

Fragrance Profile Of Myristica Frangans

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ABSTRACT

Nutmeg is the common name for *Myristica fragrans* Houtt., an evergreen tree that grows naturally in Indonesia and is grown in tropical areas like India, Malaysia, Grenada, and Sri Lanka. The plant produces two main spices: nutmeg (the seed kernel) and mace (the aril). Both contain 5–15% essential oil that is high in monoterpenes (like sabinene, α -pinene, and β -myrcene), phenylpropanoids (like myristicin, safrole, and elemicin), and other compounds like eugenol and caryophyllene. The yield of essential oils varies depending on the part of the plant and the extraction method. For example, hydrodistillation or supercritical CO₂ fluid extraction (SCFE) yields 0.7–3.2% from leaves, 8.1–10.3% from mace, 0.3–12.5% from seeds, and 6.2–7.6% from kernels. SCFE is faster (15–60 minutes) and has a similar chemical profile to traditional water steam distillation. Nutmeg essential oil has a wide range of bioactivities, such as being an antioxidant (it fights free radicals), an antimicrobial (it fights Gram-positive and Gram-negative bacteria, fungi, and parasites). The main pharmacological actions of nutmeg oil include anti-inflammatory action through cytokine production inhibition, analgesia and anticonvulsant activities; the antitumor action, as demonstrated by its cytotoxicity on several different cell lineages. Other uses are hepatoprotective, insecticidal, and memory-enhancing, which is supported empirically by its traditional Ayurvedic, Unani, use in the treatment of digestive disorders, rheumatism, insomnia, and as an aphrodisiac. However, high dosage causes toxicity through the action of myristicin and elemicin components leading to cardiovascular, central nervous system intoxication with hallucinations and seizures, anticholinergic symptoms and gastrointestinal side effects. This review has summed up evidence conducted between 2000 and 2023 showing the promising therapeutic potential of nutmeg oil and critically the need to take the dosages carefully to reduce the adverse effects, and also recommending further mechanistic research to bring it to the next level of becoming a pharmaceutical agent.

Keywords- Fragrance profile, Hydrodistillation, nutmeg essential oil.

1.INTRODUCTION

Myristica fragrans Houtt., which is also referred to as nutmeg or Jaiphal, is a medium-sized, dioecious/monoecious evergreen fragrant plant that is a member of the Myristicaceae family. It grows naturally on the Banda Islands of the Moluccas, in Indonesia and has been propagated extensively in tropical areas, such as India, Malaysia, Grenada, Trinidad, Sri Lanka and Mauritius, South Africa and several Pacific Islands. It is a tree which normally ranges between 5 and 13 metre in height, may not exceed 20 metres, and is a fruit that is yellow and fleshy in nature resembling an apricot or a peach. Two separate spices are obtained out of this fruit nutmeg, the inner reddish brown seed-kernel, and mace, the fleshy, reddish red, net-like aril or mantle which wraps the seed-kernel. The essential oil content of nutmeg seeds varies between 4- 15% and that of mace is higher (8- 10%). Both of these ingredients have been treasured since the twelfth century in Europe both as condiments, fumigants and as medicines due to their warm slightly sweet taste and wonderful musky fragrance.

The varied therapeutic values of *M. anosmosa* have been already recorded in a large range of remedial traditions such as the Ayurveda, Unani, Tibetan, Chinese, Indian, Arab, and Jewish medicine. In centuries many parts of plants have been used to treat gastrointestinal disorders including indigestion, flatulence, diarrhoea, colic and dyspepsia, to treat insomnia, urinary incontinence, rheumatism, arthritis, headache pyocutaneous diseases, nausea and vomiting associated with cholera, ulcers of the mouth, paralysis, sexual dysfunction, skin discolourations and even as aphrodisiacs, stomachics, hypnotics, analgesics and as amenorrhoid In the Greco-Arab Unani model, which is based on Hippocratic theory of the humors (blood, phlegm, yellow bile, black bile) and their respective qualities (hot, cold, moist, dry), nutmeg is added under the concept of elements (Arkan), temperament (Mizaj), and actions (Afaal). The pharmacology of the present-day world has validated some of these traditional assertions with the hypolipidemic, hypocholesterolemic, antidepressant, antimicrobial, memory-enhancing, antioxidant and hepatoprotective properties of the plant being discovered.

The extract of the oil is carried out, either by hydrodistillation or by water-steam distillation (WSD) or by using modern supercritical CO₂ fluid extraction (SCFE). These methods produce 0.312.5 per cent. oil in the seeds, or kernels, and more in mace. Its primary bioactive compounds are myristicin (the major aromatic composition, about 10 percent as indicated by ISO 3215:1998), eugenol (4-allyl-2-methoxyphenol) and macelignan, safrole, elemicin, sabinene, -pinene and 2, -myrcene and caryophyllene. Irrespective of its therapeutic potential, excess consumption is highly perilous whereby myristicin and elemicin may trigger intoxication status with tachycardia, nausea, hallucinations, seizures and organ damage. This review presents the synthesis of ethnobotanical, phytochemical, and pharmacological findings in the period between 2000 and 2023, illustrating the prospects of *M. fragrans* to be used as a prophylaxis and therapeutic method, and the necessity of mechanistic studies to make medicinal development of *M. fragrans* safe.

II. MATERIALS AND METHODS

This integrative review is based on the evidence on *Myristica fragrans* Houtt. (nutmeg) essential oil including botanical sourcing, extraction protocols, phytoactivity, and toxicological assessment, obtained exclusively using secondary data in 6 published, pre-print, and institutional articles on the same subject (2000-2023). Original laboratory work was not done, synthesis was based upon stringent literature diligence, cross-validation, and qualitative and quantitative summarisation.

2.1 Data Sources and Search Protocol.

Structured queries in the form of literature search were used to access open access repositories (ResearchGate, Preprints.org, journal websites), and databases (Google Scholar, institutional archives):

Key words Turmeric fragrans phenols, *Myristica fragrans*, *Myristica* fragrance, Jaiphal, Javitri.

Secondary terms: extraction, hydrodistillation, supercritical CO₂, GC-MS, myristicin, sabinene, bioactivity, antioxidant, antimicrobial, toxicity, Unani, Ayurveda.

Logic Boolean: (*Myristica fragrans* and nutmeg) and (essential oil and volatile oil) and (extraction and composition and bioactivity and toxicity).

Search Engine: Proquest; Author: NOT KManaged Care Organizations, 2000-2023, October, 2020 (pp. 1-5); prohibited keywords: Investment of equal and identical significance; research in English; in-patient and out-patient programs.

2.2 Selection Criteria

Inclusion:

Research on olefinic oil obtained on a seed/kernel (5~15 percent yield), mace (8~10 percent yield), or leaf (0.73 to 2.25 percent yield).

Recovery by hydrodistillation or water steam distillation (WSD) or supercritical CO₂ fluid extraction (SCFE).

GC Package -27 compounds chemical profiling ([?]27 compounds).

Accredited bioassays (in vivo/in vitro) antioxidant, antimicrobial, anti-inflammatory, analgesic, anticonvulsant, anticancer, insecticidal, hepatoprotective, or anti-parasitic.

Toxicity (acute/chronic, LD scientific, Clinical symptoms).

Ethnopharmacological experience (Ayurveda, Unani, folklore).

Exclusion:

Non-essential oil extractions (aqueous extractions, ethanolic extractions only).

Other non-MF- equipment.

Day-in day-out conference papers, abstracts, or non PDF.

Fourth quarter 2003 or after.

Those studies which lack methodological transparency (e.g. no GC-MS parameters).

2.3 Data Extraction Framework

A standardised template then took:

Materials Botanical, Origin (Indonesia, India, Malaysia, Grenada), part used, pretreatment (drying, grinding).

III. EXTRACTION TECHNIQUES:

- Hydrodistillation/WSD: Clevenger apparatus; 3 -6 h; 1:4 material-to-water ratio; a temperature 100 C.

- SCFE: CO₂ supercritical (>7.38 MPa, >31.1 o C); 15-60 min; pressure 10-30 Mpa; temperature 40-60 o C; flow rate 1020 gm/min; separator 5-10 Mpa, 2025 o C.

Calculation of the Yields: $w/w = (\text{mass of oil} / \text{mass of dry material}) \times 100$.

Phytochemical Analysis: GC -MS (Agilent 7890A/5975C or equivalent); column: HP-5MS (30m900.25mm0.25mm), carrier, helium (1mLmin⁻¹), injector, 250 °C, oven, 50-250 °C at 5 °C/min, MS: EI mode 70eV, library, NIST/Wiley. Identification Retention index (RI) mass spectra; quantification Area normalisation.

Standard of Quality: ISO 3215:1998 (myristicin [?] 10 percent, density 0.8801.910 g/ml⁻¹, refractive index 1.4701.497, optical rotation +8 to +25⁻¹).

3.1 Bioactivity Models:

- antioxidant FRAP, DPPH (IC 50) and ABTS.
- Antimicrobial: Disc diffusion (zone mm (mm), MIC (broth dilution), MBC.
- Anti-inflammatory: carrageenan paw edema (per cent inhibition).
- Analgesic: Latency of hot plate, writhing of acetic acid.
- Toxicity: Oral LD 50 (rats), clinical case history (myristicin >0.4mg/kg⁻¹).

3.2 Data Synthesis and validation.

Quantitative: Yield (e.g. kernel: 6.2 -7.6⁻¹), compound (myristicin 4-20⁻¹) or compound percentage (sabinene 15-40⁻¹).

Qualitative: Integration of mechanisms through narrative ways (e.g. myristicin -GABA modulation; eugenol - COX inhibition).

Cross-validation GC-MS profiles compared across studies, differences (e.g. the variation of safrole) due to geography/method.

Risk of Bias: Evaluated through source hierarchy (peer reviewed 06); All GC-MS studies were compliant to the ISO standards.

IV.EXTRACTION PROCESS

Myristica fragrans Houtt. (nutmeg) Volatile oil is mostly extracted using seeds (kernel), mace (aril), leaves or flowers to produce 0.315 percent oil, and this can be used depending on the plant part harvested, location, maturity and process. The most commonly used method of commercial production is traditional hydrodistillation (also known as watersteam distillation, WSD), especially in Indonesia, the native land of oil, and modern methods based on supercritical CO₂ fluid extraction (SCFE) prove to be both productive and much environmentally friendly. These two methodologies conserve important bioactives (such as myristicin (approximately 10 per cent as per ISO 3215:1998), sabinene, α -pinene, and eugenol) but their formulations differ in subtle ways as a result of differences in polarity and volatility. Each process is described below, including its summarization of yields, operation, pros, and cons, which have been reported in the recent literature (2000-2023).

4.1 Hydrodistillation(Water-Above-SteamDistillation,WSD)

The traditional, less expensive procedure currently used widely in spice-producing areas like Indonesia, India, and Grenada is hydrodistillation by reason of its relative simplicity and ability to function on an enormous measure. It utilizes the volatility of steam to deseparate oil and nonvolatile matrices resulting in a pale yellow oil that has the typical nutmeg smell.

4.2 Procedure:

Nuts or kernels (or mace) of nutmeg, which are either mature or immature, are dried to a moisture content of less than 10 to 1, ground to 1.2 mm size to expose as much surface area as possible, and loaded, typically 2.5 -5 kg, into a distillation vessel.

4.3 Distillation:

The process is frequently done in two steps: an unpressurised step (12-24h, 100°C) which isolates light fractions (e.g., monoterpenes), after which heavier phenylpropanoids, e.g. myristicin are trapped in a pressurised step (120°C, 1bar). The condensate is broken down into an oil fraction- one which contains light and heavy components- and a hydrosol, the aqueous layer.

4.4 Post-Extraction:

The crude oil is then decanted and dried (usually using anhydrous sodium sulfate), filtered and kept in amber bottles under a blanket of nitrogen to avoid oxidative degradation. Yield is determined through (division of mass of oil divided by initial biomass) X 100 percent.

V. Yields and Variability

Seeds/kernel: 5 -12.5 % (e.g. 10 -11 % out of young Indonesian seeds).

Mace: 8.1–10.3 %.

Leaves: 0.7–3.2 %.

The mace has a higher yield compared to the seeds; at maturity, or over-drying of the seed, yield reduces; Indonesian and Indian sources typically produce a yield of 9-10%.

5.1 Advantages:

It uses cheap equipment, does not use any organic solvents and can be easily scaled to make it workable to smallholders.

5.2 Limitations:

The process is power intensive, the process typically requires 24 h time and lot of fuel, thermal degradation can remove heat sensitive compounds like myristicin, waste water discharges may be environmentally unfriendly and the process lacks selectivity and tends to extract waxes and other non volatile components.

Quality complies with ISO 3215:1998, and the density is 0.880-0.910 g/mL⁻¹, with a range of refractive indices of 1.470-1.497 and an optical rotation of +8 to +25 degrees on the standard

5.3 Supercritical Fluid Extraction (CO₂)

SCFE also uses the CO₂ in supercritical form (more than 31.1 °C and 7.38 MPa), which is a non-toxic solvent that is very compatible with thermolabile volatiles. It provides greater selectivity of non-polar substances (e.g. sabinene) and is finding favor in green production in pharmaceuticals and cosmetics.

5.4 Procedure (Lab-Scale Example):

The load material is ground nutmeg powder (2.5kg, 0.51 mm) in a stainless steel extractor vessel (about 5L).

VI. EXTRACTION

Purified (99.9%) CO₂ is pressurised to 120 -300 bar, heated to 35-50 °C and allowed to flow at 1-5 L/min in dynamic mode of operation (15-60 min). A co-solvent (510% ethanol) can be added voluntarily and can be used to boost polar extraction. Separating the effluent releases the oil through the depressurisation of 40 to 50 bar (25 to 40 °C), and CO₂ is recycled at a recovery rate of about 95 per cent.

6.1 Post-Extraction:

The crude extract is fractionated (which can usually be done through density separation) and can be refined further through molecular distillation. The yield is to be obtained by gravimetric analysis after depressurisation.

6.2 Yields and Variability:

Seeds/kernel: 1015% total extract (8090% of it essential oil; to 90% purity optimum conditions). Yields of this sort are comparable to those of WSD (1012 -13 %) but can be achieved in a fraction of the time; even larger yield (up to 18 -1 -1 %) with co-solvents. Optimisation of yield is done by modifying pressure and temperature (e.g., 250 bar/45 °C is the maximum yield of myristicin) and by minimising the particle size to less than 0.5 mm which, again, can increase yield by 20-30 per cent.

6.3 Advantages

The SCFE process is significantly quicker, 1560 min vs. 24 h, and does not undergo thermal degradation, the residue of the solvent is negligible due to the complete extraction of CO₂ that gives it greater purity and selectivity. The process is both environmentally friendly, with the re-use of CO₂ and it has low effluent.

6.4 Limitations

Initial capital expenditures are high (more than US 50, 000); to optimise a process, it requires experience; extraction of lipids and co-extraction of additional molecules are likely to give a yellow colour requiring additional refining.

GC-MS (25-38 compounds) demonstrates the presence of myristicin (range 16 to 30percent) and sabinene (maximum 30percent)- more so in SCFE as compared to WSD. The chromatographic prints satisfy the ISO requirements and are characterized by an improved ability to retain bioactive components, such as antioxidant activity.

VII.COMPARISON AND MAXIMIZATION.

7.1 Yield/Composition:

WSD is mainly conducive to polar compounds despite the fact that non-polar compounds like sabinene and eugenol are extracted better by SCFE. With regard to overall composition, the two methods share an overlap of 80-90% the SCFE may offer a 12% compromise with 1-2% proportion higher yield, and require 90 percent less time and energy.

7.2 Sustainability:

SCFE produces lower CO₂ emissions because of the recycled solvent and little use of water, which makes it the most suitable in production of oil on export.

7.3 Emerging Variants:

Similar yields (8-10% -Lu) are achieved in microwave-assisted hydrodistillation (30-60 minutes) compared to ultrasound-enhanced SCFE (15% higher).

VIII. CHALLENGES

Geographic origin variability has remained, Indonesian material typically produces more oil than Indian samples, and a standardisation procedure and precise quantification of myristicin were necessary (to 35 to 50 percent depending on ISO 3215:1998).

IX.FUTURE

Cost-effective and efficient hybrid processes that integrate WSD and SCFE might be the way out. Economic analysis indicates that an ROI of SCFE in above one tonne per annum production scale takes up to two or three years.

Botanical Description

Myristica fragrans Houtt. (family Myristicaceae), hereafter referred to as nutmeg or Jaiphal (Sanskrit and Hindi: Jaiphal) and Jatiphala or Javitri when representing the aril or mace, is, in fact, the only member of the genus *Myristica* to produce two spices out of the same fruit: the dried seed or kernel is nutmeg and the dried crimson aril is mace. The plant is a medium-size to large, aromatic, perennial, dioecious (some rare cases of monoecious) evergreen tree, 8 to 20 metres high, (usually 10 to 15 metres) with a straight trunk of 30 to 60 centimetres in diameter, lacking bud scales, dark grey to blackish in colour, with longitudinal fissures on the trunk and dense pyramidal or conical crowns. It has reddish-brown wood which is middle hard.

The leaves are introduced in pairs, and are simple, stipuleless, and carried on petioles of length 1 to 1.5 centimetres. Their laminae are elliptic lanceolate through to oblong lanceolate, 5-15cm long and 2-6cm wide with whole margins and acute to an acute apex. Adaxial surface is dark green, glossy and abaxial surface is glaucous with a clear midrib bearing 8 to 12 pairs of lateral veins.

The structure of the inflorescence is axillary, racemose or umbelliform, and has brachyblasts. They are small, 4 to 6 millimetres in diameter, unisexual, urceolate or campanulate and pale yellow or cream and fragrant, without petals; the perianth is ternary-lobed and fleshy. Male flowers are found in 5 to 15 clusters with the anthers containing nine to twelve which form a column. The female flowers are single or form one to three groups, have a superior ovary, single ovule and have a bilobed stigma.

The fruits are pendulous, globose to pyriform, soft, and yellow, 6 to 9 centimetres long, and 4 to 6 centimetres diameter. They are slick, thick and fleshy-skinned with a longitudinal suture dehiscent into two valves during maturity, thus exposing the polished brown seed covered by a bright scarlet to crimson, lacinate (immensely subdivided, net-like) aril, also known as mace. The seed itself is great, 2 to 4 centimetres in length, ovoid to oblong, and is covered by a hard, reticulately-wrinkled, dark brown shell, enclosed by a ruminant endosperm, which surrounds the embryo. The inner kernel or nutmeg is spotted with reddish-brown.

Pollination is entomophilous with beetles of genus *Formicimimus* being its main mediators. Since the species is largely dioecious, to have fruit setting success in plantations there has to be a ratio of one male to every ten females; monoecious are rare. Propagation depends mostly on the fresh seeds that have a low viability of two to three weeks, but grafting and approach grafting methods have been used to produce elite clones

Ecology and Distribution *M. fragrans* is self-introduced on the Banda Islands (Moluccas, or Spice Islands), the territory of Indonesia. It has grown massively in the humid tropical lowlands at altitudes of up to 500 metres with rainfall of over 2000 millimetres in a year, well-drained loamy soils and partial shade in the early stages of development. Indonesia (producing 70 to 80 percent of the world output), Grenada, India (especially Kerala and Tamil Nadu), Sri Lanka, Malaysia, and many of the Caribbean islands, are major centres of production. The species begins producing in seven-nine years, full production is realized in fifteen-twenty years and the species remains productive between 50-70 years.

Diagnostic Features The characteristic of *M. fragrans* is dioecious habit, red lacinate aril, ruminant endosperm, and typical volatile oil aroma the features of which are sure to prevent confusion with other Myristicaceae, e.g. *Virola*, *Knema*, and *Horsfieldia*.

X. PERFUMERY AND COSMETICS:

A key product of the fragment of the kernel and the mace of *Myristica fragrans* Houtt. kernel and mace, nutmeg essential oil (NEO) is a multifunctional ingredient in the fragrance as well as the cosmetic industries, because of its warm, spicy-sweet, woody, and balsamic smell. Characteristics like rich, exotic, tenacious and slightly camphorous, with citrus like characteristics are common descriptions of the aroma. Its olfactive properties are due to its major components like myristicin (Tipping a narcotic warmth to it), sabinene (adding a piney-spicy aroma to it), 2-pinene and 2-pinene (providing a terpenic freshness to it) eugenol (endowing it with a tenor of clove-spice), and terpinen-4-ol (giving it a woody-nutmeg nuance). In commercial formulations, impurity is usually corrected or is in low -safrole/myristicin forms to address safety standards, such as that the IFRA guidelines restrict the use of safrole to a level less than 0.01 -1 in cosmetic or finished products because of its genotoxicity. Geographic provenance such as Indonesian or East Indian provenance is favored over other provenances due to better tenacity and distillation methodology with steam-distilled oil being the most desirable choice to use in perfumery.

10.1 In Perfumery

NEO is mainly used as a middle-base note giving the compositions warmth, sophistication and fixation. It combines top notes like citrus, lavender, with heart/base notes like woods, resins, and vanilla, therefore, adding a spicy exotic touch that does not oppress the mixture in general. 10.2 Key applications include:

Oriental and Amber Fragrances: Adding balsamic-sweet richness: a characteristic of powdery ambers and gourmand compounds (e.g. with vanilla, tonka, labdanum, etc.).

Fougere and Chypre Compositions: This is an ingredient necessary to total spicy warmth when applied in masculine fougere compositions and enhances lavender-oakmoss structures as has been seen in the father of the classics, like natural Brut or Old Spice.

Spicy and Woody Accords: introducing a hardworking spicy-sweet heart into the modern perfumes: it is well matched with black pepper, cardamom, clove, rosemary, citrus, including bergamot and orange, and florals, including rose and geranium.

Usage Levels: 0.1 (varying) -5 percent in concentrates, found in premium niche products (e.g. Creed Bois du Portugal) and mass-market male colognes.

Special Variants include mace oil which has a lighter nuance, less spicy and more flowery, and East Indian nutmeg is better because it is richer.

According to Good Scents Company NEO is a balsamic, fresh, tenacious citrus enhancer and is widely used in oriental, amber, and powdery bases.

10.2 In Cosmetics

NEO performs 2 roles as a fragrance component, and a functional nutrient, relying on antimicrobial, antioxidant, and anti-inflammatory effects of myristicin and eugenol as well as terpenes to make products resistant and offer skin benefits to the product. It has incorporated the following product categories:

Soaps, Detergents, and Bath Products: Delivers a warm, spicy fragrance to artisanal or bar soaps, shower gels and candles; can have antiseptic properties, thus fitting acne or medicine-based soaps (0.528 per cent).

(Creams, Lotions, Serums) Antioxidant/anti-inflammatory activities prevent the occurrence of oxidative stress and calm inflamed skins; used in antioxidant eastern or men-grooming roles to give them a warm feeling.

Hair Care and Oral Care: Oral antimicrobial activity on toothpastes and mouthwash is not significant, used as an aromahead in shampoos and conditioners.

Men Cosmetics: The Cosmetics are the main ingredient in after shaves, beard oils and fragrances to provide a spicy masculine aroma.

Usage Levels and Safety: 0.011 per cent in leave-on products (IFRA Category 4); well-tolerated, phototoxicity is said to be rare; the EU Cosmetic Regulation has no objection to its use as INCI: Myristica Fragrans Kernel Oil.

Its inherent nature is compatible with the current trends in clean beauty and is often certified organic in high-end lines. NEO increases the effects of relaxation and circulation in aromatherapy-based cosmetics.

The combination of the characteristics of aromatic, functional and luxury spices, in general, provides NEO with a long-term demand in the market, despite the use of artificial substitutes, e.g., myristicin isolates to achieve consistency.

XI.SAFETY AND TOXICOLOGY

Historically known as nutmeg essential oil (NEO), Myristica fragrans Houtt. essential oil (MFEO) is mostly considered to be safe at low therapeutic or culinary levels (i.e. 0.1-0.5g powdered nutmeg or less than 0.1mL mom n oil a day). Its use as a flavouring agent was approved by Generally Recognised as Safe (GRAS) designation by the U.S. Food and Drug Administration, reference FEMA 2793, to make use of it as a flavouring substance. On the other hand, a very high dose, about 515g of whole nutmeg powder or 1-3 mL of pure oil, causes a severe intoxication which may be life-threatening. The toxic agents that cause this negative effect are primarily the phenylpropanoid components myristicin (430 -percent of the oil), safrole (0.24), and elemicin (0.53). These are hepatic metabolised by the cytochrome P450 (CYP1A2, CYP2E1) into psychoactive amphetamine like derivatives (e.g. MDMA of myristicin) and reactive intermediates. The ensuing changes in neurons are the overstimulation of serotonergic, inhibition of GABAergic transmission, and, thereby, the oxidative stress. Other effects that have been associated with chronic exposure (specifically with safrole) are hepatotoxicity and carcinogenicity, leading to regulatory restrictions in numerous jurisdictions.

11.1 Acute Toxicity

Lethal and toxic doses: MFEO oral LD 50 in rodents is between 2000 and 3000mg/kg, and myristicin on its own has an LD 50 of around 10001200mg/kg (mice and rats). The LD 50 of safrole is approximately 1950mg kg -1 (rats). In humans, a toxic dose has been estimated at approximately 5g of nutmeg powder, or 200 400mg myristicin. The hallucinogenic effects occur within 5-15g and death after consumption is very infrequent and has been observed with more than 20-50g dosage, which leads to multi-organ failure in most cases. Clinical symptoms in children have been shown to be drove by even a dose of 1200-1500 mg.

Onset and course: Its symptomatology occurs 2-8 hours after ingestion with a peak of 6 -12 hours and recovers in 24-72 hours with supportive care.

Symptom Categories (dose-dependent and felt to attribute to myristicin /elemicin overdose):

- Central Nervous System (CNS): Euphoria, anxiety, visual and auditory hallucinations that are reminiscent of mescaline, agitation, delirium, drowsiness, seizures, and coma. These mechanisms include NMDA receptor modulation and augmented release of serotonin and dopamine and inhibition of monoamine oxidase.
- Cardiovascular: Tachycardia, palpitations, hypertension and then with a drop in blood pressure and flushing.
- Gastrointestinal: Massive nausea, vomiting, epigastric pain and diarrhea which indicate a local irritant effect.
- Anticholinergic: bizizinn (dried-out mouth), mydriasis, ataxia vision, and urinary retention.
- Miscellaneous: Hyperthermia or hypothermia, diaphoresis, metabolic acidosis and a distinctive doom anxiety.

Treatment: There is none in particular. Gastric lavage or activated charcoal administration should be done within the two hours after intake. Benzodiazepines have been recommended as a part of agitation or the control of seizures. The use of intravenous hydration is important, and clinicians are to be on par with the appearance of rhabdomyolysis and renal failure. Most of the cases self-approach; the deaths (fewer than 1% of reported cases) are usually those caused by suffocation or shock.

Case Evidence A 10-50 cases of poison control data, 2000-2020 reported most of the cases of the recreational use (such as a social media-promoted lab-packaged nutmeg high). One pediatric fatal case was as a result of 7.5 g of nutmeg ingestion.

11.2 The Chronic and Sub-Chronic Toxicity.

Hepatotoxicity: The sub-toxic rodent (90days, 100500 mg/kg MFEO) animal studies show increased liver enzymes (ALT/AST), centrilobular necrosis, and bile duct hyperplasia. Such results are attributed to the presence of safrole metabolites and myristicin that develop DNA adducts. There are few reports in humans, which include jaundice after extensive high dosage (>12 days⁻¹) over several weeks.

Carcinogenicity whereby, the International Agency on Research concerning Cancer is of the opinion Safrole to be categorized in Group 2B (Possibly Carcinogenic to Humans) due to evidence of forestomach and liver cancer in rodents. When the Ames test was conducted with S9 activation, myristicin was genotoxic. No etiological connection to human malignancy has been explored but the European Food Safety Authority advises the avoidance of safrole in feed and food additives.

Reproductive/Developmental toxicity: Umbilical contractions encountered, rat experimentation reveals embryotoxicity at doses of more than 500 mg/kg. The use is therefore contraindicated during pregnancy.

Other warning signs: Chronic MAO inhibition: Chronically inhibited drugs can raise psychiatric disorders, patch test and sensitisation in the skin is rare, with a victimization lower than 1% of users.

Safe Working Regulations.

Food/Flavoring: FEMA list of GRAS indicates that a maximum amount of 0.025% MFEO than 0.025%, in baked goods, is allowed. The European Union restricts safrole to 1 mg/kg⁻¹ of food and 0.05 mg/kg⁻¹ of drinks and it is prohibited in some infant formula.

Cosmetics/Perfumery: The International Fragrance outlines safrol containing 0.01 on leaves (Category 4) in leave-on products (Fischer 3). Myristicin is not restricted, but controlled as it has a psychoactive effect. The product Industry Name (INCI) is Myristica Fragrans Korean Oil.

Medicinal use: Traditional Ayurvedic and Unani texts warn of moderate dose (250500 mg of powder a day) and do not recommend in epileptic, hepatic dysfunction or child below six years, etc.

Mitigation measures: The use of low-myristicin/safrole crop varieties, rectified/desafrolised oil use in industries and campaigns against abuse should be taken seriously by people.

To sum it up, MFEO may be safely used both in the traditional and the culinary circles and in moderate and low concentrations. Still, abusive consumption is an important threat, which underlines the importance of strict dosage control and additional pharmacokinetic studies of its bioactive metabolites.

XII.CONCLUSION

This integrative update of the research in 2000-2023 provides solid evidence that *Myristica fragrans* essential oil can be considered a powerful and versatile natural product, a concentrated source of antioxidant, antimicrobial, anti-inflammatory, pain killer, anticonvulsive, hepatoprotective, memory-enhancing, and cytotoxic effects, and as such, scientifically supports centuries old Ayurvedic, Unani and other traditional uses of the product in digestive, rheumatic. Besides its therapeutic value, the extraction methodology of the oil is of the supreme significance: supercritical CO₂ extraction will definitely beat the conventional use of hydro steam distillation in terms of its yield, rate of processing, conservation of bioactives, and eco-friendliness sociability, and is in compliance with the ISO 3215:1998 benchmarks. However, the arylpropanoids, the production of which can also be attributed to many of its salutary effects, are also causative of dose-dependent acute psychoactivity, anticholinergic toxicity, possible hepatotoxicity and carcinogenicity (safrole), hence providing a tight regulatory limit and limited safety margin. In turn, any complete pharma/nutraceutical exploitation of this resource is subject to the availability of low-myristicin/safrole chemotypes or corrected oils, the implementation of strictly designed human pharmacokinetic/toxicodynamic experiments, and the conduction of adequately controlled clinical trials within the safety of defined doses (about 250500mg day⁻¹ of the powder equivalent). Accordingly, though the idea of radically changing the role of nutmeg oil as a treasured spice and fragrance to a contemporary evidence-based botanical medicine is indisputable, this progress must be accompanied by the invariable principle of thorough moderation of the practice.

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