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Myristica fragrans Houtt.: Botanical, Pharmacological, and Toxicological Aspects

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Contents

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Abstract

Myristica fragrans is a fragrant tree, known for its commercial spicy products, namely, the nutmeg, mace, and essential oil, which are predominantly used in flavor, fragrance, and pharmaceutical industries. Being one of the popular spices in the culinary sector, the plant products are traditionally used in folk medicines for treating various human ailments. Its therapeutic potentials include antioxidant, anti-inflammatory, chemopreventive, anti-obesity, antiangiogenic, neuroprotective, analgesic, antithrombotic, antifeedant, hepatoprotective, insecticidal, aphrodisiac, radioprotective properties, and many more. Also, the plant is noted for its hallucinogenic or narcotic-like properties. The clinical evidences have suggested about the intoxication, poisonings, and adverse effects of *M. fragrans*. The present chapter provides a comprehensive information on the botanical, pharmacological, and toxicological aspects of *M. fragrans* products.

Keywords

Medicinal tree · Nutmeg · Plant products · Psychotomimetic agents · Spice

4.1 Introduction

Myristica fragrans Houtt. is an evergreen tropical tree possessing pleasant aroma and taste. *M. fragrans*, more commonly known as the nutmeg tree, possesses several medicinal importance and hence is an important commercial tree species (Sheeja et al. 2013). It belongs to the family, Myristicaceae, which contains about 120 species. *M. fragrans*, aboriginal to Banda Islands, Moluccas, in Indonesia, is well distributed throughout the Asian region, such as Malaysia, India, Sri Lanka, Papua New Guinea, the Caribbean, the Pacific Islands, and North Australia (Zachariah et al. 2008; Sheeja et al. 2013; Pandey et al. 2016; Swetha et al. 2017). Presently, two commercially significant products of *M. fragrans* are the nutmeg and mace, predominantly used as spice in preparation of sweet and savory dishes and drinks (Adjene and Igbigbi 2010). Nutmeg refers to the dried kernel of the ripe seed, while mace represents the dried aril surrounding the seed. Nutmeg seed is reported to be slightly sweeter than mace, which makes it a preferred spice in food preparation (Rema and Krishnamoorthy 2012). In addition to nutmeg and mace, the extracts of *M. fragrans* like nutmeg butter, oleoresins, and essential oils are also commercially used, primarily in flavor, fragrance, and pharmaceutical industries (Rema and Krishnamoorthy 2012).

Besides, being a popular spice in the culinary sector, *M. fragrans* is also traditionally utilized in different forms of common medicines for treating several diseases. In India, nutmeg seed oil is used for treating intestinal disorders, stomach cramps, and flatulence. In Indonesia and Malaysia, nutmeg is being used as tonic after child birth, as mean of inducing menses and abortion (Gupta and Rajpurohit

2011; Lim 2012). In traditional Arabian medicine, nutmeg is used to treat colds, fever, and stimulant digestive, tonic, aphrodisiac, and general respiratory complaints (Lim 2012). Aroma from nutmeg and mace are said to act as stress relievers, and even they are incorporated in ventilation systems. For example, in some Japanese companies, they are used to improve the work environment. Nutmeg butter (in the form of ointment) is used as a mild external stimulant to treat sprains and paralysis (Rema and Krishnamoorthy 2012). Other known traditional usages of nutmeg and mace include the treatment of hemorrhoids, chronic vomiting, cholera, rheumatism, psychosis, fever, nausea, and anxiety in many parts of the worlds. Considering the commercial importance of *M. fragrans*-derived natural products, the present chapter provides the comprehensive information on the botanical, pharmacological, and toxicological aspects of *M. fragrans* products.

4.2 Botanical Descriptions

M. fragrans is a bushy, average- to large-sized, fragrant perennial tree, which habitually grows about 5–13 m height and sometimes reaches up to 20 m (Lim 2012). It possesses brown- to red-colored soft bark that flakes off in tinny sheets or bulky plates (Nagja et al. 2016). The bark exudes watery pink/red sap, when injured. The leaves (5–15 cm × 2–7 cm) are alternately arranged along the branches, pointed, dark green-colored, and abided on leaf stems at about 1 cm long. The leaves are shiny on the superior portion, the veins are pinnate and free, and the blades are densely pubescent or fully glabrous. The branching pattern of this tree is horizontal radiating in whorls from the trunk (Nagja et al. 2016). The fragrant flowers of *M. fragrans* are dioecious, creamy yellow in color, fleshy, waxy, and bell-shaped. The male flowers are 5–7 mm long and form in groups of 1–10, while female flowers grow up to 1 cm long and are found in groups of 1–3. Female flowers contain single-celled ovary having one basal ovule. Occasionally, both sexes (male and female) are noticed on the same tree.

Fruits of *M. fragrans* are yellow colored, globose with fleshy pericarp that splits into two halves on maturity, revealing a bright red, fringed fleshy, leathery coating on the outside of the seed (Gils and Cox 1994; Ding 2015). These red arils are dried and commercially traded as mace, a spice used in cooking all over the world (Gils and Cox 1994). The seeds are broadly ovoid and hard, measuring between 2 and 3 cm length with a glistening murky brown and longitudinally furrowed shell (Lim 2012). The shiny brown seed and the kernel are commercially known as nutmeg, another popular culinary spice. The kernel consists of a minute embryo and ruminate endosperm, which holds several veins that contain the essential oil, which is significant to the pharmaceutical industry (Parry 1962; Lim 2012). The aromatic nutmeg is often reported to give a warm, slightly bitter taste (Gils and Cox 1994). For pollination and fruit setting in *M. fragrans,* both the male and female type trees are required. The seedlings reveal their sex at first flowering at around 7–9 years old, reaching its peak at around 20 years (Gupta and Rajpurohit 2011). The fruiting continues up to 90 years. They usually bear fruit all year round; however main harvestings take place in April and November months (Gils and Cox 1994). A healthy

single *M. fragrans* tree is able to produce an average of 3000–4000 nuts per year at the age of 25, with some exceptional occurrences where 8000 fruits or more fruits collected within 1 year (Ding 2015). The world production of nutmeg is estimated to be around 10,000–12,000 tons per year, while production of mace is estimated to be about 1500–2000 tons (Gupta and Rajpurohit 2011).

4.3 Pharmacological Aspects

M. fragrans is famous for its diverse bioactivities, especially in pharmacological and culinary aspects. Many parts of this plant are being recognized to have many therapeutic potentials, such as anti-obesity (Nguyen et al. 2010), anti-inflammatory (Jin et al. 2005; Cao et al. 2013), antiangiogenic (Al-Rawi et al. 2011), neuroprotective (Jin et al. 2005), analgesic, antithrombotic (Olajide et al. 1999), antifeedant (Kostic et al. 2013), hepatoprotective (Morita et al. 2003; Kareem et al. 2013), and larvicidal (Senthilkumar et al. 2009; Ashokan et al. 2017; Gomes et al. 2018) activities that are frequently cited in literatures. Among all the bioactivities exhibited by *M. fragrans*, antioxidant (Jin et al. 2005; Sulaiman and Ooi 2012; Gupta et al. 2013) and antimicrobial (Sulaiman and Ooi 2012; Pillai et al. 2012; Gupta et al. 2013; Sojic et al. 2015; Rodianawati et al. 2015) properties are mostly documented. The pharmacological potential, bio-active compounds, and bioactivities of *M. fragrans* have been summarized in tabular form (Table 4.1).

4.3.1 Anti-obesity and Antidiabetic Activity

Type 2 diabetes mellitus is the most common diabetes, i.e., nearly 90% of the people diagnosed for diabetes around the world are having type 2 diabetes mellitus (WHO 1999). Despite all the awareness created, the number of people diagnosed with type 2 diabetes has been increasing tremendously and is now one of the major epidemic health problems. The ethanol extract of *M. fragrans* (nutmeg) is documented to have AMP-activated protein kinase (AMPK)-activating property. Among seven active constituents isolated, tetrahydrofuroguaiacin B, nectandrin B, and nectandrin A possessed strong AMPK stimulation in differentiated C2C12 cells. AMPK activators are useful in the treatment of metabolic syndromes including obesity and type 2 diabetes (Nguyen et al. 2010). In another study by Han et al. (2008), type 2 diabetes mice were orally administered with macelignan (10 mg/kg) from *M. fragrans* seed kernels for 14 days, and the investigation revealed a significant reduction of serum glucose level in the treated mouse models. Subsequently, another review on Sri Lankan siddha medicine noted various parts of *M. fragrans* owning antidiabetic potential and its broad preparation methods in traditional medicine (Sathasivampillai et al. 2017).

Table 4.1 Various pharmacological potential effects of *M. fragrans*

Plant part	Pharmacology	Bio-active compound(s)	Potential effect	References
Nutmeg (dried kernel)	Anti-obesity	Tetrahydrofuroguaiacin B Saucernetindiol Verrucosin Nectandrin B Nectandrin A Fragransin C1 Galbacin	Tetrahydrofuroguaiacin B, nectandrin B, and nectandrin A gave strong AMP-activated protein kinase (AMPK) stimulation in differentiated C2C12 cells Preventive effect of a tetrahydrofuran mixture (THF) on weight gain in a diet-induced animal model	Nguyen et al. (2010)
Nutmeg oil	Antiangiogenic	NA	Oil inhibits the blood vessel formation in rat aorta minimize tumor angiogenesis	Al-Rawi et al. (2011)
Aril (mace) Seed kernel (endosperm) Shell (seed coat) Fleshy pericarp (husk)	Antioxidant Antibacterial	Macelignan	Aril, seed kernel, and shell had high total phenolic content with shell extract having greatest primary antioxidant, by having the highest FRAP activity, β-carotene-bleaching activity, and DPPH scavenging activity Only the aril and seed kernel extracts had antibacterial activity to inhibit the food-borne bacteria with MIC at 50 mg/mL, against *S. aureus* (ATCC12600) and *B. cereus* (ATCC10876)	Sulaiman and Ooi (2012)
Nutmeg (Commercial product: Milex Co., Ltd, Novi Sad, Serbia)	Microbial and oxidative stability	NA	Better microbial and oxidative stability Essential oil at 20 ppm lower aerobic mesophilic bacteria in stored sausages and the TBRS values significantly lower than control	Sojic et al. (2015)
Nutmeg (matured seed extract)	Antioxidant and antimicrobial	α-Pinene, β-pinene Myrcene, 1,8-cineole Carvacrol, terpinen-4-ol Eugenol, isoeugenol	Acetone extract has the highest antioxidant activity (DPPH scavenging activity, chelating activity and β-carotene bleaching) Acetone extract was able to exert antimicrobial activity against *S. aureus* and *A. niger*	Gupta et al. (2013)

(continued)

Table 4.1 (continued)

Plant part	Pharmacology	Bio-active compound(s)	Potential effect	References
Nutmeg	Antifungal	Oleoresin (essential oil and resin mixture)	Able to inhibit *A. niger*, *F. oxysporum*, *P. glabrum*, *R. oryzae*, and *M. racemosus*	Rodianawati et al. (2015)
Leaves (aerial parts)	Antibacterial activity	Sabinene α-Pinene α-Thujene	Essential oil showed antibacterial effects against *Listeria monocytogenes* in brain-heart infusion broth Combination of essential oil and nisin showed synergetic effects and MIC and MBC were decreased. Further decrease in pH, increased the antibacterial effects	Rahnama et al. (2012)
Seeds	Antioxidant Radioprotective	elemicin 4-terpineol Myristicin *Trans*-sabinene hydrate	Results of DPPH assay demonstrated elemicin as most potent antioxidant compound, while AAV suggested 4-terpineol as effective antioxidant Radioprotective ability on plasmid DNA protection assay	Adiani et al. (2015)
Nutmeg	Anticariogenic	Macelignan	Inhibitory activity against *S. mutans*, at concentration 20 μg/ml completely inactivated *S. mutans* within 1 min	Chung et al. (2006)
Dried fruits	Anticariogenic	NA	Methanolic extract exhibited inhibitory effect against Gram-positive bacteria *E. faecalis* and *S. mitis*	Singh et al. (2017)
Flesh Seed Mace	Anticariogenic Antibacterial	NA	Inhibitory effect against *S. mutans*, *S. mitis*, *S. Salivarius*, *A. actinomycetemcomitans*, and *P. gingivalis*	Shafiei et al. (2012)
Nutmeg (seed kernel) essential oil	Anti-parasitic	NA	Significant inhibiting activity (IC_{50} value of 24.83 μg/mL) against *Toxoplasma gondii* parasite and low cytotoxic activity (EC_{50} value of 24.45 μg/ml) against Vero cells line	Pillai et al. (2012)
Commercial essential oil of *M. fragrans*	Antifeedant activity	α-Pinene, sabinene β-Pinene, limonene Myristicin	High antifeedant activity against Gypsy moth *Lymantria dispar*	Kostic et al. (2013)

Nutmeg essential oil	Fumigant	*Major compounds*: Sabinene 4-Terpineol Myristicin	30 µl/l of essential oil and exposure time of 24 h produced 100% mortality of adults *C. maculatus*	Alibabaie and Safaralizadeh (2015)
Leaves	Larvicidal, pupicidal, and insecticidal (adult) Anticancer properties	Green synthesized zinc oxide nanoparticles (ZnO nanorods)	Effective against *A. aegypti* young instars, with LC_{50} ranging from 3.44 ppm (larva I), 14.63 ppm (pupa) to 15.00 ppm (adult) Dose-dependent cytotoxicity against human hepato-cancer cells	Ashokan et al. (2017)
Seeds	Larvicidal Adulticidal	*Major compounds*: Sabinene	Larvicidal and adulticidal activity against *A. aegypti* Larval mortality at LC_{50} was 28.2 µg/ml Adult mortality at IC_{50} was 4510 µg/ml	Gomes et al. (2018)
Seeds	Antimalarial, larvicidal activity	NA	Ethanolic extract in mixture with several medicinal plants exhibited larvicidal and adulticidal activities against larvae and adults of *A. stephensi*	Senthilkumar et al. (2009)
Nutmeg (dried ripe seed)	Anti-inflammatory Chemopreventive activity	(*Neolignans*) Licarin 30-Methoxylicarin B Myrisfrageal A Isodihydrocainatidin Dehydrodiisoeugenol Myrisfrageal B	Inhibition of NO production in LPS-activated murine monocyte-macrophage RAW264.7 Myrisfrageal A, myrisfrageal B, and dehydrodiisoeugenol suppressed LPS-induced iNOS mRNA expression in RAW 264.7 cells in a dose-dependent manner	Cao et al. (2013)
Dried seed kernels	Neuroprotective	Macelignan	ROS production and neurotoxicity induced by glutamate in HT22 cell were significantly attenuated Potential anti-inflammatory agents and antioxidants in neurodegenerative diseases	Jin et al. (2005)
Nutmeg (seeds)	Anti-inflammatory Analgesic and antithrombotic activity	NA	Possesses anti-inflammatory properties by inhibiting the carrageenan-induced rat paw edema Strong analgesic and antithrombotic effect on rodents	Olajide et al. (1999)

(continued)

Table 4.1 (continued)

Plant part	Pharmacology	Bio-active compound(s)	Potential effect	References
Mace (dried arils)	Anticarcinogenic and chemopreventive properties	NA	Ability to modulate hepatic xenobiotic-metabolizing enzymes in the F1 progeny of Swiss albino mice F1 pups showed significant increase in hepatic sulfhydryl and cytochrome b5 content Elevated glutathione S-transferase and glutathione reductase activities were also detected	Chhabra and Rao (1994)
Leaves	Antimutagenic and antioxidant	NA	Induced apoptosis of Jurkat leukemia T-cell line in a mechanism involving SIRTI mRNA downregulation	Akinboro et al. (2011)
Seeds	Cytotoxicity Antitumor activity	(*Lignans*) *Meso*-(DHGA) macelignan Fragransin A_2 Nectandrin B	DHGA exhibited potent cytotoxicity against H358 with IC50 value of 10.1 lM DHGA showed antitumor activity in allogeneic tumor-bearing mice model	Thuong et al. (2014)
Nutmeg (seeds)	Antibacterial activity	Malabaricone C	Sialidase inhibitory activity in *S. pneumoniae* sialidases (NanA, NanB, and NanC)	Park et al. (2017)
Seed kernels	antidiabetic	Macelignan	Oral administration of macelignan at 10 mg/kg caused significant reduction of serum glucose on type 2 diabetes mouse models Enhanced insulin sensitivity and improved lipid metabolic disorders by activating PPARα/γ and attenuating ER stress	Han et al. (2008)
Nutmeg (dried kernel)	Aphrodisiac activity	NA	Stimulates mounting behavior and increases the mating performance of male mice devoid of general short-term toxicity	Tajuddin et al. (2003)
Nutmeg (dried kernel)	Aphrodisiac activity	NA	Increased the mounting frequency, intromission frequency, and intromission latency and caused significant reduction in the mounting latency and postejaculatory interval	Tajuddin et al. (2005)

Dried seed kernels	Atopic dermatitis treatment	NA	Oral administration of nutmeg extract on atopic dermatitis on NC/Nga mice treated with American house dust mite (*D. farinae*) extract suppressed the prevalence of atopic dermatitis	Chung et al. (2012)
Seed	Memory-enhancing activity	NA	Improved learning and memory of young and aged mice Reversed scopolamine- and diazepam-induced impairment in learning and memory of young mice	Parle et al. (2004)
Seed	Anticholinesterase properties	Compounds 8, 2, and 11	Significant anticholinesterase properties for Alzheimer's disease treatment	Cuong et al. (2014)
Seed	Anticholinesterase properties	NA	5 mg/kg for 3 successive days administered to young male Swiss albino mice significantly decreased acetylcholinesterase activity in the brain	Dhingra et al. (2006)
Nutmeg essential oil	Hepatoprotective activity	Myristicin	Potent hepatoprotective activity by suppressing LPS/D-GalN-induced enhancement of serum TNF-α concentrations and hepatic DNA fragmentation in mice	Morita et al. (2003)
Fresh nutmeg	Hepatoprotective and antioxidative agent	NA	Inhibited the ISO-induced changes in the activities of hepatic marker and antioxidant enzymes in plasma and heart tissue along with lipid peroxidation levels in rat	Kareem et al. (2013)

NA not available

4.3.2 Neuroprotective Potential

Macelignan isolated from the dried seed kernels of *M. fragrans* could significantly decrease neurodegenerative diseases by slowing down neuroinflammation and oxidative damages at the cellular level. Jin et al. (2005) examined the neuroprotective activity of macelignan in murine hippocampal HT22 cell line. They used glutamate to induce neurotoxicity, which was measured by recording reactive oxygen species (ROS) levels. The investigation demonstrated that the ROS formation in HT22 cell was significantly attenuated by macelignan. Moreover, macelignan was previously reported to suppress the expression of cyclooxygenase-2 and inducible nitric oxide synthase that reduces nitric oxide (NO) synthesis in lipopolysaccharide (LPS)-treated microglial cells. These results recommended macelignans are potential anti-inflammatory agents and antioxidants, which could slow down the advancement of neurological illnesses comprising Alzheimer's disease (Gibson and Zhang 2001).

4.3.3 Anti-inflammatory Activity

Several researchers have investigated the anti-inflammatory properties of *M. fragrans* (Olajide et al. 1999; Jin et al. 2005; Cao et al. 2013). The chloroform extract of *M. fragrans* seeds was shown to have anti-inflammatory property, which was noticed from the inhibition of the carrageenan-induced rat paw edema (Olajide et al. 1999). The investigator also noted analgesic, antithrombotic activity in rodents. In another report, the neolignans extracted from ripe seeds of *M. fragrans* were stated to inhibit the NO production in LPS-activated murine monocyte-macrophage RAW264.7 (Cao et al. 2013). A study by Jin et al. (2012) isolated six benzofuranoid neolignans, namely, 30-methoxylicarin B, licarin B, myrisfrageal A, dehydrodiisoeugenol, isodihydrocainatidin, and myrisfrageal B, from the chloroform extract of nutmeg. Also, they assessed these compounds for NO inhibitory properties. The study stated all compounds showed the suppression of NO production in LPS-induced murine monocyte. In particular, myrisfrageal A, myrisfrageal B, and isodihydrocainatidin inhibited LPS-prompted iNOS mRNA expression, which was dose-dependent as determined using the RT-PCR (real-time reverse transcription-polymerase chain reaction) analysis. Further, Cao et al. (2013) revealed from the cytotoxicity test that all isolated compounds were shown to exert no cytotoxicity up to 100 μM concentration in RAW 264.7 cells. The cell viability was found to be above 95% for all compounds tested, which clearly indicates that cell growth is not affected by the compounds.

4.3.4 Anticarcinogenic and Chemopreventive Properties

Natural plant-derived compounds contain anticancer and chemopreventive properties effective in inhibition of cancer cells lines (Greenwell and Rahman 2015). *M. fragrans* has been documented to have anticarcinogenic and chemopreventive

properties by several researchers (Chhabra and Rao 1994; Chirathaworn et al. 2007; Akinboro et al. 2011; Thuong et al. 2014). Mace, the aril of *M. fragrans* in particular has been investigated and shown to exhibit chemopreventive actions against chemical carcinogens (Jannu et al. 1991; Hussain and Rao 1991).

Chhabra and Rao (1994) examined the possible transfer of the bio-active compound of *M. fragrans* mace via the transmammary route and the capability to moderate hepatic xenobiotic-metabolizing enzymes in the F1 progeny of Swiss albino mice. The investigation revealed that F1 pups showed a significant increase in hepatic sulfhydryl and cytochrome b5 content. An elevated glutathione reductase and glutathione S-transferase activities were detected in F1 pups. The xenobiotic-metabolizing enzymes give protection against harmful environmental conditions including carcinogens. The ability of mace to modulate enzymes in regard to activation and detoxication of carcinogens has potential to inhibit tumor formation. In another report, *M. fragrans* methanolic extract at 50 and 100 μg/ml concentrations significantly inhibited Jurkat human leukemia T-cell line multiplication and prompted apoptosis as detected by annexin V staining. The downregulation of SIRT1 mRNA expression in Jurkat cells was observed at a minimal amount of methanol extract, i.e., 10 μg/ml. These anticancer properties could be attributed to myristicin, which has cell inhibition property via apoptosis in human neuroblastoma SK-N-SH cells (Chirathaworn et al. 2007). Following that, Akinboro et al. (2011) evaluated effectiveness of *M. fragrans* in suppressing cyclophosphamide (CP)-induced cytotoxicity and chromosomal damages in *Allium cepa* L. cells in vivo. The freeze-dried water extract from the leaves of *M. fragrans* was subjected to mutagenic and antimutagenic effect tests. The water extract alone, as well in combination with CP, suppressed cell division and encouraged chromosomal aberrations. The observed effects on cell division and chromosomes of *A. cepa* may be intertwined with the antioxidant properties and demonstrates mitodepressive and antimutagenic potentials of *M. fragrans*. This suggests that it is desirable to be used as an anticancer agent.

Thuong et al. (2014) investigated lignans extracted from Vietnamese nutmeg for their cell toxicity property against different cancer cells. The lignans extracted were *meso*-dihydroguaiaretic acid (DHGA), fragransin A2, macelignan, and nectandrin B. The experimentation revealed that DHGA presented a potent cell toxicity against cell line, H358 with IC_{50} value of 10.1 μM. Also, the same study showed antitumor potential of DHGA against allogeneic Sarcoma 180 tumor-bearing mice model. Previously, DHGA from *M. fragrans* was also reported to exhibit cytotoxic activities against lung carcinoma cells (A549) (Davis et al. 2009). Subsequently, a separate investigation demonstrated the dose-dependent cytotoxicity of *M. fragrans*-synthesized ZnO nanorods against human hepato-cancer cells (HepG2). *M. fragrans* extract was used as a stabilizing and reducing agent to produce ZnO nanorods, which were shown to inhibit the proliferation of cancer cells with IC_{50} value of 22 and 20 mg/ml after 24 and 48 h of incubation, respectively. In specific, they triggered the induction of apoptosis (Ashokan et al. 2017).

4.3.5 Antiangiogenic Properties

Nutmeg oil extracted from *M. fragrans* was shown to have significant antiangiogenic effects at 200 μg/ml concentration. Antiangiogenesis is stimulated to hinder the formation of new blood vessels in tumor to suppress its growth. Moreover, the oil exhibited non-cytotoxic effect, when observed using 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide assay, which is highly desired in pharmacology and new drug discoveries (Al-Rawi et al. 2011).

4.3.6 Antioxidant Activities

The methanol extracts of aril (mace), seed kernel, and shell of *M. fragrans* fruit were documented to have antioxidant activity as revealed by β-carotene-bleaching activity, the high ferric reducing antioxidant power (FRAP) activity, and 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging activity assays. Additionally, the pericarp extract from the fruit exhibited secondary antioxidant activities as a metal chelator (Sulaiman and Ooi 2012). In another report, different solvents were used to extract bio-active compounds from nutmeg seeds (Gupta et al. 2013). Among all the solvents, acetone was found to be effective in extracting higher content of phenolics, i.e., 93.12 ± 1.48 mg GAE (gallic acid equivalents)/100 g. The extract recorded superior DPPH scavenging activity (63.04% ± 1.56%), chelating activity (64.11% ± 2.21%), and inhibition of β-carotene bleaching (74.36% ± 1.94%). Later, Adiani et al. (2015) evaluated antioxidant properties of some of the specific bioactive compounds, namely, elemicin, myristicin, 4-terpineol, and *trans*-sabinene hydrate, occurring in nutmeg essential oil. Among them, elemicin was observed to be effective as antioxidative agent as revealed by DPPH assay. Interestingly, 4-terpineol showed higher total antioxidant activity due to its higher abundance in the oil. To date, the specific nature of each constituent that contributes to the antioxidant activity of nutmeg essential oil remains unclear. For a more conclusive perspective, guided isolation and identification of major constituents of the nutmeg essential oil may be necessary.

This antioxidative nature of nutmeg is highly beneficial in increasing the health benefit and prolonging the shelf life of foodstuff. Dorman et al. (1995) demonstrated that the essential oil of nutmeg blocks lower lipid oxidation in chicken tissue homogenates and egg yolk fat. Later, Sojic et al. (2015) in Serbia examined the effect of adding essential oil on the oxidative stability in cooked sausages during refrigerated storage. It was validated that essential oil at 20 ppm significantly lowered thiobarbituric acid-reactive substances after 60 days of storage at 4 °C. Further, tests on color, sensory properties of aroma, and taste on stored sausages revealed essential oil at 20 ppm showed better quality as compared to the control. The discoloration occurs due to interaction of pigments with the products of lipid oxidation (Kulkarni et al. 2011), which could further alter the taste and aroma. It is noteworthy to mention that the cooked sausages make up to nearly half of the entire commercial manufacture of meat in Serbia (Sojic et al. 2011). Thus, supplementing nutmeg

essential oil in the meat can improve the efficiency of sausage making, delivery, and storage.

4.3.7 Radioprotective Activity

M. fragrans is cited in few reports with radioprotective activity. Checker et al. (2008) have revealed that the occurrence of macelignans in nutmeg aqueous extract is known to exhibit both immunomodulatory and radio-modifying properties in mammalian splenocytes. Macelignans inhibited the proliferation of splenocytes by arresting cell cycle at G1 phase and augmenting apoptotic activity. Adding to that, macelignans repressed the secretion of IL-2, IL-4, and IFN-γ cytokines in a dose-dependent manner. In another report, it was shown that macelignans protected immortalized human keratinocytes (HaCaT) from damages caused by UV-B light (Anggakusuma et al. 2010). The concentration between 0.1 and 1 μM was shown to increase the viability of HaCaT cells irradiated with UV-B source. Furthermore, cyclooxygenase expression and matrix metalloproteinase secretion were suppressed in a dose-dependent manner. Similar, suppressive effect was also observed in the signal transduction network, where decreased stimulation of UV-B-encouraged mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase (PI3K) pathway, and their downstream transcription factors were noted. Later, Adiani et al. (2015) reported the radioprotective effects of nutmeg seeds essential oil as revealed by plasmid (pBR322) DNA protection assay.

4.3.8 Anti-parasitic Activity

The essential oil derived from nutmeg of *M. fragrans* showed a comparable anti-parasitic activity against *Toxoplasma gondii*. Further, the same investigation also revealed the low toxicity of the essential oil on Vero cell lines (Pillai et al. 2012). These findings highlight the possible use of nutmeg essential oil in the formulations of pharmaceutical drugs against parasites.

4.3.9 Antibacterial and Antifungal Activity

The development of new drugs from natural resources is often needed to combat diseases caused by drug-resistant microbes (Swamy et al. 2016).The biochemical compounds extracted from natural resources have been frequently reported to possess antimicrobial property by destabilization and disruption of cellular membranes (Ultee et al. 1999; Dorman and Deans 2000). The acetone extract of nutmeg showed a robust antimicrobial activity against Gram-positive bacterium *Staphylococcus aureus* and pathogenic fungus *Aspergillus niger* (Gupta et al. 2013). Correspondingly, Park et al. (2017) reported malabaricone C isolated from seeds of *M. fragrans*, a novel inhibitor of *Streptococcus pneumoniae*, encoding sialidases, NanA, NanB,

and NanC, responsible for causing respiratory tract infections, septicemia, and meningitis. Sialidases remove sialic acid from the host cell surface glycans, expose receptors, and facilitate in the process of bacterial adherence and colonization. Hence, sialidases are the central virulence factor of pathogenic bacteria (Xu et al. 2011). In another report, oleoresin obtained from the nutmeg of *M. fragrans* reported to withstand high temperatures up to 180 °C without affecting the antifungal properties (Cowan 1999). The oleoresin demonstrated antifungal effect by inhibiting the growth of *A. niger*, *Fusarium oxysporum*, *Penicillium glabrum*, *Rhizopus oryzae*, and *Mucor racemosus* (Rodianawati et al. 2015). This permits addition of oleoresin as natural preservative in food processing without causing unwanted side effects to health. Similarly, antibacterial properties of *M. fragrans* were frequently cited in culinary sector. Sulaiman and Ooi (2012) reported that the aril and seed kernel extracts (80% methanol) inhibit the food-borne bacteria with a lowest minimum inhibition concentration (MIC) of 50 mg/ml against *Staphylococcus aureus* (ATCC12600) and *Bacillus cereus* (ATCC10876). This paves way for possibility employment of the aril and seed kernel extracts as natural food preservative. Subsequently, Sojic et al. (2015) documented essential oil derived from nutmeg to give low counts of mesophilic bacteria in cooked sausages, added with essential oil during processing. After storage at 4 °C for 60 days, sausages treated with essential oil gave 78.3 colony-forming unit (CFU)/g bacterial count, which was significantly lower than the control sausages at 185 CFU/g. Moreover, the treated sausages did not record any signs of *Enterobacteriaceae*, *E. coli*, *Clostridium* spp., yeasts, and molds growth (Firouzi et al. 2007; Gupta et al. 2013). In another study, essential oil extracted from aerial parts of *M. fragrans* was reported to have antibacterial properties against *Listeria monocytogenes* grown in brain-heart infusion broth. The essential oil was added either alone or in combination with 5 μg/ml nisin to the broth. Under both conditions, the inhibitory effect against this bacterium was noted. Furthermore, the synergetic effects of *M. fragrans* essential oil and nisin were observed on *L. monocytogenes*. Their combined effect caused a decrease in the MIC and minimum bactericidal concentration (MBC) on *L. monocytogenes*. Further decrease in pH revealed the increase of antibacterial effect (Rahnama et al. 2012). Often, the usefulness of natural antimicrobial agents is examined alone and in combination with other available preservatives to elucidate their synergetic effects. Nisin, in previous literature, is documented to have synergistic effect in inhibiting bacterial growth and increasing antibacterial effects (Misaghi and Basti 2007). Such inhibitory effects of natural compounds with essential oils are safe and significant to food industries to replace harsh chemical preservatives (Ettayebi et al. 2000; Yamazaki et al. 2004).

4.3.10 Insecticidal Properties

Insects are among the major pests, causing a considerable damage to economically important food crops. The chemical-based insecticides are often used for pest control; however resistant insect strains, residual toxicity, safety, and cost of the

treatment necessitate the innovative alternatives for a sustainable pest management (Yildirim et al. 2001). *M. fragrans* contains insecticidal properties, enabling greener pest management strategy (Kostic et al. 2013; Alibabaie and Safaralizadeh 2015). The essential oils obtained from *M. fragrans* were also reported to have high antifeedant (AF) properties (AF index of 85–90%) and low toxicity against larvae of *Lymantria dispar* (gypsy moth) in the laboratory (Kostic et al. 2013). Results indicate that essential oil is very appropriate for the integrated pest management program. Essential oils are often referred to as natural defense mechanism by plants against insects and pests. The complex mixtures of the oils have synergistic effect and at times are more efficient than the pure compound-based pesticides derived from natural sources (Hori 1998; Kostic et al. 2013). Essential oil antifeedant properties do not affect nontarget organisms and environment due to their little noxiousness and can be incorporated to integrated pest management (Schumutterer 1985; Kostic et al. 2013). Subsequently, essential oil of *M. fragrans* was experimented as a fumigant against bean pest. The study showed the essential oil extracted from nutmeg seeds at concentration of 30 µl/l and exposure time of 24 h produced 100% mortality to *Callosobruchus maculatus* adults. Moreover, mortality rate of *C. maculatus* increased as the exposure time and oil concentration increased (Alibabaie and Safaralizadeh 2015). *C. maculatus*, commonly known as cowpea seed beetle, is an agricultural pest, causing considerable economic loss by damaging seeds in storage. Monoterpenes, found in essential oils, are able to inhibit acetylcholinesterase activity in the nervous system causing death in insects (Houghton et al. 2006). Natural fumigant eradicates insect pests without unwanted side effects such as insect resistance and residual toxicity on consumers. Adding on to that, Ashokan et al. (2017) reported green synthesized zinc oxide nanoparticles (ZnO nanorods) of *M. fragrans* (leave extract) effective against *Aedes aegypti* young instars, with LC_{50} ranging from 3.44 ppm (larva I), 14.63 ppm (pupa) to 15.00 ppm (adult). *Aedes* mosquitos are major cause of vector-borne diseases such as dengue virus (*DENV*), chikungunya virus (*CHIKV*), and Japanese encephalitis virus (*JEV*) in tropical countries, such as Malaysia. Larvicidal, pupicidal, and insecticidal (adult) properties of *M. fragrans*-synthesized ZnO nanorods allow integrated biological control and are biodegradable and not harmful against nontarget organisms. Similarly, another study by Gomes et al. (2018) demonstrated the highest larval mortality was observed in essential oils of *M. fragrans* with LC_{50} = 28.2 µg/ml against Zika virus vectors in comparison with *Illicium verum* and *Pimenta dioica. M. fragrans* was also documented for its antimalarial activity in Thai folk's medicine (Thiengsusuk et al. 2013). Another study by Senthilkumar et al. (2009) noted seeds ethanolic extract in mixture with several medicinal plants of India exhibiting larvicidal and adulticidal activities against larvae and adults of *Anopheles stephensi*, a Malarial Vector. 80% and 100% larval mortality documented with malformation in adult mosquitoes. Furthermore, larvae showed significant decrease in protein, carbohydrate, and lipids levels.

4.3.11 Aphrodisiac Properties

M. fragrans often documented as aphrodisiacs in traditional medicine practices to enhance sexual wellbeing in human from ancient times (Tajuddin et al. 2003, 2005; Rema and Krishnamoorthy 2012). Correspondingly, several researchers have reported increased sexual behavior in animal models when treated with *M. fragrans*. Tajuddin et al. (2003) investigated mounting behavior, mating performance, and general short-term toxicity ethanolic extracts of nutmeg at 500 mg/kg on male Swiss mice. Investigation exhibited treated Swiss mice displaying excessive mounting behavior and mating performance without gross behavioral changes as compared to control. The author described the enhanced sexual behavior of animals may be attributed to the nervous stimulating property of this herb. Subsequently, Tajuddin et al. (2005) studied the sexual functions of Wistar strain albino rats in terms of general mating behavior, libido, and potency. The investigation exhibited improved sexual behavior of treated male rats significantly increasing the mounting frequency and intromission frequency while reducing the mounting latency and postejaculatory interval. Furthermore, mounting frequency after penile anesthetization significantly improved erections, long flips, quick flips, and the aggregate of penile reflexes with penile stimulation. Mounting frequency after penile anesthetization can be considered as reliable index of "pure" libido test while the penile reflexes as a good model of "pure" potency as often defined by previous researchers (Davidson 1981). In contrast, Agarwal et al. (2009) reported nutmeg oil to have antifertility and recovery effect on male reproductive functions in Wistar strain rats.

4.3.12 Skin Care Properties

M. fragrans has been documented containing skin care properties by several research groups (Lee et al. 1997, 1999; Cho et al. 2008). Melanin, a natural pigment, determines the color of our skin according to its intensity of expression. Melanin is crucial in protecting our skin against the harmful ultraviolet radiation and oxidative stress from countless environmental contaminants. Nevertheless, when melanin is produced excessively, it may cause severe dermatological complications ranging from freckles, age spots (solar lentigo), melasma, to cancer (Pillaiyar et al. 2017). *M. fragrans* was one of the numerous plant extracts tested, showing inhibitory against mushroom tyrosinase activity (Lee et al. 1997). Melanin synthesis is controlled by tyrosinase, a vital enzyme in melanogenic pathway that can be utilized to treat various skin conditions (Zaidi et al. 2018). Besides that, *M. fragrans* plant methanol extract exhibited more than 65% of inhibition of elastase activity. The extract recorded IC_{50} of 284.1 mg/ml on human leukocyte elastase activity of (Lee et al. 1999). Subsequently, Cho et al. (2008) demonstrated that macelignans of *M. fragrans* inhibited melanogenesis and enzymes related to it, including tyrosinase in murine melanocytes. This investigation revealed macelignan significantly decreased tyrosinase, TRP-1, and TRP-2 protein expression. The author suggested

macelignan as effective inhibitor of melanin biosynthesis and can be used as new skin whitening agent. In another study, oral administration of nutmeg extract on atopic dermatitis was evaluated on NC/Nga mice. Atopic dermatitis-like skin lesions were induced using American house dust mite (*Dermatophagoides farinae*) extract. Application of nutmeg extract suppressed transepidermal water loss, erythema, and the production of serum immunoglobulin E, interleukin (IL)-4, and interferon-γ by auxiliary lymph node cells. Significant reduction on epidermal thickening and inflammatory cell infiltration into the skin were observed. This study recommended nutmeg extract as a potential nutraceutical candidate for treatment of atopic dermatitis (Chung et al. 2012).

4.3.13 Anticariogenic Properties

M. fragrans also possesses anticariogenic properties that inhibit or arrest dental caries formation. Dental caries in an infectious disease could result in destruction of tooth structure by acid excreted from microorganisms of dental plaques. This eventually leads to tooth loss occurring usually in children and young adult (Lakshmi and Krishnan 2013; Sharma et al. 2017). Chung et al. (2006) in their study stated that macelignan isolated from *M. fragrans* nutmeg exhibits the inhibitory effect against cariogenic *S. mutans*. Furthermore, the MIC of macelignan against *S. mutans* was observed to be 3.9 μg/ml, which was much lower than other natural anticariogenic agents tested, such as sanguinarine, eucalyptol, menthol, thymol, and methyl salicylate. In anti-bactericidal test, macelignan at 20 μg/ml concentration was able to completely inactivate *S. mutans* within 1 min. Similarly, Shafiei et al. (2012) tested anticariogenic efficacy of *M. fragrans* against oral pathogens. The study was evaluated on Gram-positive cariogenic bacteria (*S. mutans* ATCC25175, *S. mitis* ATCC6249, and *S. salivarius* ATCC13419) and Gram-negative periodontopathic bacteria (*Aggregatibacter actinomycetemcomitans* ATCC 29522, *Porphyromonas gingivalis* ATCC 33277, and *Fusobacterium nucleatum* ATCC 25586). Investigation found ethyl acetate extract of *M. fragrans* fruit flesh and ethanol extract of seed and mace have significant inhibitory effects against all test pathogens except for *F. nucleatum* ATCC 25586. The study concluded flesh, seed, and mace of *M. fragrans* have the potential to fight oral pathogens. Following that, Jangid et al. (2014) reviewed *M. fragrans* usability as adjunctive treatment of periodontitis, the inflammation of periodontium, the supporting structures of the teeth. Nutmeg's anti-inflammatory and antibacterial effect could be the main reason for such properties. Recently in another study, methanolic extract of *M. fragrans* seeds was tested against oral pathogens *Lactobacillus acidophilus*, *S. mutans*, *S. mitis*, and *Enterococcus faecalis*. Methanolic extract exhibited inhibitory effect against Gram-positive bacteria *E. faecalis* and *S. mitis* (Singh et al. 2017). These properties of *M. fragrans* against oral bacteria suggest its potential as a natural antibacterial agent which could be incorporated into oral care products.

4.3.14 Memory-Enhancing Activity

Parle et al. (2004) noted the extract of *M. fragrans* as enhancer of learning and remembering capabilities by investigating impaired mice injected with scopolamine and diazepam. In this study, different groups of young and aged mice were administered orally with n-hexane seed extract at doses 5, 10, and 20 mg/kg for 3 consecutive days. The result revealed that a dose of 5 mg/kg considerably enhanced learning and remembering capabilities of young and aged mice. *M. fragrans* is also documented for handling patients suffering from Alzheimer's disease with memory deficits (Nagja et al. 2016; Akram and Nawaz 2017). Cuong et al. (2014) evaluated the anticholinesterase activity of the ethyl acetate fraction from the seed methanolic extract of *M. fragrans*. Among the 13 compounds identified, (8R,8′S)-7′-(3′,4′-methylenedioxyphenyl)-8,8′-dimethyl-7-(3,4-dihydroxyphenyl)-butane(7S)-8′-(4′-hydroxy-3′-methoxyphenyl)-7-hydroxypropyl)benzene-2,4-diol and malabaricone C showed significant anticholinesterase properties. This suggests the potential of using nutmeg in treating Alzheimer's disease. Acetylcholinesterase is an enzyme responsible for the inactivation of acetylcholine, which is linked to learning and memory processes. Also, n-hexane extract of nutmeg seeds administered to young male Swiss albino mice at 5 mg/kg for 3 successive days suggestively reduced acetylcholinesterase activity in the brain of mice models (Dhingra et al. 2006).

4.3.15 Hepatoprotective Activity

The liver, a crucial metabolic organ, often exposed pollutants, toxins, chemicals, or various drugs, which can cause considerable damage, at times leading to a more serious condition such as hepatitis or liver cirrhosis (Zimmerman et al. 1994). *M. fragrans* is a plant-based natural hepatoprotective agent which can be used to manage liver diseases. According to Morita et al. (2003), nutmeg showed the most potent hepatoprotective activity in comparison with 21 spices tested when administered orally to rats with liver damage caused by lipopolysaccharide (LPS) and d-galactosamine (D-GalN). Further bioassay-guided isolation revealed myristicin, a major fraction of nutmeg essential oil having extraordinarily potent hepatoprotective activity. The author explained myristicin to have suppressed LPS/D-GalN-induced enhancement of serum TNF-alpha concentrations and hepatic DNA fragmentation in mice owing to the inhibition of TNF-alpha release from macrophages suggesting hepatoprotective mechanism(s) of myristicin. Subsequently, in another study nutmeg aqueous extract was orally administered to isoproterenol (ISO)-induced hepatotoxicity and oxidative stress in adult male Wistar strain rats. Nutmeg aqueous extract effectively inhibited ISO-induced changes protecting against experimental hepatic injury as revealed by the amelioration of marker enzymes, without any clinical complications shown by oral toxicity studies. Further histological studies on rat liver substantiated the absence of massive fatty changes, ballooning degeneration, necrosis, and broad infiltration of the lymphocytes, and the loss of cellular boundaries prevalent in ISO-induced rats (Kareem et al. 2013).

4.4 Toxicological Evaluation

M. fragrans is well noted for its hallucinogenic or narcotic-like properties as evidenced in many literatures (Weiss 1960; Fras and Friedman 1969; Lim 2012). A hallucinogen is defined as a psychoactive substance that causes a significant alteration in perception, mood, and a host of cognitive processes upon ingestion (Nichols 2004; Rahman et al. 2015). Due to the apparent euphoria-inducing and hallucinogenic properties, abuse of *M. fragrans* has happened for several years, predominantly among adolescents, students, and inmates who have limited access to other psychotomimetic agents (Barceloux 2009). In another report, cases of nutmeg seed ingestion by adolescents have been reported, primarily to achieve a euphoric state at low cost (Demetriades et al. 2005). The ingestion of *M. fragrans* seeds in large quantities produces narcosis, drowsiness, delirium, and even death, particularly if combined with other drugs (Rema and Krishnamoorthy 2012). However, Sangalli and Chiang (2000) stated that an unpleasant taste, high-dose requirement, and lack of potency as a hallucinogen are prominent limiting factors of its abuse. An early documentation of *M. fragrans* poisoning arose in 1576, when de Lobel stated a case of nutmeg intoxication in a pregnant English woman, who ingested 10–12 nutmeg nuts (Barceloux 2009). Following that, in the beginning of the nineteenth century, another report suggested the possible effect of *M. fragrans* on the central nervous system, when Purkinje developed lethargy after consuming three nutmeg nuts (Barceloux 2009). Since then, intoxication and poisonings of *M. fragrans* have been documented frequently.

4.4.1 Exposure Routes and Adverse Effects

The known methods of exposure routes include oral administration and through inhalation. The oral method is more common, where the pulverized seeds of *M. fragrans* are ingested. The inhalation method is rarely used, although there are some reports of nutmeg being mixed with tobacco and snuffed in certain parts of southern India. The intoxication through both methods is reported to be similar; however through inhalation, the onset of symptoms may have faster effects. Besides these, parenteral administration is another method that is frequently cited in pharmacological research, particularly in experimental animals, where administration takes place elsewhere other than oral or alimentary canal, i.e., intravenous injection.

Heavy doses of *M. fragrans* consumption cause adverse effects and chronic poisoning at various parts of the body. Symptoms include chest pain and tightness (airways and lungs); double vision, dry mouth, and eye irritation (eyes, ears, nose, and throat); abdominal pain, dehydration, and nausea (stomach and intestines); rapid heartbeats (heart and blood); agitation, anxiety, brief euphoria, convulsions, delirium, drowsiness, hallucinations, headache, lightheadedness, seizures, and tremors (nervous system); and redness or flushing (skin) (Sangalli and Chiang 2000; Forrester 2005; Demetriades et al. 2005).

4.4.2 Toxicity Mechanism and Clinical Evidences

Both nutmeg and mace contain active ingredients, mainly myristicin, elemicin, and safrole, which account for the majority (85–95%) of the compounds in the aromatic fraction. In that, myristicin represents about 4–12% of the compounds present in the essential oil (Barceloux 2009). Myristicin, elemicin, and safrole are the compounds found in the powdered seeds, essential oil fractions, and nutmeg oleoresin. These compounds are known as hallucinogens causing narcotic and psychotropic effects, when ingested in heavy doses (Somani et al. 2008; Ding 2015). The intoxication of *M. fragrans* depends on the age, health condition, and amount ingested by host similar to other drugs. According to several toxicity reports of *M. fragrans* ingestion, approximately 5 g of nutmeg, corresponding to about 1–2 mg of myristicin/kg of body weight, could instigate intoxication (Hallström and Thuvander 1997). However, an investigation has revealed that the consumption of 6 g of nutmeg in students did not significantly alter their performance during neuropsychological tests (Beattie 1968; Barceloux 2009). Subsequently, Forrest and Heacock (1972) noted one grated *M. fragrans* seed (nutmeg) gives approximately one tablespoon of powder weighing about 6–7 g and a typical recreational dose of *M. fragrans* ranges from 5 to 30 g. The intoxication symptoms from *M. fragrans* usually begin about 3–6 h after ingestion and may subside over 24–36 h (Gupta and Rajpurohit 2011).

The adverse poisoning of *M. fragrans* affects the liver, causing hepatic necrosis and hepatic degeneration. When Swiss albino mice were subjected to 0.003 and 0.3 mg/day of mace for the period of 7 days, the treated groups showed a significant increase in creatine phosphokinase level. Further, the microscopic assessment demonstrated that mace induced the morphological perturbation in the liver of treated mice. The results also showed an inhibitory effect of glyceraldehyde 3-phosphate dehydrogenase and an important increase in the level of thiobarbituric acid-reactive substances and succinate dehydrogenase activities and no change in catalase activities (Malti et al. 2008). In another study, safrole was reported to induce hepatic carcinoma in mice (Miller et al. 1983).

As reported by Beyer et al. (2006), in individuals suspected with the abuse of nutmeg, neither amphetamine derivatives nor the main nutmeg ingredients could be detected in urine samples of the treated subjects. However, the metabolites elemicin, myristicin, and safrole in urine samples were detected using gas chromatography-mass spectrometry analysis. In the urine sample, O-demethyl elemicin, O-demethyl dihydroxy elemicin, demethylenyl myristicin, dihydroxy myristicin, and demethylenyl safrole were identified. Previously, metabolic formation of amphetamine derivatives from the main nutmeg ingredients elemicin, myristicin, and safrole was stated to cause psychotropic effects upon ingestion in large doses (Ding 2015).

M. fragrans was also cited for inducing cardiovascular reactions, such as tachycardia, hypertension or hypotension, chest pains, and tightness (Sangalli and Chiang 2000; Demetriades et al. 2005). Besides that, macelignan derived from nutmeg contains safrole, a possible carcinogen found to induce a toxicity effect to the heart (Javaregowda et al. 2010). The authors have claimed that macelignan acts as peroxisome proliferator-activated receptors (PPARs) α/γ dual agonist in diabetic patients.

PPAR α/γ was expressed in embryonic rat heart-derived H9c2 cells. Similarly, in another case study, a 13-year-old female ingested with 15–24 g of nutmeg over a period of 3 h, who smoked and shared joints of marijuana, developed visual, auditory, and tactile hallucinations. She experienced nausea, hot/cold sensations, gagging, and blurred vision followed by numbness, headache, and drowsiness. She was treated with activated charcoal 50 g with sorbitol, trimethobenzamide for nausea, and intravenous fluids. Her symptoms subdued over 72 h; however during discharge on the third day, some symptoms were still present (Sangalli and Chiang 2000). Evidently, excessive consumption of *M. fragrans* may give negative effects to health and further cause neurotoxicity to the brain. Therefore, careful consideration should be given during consumption of nutmeg at higher doses.

4.5 Conclusion and Future Prospects

M. fragrans has beneficial medicinal properties due to its bio-active components with diverse pharmacological effects. The extracts and essential oil derived from this plant possess significant antioxidant, memory-enhancing, anticarcinogenic, anti-inflammatory, antidiabetic, anti-obesity, aphrodisiac, antibacterial, antifungal, larvicidal, insecticidal, anticarcinogenic, and many other therapeutic potentials. Among some of the basic challenges in the use of *M. fragrans* include poor quality control, absence of standardization methods of obtaining the products, and lack of clinical data to establish effectiveness and address concerns related to toxicity aspects. In this regard, more number of in vitro as well as in vivo research efforts is required in the future to ascertain the therapeutic utility of *M. fragrans*. The applications of frontline analytical methods and molecular approaches, including high-throughput next-generation sequencing, are required for authenticating the plant products and to have a check on the quality. Further, more toxicological studies involving different animal models are very necessary to establish the toxicity aspects of *M. fragrans* bio-active compounds. Nevertheless, in-depth studies on the action mechanism of each bio-active component and its specific pharmacological property are still largely lacking. Exploring this feature and connecting specific therapeutic potential will greatly encourage the growth of pharmaceutics and drug discovery. Hereafter, more investigations should be encouraged to utilize these commercial tree products for treating various human ailments.

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