et al*. 2001). Nematicidal activity of *M. fragrans* seed against *Meloidogyne incognita* has been reported (Gotke & Maheswari 1990).

Phytochemical studies

Satyavathy *et al*. (1987) and Thakur *et al*. (1989) have reviewed the phytochemistry of *M. fragrans*. The seed contains about 10% essential oil (Verghese 2001; Maya *et al*. 2004), which is mostly composed of terpene hydrocarbons (α-pinenes, camphene, p-cymene, sabinene, β-phellandrene, γ-terpinene, limonene, myrcene (60% to 90%), terpene derivatives (linalool, geraniol, terpineol-5% to 15%) and phenylpropanes (myristicin, elemicin, safrole-2% to 20%). The presence of myristicin and elemicin, in the seed of *M. fragrans* is one of the reasons for its intoxicating effects (Sonavane *et al*. 2001). Myristicin constitutes 4%–6% of nutmeg and mace essential oil and is responsible for most of its pharmacological effects. Oil of mace (up to 12% in the spice) contains the same aroma components in slightly different amounts. Although essential oils are the same in both seed and mace, the flavours are different. In addition to the known monoterpene hydrocarbons, α-p-dimethylstyrene has been identified along with seven esters, eight sesquiterpene hydrocarbons and two unsaturated aliphatic compounds namely, 3-methyl -4-decan-1-ol and its acetate (Schenk & Lamparsky 1981).

Gopalakrishnan (1992) has made extensive studies on the composition of nutmeg and mace. The seeds also contain 25%–30% fixed oils (myristic, stearic, palmitic, oleic, linoleic and lauric acids). Besides, the seeds contain saponins, polyphenols, tannins, epicatechin, triterpenic sapogenins and fats (Varshney & Sharma 1968; Sathyavathy *et al*. 1987). Nutmeg has also been reported to contain calcium, phosphorous, iron, thiamine, riboflavin and niacin (Gopalan *et al*. 1984). Chromatography of the nutmeg extract revealed the presence of epicatechin and cyanidin (Gopalakrishnan & Mathew 1983). Kim & Park (1991) isolated Licarin B from the seeds of *M. fragrans*. Malabaricone C isolated from nutmeg had significant antibacterial effects (Shinohara *et al*. 1999).

The colour of mace is an important factor, influencing its commercial value. The red pigment of mace was identified to be lycopene by thin layer chromatography and absorption studies (Gopalakrishnan 1979). The neolignans, fragnasol C and D and myristicanol A and D have been isolated from

mace (Rastogi & Mehrotra 1995; Miyasawa *et al*. 1996). A neolignan, characterized as dihydro-di-isoeugenol was isolated from the hexane and chloroform extracts of *M. fragrans* arils (Purushothaman & Sarada 1980). Five phenyl propanoids had been reported from the seed kernel of the plant (Irogi *et al*. 1973). Dihydroguaiaretic acid has been isolated from the mace of nutmeg (Park *et al*. 1998).

The fresh pericarp of the ripe fruit contains an acidic astringent juice with an aromatic flavour. The composition of the fruit rind was found to contain proteins, fats, minerals, phosphorous, iron and carotene (Anonymous 1962; Gopalan *et al*. 1984). The rind contained up to 14% pectin and 27% fibre (Preethi & Krishnankutty 1986; Gopalakrishnan 1992). Perhaps, the high pectin content of the pericarp is responsible for its antidiarrhoeal effects, reported in ayurvedic treatises.

The major chemical composition of nutmeg, mace and pericarp are given in Table 1.

Conclusion

There is significant evidence for the pharmacological basis of the traditional medicinal use of *M. fragrans*. Though the existing chemical and pharmacological literature on *M. fragrans* is impressive, more topics remain open to future investigation like characterization of the still unexplored phytochemicals, their mechanisms of action and the clinical efficacy in long term trials with special reference to herbal formulations developed from *M. fragrans* for insomnia, heart disease, peptic ulcers and oral care. The high quantity of pectin present in *M. fragrans* pericarp, can be put to use in the

Table 1. Chemical composition of *Myristica fragrans* fruit

Chemical composition	Part of the fruit	References
Proteins	Seed, mace	Gopalakrishnan (1992)
Sugars	Seed, mace	Gopalakrishnan (1992)
Starch	Seed, mace	Gopalakrishnan (1992)
Myristicin	Seed, mace	Satyavathy *et al*. (1987)
Elemicin	Seed	Satyavathy *et al*. (1987)
Safrole	Seed	Satyavathy *et al*. (1987)
Fixed oils	Seed	Gopalakrishnan (1992)
Saponins	Seed	Varshney & Sharma (1968)
Tannins	Seed	Varshney & Sharma (1968)
Epicatechin	Seed	Varshney & Sharma (1968)
Monoterpene alcohols	Seed	Schenk & Lamparsky (1981)
Fats	Seed, pericarp	Varshney & Sharma (1968)
Calcium	Seed	Gopalan *et al*. (1984)
Phosphorous	Seed, pericarp	Gopalan *et al*. (1984)
Iron	Seed, pericarp	Gopalan *et al*. (1984)
Thiamin	Seed	Gopalan *et al*. (1984)
Riboflavin	Seed	Gopalan *et al*. (1984)
Niacin	Seed	Gopalan *et al*. (1984)
Epicatechin	Seed	Gopalakrishnan & Mathew (1983)
Cyanidin	Seed	Gopalakrishnan & Mathew (1983)
Licarin B	Seed	Kim & Park (1991)
Malabaricone C	Seed	Shinohara *et al*. (1999)
Neolignans	Mace	Miyasawa *et al*. (1996)
Dihydroguaiaretic acid	Mace	Park *et al*. (1998)
Carotene	Pericarp	Gopalan *et al*. (1984)
Pectin	Pericarp	Preethi & Krishnankutty (1986)
Phenyl propanoid ethers	Seed	Krishnamoorthy & Rema (2001)

preparation of jams and jellies and development of natural and safe plasma substitutes and antidiarrrhoeal agents.

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