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Review Article

Myristica fragrans (Nutmeg): A Brief Review

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Abstract : *Myristica fragrans* is commonly named nutmeg or mace belongs to family Myristicaceae. It is an aromatic evergreen tree with spreading branches and a yellow fleshy fruit similar in appearance to an apricot or peach. *Myristica fragrans* essential oil has antimicrobial, antiseptic, antiparasitic, anti-inflammatory, and antioxidant properties. We have recently demonstrated that hydrodistillation of nutmeg essential oil by applying magnesium aluminometasilicate as an excipient significantly increases both the content and amount of bioactive substances in the oil and hydrolats. In this study, we aimed to compare the antioxidant, antimicrobial, and anti-inflammatory activity of hydrolats and essential oil obtained by hydrodistillation in the presence and absence of magnesium aluminometasilicate as an excipient. 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 or mace, Myristicaceae.

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 amenorrheal agents [7,8]. The aim of this review is to emphasize on the various pharmacological activities of *Myristica fragrans*. The toxicity of nutmeg seeds at high doses has been reported, mainly due to myristicin oil and elemicin, causing tachycardia, nausea, vomiting, agitation, and hallucinations. However, these effects are related to the abuse of the spice and are not observed at usual low concentrations [9]. There are many studies on the beneficial effects of nutmeg seed and various nutmeg seed extracts. One of the most prominent biological activities of the nutmeg preparations is antibacterial. Nutmeg seed lignans exert antimicrobial activity on Bacillus subtilis, Staphylococcus aureus, and Shigella dysenteriae[10]. Ethanol and acetone extracts of nutmeg crust have strong antibacterial activity against gram-positive bacteria Staphylococcus aureus [5]. Ethyl

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acetate extracts of flesh of the nutmeg fruit have inhibitory potential against both gram-positive and gram-negative bacteria with a minimum inhibitory concentration (MIC) ranging from 0.625 to 1.25 mg/mL [11]. Used for the preservation of sweets, nutmeg methanol extracts inhibit growth of Staphylococcus aureus, Aspergillus niger, Saccharomyces cerevisiae, and Escherichia coli at MIC between 250 and 300 mg/mL [12]. However, there are only a few studies on the biological activity of nutmeg essential oil. Takikawa et al. showed a higher antibacterial effect of essential nutmeg oil on pathogenic compared to non-pathogenic strains of Escherichia coli [13]. Furthermore, nutmeg essential oil decreased the growth and survival of Yersinia enterocolitica and Listeria monocytogenes in broth culture [14]. Nutmeg oil preparations are also known for their antioxidant capacity. Using the 2,2-diphenyl-1- picrylhydrazyl (DPPH) free radical scavenging assay, Piaru et al. reported a significant antioxidant activity of nutmeg oil [15]. The antioxidant properties are often related to the alleviation of inflammation. Nutmeg oil diminished chronic inflammation and pain through the inhibition of COX-2 expression and substance P release in vivo [16]. In another study, nutmeg oil suppressed reactive oxygen species (ROS) production in human neutrophils stimulated by PMA (phorbol 12-myristate 13-acetate) [17] and mildly inhibited phagocytosis in human neutrophils [18]. However, there is no published research on the effect of nutmeg seed essential oil on virus-triggered inflammatory response. Hydrodistillation is a popular method used for the preparation of essential oils. However, hydrodistillation with excipients is not widely used—we have found just three studies applying this method so far [19-21]. Therefore, we have applied magnesium aluminometasilicate in hydrodistillation as the new excipient and have tested its effects on the nutmeg essential oil yield and its composition [22]. Aluminometasilicate is widely used as a disintegrator in the manufacturing of tablets. Furthermore, this compound is non-toxic and inexpensive, as the price is ~300 eur for 25 kg. Magnesium aluminometasilicate has significantly increased both the yield and composition of some chemical compounds (sabinene, α-pinene, and limonene). The use of the excipient also increased the essential oil yield by about 61% (hydrodistillation with water—the yield is 0.79 ± 0.04 g, using 1% excipient—1.29 ± 0.05 g; the nutmeg quantity was 15 g, the water content was 300 mL) [22]. The increased amount of active substances suggests that oil preparations with aluminometasilicate might have stronger biological activities. Therefore, in this study we compared the antioxidant, antimicrobial, and anti-inflammatory properties of *Myristica fragrans* seed essential oil preparations with and without aluminometasilicate.

Figure 1: Nutmeg (*Myristica fragrans*)

PHYTOCHEMISTRY

The main constituents of M. fragrans are alkyl benzene derivatives (myristicin, elemicin, safrole, etc.), terpenes, alpha-pinene, beta-pinene, myristic acid, and trimyristin.[23] Myristicin (5-allyl-1-methoxy-2,3 (methylenedioxy benzene) is a flavoring plant constituent and has been known to produce significant psychopharmacological responses. [24] Mace contains a volatile oil 8-17 %, a fixed oil, resin, fat, sugar, destrin, and mucilage. The essential oil of mace is yellowish with the odor of mace and consists of macene.

PHARMACOLOGY

Antioxidant activity

Nutmeg possesses antioxidant activity due to the presence of various compounds including β-caryophyllene and eugenol, having hydrogen atoms in the allylic or benzylic positions. Because of the comparatively simple abstraction of atomic hydrogen from these functional groups, these compounds have high antioxidant activity. The abstraction of atomic hydrogen is done by peroxy radicals that produced under oxidative stress. In another view, role of Eugenol in nutmeg favors the antioxidant property by promoting the activities of superoxide dismutase, catalase, glucose-6-phosphate dehydrogenase, glutathione peroxidase and glutamine transferase enzymes [23]. The compounds having catechol like structure as in caffic acid are considered to be good antioxidants as they easily donate electrons or phenolic hydrogen to the acceptors, such as lipid peroxyl groups or reactive oxygen species. Calliste *et al*., (2010) stated that lignan derivatives are considered as a class of compounds that shows the antioxidant potential of nutmeg seeds [24]. After absorption of lignans and their glycosides into the body, they are metabolized to produce biologically active compounds having catechol structures that are responsible of high antioxidant property of nutmeg seeds.

Immuno-modulatory and radio-protective activities

The lignans present in fresh nutmeg and mace show radio modifying and immune modulatory properties, present in the aqueous extract of fresh nutmeg mace These properties found in cell free systems and protected PUC18 plasmid against radiation that induced DNA damage. The mammalian splenocytes in response to polyclonal T cell mitogen concanavalin A (Con A) proliferate. This process is inhibited by these mace lignans which was due to G1 phase of cell cycle and augmentation of apoptosis as presented by increase in pre G1 cells. The increase in activation of induced cell death by mace lignans was depending on the dosage. Splenocytes are protected by mace lignans against radiations. These radiations induced by producing intracellular reactive oxygen species depending on the dose. Mace lignans was not cytotoxic for lymphocytes. On the other hand, in splenocytes the radiation-induced DNA damage is inhibited by decreasing DNA fragmentation [25].

Antimicrobial activity

The essential oil and different extracts of aromatic plants have shown strong antimicrobial activity against variety of fungi as well as bacteria [26]. Narasimhan et al (2006) demonstrated the antibacterial activity by preparing chloroform extract of nutmeg against both gram negative and gram positive bacteria. They found myristic acid and trimyristin are the main antibacterial compounds extracted from nutmeg seeds. Researchers isolated three lignans (meso-dihydroguaiaretic acid, nectandrin-B and erythroaustrobailignan-6) showing antifungal activity, from the methanolic extract of nutmeg seeds [27]. The development of wheat leaf rust and rice blast was suppressed by these three lignans. Some compounds like carvacrol, γ-cymene, αpinene, β-pinene, and β-caryophyllene are reported to be antimicrobial present in essential oil of nutmeg seeds [28]. Some plant phenolics are also reported for antimicrobial activity. Antifungal and anti-inflammatory activities of plant essential oil are due to the presence of β-caryophyllene [29]. α-Pinene and β-pinene which are monoterpene hydrocarbons are also antimicrobial agents. They are considered to be involved in membrane disruption [30]. Carvacol is another significant compound for antimicrobial activity. Carvacol works in the same way as the other phenolic compounds, which work through membrane destruction, resulting in an increase in permeability of membrane to potassium ions and protons, proton-motive force disruption and intracellular ATP pool depletion. γCymene (a precursor of carvacrol) could also be an important component. It has been demonstrated that γcymene works synergistically with carvacrol in membrane enlarging, which results weakening of the membrane while alone shows weak antibacterial activity [31]. It has been proposed that antimicrobial activity is due to the minor and major both compounds; while it is feasible that the major compound controlled by other minor compounds [32].

Anti-carcinogenic and hepatoprotective activity

Nutmeg shows resistance against carcinogenic elements. Hussain and Rao, (1991) reported that, in Swiss albino mice uterine cervix, 3-methylcholanthrene -induced carcinogenesis could be prohibited by mace oral administration [33]. Nutmeg also shows hepato-protective activity. This property observed in rats with damaged liver, by giving nutmeg in their diets. Kyriakis *et al*., (1994) studied on the activities of hepatic carcinogen-metabolizing enzymes, like aryl hydrocarbon hydroxylase, cytochrome P450, and acid soluble sulphhydryl and glutathione-Stransferase level in albino mice and checked the influence of essential oil from nutmeg [34]. They found that the essential oil hinders the activities of the host enzymes related with detoxication and activation of xenobiotic components, as well as mutagens and chemical carcinogens.

Anti-inflammatory activity

Several authors reported anti-inflammatory activity of nutmeg as well as its oil [35]. Similar to non-steroidal anti-inflammatory drugs, pharmacological activities also exhibited by nutmeg oil [36]. But anti-inflammatory activity is shown only by petroleum ether extracts. The total extract of nutmeg activated an enzyme that is AMP-activated protein kinase enzyme (potential therapeutic target) for curing the metabolic syndrome including type-2 diabetes and obesitys. Seven compounds like tetrahydrofuroguaiacin B, 2,5-bis-aryl-

3,4-dimethyltetrahydrofuranlignans, fragransin C1, saucernetindiol, nectandrin B, verrucosin, galbacin and nectandrin A were isolated from this extract as an active constituents. Some of the isolated compounds produced strong AMPK stimulation in differentiated C2C12 cells, at 5μM concentration. Nutmeg and its active components not only used to treat type-2 diabetes and obesity but also for the development of agents other metabolic disorders [37-39].

CONCLUSION

Myristica fragrans is used for various medicinal properties. Nutmeg essential oil preparations with aluminometasilicate have stronger anti-inflammatory activity in Poly I:C-affected fibrolast cell culture. The oil with the excipient has a higher degree of cytoprotection from Poly I:C-induced necrosis, and both the oil and hydrolats with excipient more efficiently prevent IL-6 release compared to the preparations without aluminometasilicate. The fruit and seed extracts show various activities like hepatoprotective activity, anti-oxidant activity, memory enhancing activity, anticancer activity, aphrodisiac activity, anti-diabetic activity, antidepressant activity, hypolipidaemic and hypocholesterolemic effect, anti-microbial activity, anti-bacterial, anti-inflammatory and anticarcinogenic 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.

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