

REVIEW

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Nutmegs and wild nutmegs: An update on ethnomedicines, phytochemicals, pharmacology, and toxicity of the *Myristicaceae* species

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Funding information

Council of Scientific and Industrial Research, Ministry of Science & Technology, Govt. of India, New Delhi; Department of Biotechnology (DBT), Govt. of India, New Delhi, Grant/Award Number: BT/PR27725/NER/95/1349/2018; Department of Science & Technology, Govt. of India, Grant/Award Number: DST/INSPIRE Fellowship/2017/IF170731

Prized medicinal spice true nutmeg is obtained from *Myristica fragrans* Houtt. Rest species of the family *Myristicaceae* are known as wild nutmegs. Nutmegs and wild nutmegs are a rich reservoir of bioactive molecules and used in traditional medicines of Europe, Asia, Africa, America against madness, convulsion, cancer, skin infection, malaria, diarrhea, rheumatism, asthma, cough, cold, as stimulant, tonics, and psychotomimetic agents. Nutmegs are cultivated around the tropics for high-value commercial spice, used in global cuisine. A thorough literature survey of peer-reviewed publications, scientific online databases, authentic webpages, and regulatory guidelines found major phytochemicals namely, terpenes, fatty acids, phenylpropanoids, alkanes, lignans, flavonoids, coumarins, and indole alkaloids. Scientific names, synonyms were verified with www.theplantlist.org. Pharmacological evaluation of extracts and isolated biomarkers showed cholinesterase inhibitory, anxiolytic, neuroprotective, anti-inflammatory, immunomodulatory, antinociceptive, anticancer, antimicrobial, antiprotozoal, antidiabetic, antidiarrhoeal activities, and toxicity through in-vitro, in-vivo studies. Human clinical trials were very few. Most of the pharmacological studies were not conducted as per current guidelines of natural products to ensure repeatability, safety, and translational use in human therapeutics. Rigorous pharmacological evaluation and randomized double-blind clinical trials are recommended to analyze the efficacy and therapeutic potential of nutmeg and wild nutmegs in anxiety, Alzheimer's disease, autism, schizophrenia, stroke, cancer, and others.

KEYWORDS

biomarkers, ethnomedicine, *Myristicaceae*, nutmegs, pharmacology, toxicity

ABBREVIATIONS: 1,2-DdeHGA, (+)-trans-1,2-dihydrodehydroguaiaretic acid; A-357 cell lines, epidermal skin cancer; A-549 cell lines, human lung cancer; AChE, acetylcholinesterase inhibition; BChE, butyrylcholinesterase inhibition; CNS, central nervous system; deHGA, dehydroguaiaretic acid; EA-6, erythro-austrobailligan-6; EME, eugenol methylether; HD, hydrodistillation; HT-29 cell lines, human colon cancer; IEME, isoeugenol methylether; iso-E, isoeugenol; KLAR 5 CB, KLAR 5 endophytic fungus culture broth; MCF-7 cell lines, human breast cancer; MDHGA, mesodihydroguaiaretic acid; Me-E, methyleugenol; Me-iso-E, methylisoeugenol; MeO-E, methoxyeugenol; RCT, randomized clinical trial; RDBCT, randomized double-blind clinical trial; RDBD, randomized double-blind design; SCFE, super critical fluid extraction; SD rats, Sprague–Dawley rats; TA-5, threo-austrobailligan-5; UDS, unscheduled DNA synthesis.

1 | INTRODUCTION

Global trend on the use of herbal medicine is on the rise (Ahn, 2017; Williamson, Liu, & Izzo, 2020). There is an increase in the use of culinary spice as botanicals for health and wellness and herbal drugs (Chanda, Kushwaha, & Tiwari, 2011). Nutmeg is an ancient aromatic spice used almost in every cuisine in the globe (Agbogidi and Azagbaekw, 2013). Global exporters of nutmegs are Indonesia, Sri Lanka, Vietnam, Grenada, India, and Netherlands. Nutmeg has a long history of usage in almost all

the traditional medicinal systems in the tropical and temperate world (Gordon, 2020). True nutmeg and mace are obtained from seeds and aril of *Myristica fragrans* Houtt. (Sinclair, 1958). Apart from true nutmeg other species of *Myristica*, *Knema*, *Virola* and other genera of the family *Myristicaceae* R. Br. are known as wild nutmegs (Howe and Vande Kerckhove, 1981; Weiss 2002; Hake et al., 2009; Sheeja et al., 2014; Maya, Zachariah, Krishnamurthy, Rema, & Krishnamoorthy, 2015; Audrey et al., 2017; Banik & Bora, 2016; Prabha et al., 2019). Nutmeg and wild nutmeg fruits possess a single seed covered by juicy red or yellow aril (Banik & Bora, 2016; Banik, Bora, Kumar, & Bezbaruah, 2017). Both mace and nutmeg contain two types of oils as major components, "nutmeg oil," and "nutmeg butter" (De Wilde, 2000). Nutmeg oil is used as a natural flavoring agent in foods, beverages, and the perfumery industry for topical applications. Nutmeg butter mostly contains trimyristin, unsaponifiable constituents, resinous material, linolenic, oleic, formic, acetic, cerotic acids, and others. Trimyristin and its derivatives namely, myristic acid, myristyl alcohol, and glycerol are commercially used in personal care products, food and beverage additives, preservatives and paints and greases, and so forth (Marcelle, 1995; Singh et al., 2003). Traditionally, *Myristicaceae* species had been used in ethnomedicines and psychotomimetic agents (Alrashedy & Molina, 2016; Nagano, 2009; Schultes & Farnsworth, 1980). The present study was focused to critically review the ethnomedicinal, phytochemical and pharmacological potential, safety, and toxicity of the nutmegs and wild nutmegs for their contemporary use in herbal therapeutics. References were retrieved from books (De Wilde, 2000; Hooker, 1890; Warburg, 1897), scientific databases namely, www.pubmedcentral, www.google scholar, https://www.jstor.org/, https://www.biodiversitylibrary.org/, Ph.D. thesis (Maya, 2005), webpage (TKDL, 2001), regulatory guidelines (Federal Register, 2010) using the keywords namely, *Myristicaceae*, nutmeg, wild nutmeg, psychotomimetic agent, ethnomedicine, phytochemicals, pharmacology, biological activity as per stated sections, toxicity, clinical trial, industrial uses during (1683–April, 2020).

2 | BOTANICAL ASPECTS

2.1 | Taxonomy, description, and geographical distribution

The nutmeg family *Myristicaceae* R. Br. *nom. Cons.* is currently placed under the order Magnoliales Juss. ex Bercht. and J. Presl., the clades Magnoliids and Mesangiosperms (Chase et al., 2016). The genus *Myristica* Gronov. was described in the 18th century (Gronovius, 1755) followed by *Myristica fragrans* Houtt., the commercial "true" nutmeg (Houttuyn, 1774). Trees are tall, straight with characteristic horizontal branches, occasional knee roots, bark oozing red latex. Fruits with single seed covered by aril. (Rheede tot Drakestein & Casearius, 1683; Hooker, 1890; Warburg, 1897; Sinclair, 1961; 1969; 1975; De Wilde, 2000). Nearly 20 genera and 500 species of *Myristicaceae* are distributed from Africa to South East Asia, America, Australia, and New Guinea (Li & Wilson, 2008).

3 | TRADITIONAL USES

3.1 | Psychotomimetic agent

Nutmegs and wild nutmegs were used as natural hallucinogens, narcotics and medico-spiritual agents (Tables 1 and 2). Several species of the genus *Virola* namely, *Virola calophylla*, *V. calophylloidea*, *V. carinata*, *V. elongata*, and others were used in hallucinogenic snuff, smoke, vapor, drinks, and oral pellets in ceremonial practices by aboriginal Amerindians in Central and South America (Schultes, 1969a, 1969b; Schultes, 1976; McKenna et al., 1984a, 1984b; Martinez & Cuca, 1995). Resins of *V. elongata* were used as snuff in endocannibalistic rituals, *V. theiodora* for oral pellets and arrow poison by Yekwana Indians (Gottlieb, 1979; Holmstedt et al., 1980; McKenna & Riba, 2016; Schultes, 1982). *Scyphocephalum ochocoa*, *Pycnanthus angolensis*, and others were used in medico-spiritual treatments (Quiroz, 2015). However, most of the references lacked information on the preparation of psychotomimetic formulation, dosage, route, and duration of administration and others.

3.2 | Ethnomedicine

Nutmeg was documented in Thai, Burmese, Malayan, Vietnamese, and Indian traditional medicines (Nagano, 2009). It was used in Unani to treat melancholia and Ayurveda for all types of complications

TABLE 1 Relevant synonyms of the reviewed nutmeg and wild nutmegs of *Myristicaceae*

Scientific names	Relevant synonyms	References
<i>Coelocaryon preussii</i> Warb.	<i>Coelocaryon klainei</i> Pierre ex Heckel	www.theplantlist.org
<i>Iryanthera hostmannii</i> (Benth.) Warb.	<i>Iryanthera ulei</i> Warb.	www.theplantlist.org
<i>Myristica beddomei</i> subsp. <i>ustulata</i> W.J. de Wilde	<i>Myristica dactyloides</i> sensu J. Sinclair non Gaertn.	(Banik et al., 2017)
<i>Myristica magnifica</i> Bedd.	<i>M. fatua</i> var. <i>magnifica</i> (Bedd.) Sinclair	www.theplantlist.org
<i>Otoba novogranatensis</i> Moldenke	<i>Dialyanthera otoba</i> (Humb. & Bonpl.) Warb. <i>Myristica otoba</i> Humb. & Bonpl.	www.theplantlist.org
<i>Pycnanthus angolensis</i> (Welw.) Warb.	<i>Pycnanthus kombo</i> Warb.	www.theplantlist.org
<i>Virola elongata</i> (Benth.) Warb.	<i>Virola cuspidata</i> (Benth.) Warb.	www.theplantlist.org
<i>Virola theiodora</i> (Spruce ex Benth.) Warb.	<i>Virola rufula</i> Warb.	www.theplantlist.org

TABLE 2 Ethnomedicinal and psychotomimetic uses of nutmeg and wild nutmegs (*Myristicaceae*)

Scientific names	Name of the user country/continents	Health ailments /indications of use	Plant parts used	Mode of consumption	References
<i>Coelocaryon preussii</i> Warb.	Africa	Paralysis, diabetes, diarrhea, dysentery, piles, high pressure, venereal, respiratory diseases, psychotomimetic	Ba, See	Oral	(Akoubet et al., 2017; Quiroz, 2015)
<i>Compsonura capitellata</i> (A. DC.) Warb.	SE Ecuador, Amazon, Colombia	Mental disorder, tranquilizer, erratic behavior, convulsion, wounds, psychotomimetic	Ba, Le	Drink (Infusion), inhalation	(Ballesteros, Bracco, Cerna, Vita Finzi, & Vidari, 2016; Gottlieb, 1979)
<i>Horsfieldia glabra</i> (Reinw. ex Blume) Warb.	China, Indonesia, Thailand	Sores and boils	Le, Ba, See	N/R	(Wiat, 2007)
<i>Horsfieldia irya</i> (Gaertn.) Warb.	Sri Lanka, Thailand, New Guinea, India	Pimples, stomach pain, diarrhea, sore throat, ulcer, snake bite	La, R, Ba, Fr	Oral, Ba. decoction (Gargling)	(Banik & Bora, 2016; Gonzalez et al., 2002; Lu et al., 2014; Wimalasena & Karunawansa, 1994)
<i>Horsfieldia kingii</i> (Hook.f.) Warb.	India	Stimulant, mouth sores, intoxicant, dysentery, edible nuts	La, Fr, See	Oral	(Banik & Bora, 2016; Barukial & Sarmah, 2011)
<i>Iryanthera hostmannii</i> (Benth.) Warb.	Peru, Venezuela, Colombia	Anemia, diarrhoea, fever, malaria, mouth, and wound infection, ulcer, psychotomimetic	Ba, Le, Re, Fr, See	Inhale (snuff), drink (decoction)	(Cuca, Bernal, Coy, & Coy, 2009)
<i>Iryanthera juruensis</i> Warb.	Brazil, Ecuador	Fungal infection, aphthous stomatitis, scabies, wounds, changes in the state of CNS	Ba, Le, La, See	Roasted see. (Oral), beverages of crushed Le. (drinks)	(Aponte et al., 2007; E. W. Davis & Yost, 1983; Silva Dulce, Zhang, Santos, Bolzani, & Nair, 2007)
<i>Iryanthera macrophylla</i> Warb.	Peru	Psychotomimetic	Ba, Le, Re, Fr, See	Inhale (snuff)	(Holmstedt et al., 1980; McKenna, 1984)
<i>Knema angustifolia</i> (Roxb.) Warb.	India, Thailand	Dysentery, cancer, whole-body tonic, astringent, mouth ulcers	Ba, Re	Ba. (Drink)	(Banik & Bora, 2016; Khare, 2008; Phadungkit, Rattarom, & Rattana, 2010)
<i>Knema attenuata</i> Wall.	India	As an ingredient in 'Aswagandha nei' in several discomforts	Ba	N/R	(Vinayachandra & Chandrashekar, 2014)
<i>Knema erratica</i> (Hook.f. & Thoms.) J. Sinclair	Lao PDR, India	Mouth sore, dysentery	Ste, Le, La	N/R	(Banik & Bora, 2016)
<i>Knema furfuracea</i> Warb.	Thailand, Malaysia, Singapore	Sore, pimples, cancer	Ba	N/R	(Salleh & Farediah, 2017)
<i>Knema globularia</i> (Lam.) Warb.	Thailand	Blood tonic, skin diseases, scabies	Ba, R, See	N/R	(Salleh & Farediah, 2017)
<i>Knema laurina</i> (Blume) Warb.	Malaysia	Rheumatism, digestive problems, inflammation, fever, wound	Ba, Le	N/R	(Hake et al., 2009; Phadungkit et al., 2010; Salleh & Farediah, 2017)
<i>Knema tenuinervia</i> subsp. <i>setosa</i> W.J. de Wilde	Thailand	Cancer	Ba	N/R	(Pinto & Kijjoo, 1990)

(Continues)

TABLE 2 (Continued)

Scientific names	Name of the user country/continents	Health ailments /indications of use	Plant parts used	Mode of consumption	References
<i>Myristica andamanica</i> Hook.f.	India	Fever, malaria, stimulant, bleeding, skin infection, stomach disorder	Ba, Le, Fr, See	(Water extract) Oral, (Fr. powder and oil mixture) topical	(Rajasekharan & Rao, 2019; Sharma, Abirami, & Chander, 2018; Sheeja et al., 2014)
<i>Myristica beddomei</i> subsp. <i>ustulata</i> W.J. de Wilde	India	Diabetes, skin diseases, bronchitis, constipation, dysmenorrhea, spermatorrhea, anti-emetic, aphrodisiac, spasmolytic	Fr, See, Ar	N/R	(Koperuncholan & John, 2011; Subha et al., 2013)
<i>Myristica fragrans</i> Houtt.	Myanmar, India, Malaysia, Indonesia, Vietnam, Europe, Australia, Africa	Nervous disorder, stomach disorder, stimulant, blood purifier, rheumatism, inflammation, psychotomimetic, aphrodisiac, menstrual disorder, sedative, narcotic, toxic, sarcophagous	Ba, Fr (Pericarp), See, Ar	Oral, hot drink, topical (Spice powder, oil, spicy pericarp)	(Alrashedy & Molina, 2016; Benzeid et al., 2018; DeFilipps & Krupnick, 2018; Khare, 2008; Nagaraju et al., 2013)
<i>Myristica malabarica</i> Lam.	India	Rheumatism, stimulant, topical application, cough, inflammation, tumor, diarrhea, febrifuge, ulcer	Le, Fr	Oral	(Chelladurai & Ramalingam, 2017; Khare, 2008)
<i>Osteophloeum platyspermum</i> (Spruce ex DC.) Warb.	Brazil	Cough and cold, asthma, psychotomimetic	Ba, Le, Re	Drink, Smoke	(McKenna, 1984; Schultes, 1980)
<i>Otoba novogranatensis</i> Moldenke	Colombia	Liver problems, skin diseases	Re		(Bussmann, Paniagua Zambrana, Romero, & Hart, 2018)
<i>Otoba parvifolia</i> (Markgr.) A. H. Gentry	Ecuador, Central, South America,	Fungal infection	See	Inhale (snuff)	(J. Weiss, 2019)
<i>Pycnanthus angolensis</i> (Welw.) Warb.	Central Africa	Respiratory disease, fever, leprosy, wound healing, inflammation, pain, lactation, female sterility, stomach problem, osteoarthritis, diabetes, cognitive disease, cancer, poison antidote, psychotomimetic	W, Ba, Le, See	Topical (Bath), kombo butter	(Achel, Alcaraz, Adabo, Nyarko, & Gomda, 2012; Gustafson, Wu, Asante-Dartey, & Simon, 2013; Quiroz, 2015)
<i>Scyphocephalum mannii</i> (Benth. & Hook.f.) Warb.	Central Africa	Unspecified diseases, psychotomimetic	Ba	N/R	(Quiroz, 2015)
<i>Scyphocephalum ochocoa</i> Warb.	Central Africa	Vaginal infection, female fertility, gonorrhea, rheumatism, febrile body ache, excessive milk secretion, inflammation, breast, stomach, skin, liver cancer, unspecified diseases, psychotomimetic	Ba, See	Ba. decoction, ste. bath, oral (roasted see.)	(Ngoua-Meye-Misso et al., 2018; Quiroz, 2015)

TABLE 2 (Continued)

Scientific names	Name of the user country/continents	Health ailments /indications of use	Plant parts used	Mode of consumption	References
<i>Staudtia kamerunensis</i> var. <i>gabonensis</i> (Warb.) Fouilloy	Central Africa	Dysentery, skin infection, arrow poison antidote, psychotomimetic	Ba	Drink	(Musuyu et al., 2012; Quiroz, 2015)
<i>Virola bicuhyba</i> (Schott ex Spreng.) Warb.	Brazil	Brain stimulant	See	N/R	(Kobelnik, Fontanari, Soares, Figueiredo, & Ribeiro, 2013)
<i>Virola calophylla</i> (Spruce) Warb.	Colombia	Psychotomimetic, skin infections	Ba, R, Le, Fr, See	Inhale (snuff)	(E. W. Davis & Yost, 1983; Holmstedt et al., 1980; McKenna, 1984)
<i>Virola calophylloidea</i> Markgr.	Colombia, Peru	Fungal infections, psychotomimetic	Ba, Re, Le	Inhale (Snuff)	(E. W. Davis & Yost, 1983; Holmstedt et al., 1980)
<i>Virola carinata</i> (Spruce ex Benth.) Warb.	Colombia	Psychotomimetic	Ste, Ba, Le, Re	Inhale (Snuff)	(Holmstedt et al., 1980)
<i>Virola elongata</i> (Benth.) Warb.	Brazil, Peru, Colombia, Orinoco	Stimulant, psychotomimetic	W, R, Ba, Le, Re	Inhale (Snuff); oral paste, pellete, salt	(Alrashedy & Molina, 2016; McKenna, 1984)
<i>Virola michelii</i> Heckel	Brazil	Fungal disease, skin infection, medicinal plaster, psychotomimetic	Ba, Le, Re	Inhale (Snuff)	(Carvalho et al., 1999; Morais et al., 2009)
<i>Virola pavanis</i> (A. DC.) A.C. Sm.	Peru, Ecuador	Analgesic, psychotomimetic, kidney, tooth ailments	Ba, Le, Re, Fr (Pericarp), Ar	Inhale (Snuff), oral (drink)	(Ballesteros et al., 2016; McKenna, 1984)
<i>Virola peruviana</i> (A. DC.) Warb.	Colombia, Peru	Psychotomimetic	Ba, Re	Inhale (Snuff)	(Holmstedt et al., 1980)
<i>Virola sebifera</i> Aubl.	Ecuador	Carminative, psychotomimetic	Le, Flw	Inhale (Snuff)	(Ballesteros et al., 2016)
<i>Virola surinamensis</i> (Rol. ex Rottb.) Warb.	Brazil, South America	Inflammation, skin infection, cancer, stomach disorder	Ba, Re,	Inhale (Vapour; Snuff), drink (tea)	(Hiruma-Lima et al., 2009)
<i>Virola theiodora</i> (Spruce ex Benth.) Warb.	Brazil, Colombia, Venezuela	Psychotomimetic	Ba, R	Inhale (Snuff)	(Holmstedt et al., 1980)

Abbreviations: Ar, Aril; Ba, Bark; Flw, Flowers; Fr, Fruit; La, Latex; Le, Leaves; R, Roots; Re, Resin; See, Seeds; Sh, Shoot; Ste, Stem; W, Wood.

(TKDL, 2001). Ethnomedicinally nutmegs and wild nutmegs were used to treat the nervous disorder, menstrual complications, rheumatism, asthma, skin infection, as a stimulant, aphrodisiac, abortifacient, blood purifier, antitumor, antidiarrhoeal agents, and others (Khare, 2008; Latha et al., 2005). Bark decoction of *Compsonura* and *Iryanthera* was used as a topical wash to clean wounds (Gottlieb, 1979), *Virola elongata* in rheumatism, joint tumors, toothache, colic, dyspepsia (Alrashedy & Molina, 2016; Gottlieb, 1979; Holmstedt et al., 1980; McKenna, 1984), *Virola bicuhyba* as brain stimulant (Oliveira et al., 2011; Schultes, 1988), *Knema elegans*, *K. furfuracea* to cure cancer, mouth sore, dysentery (Henkin et al., 2017; Murray, Faraoni, Castro, Alza, & Cavallaro, 2013; Phadungkit et al., 2010; Pinto & Kijjoa, 1990) and *Staudtia kamerunensis* var. *gabonensis* as antidote of poison (Musuyu et al., 2012) (Tables 1 and 2). Several references lack

updated scientific and vernacular names of species, preparation of formulation, dosage, route, and duration of administration and others.

4 | PHYTOCHEMICALS

Major oleochemicals reported in *Myristicaceae* are namely, essential (EO), and fixed oils. Major phytochemicals reported in *Myristicaceae* are namely, terpenes (1–30), triglyceride, long-chain fatty acid and derivatives (31–45), phenolics and phenylpropanoids (46–59), diaryl long-chain alkanes (60–79), lignan, neolignan and derivatives (80–120), flavonoids and lignoflavonoids (121–138), coumarins (139–142), indole alkaloids (143–159) and others (160) (Table 3 and Table S1). Structures of representative biomarkers of each group were redrawn

TABLE 3 Phytochemicals of the family *Myristicaceae*

Scientific names	Significant biomarkers/hallucinogens	References
<i>Coelocaryon preussii</i> Warb.	β -sitosterol (22), stigmaterol (21)	(Akoubet et al., 2017)
<i>Horsfieldia glabra</i> (Reinw. ex Blume) Warb.	4-vinylphenol (46)	(Chaichana, 2016)
<i>Horsfieldia irya</i> (Gaertn.) Warb.	1-(2,6-dihydroxyphenyl) dodecan-1-one (41), 2-(6-phenylhexyl)-8-hydroxy-5,6,7,8-tetrahydrochromone (139), 2-(6-phenylhexyl)-5,7-dihydroxychromone (142), 5,7-dihydroxy-2-n-nonylchromen-4-one (141), 8-hydroxy-2-n-nonyl-5,6,7,8-tetrahydrochromon (140), asarinin (98), dihydrocubebin (84), horsfieldin (91), myristic acid (36), trimyrustin (31)	(Gonzalez et al., 2002; Wimalasena & Karunawansa, 1994)
<i>Horsfieldia kingii</i> (Hook.f.) Warb.	Horsfielane A (123), Horsfielenide A (133), Horsfielenide B (134), Horsfielenide D (131) Horsfielenide E (132), maculatin (92), bursehernin (82)	(B. Liu et al., 2019; B. Liu, Chen, Tian, & Zhan, 2019)
<i>Horsfieldia spicata</i> (Roxb.) J. Sinclair	Myristicyclins A (124), Myristicyclins B (125)	(Lu et al., 2014)
<i>Horsfieldia superba</i> Warb.	5-MeO-DMT (143), Horsfiline (158), 6-MeO-2-MTHC (154)	(Kam, 1999)
<i>Iryanthera hostmannii</i> (Benth.) Warb.	Iryantherin A (135), Iryantherin B (136), Iryantherin C (137), Iryantherin D (138), Ba: 5-MeO-DMT (0.013%) (143); Le EO: α -cadinol (7.8%) (16), α -muurolol (13.2%) (17), guaialol (4%) (13), limonene (3.3%) (1), oplopanone (3.7%) (26), spathulenol (12.1%) (15)	(Conserva, Yoshida, Gottlieb, Martinez, & Gottlieb, 1990; Cuca et al., 2009; Holmstedt et al., 1980)
<i>Iryanthera juruensis</i> Warb.	Tocotrienol (26), myristic acid (36), juruenolic acid (33), guaiaicin (90), verrucosin (118), sargachromenol (27), sargaquinoic acid (29)	(Moraes et al., 2009; Silva Dulce et al., 2007)
<i>Knema attenuata</i> Wall.	Attenuol (100)	(Salleh & Farediah, 2017)
<i>Knema glauca</i> Warb.	Malabaricone A (60), Dodecanoylphloroglucinol (44), 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one (66)	(Salleh & Farediah, 2017)
<i>Knema elegans</i> Pierre	Myristinins A (126), Myristinins D (127), 2-hydroxy-6-(12-phenyldodecyl)-benzoic acid (69), 3-(12-phenyldodec-8-enyl)-phenol (72), 2,4-dihydroxy-6-(10-phenyldodecyl)-acetophenone (67)	(Salleh & Farediah, 2017)
<i>Knema furfuracea</i> Warb.	Furfuracin (87), Ginkgolic acid (32), 2-hydroxy-6-(12-phenyldodecyl)-benzoic acid (69), 3-(12-phenyldodecyl)-phenol (73), deHGA (85), 1,2- DdeHGA (81)	(Salleh & Farediah, 2017)
<i>Knema globularia</i> (Lam.) Warb.	Kneglomeratanone A (42), kneglobularic acid A (79)	(Salleh & Farediah, 2017)
<i>Knema laurina</i> (Blume) Warb.	Brefeldin A (160), 2-hydroxy-6-(10'-[Z]-heptadecenyl) benzoic acid (68), 8-deoxytrichothecin (11), 7- α -hydroxytrichodermol (10)	(Salleh & Farediah, 2017)
<i>Knema tenuinervia</i> subsp. <i>setosa</i> W.J. de Wilde	2,4-dihydroxy-6-(10-phenyldodecyl)-acetophenone (67), 3-(8-pentadecenyl)-phenol (43)	(Pinto & Kijjoa, 1990)
<i>Myristica argentea</i> Warb.	MDHGA (93), EA6 (86), Nectandrin-B (106), licarin A (113), licarin B (114), machilin C (115), safrole (59), EME (49), elemicin (56), eugenol (50), IEME (51), MeO-E (54)	(Filleur, Le Bail, Duroux, Simon, & Chulia, 2001; Filleur, Pouget, Allais, Kaouadji, & Chulia, 2002)
<i>Myristica beddomei</i> subsp. <i>Ustulata</i> W.J. de Wilde	β -caryophyllene (18), α -cadinol (16), globulol (12), δ -cardinene (9), 1,5,9,9-tetramethyl-Z,Z,Z-1,4,7-cycloundecatriene (30)	(Vidhya et al., 2015)
<i>Myristica cinnamomea</i> King	Malabaricone A (60), Malabaricone B (61), Malabaricone C (62) & Malabaricone E (64), maingayic acid B (45)	(Wahab et al., 2016)
<i>Myristica fatua</i> Houtt.	Malabaricone B (61), Malabaricone C (62), (7S, 8R, 80S, 70S) 7,70-bis(3-hydroxy-5-methoxyphenyl)-8,80-dimethylbutane-7,70-diol, (80), 3'-hydroxydemethylidactylidin (77)	(Fajriah, Darmawan, Megawati, Kosela, & Hanafi, 2017; Megawati & Darmawan, 2017)
<i>Myristica fragrans</i> Houtt.	Myristicin (32.8%) (58), Elemicin (56), isoelemicin (17.68%) (57), Safrole (4.1%) (59), Me-E (8.13%) (52), eugenol (50), Me-iso-E (53), trans-isoeugenol (2.76%) (55), dehydrodiisoeugenol (4.06%) (48), MeO-E (54), α - pinene (9.8%) (3), β -pinene (9.4%) (4), sabinene (16.01%) (2), linalool (7), linoleic acid (4.12%) (35), geraniol (6), 4-terpeniol (12.08%) (5), palmitic acid (2.8%) (38), virolane (71), myticaganal A (116), myticaganal C (117)	(Chumkaew & Srisawat, 2018; Francis, Suresh, & Nair, 2014; Kalbhen, 1971; Maya et al., 2004; Maya, 2005; Ogunwande, Olawore, Adeleke, & Ekundayo, 2003; Singh, Marimuthu, De Heluani, & Catalan, 2005; Muchtaridi et al., 2010; Valente, Jham, Dhingra, & Ghiviriga, 2011)

TABLE 3 (Continued)

Scientific names	Significant biomarkers/hallucinogens	References
<i>Myristica magnifica</i> Bedd.	Malabaricone B (61), Malabaricone C (62), Promalabaricone B (65)	(Prabha et al., 2018; Prabha et al., 2019)
<i>Myristica malabarica</i> Lam.	Malabaricones A (60), Malabaricones B (61), Malabaricones C (62), Malabaricones D (63), β -caryophyllene (18), linalool (7), α -humulene (8); α -hydroxydihydrochalcone (70), nerolidol (14), δ -cardinene (9), myristic acid (19.06%) (36), stearic acid (57.64%) (39)	(Banerjee, Bauri, Guha, Bandyopadhyay, & Chattopadhyay, 2008; Chelladurai & Ramalingam, 2017; Maya et al., 2015; Talukdar, Jain, De, & Krishnamurthy, 2000; Zachariah et al., 2008)
<i>Osteophloeum platyspermum</i> (Spruce ex DC.) Warb.	NMT (149); DMT (148), 5-MeO-DMT (143), 5-OH-DMT (146)	(Holmstedt et al., 1980; McKenna, 1984)
<i>Otoba novogranatensis</i> Moldenke	Tryptamine (150), Otobain (94)	(Gottlieb, 1979; Zhou & Xie, 2011)
<i>Otoba parvifolia</i> (Markgr.) A. H. Gentry	Tocotrienol (26)	(Ferreira et al., 1989; J. Weiss, 2019)
<i>Pycnanthus angolensis</i> (Welw.) Warb.	Talaumidin (96), myristoleic acid (37), cetyl myristoleate (40), tocotrienol (26), dihydroguaiaretic acid (85), pycnanolide A (119), pycnanolide B (120), pycnanthulignene A (109), pycnanthulignene B (110), pycnanthulignene C (111), pycnanthulignene D (112), pycnanthuquinone A (23), pycnanthuquinone B (24), pycnanthuquinone C (25), 2'-hydroxyformononetin (130), sargahydroquinoic acid (28), sargachromenol (27), sargaquinoic acid (29)	(Achel et al., 2012; Gustafson et al., 2013)
<i>Scyphocephalum ochocoa</i> Warb.	Ocholignan A (107), ocholignan B (108), ochocinone A (74), ochocinone B (75), α -amyrine (19), β -amyrine (20), oleiferinone (76)	(Foundikou et al., 2018; Hu et al., 2005; Ngoua-Meye-Misso et al., 2018)
<i>Virola bicuhyba</i> (Schott ex Spreng.) Warb.	Laruric acid (35%) (34); myristic acid (40%) (36)	(Kobelnik et al., 2013)
<i>Virola calophylla</i> (Spruce) Warb.	T (150), MMT (149), MTHC (158), Le: DMT (0.15%) (148), NMT (0.006%) (149) Ba: 5-MeO-DMT (143)	(Farnsworth, 1968; Holmstedt et al., 1980; McKenna, 1984)
<i>Virola calophylloidea</i> Markgr.	5-MeO-DMT (143), 5-MeO-MMT (144); Le: DMT (0.001%) (148)	(Holmstedt et al., 1980)
<i>Virola carinata</i> (Spruce ex Benth.) Warb.	5-MeO-DMT (143), Le: DMT (0.001%) (148)	(Holmstedt et al., 1980)
<i>Virola elongata</i> (Benth.) Warb.	T (150), MMT (149), 5-MeO-MMT (144), MTHC (158), 5-MeO-THC (154), 6-MeO-2-MTHC (155), 6-MeO-tetrahydro Harman (156), 6-MeO-harmaline (152), 6-MeO-harman (153); 6-MeO-DMT (147), 5-MeO-DMT (ca. 8%) (143); Phloem: 5-MeO-DMT (0.001%) (143); Le: DMT (0.001%) (148)	(Cassady, Blair, Raffauf, & Tyler, 1971; Holmstedt et al., 1980; McKenna, 1984)
<i>Virola michelii</i> Heckel	Titonine (128), 7,3,4-trimethoxy flavone (122), 7,3'-dimethoxy-4'-acetylflavone (121), eudesmin (99), phylligenol (95)	(Carvalho et al., 1999; Morais et al., 2009)
<i>Virola multinervia</i> Ducke	5-MeO-DMT (143), Ba: DMT (0.001%) (148)	(Holmstedt et al., 1980)
<i>Virola pavanis</i> (A.DC.) A.C. Sm.	DMT (148), 5-MeO-DMT (143), MMT (149), carinatidin (102), carinatidin (101), dihydrocarinatidin (105), dihydrocarinatidin (104), dehydrodieugenol (47), galgravin (89), nectandrin B (106), galbelgin (88), verrucosin (118), carinatone (103)	(Holmstedt et al., 1980; McKenna, 1984; Morais et al., 2009)
<i>Virola peruviana</i> (A. DC.) Warb.	DMT (148), 5-MeO-T (145), 6-MeO-2-MTHC (155), 6-OH-DMTHC (157); Paste: 5-MeO-DMT (0.001%) (143)	(Holmstedt et al., 1980)
<i>Virola sebifera</i> Aubl.	DMT (148), 5-MeO-DMT (143), MMT (149); 5-MeO-MMT (144)	(Holmstedt et al., 1980; McKenna, 1984)
<i>Virola surinamensis</i> (Rol. ex Rottb.) Warb.	DMT (148), 5-MeO-DMT (143), Elemicin (56), Virolin (97), Surinamensin (78), Veraguesin (129), Le EO: Safrole (4.6%) (59)	(Holmstedt et al., 1980; Lopes et al., 1999; Saraiva, 2012)
<i>Virola theiodora</i> (Spruce ex Benth.) Warb.	MMT (149), DMT (148), 5-MeO-MMT (144), 5-MeO-DMT (143), Ba (0.19%); R (0.13%); Le (0.1%), 5-MeO-THC (154), 6-MeO-DMT (147), MTHC (158), β -carboline (151)	(Holmstedt et al., 1980; Schultes, 1977; Schultes et al., 1977)

by using ChemDraw software (version 18.2) (Figure 1) and PubChem Compound IDs were provided (Table S1).

Oils: EO content reported in nutmeg seeds were 7–16% and arils 4–17%. Major components were hydrocarbon and oxygenated

monoterpenes and sesquiterpenes (60–80%) namely, sabinene (2), α - and β -pinene (3–4), β -caryophyllene (18), α -humulene (8) and terpene alcohols (5–15%) namely, linalool (7), geraniol (6), 4-terpineol (5). Seeds yield about 25–30% nutmeg butter containing trimyristin (31),

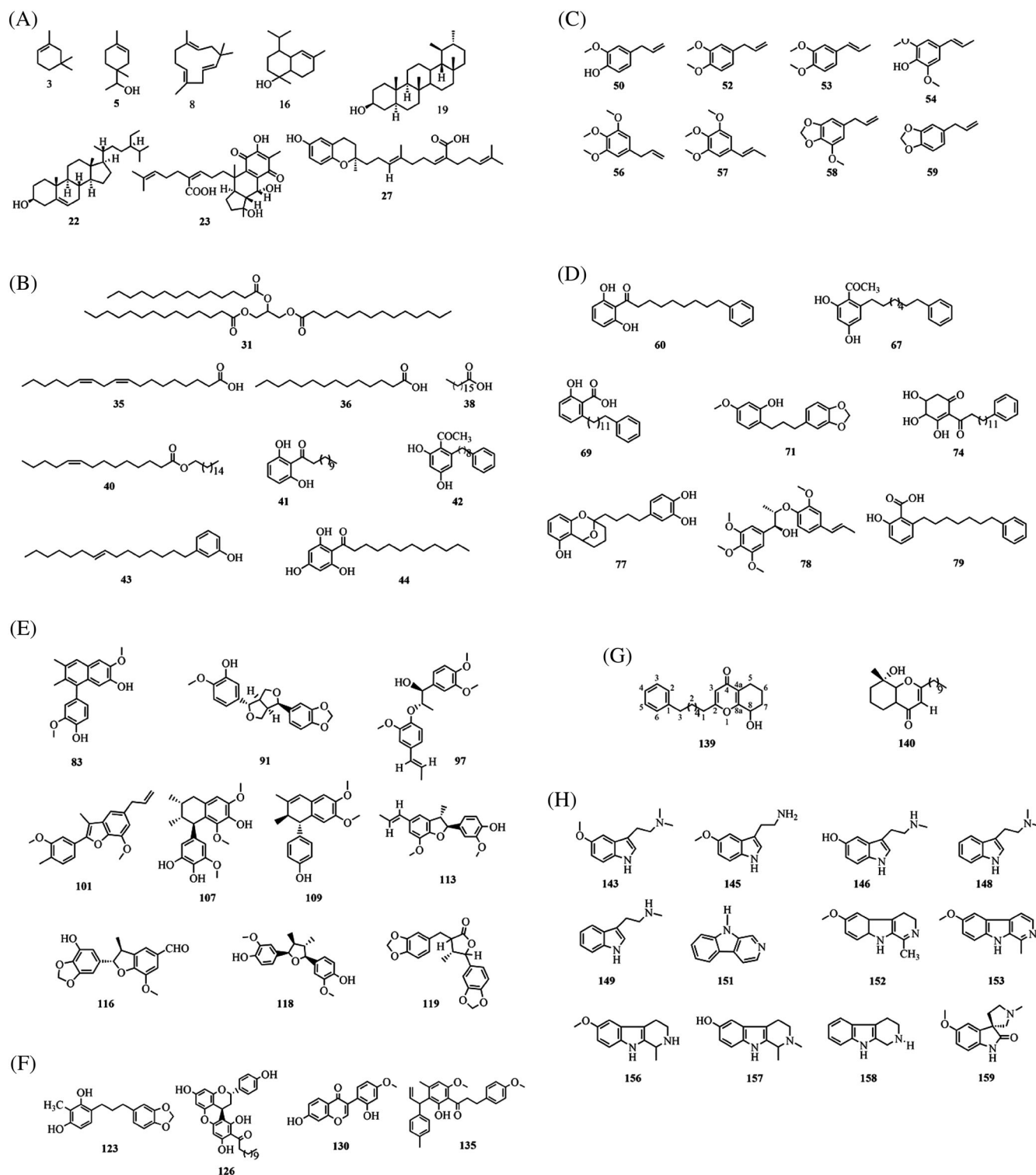


FIGURE 1 Bioactive molecules of major phytochemicals in *Myristicaceae* members: (a) Terpenes; (b) Triglyceride, long-chain fatty acid, and derivatives; (c) Phenolics and phenylpropanoids; (d) Diaryl long-chain alkanes. (e) Lignan, neolignan, and derivatives; (f) Flavonoids and lignoflavonoids; (g) Coumarins, (h) Indole alkaloids

lauric (34), linoleic (35), myristic (36), oleic, palmitic (38), and stearic acids (39) (De Wilde, 2000; Frank, Roberts, Snell, Yates, & Collins, 1971; Hima Sai Bindu, Rubesh Kumar, Duganath, & Devanna, 2013; Morsy, 2016; Saputro, Andarwulan, & Faridah, 2016).

Terpenes (1–30): Terpenes reported in the *Myristicaceae* belong to hydrocarbon and oxygenated monoterpenes namely, limonene (1) and geraniol (6), hydrocarbon and oxygenated sesquiterpenes namely, δ -cardinene (9) and globulol (12), triterpenes (19–20), sterols (21–22) and other terpenes comprising terpenoid-quinone (23–25), tocotrienol (26), tocotrienol derivatives (27–29) and others.

Triglyceride, long-chain fatty acid and derivatives (31–45): Trimyristin (31), the triglyceride, –juruenolic (33), myristic (36), ginkgolic acids (32), cetyl myristoleate (40), the fatty acid ester and aryl alkanone (41), acetophenone (42), acylphenols (44–45) were reported.

Phenolics and phenylpropanoids (46–59): Allylbenzenes namely, eugenol (50), dehydriedieugenol (47), dehydriedioeugenol (48), methyleugenol (52), and phenylpropanoids namely, myristicin (58), elemicin (56), safrole (59), and others were reported as one of the major biomarkers in the *Myristicaceae*.

Diaryl long-chain alkanes (60–79): Diphenylalkanes namely, Malabaricones A–E (60–64), acylphenol like 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one (66), alkylresorcinols namely, ochocinone A–B (74–75), diaryl nonanoid like 3''-hydroxydemethyldactyloidin (77), diaryloctane namely, kneglobularic acid A (79) and others were reported.

Lignan, neolignan and derivatives (80–120): (7S, 8R, 80S, 70S) 7,70-bis(3-hydroxy-5-methoxyphenyl)-8,80-dimethylbutane-7,70-diol (80), 1,2- DdeHGA (81), horsfieldin (91) and others were reported as lignans, carinatidin (101), carinatin (102), nectandrin-B (106) as lignoids, ocholignan A–B (107–108) as cyclolignans, pycnanthulignene A – D (109–112) as cyclolignene derivatives, licarin A (113), myticaganal C (117) as neolignans, pycnanolide A–B (119–120) as lignan lactones were reported in the *Myristicaceae*.

Flavonoids and lignoflavonoids (121–138): Flavonoids namely, 7-,3'-dimethoxy-4'-acetylflavone (121), horsfieldane A (123), myristicyclins A–B (124–125), myristinins A, D (126–127), isoflavone namely, 2'-hydroxyformononetin (130), diarylpropanes namely, horsfieldenide A–B (133–134), D–E (131–132), lignoflavonoids namely, iryantherin A – D (135–138) were reported.

Coumarins (139–142): Coumarins reported in the *Myristicaceae* were namely, 2-(6-phenylhexyl)-8-hydroxy-5,6,7,8-tetrahydrochromone (139), 8-hydroxy-2-n-nonyl-5,6,7,8-tetrahydrochromone (140), 5,7-dihydroxy-2-n-nonylchromen-4-one (141) and others.

Indole alkaloids (143–159): Indole alkaloids are one of the major phytochemicals reported in the family *Myristicaceae* which can be categorized as tryptamine derivatives namely, tryptamine (T) (150), N'-methyltryptamine (NMT or MMT) (149), 5-methoxy N-methyl tryptamine (5-MeO-NMT or 5-MeO-MMT) (144), N'-N'-dimethyl tryptamine (DMT) (148), 5-methoxy N-N- dimethyl tryptamine (5-MeO-DMT) (143), 6-methoxy N-N- dimethyl tryptamine (6-MeO-DMT) (147), 5-hydroxy dimethyltryptamine (5-OH-DMT) (146), 5-methoxytryptamine (5-MeO-T) (145) and β -carbolines (151) and harmala alkaloids namely, 6-methoxy-1-methyl- β -carboline (6-MeO-harman) (153), 1-methyl-6-methoxy-dihydro- β -carboline (6-MeO-har-

malan) (152), 2-methyl-1,2,3,4-tetrahydro- β -carboline (MTHC) (158), 2-methyl-5 hydroxy-1,2,3,4-tetrahydro- β -carboline (5-MeO-THC) (154), 6-methoxy-2-methyl-1,2,3,4-tetrahydro- β -carboline (155) and 1, 2-dimethyl-6 hydroxy-1,2,3,4-tetrahydro- β -carboline (6-OH-DMTHC) (157) and oxindole alkaloid namely, horsfieldin (159). Harmane bases namely, 6-methoxyharman (153), 6-methoxyharman (152), 2-methyl-6-methoxy-1,2,3,4-tetrahydro- β -carboline (6-MeO-tetrahydroharman) (156) were reported in trace amounts in *Myristicaceae* paste and snuff (Holmstedt et al., 1980; McKenna, 1984).

Others: Brefeldin A (160), an endophytic fungal polyketide biomarker was reported from *Knema laurina* (Salleh & Farediah, 2017).

5 | PHARMACOLOGY

Pharmacological evaluation of the plant extracts, essential oil, major biomarkers was critically reviewed for biological activities through in vitro, in vivo studies to the best of our knowledge (Figure 2).

5.1 | Inhibitory activity of cholinesterases and MAO

Inhibitory activity of cholinesterases and MAO were reviewed by AChEI, BChEI in vitro, MAOI in vivo studies and others (Table 4). Only

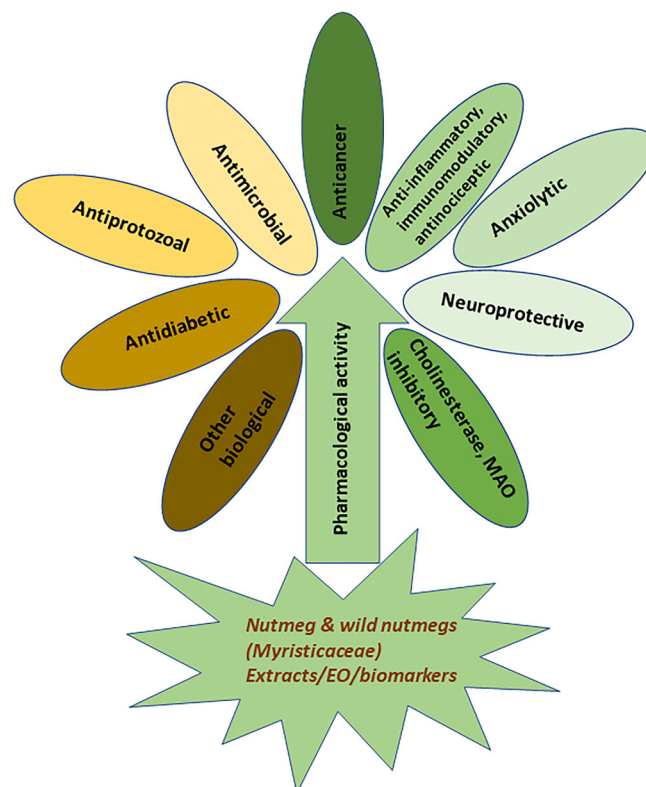


FIGURE 2 General scheme of pharmacological activity of nutmeg and wild nutmegs (*Myristicaceae*) [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Inhibitory activity of cholinesterases and MAO

Scientific name of the species	Parts used	Type of assay/study	Compound/extract	Mode of action	Observations	References
<i>Knema laurina</i>	Bark	In vitro assay	2-hydroxy-6-(10'[Z]-heptadecenyl benzoic acid)	AChEI	IC ₅₀ value of 0.57 ± 0.02 µM	(Akhtar et al., 2011)
<i>Myristica cinnamomea</i>	Fruits	In vitro assay	Malabaricone B from EtOAc extract	AChEI	IC ₅₀ value 1.84 ± 0.19 µM	(Wahab et al., 2016)
<i>M. cinnamomea</i>	Fruits	In vitro assay	Malabaricone C from EtOAc extract	AChEI	IC ₅₀ value 1.94 ± 0.27 µM	(Wahab et al., 2016)
<i>M. cinnamomea</i>	Fruits	In vitro assay	Malabaricone B from EtOAc extract	BChEI	IC ₅₀ value 1.76 ± 0.21 µM	(Wahab et al., 2016)
<i>M. cinnamomea</i>	Fruits	In vitro assay	Malabaricone C from EtOAc extract	BChEI	IC ₅₀ value 2.80 ± 0.49 µM	(Wahab et al., 2016)
<i>M. fragrans</i>	—	In vitro assay	Nutmeg powder (500 mg/kg)	MAOI	Tryptamine potentiation	(Tруitt Jr, Duritz, & Ebersber, 1963)
<i>M. fragrans</i>	—	In vivo study among 54 rats	Myristicin 1 g/kg (oral dose)	MAOI	Reduced intravenous dose of tryptamine and increased 5-HT in brain	(Tруitt Jr et al., 1963)

two assays showed significant AChEI with half-maximal inhibitory concentration (IC₅₀) value of 0.57 ± 0.02 µM of 2-hydroxy-6-(10'[Z]-heptadecenyl) benzoic acid isolated from *Knema laurina* (Akhtar et al., 2011) and AChEI and BChEI with IC₅₀ 1.84 ± 0.19–2.80 ± 0.49 µM of Malabaricone B and C from *Myristica cinnamomea* (Wahab et al., 2016). In vivo study with 1 g/kg oral dose of myristicin from *M. fragrans* exhibited MAOI in 6 out of 54 experimental rats where the study lacked the health and sex status of the experimental animals and the approval of ethical clearance and guidelines from the committee for use of laboratory animals (Tруitt Jr et al., 1963).

5.2 | Neuroprotective activity

Only two studies showed neuroprotective activity by inhibition of release of nitric oxide (NO), cytokines, chemokines, reduction in neuronal damage due to glutamate, BV-2 Microglial cell (MGC), reduction in NF-κB translocation, O₂-glucose deprivation in vitro, infarct volume in vivo against post-stroke brain damage, neurogenesis with ethanolic leaf extract in vitro (Gustafson et al., 2013; Hake et al., 2009) (Table 5). In a mixed study, EtOH leaf extract of *Knema laurina* showed, dose-dependent decrease in NO release from lipopolysaccharide (LPS) activated MGC compared to control, approx. 36.5% protection against glutamate damage at 150 µg/ml, reduction in neuronal damage, IL-6 release, expression of Intercellular Adhesion Molecule 1, inhibition of NF-κB, ERK-1/2, Ikb, showed neurogenesis and reduced infarct volume at 30 mg/kg in stroke model of SD rats (Hake et al., 2009). However, in vitro assay was carried out with only extracts (Hake et al., 2009) and effective concentration of isolated biomarkers was as high as 30 mg/kg in in vivo studies, which had moderate translational relevance to human dosage (Gustafson et al., 2013; Izzo et al., 2020).

5.3 | Anxiolytic activity

Anxiolytic activity was reviewed by parameters namely, increase in rearing, and ambulations, reduction in locomotor activity, experiments on the elevated plus-maze and others in only three in vivo studies (Table 6). In study among 40 male Albino mice, *M. fragrans* at 25 and 50 mg/kg, exhibited improvements in anxiety-related parameters like increased numbers of rearing and ambulations and decreased grooming and fecal pellets in dose-dependent manner compared to vehicle control. Fifty milligram per kilogram water extract exhibited anxiolytic activity comparable to 2 mg/kg of Diazepam (Nagaraju et al., 2013). However, the studies lacked inclusion of mice of both sexes while the second was conducted with only water extract for very short duration that is, 7 days, the third used synthetic myristic acid (Contreras et al., 2014; Nagaraju et al., 2013).

5.4 | Antiinflammatory, immunomodulatory activity, and antinociceptive effect

Antiinflammatory activity was reviewed by inhibition of enzymes COX-1, COX-2, the release of NO, cytokines, chemokines, by assays namely, protein denaturation, membrane stabilization in vitro, inhibition of mouse edema induced by carrageenan, 12-O-tetrahydrodecanylphorbol-13-acetate (TPA) in vivo, immunomodulatory activity by myeloperoxide burst assay in vitro and analgesic activity by a reduction in acetylsalicylic acid-induced writhing numbers and formalin-induced injured arm licking in vivo studies in altogether six studies and two literature reviews (Table 7). 7,4' dimethoxyflavone, tithonine, fasciculiferin, farnisine from methanolic leaf extract of *Iryanthera juruensis* at 100 ppm inhibited enzymes COX-1, COX-2 by 50–65%, sargaquinoic acid, guaiacin from seed hexane extract at

TABLE 5 Neuroprotective activity

Scientific name of the species	Parts used	Type of assay/study	Compound/extract	Mode of action	Observations	References
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Inhibition of NO release	Decrease in NO release from LPS-activated MGC compared to control	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Inhibition of NO release	IC ₅₀ value 14.8 µg/ml in BV-2 MGC	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Dose-dependent protection against glutamate damage	Approx. 36.5% protection at 150 µg/ml, 19.9% protection at 75 µg/ml	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Reduction in MGC mediated neuronal damage	15 and 30 µg/ml reduced primary damage and 75 µg/ml secondary damage	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Reduction of IL-6 release, ICAM-1 expression,	Reduction of IL-6, at 300 µg/ml of ICAM-1 expression	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Inhibition of NF-kB translocation, ERK-1/2, Ikb phosphorylation	at 15 µg/ml inhibition of NF-kB translocation, ERK-1/2, at 30 µg/ml Ikb phosphorylation	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vitro	EtOH extract	Neurogenesis	30 µg/ml in OGD model of brain tissue exhibited approx. 1.8 fold neurogenesis	(Hake et al., 2009)
<i>K. laurina</i>	Leaves	In-vivo	EtOH extract	Prevention against post stroke brain damage	Reduced infarct volume at 30 mg/kg, 24 hr after in MCAO ischemia model of SD rats (250–280 g).	(Hake et al., 2009)
<i>Pycnanthus angolensis</i>	Seeds	In-vivo	Sargahydroquinoic acid	Reduced neuronal damage	30 mg/kg reduced brain infarct volume, 48% neuronal damage in mice after 24 hrs	(Gustafson et al., 2013)
<i>P. angolensis</i>	Seeds	In-vivo	1-4-diacetyl sargahydroquinoic acid	Reduced neuronal damage	30 mg/kg reduced brain infarct volume, 54% neuronal damage in mice after 24 hrs	(Gustafson et al., 2013)

100 ppm inhibited enzyme COX-1 by 60–65% against Celebrex and Aspirin as reference (Silva Dulce et al., 2007). Ochocinone A, Ochocinone B, and Oleiferinone from methanolic leaf extract of *Scyphocephalum ochocoa* exhibited immunomodulatory activity through myeloperoxidase oxidative burst assay with IC₅₀ value ranging approx. <1–2.91 µg/ml in polymorphonuclear neutrophils (PMNs), macrophages and TNF-α inhibition approx. 39–73% at 25 µg/ml and NO inhibition 81–110% (Foundikou et al., 2018). Ethanol water extract of bark of *Scyphocephalum ochocoa* exhibited IC₅₀ value 34.775 ± 2.543 µg/ml against protein denaturation and membrane stabilization by water extract exhibiting hypotonicity and heat mediated hemolysis of RBC with IC₅₀ value 56.713 ± 0.492 µg/ml and 36.793 ± 0.529 µg/ml (Ngoua-Meye-Misso et al., 2018). Carrageenan-induced paw edema was inhibited by seed oil of *M. fragrans* by 75%, formalin-induced injured arm licking time in rodents was reduced by seed oil and adrenaline injected anti-thrombotic protection by 96% as referral to acetylsalicylic acid

(Olajide et al., 2000) and chloroform extract of seeds of *M. fragrans* showed a reduction in the acetylated salicylic acid-induced writhing numbers approx. 11–7 (Olajide et al., 1999). Out of three in vivo studies, one used chloroform extract (Olajide et al., 1999), one exhibited gastric mucosal ulceration with seed oil and indomethacin (Olajide et al., 2000) while the other was conducted only on male mice (Carvalho et al., 1999). In vitro assay of antiinflammatory activity was carried out with only extracts (Ngoua-Meye-Misso et al., 2018), whereas reviewed references lacked effective concentration of Kombo butter of *Pycnanthus angolensis* (Gustafson et al., 2013) and biomarkers of *Knema glauca* (Rangkaew et al., 2009).

5.5 | Anticancer activity

Anticancer activity of *Myristicaceae* members was critically reviewed on cytotoxicity, inhibition of DNA polymerase-β, the anti-angiogenic

TABLE 6 Anxiolytic activity

Scientific name of the species	In vivo study	Compound/ extract	Mode of action	Observations	References
<i>M. fragrans</i>	Weel cage study among 2-3 months old male mice of 25-30 g for 30-180 minutes	0.5 mL seed EO inhalation	Reduction in cage movement	Reduced approximately 69% cage movement compared to approximately 58% of lavender oil and 0% in control after 75 minutes	(Muchtaridi et al., 2010)
<i>M. fragrans</i>	Weel cage study among 2-3 months old male mice of 25-30 g for 30-180 minutes	0.5 ml Myristicin inhalation	Reduction in cage movement	Reduced approximately 86% cage movement after 75 minutes	(Muchtaridi et al., 2010)
<i>M. fragrans</i>	Weel cage study among 2-3 months old male mice of 25-30 g for 30-180 minutes	0.5 ml Safrole inhalation	Reduction in cage movement	Reduced approximately 90% cage movement after 75 minutes	(Muchtaridi et al., 2010)
<i>M. fragrans</i>	Weel cage study among 2-3 months old male mice of 25-30 g for 30-180 minutes	0.5 ml 4-terpineol inhalation	Reduction in cage movement	Reduced approximately 79% cage movement after 75 minutes	(Muchtaridi et al., 2010)
<i>M. fragrans</i>	Open field model among 1-2 months old 40 male Albino mice of 18-35 g - 7 days	25 mg/kg water extract	Reduced anxiety	Increased numbers of rearing (approx. 12), ambulation (approx. 71) than control (approx. 4 and 33). Decreased grooming (approx. 4), fecal pellets (approx. 3) numbers than vehicle control.	(Nagaraju et al., 2013)
<i>M. fragrans</i>	Open field model among 1-2 months old 40 male Albino mice of 18-35 g - 7 days	50 mg/kg water extract	Anxiolytic activity comparable to 2 mg/kg Diazepam	Increased numbers of rearing (approx. 16), ambulation (approx. 94) than control (approx. 4 and 33). Decreased dose-dependent grooming (approx. 2), fecal pellets (approx. 2) numbers than vehicle control (approx. 10 and 7).	(Nagaraju et al., 2013)
—	11-12 weeks old 149 male Wister rats of 200-250 g	Myristic acid (30 µg/ml)	Reduced anxiety under elevated plus maze (8 fatty acids mixture like human amniotic fluid, individual 8 fatty acids, Diazepam	Enhanced anxiolytic parameters with Myristic acid, reduced anxiety index.	(Contreras et al., 2014)
—	11-12 weeks old 149 male Wister rats of 200-250 g	Myristic acid	Dose-dependent (at 10-60 µg/rat) anxiolytic effect by Locomotor activity test	Reduction in crossing number (approx. 68-29), activity time (approx. 147-79 sec), increased resting time (152-214 sec) (at 10-60 µg/rat) respectively compared to vehicle control approx. 51 crossing number, activity 108 sec and resting time 191 sec.	(Contreras et al., 2014)

activity of plant extracts, EO, biomarkers against several cell lines with lowest IC₅₀ values (<1-16.53 µg/ml, <1-26 µM approx.) assay type, toxicity in normal cells, use of reference drugs in altogether 14 studies and 1 review (Table 8). Kneglomeratanone A from methanolic extract of the root of *K. globularia* exhibited IC₅₀ value 16.53 µg/ml against human

lung cancer (NCI-H187) and 48.03 µg/ml in normal (Vero) cell lines using ellipticine as reference. Kneglobularone A from hexane extract showed IC₅₀ value 13.07 µg/ml against KB and 10.43 µg/ml against NCI-H187 and 8.23 µg/ml in normal Vero cell lines using doxorubicin as reference (Salleh & Farediah, 2017). 2',4'-dihydroxy-6-methoxy-3,4-methyl

TABLE 7 Antiinflammatory, immunomodulatory activity, and antinociceptive effect

Scientific name	Plant part	Extract/compound	Control/Ref. drug	Activity	Concn.	Observations	References
<i>Myristica fragrans</i>	Seed	Chloroform		Antiinflammatory	50–200 mg/kg	Carrageenan-injected paw edema inhibition (38–66%) - male Swiss albino mice (20–28 g), Wistar rats (170–270 g)	(Olajide et al., 1999)
<i>M. fragrans</i>	Seed	Chloroform		Analgesic	50–200 mg/kg	Reduction of acetylsalicylic acid influenced writhing numbers approx. 11 to 7	(Olajide et al., 1999)
<i>M. fragrans</i>	Seed	Chloroform	Tween 80 - control	Anti-thrombotic	50–200 mg/kg	Protection in adrenaline and ADP injected thrombosis approx. 86–90%	(Olajide et al., 1999)
<i>M. fragrans</i>	Seed	Seed oil	Tween 80 - control, Indomethacin - reference	Antiinflammatory	40 mg/kg	75% inhibition of Carrageenan-injected edema - male Albino rats (200–280 g), Swiss albino mice (22–30 g)	(Olajide, Makinde, & Awe, 2000)
<i>M. fragrans</i>	Seed	Seed oil	Do	Analgesic	40 mg/kg	Reduction of acetic acid injected writhing numbers approx. 17	(Olajide et al., 2000)
<i>M. fragrans</i>	Seed	Seed oil	Do	Analgesic	40 mg/kg	Reduced formalin induced injured arm licking time approx. 9 sec.	(Olajide et al., 2000)
<i>M. fragrans</i>	Seed	Seed oil	Do	Reduction in hyperpyrexia	40 mg/kg	Reduced fever caused by Yeast	(Olajide et al., 2000)
<i>M. fragrans</i>	Seed	Seed oil	Acetylsalicylic acid (ASA)	Anti-thrombotic		Protection approx. 96% in adrenaline, ADP injected thrombosis	(Olajide et al., 2000)
<i>Viola michellii</i>	Leaves	7,4'-dimethoxy-3'-hydroxyflavone, titonine derivative (Hexane extract)		Antiinflammatory, Analgesic	10 mg/kg	Inhibited approx. 46% carrageenan-injected paw edema, reduced writhing numbers - male Wistar rats, male albino mice	(Carvalho et al., 1999)
<i>V. michellii</i>	Leaves	7,4'-dimethoxy-3'-acetylflavone, titonine derivative		Antiinflammatory	10 mg/kg	Inhibited approx. 78% carrageenan-injected paw edema	(Carvalho et al., 1999)
<i>Iryanthera juruensis</i>	Methanolic leaf	7,4' dimethoxyflavone	Celebrex (7 ppm), Aspirin (180 ppm)	Antiinflammatory	100 ppm	Inhibited COX-1 by 65%	(Silva Dulce et al., 2007)
<i>I. juruensis.</i>	Methanolic leaf	Fasciculiferin	Celebrex (7 ppm), Aspirin (180 ppm)	Antiinflammatory	100 ppm	Inhibited COX-1 by <60%, COX-2 by 51%	(Silva Dulce et al., 2007)
<i>I. juruensis.</i>	Methanolic leaf	Tithonine	Celebrex (7 ppm), Aspirin (180 ppm)	Antiinflammatory	100 ppm	Inhibited COX-1 by <60%, at 10 ppm LPO by 86%	(Silva Dulce et al., 2007)
<i>I. juruensis</i>	Seeds hexane	Sargaquinoic acid	Celebrex (7 ppm), Aspirin (180 ppm)	Antiinflammatory	100 ppm	Inhibited COX-1 by 60%	(Silva Dulce et al., 2007)
<i>I. juruensis</i>	Seeds hexane	Guaiacin	Celebrex (7 ppm), Aspirin (180 ppm)	Antiinflammatory	100 ppm	Inhibited COX-1 by 65%, LPO by 99%	(Silva Dulce et al., 2007)
<i>Knema glauca</i>	EtOAc extracts -leaves, fruits	Myristinins A, Myristinins B		Antiinflammatory		Inhibited COX-1, COX-2	(Rangkaew, Suttisri, Moriyasu, & Kawanishi, 2009)

(Continues)

TABLE 7 (Continued)

Scientific name	Plant part	Extract/compound	Control/Ref. drug	Activity	Concn.	Observations	References
<i>Pycnanthus angolensis</i>	Seed fat	Kombo butter, Sargahydroquinolic acid, Sargachromenol		Antiinflammatory		Inhibited NO; iNOS mRNA, protein; COX2 protein	(Gustafson et al., 2013)
<i>P. angolensis</i>	Seed fat	Sargachromenol	Indomethacin - reference	Antiinflammatory		Inhibits 12-O-TPA raised edema	(Gustafson et al., 2013)
<i>Scyphocephalum ochocoa</i>	Methanolic leaf	Ochocinone A, Ochocinone B, Oleiferinone	Luminol, Lucigenin, Ibuprofen -reference	Immunomodulatory	<1–2.91 µg/ml	Myeloperoxide oxidative burst IC ₅₀ value approx. <1–2.91 (PMNs), <1–1.83 (macrophages) against Luminol, approx. <1–2.71 (PMNs), <1–2.37 (macrophages) against Lucigenin; Ibuprofen approx. 13–14 µg/ml	(Foundikou et al., 2018)
<i>S. ochocoa</i>	Methanolic leaf	Ochocinone A, Ochocinone B, Oleiferinone		Antiinflammatory	25 µg/ml	Inhibition of TNF-α approx. 39–73%, NO >81%	(Foundikou et al., 2018)
<i>S. ochocoa</i>	Ethanol water extract (bark)			Antiinflammatory	100 µg/ml	Inhibition of approx. 65–66% protein denaturation; IC ₅₀ value 34.775 ± 2.543 µg/ml	(Ngoua-Meye-Misso et al., 2018)
<i>S. ochocoa</i>	Water extract (bark)		Sodium diclofenac - reference	Antiinflammatory	100 µg/ml	Membrane stabilization through hemolysis of RBC (approx. 65–66% albumin denaturation; IC ₅₀ value induced by hypotonicity, heat–56.713 ± 0.492; 36.793 ± 0.529 µg/ml)	(Ngoua-Meye-Misso et al., 2018)

TABLE 8 In vitro assays on cytotoxicity of nutmeg and wild nutmegs of *Myristicaceae*

Scientific name of the species name	Extract	Plant part	Conc./IC ₅₀ /GI ₅₀ value	Compound	Reference drug	Cancer cell line	IC ₅₀ value in normal cell line	Assay type	References
<i>K. furfuracea</i>	NR	Bark	1.85 µg/ml	3-(12-phenyldodecyl)phenol	–	A-549	–	–	(Salleh & Farediah, 2017)
<i>K. furfuracea</i>	NR	Bark	2.62 µg/ml	3-(12-phenyldodecyl)phenol	–	HT-29	–	–	(Salleh & Farediah, 2017)
<i>K. globularia</i>	MeOH	Root	16.53 µg/ml	Kneglomeratanone A	Ellipticine	NCI-H187	48.03 µg/ml in Vero	Resazurine microplate	(Salleh & Farediah, 2017; Sriphana, Yenjai, & Koatthada, 2016)
<i>K. globularia</i>	MeOH	Root	13.07 µg/ml	Kneglobularone A	Doxorubicin	KB	8.23 µg/ml in Vero	Resazurine microplate	(Salleh & Farediah, 2017; Sriphana et al., 2016)
<i>K. laurina</i>	KLAR 5 CB	Twig	0.09 µg/ml	NR	Ellipticine	KB	–	Colorimetric	(Chinworungsee, Wiyakrutta, Sriubolmas, Chuailua, & Suksamarn, 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	0.03 µg/ml	NR	Doxorubicin	BC-1	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	0.31 µg/ml	NR	Ellipticine	NCI-H187	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	Mycella		0.10, and µg/ml	NR	Ellipticine	KB	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	Mycella		0.02 µg/ml	NR	Doxorubicin	BC-1	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	Mycella		0.29 µg/ml	NR	Ellipticine	NCI-H187 cell line	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	IC ₅₀ value 0.18 µM	Brefeldin A	Ellipticine	KB	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	IC ₅₀ value 0.04 µM	Brefeldin A	Doxorubicin	BC-1	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	IC ₅₀ value 0.11 µM	Brefeldin A	Ellipticine	NCI-H187	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	IC ₅₀ value 0.88 µM	8-deoxytrichothecin	Doxorubicin	BC-1	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	IC ₅₀ value 1.48 µM	8-deoxytrichothecin	Ellipticine	NCI-H187	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. laurina</i>	KLAR 5 CB	Twig	IC ₅₀ value 1.73 µM	7-α-hydroxytrichodermol	Ellipticine	NCI-H187	–	Colorimetric	(Chinworungsee et al., 2008)
<i>K. angustifolia</i>	Ethanol	Leaves	4.55 ± 4.60 µg/ml	Polar and Phenolic compounds	–	NCI-H187	–	MTT	(Phadungkit et al., 2010)
<i>I. juruensis</i>	Diethyl ether	NR	GI ₅₀ value 8.4 µg/ml, 7.4 µg/ml	2',4'-dihydroxy-6'-methoxy-3,4-methylenedioxydihydrochalcone, 2',4'-dihydroxy-4,6'-dimethoxydihydrochalcone	–	K562	GI ₅₀ value 28.4 µg/ml, 40.4 µg/ml in Vero	Cell growth inhibition	(Aponte et al., 2007)
<i>M. fragrans</i>	Seed EO	Seed	146 µg/ml	Myristicin	–	Carco-2	–	MTT	(Piras et al., 2012)
<i>M. fragrans</i>	Seed EO by HD	Seed	167 µg/ml	EO (HD)	Myristicin	Caco-2	–	MTT	(Piras et al., 2012)
<i>M. fragrans</i>	Seed EO by SCFE	Seed	155 µg/ml	EO (SFE)	Myristicin	Caco-2	–	MTT	(Piras et al., 2012)
<i>M. fragrans</i>	Ethanol	Seed	10.1 µM	MDHGA	Taxol	H358	MDCK (normal cell)	MTT	(Thuong et al., 2014)
<i>M. fragrans</i>	EO by HD	Leaves	100 µl	EO (HD)	–	MCF-7	–	64% metabolic activity by Trypan Blue dye exclusion	(Mary, Tina, Jeeja, & Abiramy, 2012)

(Continues)

TABLE 8 (Continued)

Scientific name of the species name	Extract	Plant part	Conc./IC ₅₀ /GI ₅₀ value	Compound	Reference drug	Cancer cell line	IC ₅₀ value in normal cell line	Assay type	References
<i>M. fragrans</i>	EO by HD	Leaves	100 µl	EO (HD)	—	A-357	—	64% metabolic activity by Trypan Blue dye exclusion	(Mary et al., 2012)
<i>M. fragrans</i>	EO by HD	Fresh fruit	24.83 µg/ml	Myristicin	—	—	24.83 µg/ml in Vero	MTT	(Piaru, Mahmud, & Perumal, 2012)
<i>M. fatua</i>	Methanol	Leaves	26.19 µM, 8.33 µM	(7S, 8R, 8'S, 7'S) 7,70-bis (3-hydroxy-5-methoxyphenyl)-8,80dimethyl-butane-7,70-diol, 3''-hydroxydemethyldactyloidin	Cisplatin	MCF-7	—	Alamar Blue	(Fajriah et al., 2017)
<i>M. argentea</i>	Pet. Ether	Mace	30 µM	TA-5, EA-6, MDHGA, Malabaricanone A	—	MCF-7	—	NR assay	(Filleur et al., 2001)
<i>M. fragrans</i>	Acetone	Seeds	IC ₅₀ value 9.2 µM	Dehydodi-isoegenol	Doxorubicin	MCF-7	—	MTT	(Chumkaew & Srisawat, 2018)
<i>M. fragrans</i>	Acetone	Seeds	IC ₅₀ value 6.3 µM	Myticaganal C	Doxorubicin, Ellipticine	NCIH187	—	MTT	(Chumkaew & Srisawat, 2018)
<i>M. fragrans</i>	Acetone	Seeds	IC ₅₀ value 5.9 µM	Myticaganal C	Doxorubicin, Ellipticine	KB	—	MTT	(Chumkaew & Srisawat, 2018)
<i>K. elegans</i>	Methyl ethylketone	Wood	9 µM concn.	(+) Myristinins A, (+) Myristinins D	Bleomycin	P388D1	30% viable cells	93%, 84% DNA polymerase-β inhibition	(Deng, Starck, Li, & Hecht, 2005)
<i>M. fatua</i>	DCM	Bark	IC ₅₀ value 2.68 µg/ml and 0.71 µg/ml	Malabaricone B and Malabaricone C	—	MCF-7 cell lines	—	Alamar blue	(Megawati & Darmawan, 2017)
<i>Scyphocephalum ochocaa</i>	Methanol	Leaf	<1 µg/ml, 1.04 µg/ml	Ochocinone B, Oleiferinone	Doxorubicin	MCF cell lines	—	MTT	(Foundikou et al., 2018)

enedioxy dihydrochalcone and 2',4'-dihydroxy-4,6'-dimethoxy dihydrochalcone isolated from diethyl ether extracts of *Iryanthera juruensis* showed growth inhibition by 50% (GI₅₀) value 8.4 µg/ml and 7.4 µg/ml against human leukemia (K562) cell line compared to moderate activity in Vero cells with growth inhibitory 50% GI₅₀ value of 28.4 and 40.4 µg/ml (Aponte et al., 2007). Ochocinone B and Oleiferinone from methanolic leaf extract of *Scyphocephalum ochocoa* exhibited IC₅₀ value <1.05 µg/ml against Breast cancer (MCF) cell lines (Foundikou et al., 2018). Brefeldin A, 8-deoxytrichothecin, 7-α-hydroxytrichodermol isolated from the KLAR 5 extract of endophytic fungi from *K. laurina* twig exhibited IC₅₀ value 0.04–1.73 µM against KB, human lymphoma (BC-1), NCI-H187 cell lines (Salleh & Farediah, 2017). Myristinins A and D isolated from methyl ethylketone extracts of wood of *K. elegans* showed cytotoxicity against mouse macrophage P388D1 cells with the IC₅₀ value 9 µM and inhibited DNA polymerase-β by 93% and 84% and viable cells by 30% (Deng et al., 2005). The aqueous extract of bark of *Scyphocephalum ochocoa* at 62.5 µg/ml showed 26.66% inhibition of angiogenesis with IC₅₀ value 1.153 µg/ml in Chick Chorioallantoic Membrane model (Ngoua-Meye-Misso et al., 2018). Only seven studies included reference drugs, five included cytotoxicity of normal cell lines (Aponte et al., 2007; Deng et al., 2005; Piaru et al., 2012; Sriphana et al., 2016; Thuong et al., 2014) and four employed statistical methods to analyze the results (Foundikou et al., 2018; Piaru et al., 2012; Piras et al., 2012; Thuong et al., 2014).

5.6 | Antimicrobial activity

There were several publications on anti-microbial and anti-viral activities which mostly lack information of Minimum Inhibitory Concentration (MIC) value and the most significant activities on *Mycobacterium*, oral pathogens, enteric bacteria, and dermal pathogens were reviewed from 10 studies and 1 review work (Table 9). Malabaricone A isolated from fruits of *Knema glauca* exhibited MIC value as 25 µg/ml against *Mycobacterium tuberculosis* and Dodecanoylphloroglucinol showed IC₅₀ value 3.05 µg/ml against *Herpes simplex I* (Rangkaew et al., 2009). The EtOAc extract of fruit flesh of *M. fragrans* showed the bactericidal activity against oral pathogenic strains of *Streptococcus salivarius* (ATCC 13419) and *S. mitis* (ATCC 6249) with MIC value 0.625 mg/ml and antibacterial activity against *S. mutans* (ATCC25175), *Aggregatibacter actinomycetemcomitans* (ATCC29522), *Porphyromonas gingivalis* (ATCC33277) with 0.62–1.25 mg/ml (Shafiei, Shuhairi, Yap, Sibungkil, & Latip, 2012). The fruit EO exhibited approx. MIC value 0.03 mg/ml against *Shigella dysenteriae*, with MIC >1 mg/ml against *Salmonella typhi*, *Klebsiella pneumoniae*, *E. coli*, *Bacillus subtilis* and *Proteus vulgaris*. Trimyristin, Myristic acid and Myristicin isolated through chloroform extract of seed exhibited approx. MIC value 0.60–0.62 mg/ml against *Pseudomonas aeruginosa*, 0.6–1.25 mg/ml against *Staphylococcus aureus*, *Bacillus subtilis* and *M. luteus* (Narasimhan & Dhake, 2006; Piaru et al., 2012). Ethylacetate fraction of fruit flesh of *Scyphocephalum ochocoa* showed MIC value 16 µg/ml against methicillin resistant *S. aureus* ATCC 33591, *S. aureus* ATCC 78-13607A

(Hu et al., 2005). Inhibition zone diameter of leaf EO of *M. fragrans* was determined against pathogenic bacteria and *Candida tropicalis* by Kirby Bauer method (Mary et al., 2012). Only seven studies and one literature review were found with MIC out of which five studies and the literature review were reported with solvent extracts and essential oil without characterizing the components (Chaichana, 2016; Hu et al., 2005; Q. Liu et al., 2017; Piaru et al., 2012; Shafiei et al., 2012; Vinayachandra & Chandrashekar, 2014). However, MIC values (<25 µg/ml) of only two studies may have moderate translational relevance to the human application (Hu et al., 2005; Rangkaew et al., 2009) where the former used only extracts without characterizing the biomarkers and the later did not analyze the results statistically. The results were statistically analyzed in only four studies (Piaru et al., 2012; Shafiei et al., 2012; Singh et al., 2005; Vinayachandra & Chandrashekar, 2014).

5.7 | Antiprotozoal activity

Significant anti-protozoal activity was reviewed by in vitro assays of six studies against Malaria, *Leishmania* and *Trypanosoma* with extracts and bioactive markers (Table 10). Talaumidin isolated from dichloromethane (DCM) extract of stem of *Pycnanthus angolensis* showed an IC₅₀ value of 20.7 µg/ml against Dd₂-chloroquine-resistant *P. falciparum* and the stem extract with IC₅₀ value 1.6 µg/ml against 3D7 *P. falciparum* (Abrantes et al., 2008). Malabaricone A from n-Hexane extract of fruits, leaves of *Knema glauca* showed IC₅₀ value 2.78 µg/ml against *Plasmodium falciparum* (Rangkaew et al., 2009). Myristicyclin A from *Horsfieldia spicata* exhibited IC₅₀ value 54 µM against schizont stage of *P. falciparum* (Lu et al., 2014). Aryltetraline neolignane and tetrahydrofuran lignan of *Iryanthera juruensis* arils showed IC₅₀ value 45 µg/ml and 27 µg/ml against *Leishmania amazonensis* (Morais et al., 2009). Water extract of bark of *Staudtia kamerunensis* exhibited IC₅₀ value 38.47 µg/ml against *Trypanosoma brucei brucei* (Musuyu et al., 2012). Cytotoxicity of experimental extracts/biomarkers was conducted in only one study, which showed weak anti-protozoal effect (Musuyu et al., 2012). Results of none of the studies were statistically analyzed.

5.8 | Antidiabetic activity

Antidiabetic activity was reviewed by inhibition of α-glucosidase, α-amylase, advanced glyated end products (AGEs) and allied in vitro assays from three studies and one literature review (Table 11). Malabaricone C isolated from DCM extract of bark of *M. magnifica* showed α-amylase, α-glucosidase and advanced glyated end products (AGEs) inhibition with IC₅₀ value 10.63, 43.61, 14.99, and IC₅₀ 32.7 µM against α-amylase with Promalabaricone B (Prabha et al., 2018, 2019). Pycnanthuquinone A, B from *Pycnanthus angolensis* exhibited anti-hyperglycemic activity (Gustafson et al., 2013). Only one study showed upregulation of gene signaling pathway (Prabha

TABLE 9 Antimicrobial activity

Scientific name of the species	Plant parts	Extract/compound	Activity against	Minimum inhibitory Concn. (MIC Value)	Minimum inhibitory zone (MIZ) mm/10 µl	Reference drug	Method	References
<i>Krema glauca</i>	fruits	Malabaricone A	<i>Mycobacterium tuberculosis</i>	25 µg/ml	–	Isoniazid, Kanamycin sulfate	Alamar Blue	(Rangkaew et al., 2009)
<i>K. glauca</i>	fruits	1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one	<i>Mycobacterium tuberculosis</i>	100 µg/ml	–	Do	Do	(Rangkaew et al., 2009)
<i>K. glauca</i>	fruits	dodecanoylphloroglucinol	Herpes simplex virus type I	3.05 µg/ml	–	Do	Do	(Rangkaew et al., 2009)
<i>Myristica fragrans</i>	Fruit flesh	Ethyl acetate	<i>Streptococcus salivarius</i> (ATCC 13419), <i>Streptococcus mitis</i> (ATCC 6249)	0.625 mg/ml, (MBC-2.5 mg/ml)	–	Tetracyclin	Broth dilution	(Shafiei et al., 2012)
<i>M. fragrans</i>	Fruit flesh	Ethyl acetate	<i>Streptococcus mutans</i> (ATCC 25175)	1.25 mg/ml (MBC-20 mg/ml)	–	Tetracyclin	Broth dilution	(Shafiei et al., 2012)
<i>M. fragrans</i>	Fruit flesh	Ethyl acetate	<i>Aggregatibacter actinomycetemcomitans</i> (ATCC29522)	1.25 mg/ml	–	Metronidazole	Broth dilution	(Shafiei et al., 2012)
<i>M. fragrans</i>	Fruit EO		<i>Shigella dysenteriae</i>	0.031 mg/ml	–	Amoxycillin, Gentamycin, Chloramphenicol, Vancomycin	Tetrazolium microplate	(Piaru et al., 2012)
<i>M. fragrans</i>	Fruit EO		<i>Salmonella typhi</i>	>1 mg/ml	–	Do	Do	(Piaru et al., 2012)
<i>M. fragrans</i>	Fruit EO		<i>Escherichia coli</i>	>1 mg/ml	–	Do	Do	(Piaru et al., 2012)
<i>M. fragrans</i>	Fruit EO		<i>Klebsiella pneumoniae</i>	>1 mg/ml	–	Do	Do	(Piaru et al., 2012)
<i>M. fragrans</i>	Fruit EO		<i>Bacillus subtilis</i>	>1 mg/ml	–	Do	Do	(Piaru et al., 2012)
<i>M. fragrans</i>	Fruit EO		<i>Proteus vulgaris</i>	>1 mg/ml	–	Do	Do	(Piaru et al., 2012)
<i>M. fragrans</i>	Trimyristin	Seed chloroform extract	<i>Pseudomonas aeruginosa</i>	0.60 mg/ml	–	Salicylic acid	Tube dilution	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristic acid	Seed chloroform extract	<i>P. aeruginosa</i>	0.62 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristicin	Seed chloroform extract	<i>P. aeruginosa</i>	0.60 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Trimyristin	Seed chloroform extract	<i>Staphylococcus aureus</i>	1.00 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristic acid	Seed chloroform extract	<i>S. aureus</i>	0.75 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristicin	Seed chloroform extract	<i>S. aureus</i>	0.75 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Trimyristin	Seed chloroform extract	<i>Bacillus subtilis</i>	0.60 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristic acid	Seed chloroform extract	<i>B. subtilis</i>	1.25 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristicin	Seed chloroform extract	<i>B. subtilis</i>	1.00 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Trimyristin	Seed chloroform extract	<i>Micrococcus luteus</i>	1.25 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristic acid	Seed chloroform extract	<i>M. luteus</i>	0.75 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)
<i>M. fragrans</i>	Myristicin	Seed chloroform extract	<i>M. luteus</i>	0.625 mg/ml	–	Do	Do	(Narasimhan & Dhake, 2006)

TABLE 9 (Continued)

Scientific name of the species	Plant parts	Extract/compound	Activity against	Minimum inhibitory Concn. (MIC Value)	Minimum inhibitory zone (MIZ) mm/10 µl	Reference drug	Method	References
<i>M. fragrans</i>	Mace	Acetone extract (1,000 ppm)	<i>Bacillus cereus</i>	—	25(±0.3) mm	Ampicillin, Cloxacillin	Agar well diffusion	(Singh et al., 2005)
<i>M. fragrans</i>	Mace	Acetone extract (2,000 ppm)	<i>B. subtilis</i>	—	25(±0.3) mm	Do	Do	(Singh et al., 2005)
<i>M. fragrans</i>	Mace	Acetone extract (2,000 ppm)	<i>S. aureus</i>	—	40(±0.1) mm	Do	Do	(Singh et al., 2005)
<i>M. fragrans</i>	Mace	Acetone extract (2,000 ppm)	<i>B. cereus</i>	—	34(±0.5) mm	Do	Do	(Singh et al., 2005)
<i>M. fragrans</i>	Mace	Acetone extract (3,000 ppm)	<i>B. subtilis</i>	—	31(±1.7) mm	Do	Do	(Singh et al., 2005)
<i>M. fragrans</i>	Mace	Acetone extract (3,000 ppm)	<i>B. cereus</i>	—	47(±0.7) mm	Do	Do	(Singh et al., 2005)
<i>M. fragrans</i>	Mace	EO (3,000 ppm)	<i>B. subtilis</i>	—	26.00 mm	Do	Do	(Singh et al., 2005)
<i>M. fragrans</i>	Leaves	EO (10 µl)	<i>Enterococcus faecalis</i>	—	13 mm	—	Kirby Bauer	(Mary et al., 2012)
<i>M. fragrans</i>	Leaves	EO (10 µl)	<i>Candida tropicalis</i>	—	14 mm	—	Do	(Mary et al., 2012)
<i>Myristica argentea</i>	—	Water extract	<i>S. aureus</i>	6.2 mg/ml	—	—	—	(Q. Liu et al., 2017)
<i>M. argentea</i>	—	Water extract	<i>E. coli</i>	9.8 mg/ml	—	—	—	(Q. Liu et al., 2017)
<i>Knema attenuata</i>	Seed	Hexane	<i>S. aureus</i>	12.54 mg/ml	—	Streptomycin	Broth dilution	(Vinayachandra & Chandrashekar, 2014)
<i>K. attenuata</i>	Seed	Ethanol	<i>S. aureus</i>	12.58 mg/ml	—	Do	Do	(Vinayachandra & Chandrashekar, 2014)
<i>K. attenuata</i>	aril	Chloroform	<i>S. aureus</i>	12.56 mg/ml	—	Do	Do	(Vinayachandra & Chandrashekar, 2014)
<i>K. attenuata</i>	aril	chloroform	<i>B. subtilis</i>	12.56 mg/ml	—	Do	Do	(Vinayachandra & Chandrashekar, 2014)
<i>K. attenuata</i>	Seed	Hexane	<i>B. subtilis</i>	12.57 mg/ml	—	Do	Do	(Vinayachandra & Chandrashekar, 2014)
<i>Scyphocephalum ochocoa</i>	Fruit flesh	Ethyl acetate	Methicillin resistant <i>S. aureus</i> ATCC 33591	16 µg/ml	—	Vancomycin	Broth microdilution	(Hu et al., 2005)
<i>S. ochocoa</i>	Fruit flesh	Ethyl acetate	<i>S. aureus</i> ATCC 78-13607A	16 µg/ml	—	Do	Do	(Hu et al., 2005)
<i>Knema angustifolia</i>	Stem	Ethanol	<i>S. aureus</i> ATCC 25923	—	10.67 mm	Amoxycillin	—	(Phadungkit et al., 2010)
<i>Horsfieldia amygdalina</i>	Seed	Methanol	<i>S. aureus</i>	15.625 mg/ml	8 mm	Streptomycin	—	(Chaichana, 2016)

TABLE 10 Anti-protozoal activity

Scientific name	Extract	Plant parts	Activity against protozoa	IC ₅₀ value	Compound	Positive control	References
<i>Pycnanthus angolensis</i>	Dichloromethane	Stem	Dd2-chloroquine resistant <i>Plasmodium falciparum</i>	20.7 µg/ml	Talaumidin	Chloroquine hydrochloride	(Abrantes et al., 2008)
<i>P. angolensis</i>	Dichloromethane	Stem	3D7 <i>Plasmodium falciparum</i>	1.6 µg/ml	—	Chloroquine hydrochloride	(Abrantes et al., 2008)
<i>Knema glauca</i>	n-Hexane	Fruits, leaves	MDR <i>Plasmodium falciparum</i>	2.78 µg/ml	Malabaricone A	Dihydroartemisinin	(Rangkaew et al., 2009)
<i>Iryanthera juruensis</i>	—	Aril	<i>Leishmania amazonensis</i>	45 µg/ml	Guaiaicin	—	(Morais et al., 2009)
<i>I. juruensis</i>	—	Aril	<i>Leishmania amazonensis</i>	27 µg/ml	Verrucosin	—	(Morais et al., 2009)
<i>Staudtia kamerunensis</i>	Water	Bark	<i>Trypanosoma brucei brucei</i>	38.47 µg/ml	—	—	(Musuyu et al., 2012)
<i>Virola surinamensis</i>	Hexane	—	Promastigote stage of <i>Leishmania amazonensis</i>	CIM value 50 µg/ml	—	Amphotericin B	(Saraiva, 2012)
<i>V. surinamensis</i>	Hexane	—	Promastigote stage of <i>L. chagasi</i>	CIM value 100 µg/ml, CI ₅₀ 40 µg/ml	—	Amphotericin B	(Saraiva, 2012)
<i>Horsfieldia spicata</i>	—	—	Schizont stage of <i>P. falciparum</i>	54 µM	Myristicyclin A	—	(Lu et al., 2014)
<i>H. spicata</i>	—	—	Schizont stage of <i>P. falciparum</i>	230 µM	Myristicyclin B	—	(Lu et al., 2014)

et al., 2019) and kinetic study on inhibitory mechanism of α -glucosidase (Ramadhan & Phuwapraisrisan, 2015).

5.9 | Other biological activities

Other biological activities were reviewed from three studies. *Myristica fragrans* seed oil at 20 mg/kg reduced the number of wet feces of castor oil-induced diarrhea in mice compared to control and reference atropine (Olajide et al., 2000), whereas adverse effect like sub-acute gastric mucosal ulceration was observed in repeat dosing study with increased dose of both indomethacin and nutmeg oil (Olajide et al., 2000). Malabaricone C and B of methanolic fruit extract of *M. malabarica* reduced gastric ulcer by 88.4% and 60.3% within 3 days in indomethacin (10 mg/kg body wt./day) pretreated mice using Omeprazole (3 mg/kg/day) as reference (Banerjee et al., 2008). Extract of *Otoba parvifolia* exhibited inhibitory activity of Cyt-P450 and 1B1 polypeptide transport with IC₅₀ value of 0.65 ± 0.29 (J. Weiss, 2019).

6 | HUMAN CLINICAL TRIALS

Only seven human trials were available with herbal products of *Myristicaceae* and biomarkers (Table 12). In an open uncontrolled study for 4 weeks comprising 196 males 55 females of the average

age of 44 years, polyherbal drug Revivin which contains *M. fragrans*, 1 cap once daily improved mental state, sleep pattern, overall weakness by 70% without side effects (Usha Rani et al., 1997). In a RDBCT, commercial topical preparation of *M. fragrans* with nutmeg and mace oil and others were used in neuropathic pain of 24 male and 50 diabetic females. Topical spray three times/day for 1, 2, 4 weeks improved patients' compliance and 33% reduction in pain and improvements in sleep (Motilal & Maharaj, 2013). In a clinical trial among four healthy young men intravenous administration of bufotenine exhibited a dose-dependent psychedelic effect at 1–16 mg comparable with LSD (Fabing & Hawkins, 1956). In a clinical study comprising Autism Spectrum Disorder (ASD), schizophrenics and control groups males and females exhibited higher reference of urinary metabolites of 5-OH-DMT in Autistic and Schizophrenic patients (3–4 µg/L) compared to control (1 µg/L) reflecting the potential of diagnostic reference in diseases of transmethylation of serotonin (Emanuele et al., 2010). In two sets of multiple studies, each of the clinical trials among hallucinogen user women and men, intravenous DMT at 0.2 and 0.4 mg/kg exhibited visual hallucinatory effect, physical dissociation and significant mental change within 1.5–2 min. The hallucinogenic threshold of DMT was found at 0.2 mg/kg and at 0.05 mg/kg showed a therapeutic anxiolytic effect and at 0.3 mg/kg reduced anxiety without tolerance in non-blind and double-blind studies (Strassman, 1996; Strassman et al., 1994). In a clinical study of 380 completed participants of mixed race, gender, age and among

TABLE 11 Anti-diabetic activity

Scientific name of the species	Study type	Extract	+ve control	Plant part	IC ₅₀ value	Compounds	Activity	References
<i>M. magnifica</i>	In-vitro	DCM extract	Acarbose	bark	10.63 μ M	Malabaricone C	Inhibition of α -amylase	(Prabha et al., 2018)
<i>M. magnifica</i>	In-vitro	DCM extract	Acarbose	bark	43.61 μ M	Malabaricone C	Inhibition of α -glucosidase	(Prabha et al., 2018)
<i>M. magnifica</i>	In-vitro	DCM extract	Ascorbic acid	bark	14.99 μ M	Malabaricone C	Inhibition of AGEs	(Prabha et al., 2018)
<i>M. magnifica</i> [Auct. non <i>M. fatua</i> Houtt., sensu syn. <i>M. fatua</i> var. <i>magnifica</i> (Bedd.) Sinclair]	In-vitro	DCM extract	standard α -glucosidase	—	32.7 μ M 227.26 μ M	Promalabaricone B Promalabaricone B	Inhibition of α -glucosidase Inhibition of AGEs Hypoglycemic activity by AMPK upregulation and GLUT4 translocation	(Prabha et al., 2019)
<i>Horsfieldia macrobotrys</i>	In-vitro	methanol extract	Acarbose (IC ₅₀ 130 μ M) - Type I of Baker's Yeast	bark	5.65 μ M (in Baker's Yeast), Maltase (33.89 μ M), sucrase (47.41 μ M) of Rat intestine	Maingayone D	Inhibition of α -glucosidase	(Ramadhan & Phuwapraisrisan, 2015)
<i>Pycnanthus angolensis</i>	—	—	—	Leaves, stem	—	Pycnanthuquinone A	Anti-hyperglycemic	(Gustafson et al., 2013)
<i>P. angolensis</i>	—	—	—	—	—	Pycnanthuquinone B	Anti-hyperglycemic	(Gustafson et al., 2013)

some hallucinogen users, vaporized 5-MeO-DMT at the dosage range of 5–7, 8–12, and 13–15 mg with exposure for 35–45 min showed 80% improvements in anxiety and depression in users of mild to high narcotics (A. K. Davis et al., 2019). Only two RDBCTs were available with topical application of herbal product (Motilal & Maharaj, 2013) and intravenous synthetic DMT (Strassman et al., 1994). All the studies were conducted either in small groups, shorter duration, mostly single-blind, uncontrolled trials, devoid of the placebo effect, repeatability, safety, drug interactions and adverse effects and did not comply with the guidelines for the efficacy of the clinical trials (Izzo, Hoon-Kim, Radhakrishnan, & Williamson, 2016).

7 | POISONING AND TOXICITY

Nutmeg poisoning included recreational abuse via oral, nasal, dermal, ocular exposure and as drug admixture. The toxic dose of nutmeg was approximately 5 g, myristicin 1–2 mg/kg body wt. (Rahman, Fazilah, & Effarizah, 2015), elemicin in food upto 0.05 mg/kg (De Vincenzi, De Vincenzi, & Silano, 2004) and 0.02–1.88 mg/L of DMT, 5-MeO-DMT, harmaline, tetrahydroharmine, harmine in cardiac blood (Sklerov, Levine, Moore, King, & Fowler, 2005). Myristicin of nutmeg oil is metabolized to the controlled drugs namely, MMDA, MDMA, MMDMA (Clark, DeRuiter, & Noggle, 1996), safrole to MDA (Shulgin, Sargent, & Naranjo, 1967), elemicin to 3,4,5-Trimethoxyamphetamine (Lapoint, Dargan, & Hoffman, 2013), whereas 5-MeO-DMT, DMT were used as controlled substances in USA and UK (Federal Register, 2010; Tittarelli, Mannocchi, Pantano, & Saverio Romolo, 2015; Waller & Sampson, 2018).

In hepatocytes of 344 male Fischer rats weighing 155–240 g, myristicin showed cytotoxicity at 10^{-3} M and CytP450 mediated 1'-hydroxylation and sulfation of elemicin showed genotoxicity by UDS (Hasheminejad & Caldwell, 1994). Among male SD rats of 200–250 g myristicin at 500 μ M/kg enhanced rat liver P450 enzymes 2–10 times than control (Jeong & Yun, 1995). Physiology-based kinetic (PBK) model showed that detoxification of carcinogenic HE to 1'-hydroxyelemicin glucuronide (HEG) was more efficient than carcinogenic sulfonation to 1'-sulfoxyelemicin (HES) and increased cancer incidence of elemicin was found lesser than other alkylbenzenes (Van den Berg et al., 2012). In a human study among 21–25 years of eight men and women of 50–83 kg, C¹⁴ safrole administration showed rapid absorption within 30 min in blood plasma and 90–98% urinary and fecal elimination by 4–5 days (Benedetti, Malnoe, & Broillet, 1977). The sub-hallucinogenic dose of nutmeg powder 0.5–1.0 g showed therapeutic potential than the hallucinogenic dose of 4–5 g to 10–15 g (Khare, 2008; Panayotopoulos & Chisholm, 1970; G. Weiss, 1960). In a study among male SD rats 200–250 g, harmaline intravenous injection at 0.5 mg/kg showed first-order elimination and oral dose at 20 mg/kg exhibited blood plasma level 1.7 ± 0.5 μ g/ml and 19% bio-availability after 20 min (Guan, Louis, & Zheng, 2001). In a study among 20 male SD rats, weighing 190–260 g bufotenin was metabolized to 5-HIAA through MAO-A and was distributed in lung, heart, brain, and liver after 1 hr and was eliminated rapidly. (Fuller, Snoddy, & Perry, 1995). Though the biomarkers namely, myristicin,

TABLE 12 Clinical trials with nutmegs and biomarkers

Species	Parts used	Type of assay/study	Compound/extract	Observations	References
—	—	Clinical trial among four healthy young men with subsequent dosage of each intravenous injections of 1 mg, 2 mg, 4 mg, 8 mg to four participants and 16 mg injection to second participant	Bufotenine	Intravenous administration of bufotenine exhibited dose-dependent psychedelic effect at 4 mg/kg comparable with LSD	(Fabing & Hawkins, 1956)
—	—	Dose response study of DMT with 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg and 0.4 mg/kg among 11 subjects (one woman and 10 men), 1 week for men, 1 month for woman	Dimethyl-tryptamine fumarate	0.2 and 0.4 mg/kg dosage enhanced immediate onset of hallucinatory effect on changes in vision, physis and psyche. 0.05 and 0.1 mg/kg dosage exhibited effect on emotion and physis but not hallucinogenic.	(Strassman, Qualls, Uhlenhuth, & Kellner, 1994)
—	—	DB tolerance study with hallucinogenic dose (0.05, 0.1, 0.2 and 0.4 mg/kg) among 12 hallucinogen users	DMT fumarate and saline placebo	0.2 mg/kg dosage showed significant effects than placebo. 0.05 and 0.1 mg/kg dosage affected physical and affective functions, less perceptual changes	(Strassman, 1996)
—	—	DB tolerance study with hallucinogenic dose (0.3 mg/kg) among 13 hallucinogen users for four times at half hour intervals	DMT fumarate and saline placebo	Decrease in hallucinogen rating in 1–2 sessions with decrease responses of physiological effect on adrenocorticotropin (ACTH) and prolactin (PRL)	(Strassman, 1996)
—	—	DB tolerance study with sub-hallucinogenic dose (0.1 mg/kg) among 12 hallucinogen users	DMT/saline placebo, in combination with 30 mg oral racemic pindolol/ placebo-pindolol	Reduced responses of PRL, ACTH and increased mean arterial blood pressure	(Strassman, 1996)
<i>M. fragrans</i>	—	Open uncontrolled trial for 4 weeks among 251 patients of 44 yrs (196 male +55 female)	Revivin (polyherbal drug which contains <i>M. fragrans</i>) 1 cap/day	Improved mental state, sleeping condition and overall weakness by 70% without side effects	(Usha Rani, Naidu, Kumar, & Shobha, 1997)
—	—	Clinical study with Autism Spectrum Disorder (ASD), schizophrenics, control groups, males and females; 15 for each category and 18 in control whose urine was examined by single blind laboratory staff	5-OH-DMT	Exhibited urinary metabolites of 5-OH-DMT in Autistic and Schizophrenic patients (3–4 µg/L), higher compared to control (1 µg/L)	(Emanuele et al., 2010)
<i>M. fragrans</i>	Nut, mace	Randomized double-blind clinical trial among 74 diabetic neuropathy patients (24 male +50 females) 30–85 yrs for 1, 2, 4 weeks	Commercial topical preparation comprising nutmeg oil, mace oil, methyl salicylate, menthol, coconut oil and alcohol sprayed 3 times/day	Patients' compliance, pain, and functional interference was scored by numerical rating scales, visual analogue scales. After 1 week reduction in pain compared to placebo. After 4 weeks 33% reduction in pain and improvements in sleep in both placebo (excluding nutmeg and mace oil) and nutmeg groups	(Motilal & Maharaj, 2013)
—	—	Clinical study among 380 completed participants of mixed race, gender, age, and some hallucinogen users of >18–21 yrs, 4 months	5-MeO-DMT	5-MeO-DMT at dosage of 5–7, 8–12, and 13–15 mg by inhalation for 35–45 min, showed 80% improvement in anxiety and depression among participants with mild to high narcotics exposure	(A. K. Davis, So, Lancelotta, Barsuglia, & Griffiths, 2019)

Note: DB - Double Blind.

elemicin, safrole, DMT, 5-MeO-DMT and metabolites are mostly used as controlled substances, the toxicity threshold value of nutmeg and the biomarkers were found safer than other alkylbenzenes and relatively quicker elimination while DMT and 5-MeO-DMT exhibited therapeutic effect at sub-hallucinogenic dose.

8 | INDUSTRIAL APPLICATIONS

Estimated value of the world market of nutmeg and mace is over 140 million, annual production >12,000 MT where 70% are East Indian (Indonesia) and 20–25% West Indian (Grenada) nutmegs. Significant user countries are namely, Europe, USA, Germany, Netherlands, France and others. The major products are whole and ground nutmegs and mace, oleoresin, essential oils and nutmeg butter used in the food and in perfumery industry where myristicin and sabinene are used as chemical markers and common adulterants are *Myristica malabarica* and *M. argentea* (Farnsworth, 1968; Gottlieb, 1979; Maya, 2005; Sinclair, 1958; Singh, Sankat, & Mujaffar, 2003). One of the major by-products is wax or waxy “tallow,” seed oils of *Viola sebifera*, *V. surinamensis*, *V. bicuhyba*, *Otoba novogranatensis*, *Osteophloeum platyspermum* for candles, lanterns, and soaps (Kobelnik et al., 2013; Williams, 1960). *Myristicaceae* biomarkers namely, T, DMT, 5-MeO-DMT, 5-OH-DMT, horsfiline, myristicin exhibited futuristic scope for therapeutic and diagnostic agents in Alzheimer's disease, anxiety, depression, schizophrenia, bipolar disorder, drug addiction, PTSD, ASD, cancer, pain and others (Jossang et al., 1991; Takeda, Ikeda, Ohba, & Kondo, 1995; Winkelman, 2001; Zucchi et al., 2006; Frecska et al., 2013; Pavlovskaya et al., 2015; Tupper, Wood, Jensen, & Johnson, 2015; Gallimore & Strassman, 2016; Carlini & Maia, 2017; Reiche et al., 2018; Rucker, Iliff, & Nutt, 2018; Wahab et al., 2016). Most of the biomarkers were characterized by TLC, GC, GC-MS, ¹H, and ¹³C NMR (Conserva et al., 1990; Cuca et al., 2009; Holmstedt et al., 1980; Pinto & Kijjoa, 1990; Talukdar et al., 2000) which needs urgent upgradation.

9 | CONCLUSION AND FUTURE SCOPE

Wide use of nutmegs and wild nutmegs were presented in this review as ethnomedicine to treat diverse health ailments namely, mental, nervous, stomach, reproductive disorders, skin infections, malaria, asthma, rheumatism, as a stimulant, febrifuge, as psychotomimetic agents and others. Though nutmeg had been used in traditional systems of medicines, the review found wide gap areas for improvements in future research.

Diverse analytical techniques to be employed for isolation, identification of novel biomarkers with therapeutic significance and scientific congruence to ethnomedicinal claims.

Extensive investigations are required for promising botanical therapeutic agents from limitedly explored wild nutmegs with new indications for clinical practice.

Traditional use of nutmeg and wild nutmegs in asthma, cough and cold, rheumatism, as stimulant, body and brain tonics and others lack

pharmacological evaluations which need urgent attention. Pharmacological studies were largely focused on inflammatory, immunomodulatory, anticancer, and antimicrobial activities. Rest biological activities namely, cholinesterase inhibition, anxiolytic, and neuroprotective require extensive randomized double-blind clinical trials of biomarkers for pharmacokinetics, safety, drug interaction, toxicity, and therapeutic windows. As most of the studies do not comply with the current practice, standards and guidelines of pharmacological research on herbal products (Andrew & Izzo, 2017; Izzo et al., 2016, 2020) stringent guidelines to be followed in rigorous future research on herbal extracts and products of nutmegs and wild nutmegs as herbal therapeutics for translational use in human in neuropsychiatric, neurodegenerative, life-threatening, metabolic, infectious, and other disorders.

ACKNOWLEDGEMENTS

The study was funded by the Council of Scientific and Industrial Research, Ministry of Science & Technology, Govt. of India, New Delhi and Department of Biotechnology (DBT), Govt. of India, New Delhi (File no. BT/PR27725/NER/95/1349/2018 dated 11.01.2019). Rubi Barman, Pranjit Kumar Bora, and Phirose Kemprai acknowledge the Academy of Scientific and Innovative Research (AcSIR), Ghaziabad - 201002, Uttar Pradesh, India and CSIR-North East Institute of Science & Technology, Jorhat-785006, Assam, India (CSIR-NEIST) for the opportunity and platform to carry out the work. Rubi Barman acknowledges the Department of Science & Technology, Govt. of India for DST-Inspire Fellowship (DST/INSPIRE Fellowship/2017/IF170731) for pursuing PhD work. Dipanwita Banik acknowledges P. Pahari, Senior Scientist, CSIR-NEIST for his help in providing the PubChem ID number of a few compounds. All the authors acknowledge Director, CSIR-NEIST (NMN - 202026) for the logistics and CSIR, Govt. of India, New Delhi for overall support.

CONFLICTS OF INTERESTS

The authors have declared that there is no conflict of interests.

AUTHORS' CONTRIBUTIONS

Rubi Barman and Jadumoni Saikia retrieved and inserted all the references, retrieved the Pub Chem IDs of hallucinogenic markers, drafted the manuscript (in part). Pranjit Kumar Bora drawn the compounds, verified the Pub Chem IDs, drafted the manuscript (in part). Phirose Kemprai collected references (in part). Saikat Halder overall conceptualized the chemistry part of the manuscript. Siddhartha Proteem Saikia verified the information. Dipanwita Banik conceptualized and designed the review, verified the nomenclature of species and drafted the final manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

- Abrantes, M., Mil-Homens, T., Duarte, N., Lopes, D., Cravo, P., Madureira, M. D. C., & Ferreira, M. J. U. (2008). Antiplasmodial activity of lignans and extracts from *Pycnanthus angolensis*. *Planta Medica*, 74 (11), 1408–1412.
- Achel, D. G., Alcaraz, M., Adabo, K. R., Nyarko, A. K., & Gomda, Y. (2012). A review of the medicinal properties and applications of *Pycnanthus angolensis* (Welw) Warb. *Pharmacology*, 2, 1–22.
- Agbogidi, O. M., & Azagbaekwe, O. P. (2013). Health and nutritional benefits of nutmeg (*Myristica fragrans* Houtt.). *Scientia Agriculturae*, 1(2), 40–44.
- Ahn, K. (2017). The worldwide trend of using botanical drugs and strategies for developing global drugs. *BMB Reports*, 50(3), 111–116.
- Akhtar, M. N., Lam, K. W., Abas, F., Maulidiani, Ahmad, S., Shah, S. A., ... Lajis, N. H. (2011). New class of Acetylcholinesterase inhibitors from the stem bark of *Knema laurina* and their structural insights. *Bioorganic & Medicinal Chemistry Letters*, 21, 4097–4103.
- Akoubet, O. A., Marcelline, A. N. D., Claude, K. A. L., Sandrine, A. A.-G., Siomenan, C., Leopold, A. A., ... Dieneba, K. B. (2017). Sterols from the fruit barks of *Coelocaryon klainei* Pierre ex Heckel (Myristicaceae). *International Current Pharmaceutical Journal*, 6, 49–52.
- Alrashedy, N. A., & Molina, J. (2016). The ethnobotany of psychoactive plant use: A phylogenetic perspective. *PeerJ*, 4, e2546 23.
- Andrew, R., & Izzo, A. A. (2017). Principles of pharmacological research of nutraceuticals. *British Journal of Pharmacology*, 174(11), 1177–1194. <https://doi.org/10.1111/bph.13779>
- Aponte, J. C., Vaisberg, A. J., Rojas, R., Caviedes, L., Lewis, W. H., Lamas, G., ... Hammond, G. B. (2007). Isolation of cytotoxic metabolites from targeted peruvian amazonian medicinal plants. *Journal of Natural Products*, 71, 102–105.
- Audrey, L. J., Herman, R., Riadh, U. M., & Asri, S. M. (2017). Productivity of nutmeg (*myristica* spp.) in agroforestry system (dusung) in ambon island. future collaboration on island studies between pattimura university and kagoshima university. *Occasional Papers*, 58, 69–76.
- Ballesteros, J. L., Bracco, F., Cerna, M., Vita Finzi, P., & Vidari, G. (2016). Ethnobotanical research at the Kutukú Scientific Station, Morona-Santiago, Ecuador. *BioMed Research International*, 2016, 1–18.
- Banerjee, D., Bauri, A. K., Guha, R. K., Bandyopadhyay, S. K., & Chattopadhyay, S. (2008). Healing properties of malabaricone B and malabaricone C, against indomethacin-induced gastric ulceration and mechanism of action. *European Journal of Pharmacology*, 578, 300–312.
- Banik, D., & Bora, P. P. (2016). A Taxonomic study on the diversity of Indian *Knema* Lour. (Myristicaceae). *Taiwania*, 61, 141–158.
- Banik, D., Bora, P. P., Kumar, V. S., & Bezbaruah, R. L. (2017). Conspectus on Indian *Gymnacranthera* and *Myristica*. *Rheedea*, 27, 1–12.
- Barukial, J., & Sarmah, J. N. (2011). Ethnomedicinal plants used by the people of Golaghat district, Assam, India. *International Journal of Medicinal and Aromatic Plants*, 1, 203–211.
- Benedetti, M. S., Malnoe, A., & Broillet, A. L. (1977). Absorption, metabolism and excretion of safrole in the rat and man. *Toxicology*, 7, 69–83.
- Benzeid, H., Gouaz, F., Touré, A. H., Bouatia, M., Idrissi, M. B., Draoui, M. (2018). Inventory of toxic plants in morocco: an overview of the botanical, biogeography, and phytochemistry studies. *Journal of Toxicology*, 2018, 1–13. <http://dx.doi.org/10.1155/2018/4563735>.
- Bussmann, R. W., Paniagua Zambrana, N. Y., Romero, C., & Hart, R. E. (2018). Astonishing diversity-the medicinal plant markets of Bogota, Colombia. *Journal of Ethnobiology and Ethnomedicine*, 14, 43. <https://doi.org/10.1186/s13002-018-0241-8>
- Carlini, E. A., & Maia, L. O. (2017). Plant and fungal hallucinogens as toxic and therapeutic agents. In P. Gopalakrishnakone, C. Carlini, & R. Ligabue-Braun (Eds.), *Plant toxins, toxinology* (pp. 37–80). Dordrecht: Springer.
- Carvalho, J. C. T., Ferreira, L. P., da Silva Santos, L., Correa, M. J. C., de Oliveira Campos, L. M., Bastos, J. K., & Sarti, S. J. (1999). Anti-inflammatory activity of flavone and some of its derivatives from *Virola michelli* Heckel. *Journal of Ethnopharmacology*, 64, 173–177.
- Cassady, J. M., Blair, G. E., Raffauf, R. F., & Tyler, V. E. (1971). The Isolation of 6-methoxyharmalan and 6-methoxyharman from *Virola cuspidata*. *Lloydia*, 34, 161–162.
- Chaichana, N. (2016). Nutrition composition and analysis of medicinal herbal potential of *Horsfieldia glabra* Warb. seeds. *King Mongkut's University of Technology North Bangkok International Journal of Applied Science and Technology*, 9, 61–69.
- Chanda, S., Kushwaha, S., & Tiwari, R. K. (2011). Garlic as food, spice and medicine: A perspective. *Journal of Pharmacy Research*, 4(6), 1857–1860.
- Chase, M. W., Christenhusz, M. J. M., Fay, M. F., Byng, J. W., Judd, W. S., Soltis, D. E., ... Stevens, P. F. (2016). An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG IV. *Botanical Journal of the Linnean Society*, 181, 1–20.
- Chelladurai, P. K., & Ramalingam, R. (2017). *Myristica malabarica*: A comprehensive review. *Journal of Pharmacognosy and Phytochemistry*, 6, 255–258.
- Chinworrungsee, M., Wiyakrutta, S., Sriubolmas, N., Chuailua, P., & Suksamrarn, A. (2008). Cytotoxic activities of trichothecenes isolated from an endophytic fungus belonging to order Hypocreales. *Archives of Pharmacol Research*, 31, 611–616.
- Chumkaew, P., & Srisawat, T. (2018). New neolignans from the seeds of *Myristica fragrans* and their cytotoxic activities. *Journal of Natural Medicines*, 73, 273–277.
- Clark, C. R., DeRuiter, J., & Noggle, F. T. (1996). Analysis of 1-(3-methoxy-4, 5-methylenedioxyphenyl)-2-propanamine (MMDA) derivatives synthesized from nutmeg oil and 3-methoxy-4, 5-methylenedioxybenzaldehyde. *Journal of Chromatographic Science*, 34, 34–42.
- Conserva, L. M., Yoshida, M., Gottlieb, O. R., Martinez, V. J. C., & Gottlieb, H. E. (1990). Iryantherins, lignoflavonoids of NOVEL structural types from the Myristicaceae. *Phytochemistry*, 29, 3911–3918.
- Contreras, C. M., Rodriguez-Landa, J. F., Garcia-Rios, R. I., Cueto-Escobedo, J., Guillen-Ruiz, G., & Bernal-Morales, B. (2014). Myristic acid produces anxiolytic-like effects in Wistar rats in the elevated plus maze. *BioMed Research International*, 1–8. <https://doi.org/10.1155/2014/492141>
- Cuca, L. E., Bernal, F. A., Coy, C. A., & Coy, E. D. (2009). Essential oil composition and antimicrobial activity of fruits of *Iryanthera ulei* Warb. from Colombia. *Journal of the Chilean Chemical Society*, 54, 363–365.
- Davis, A. K., So, S., Lancelotta, R., Barsuglia, J. P., & Griffiths, R. R. (2019). 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *The American Journal of Drug and Alcohol Abuse*, 45, 161–169.
- Davis, E. W., & Yost, J. A. (1983). The ethnomedicine of the Waorani of Amazonian Ecuador. *Journal of Psychopharmacology*, 9, 273–297.
- De Vincenzi, M., De Vincenzi, A., & Silano, M. (2004). Constituents of aromatic plants: Elemicin. *Fitoterapia*, 75, 615–618.
- De Wilde, W. J. J. O. (2000). Myristicaceae. In *Flora Malesiana: Series I-Seed plants* (pp. 1–634). Netherlands: National Herbarium Nederland, Universiteit Leiden.
- DeFilipps, R. A., & Krupnick, G. A. (2018). The medicinal plants of Myanmar. *Phytokeys*, 102, 1–341.
- Deng, J.-Z., Starck, S. R., Li, S., & Hecht, S. M. (2005). (+)-Myristinins A and D from *Knema elegans*, which Inhibit DNA Polymerase beta and Cleave DNA. *Journal of Natural Products*, 68, 1625–1628.
- Emanuele, E., Colombo, R., Martinelli, V., Brondino, N., Marini, M., Boso, M., ... Politi, P. (2010). Elevated urine levels of bufotenine in patients with autistic spectrum disorders and schizophrenia. *Neuroendocrinology Letters*, 31, 101–105.

- Fabing, H. D., & Hawkins, J. R. (1956). Intravenous bufotenine injection in the human being. *Science*, 123, 886–887.
- Fajriah, S., Darmawan, A., Megawati, H. S., Kosela, S., & Hanafi, M. (2017). New cytotoxic compounds from *Myristica fatua* Houtt. leaves against MCF-7 cell lines. *Phytochemistry Letters*, 20, 36–39.
- Farnsworth, N. R. (1968). Hallucinogenic plants. *Science*, 162, 1086–1092.
- Federal Register. (2010). Drug Enforcement Administration, Rules and Regulations. Federal Register, US Government: 79296–79300.
- Ferreira, A. G., Motidome, M., Gottlieb, O. R., Fernandes, J. B., Vieira, P. C., Cojocaru, M., & Gottlieb, H. E. (1989). Farnesyl-homogentisic acid derivatives from *Otoba parvifolia*. *Phytochemistry*, 28, 579–583.
- Filleur, F., Le Bail, J. C., Duroux, J. L., Simon, A., & Chulia, A. J. (2001). Antiproliferative, anti-aromatase, anti-17B-HSD and antioxidant activities of lignans isolated from *Myristica argentea*. *Planta Medica*, 67, 700–704.
- Filleur, F., Pouget, C., Allais, D. P., Kaoudji, M., & Chulia, A. J. (2002). Lignans and neolignans from *Myristica argentea* Warb. *Natural Product Letters*, 16, 1–7.
- Foundikou, H., Mbiantcha, M., Kezetas, J.-J. B., Tchouankeu, J. C., Shaheen, F., Choudhary, M. I., ... Tchouya, G. R. F. (2018). Two new alkylresorcinol derivatives from the leaves of *Scyphocephalum ochocoea*. *Zeitschrift für Naturforschung Part B*, 73, 381–388.
- Francis, K. S., Suresh, E., & Nair, M. S. (2014). Chemical constituents from *Myristica fragrans* fruit. *Natural Product Research*, 28, 1664–1668.
- Frank, F., Roberts, T., Snell, J., Yates, C., & Collins, J. (1971). Trimyristin from nutmeg. *Journal of Chemical Education*, 48, 255–256.
- Freccsa, E., Szabo, A., Winkelman, M. J., Luna, L. E., & McKenna, D. J. (2013). A possibly sigma-1 receptor mediated role of dimethyltryptamine in tissue protection, regeneration and immunity. *Journal of Neural Transmission*, 120, 1295–1303.
- Fuller, R. W., Snoddy, H. D., & Perry, K. W. (1995). Tissue distribution, metabolism and effects of bufotenine administered to rats. *Neuropharmacology*, 34, 799–804.
- Gallimore, A. R., & Strassman, R. J. (2016). A model for the application of target-controlled intravenous infusion for a prolonged immersive DMT psychedelic experience. *Frontiers in Pharmacology*, 7, 211.
- Gonzalez, M. J., Pinto, M. M. M., Kijjoa, A., Kengthong, S., Mondanondra, I.-O., Silva, A. M. S., ... Herz, W. (2002). 5, 7-Dihydroxychromones and 8-hydroxytetrahydrochromones from *Horsfieldia irya*. *Phytochemistry*, 61, 995–998.
- Gordon, A. (2020). Market & technical considerations for spices: Nutmeg & mace case study. In *Food safety and quality systems in developing countries* (pp. 367–414). Amsterdam, Netherlands: Elsevier.
- Gottlieb, O. R. (1979). Chemical studies on medicinal *Myristicaceae* from Amazonia. *Journal of Ethnopharmacology*, 1, 309–323.
- Gronovius, J. F. (1755). *Flora Orientalis-Lugduni Batavorum*, Lugduni Batavorum: Typis Wilhelmi de Groot.
- Guan, Y., Louis, E. D., & Zheng, W. (2001). Toxicokinetics of tremorogenic natural products, harmaline and harmine, in male sprague-dawley rats. *Journal of Toxicology and Environmental Health Part A*, 64, 645–660.
- Gustafson, K., Wu, Q.-L., Asante-Dartey, J., & Simon, J. E. (2013). *Pycnanthus angolensis*: Bioactive compounds and medicinal applications. In H. Rudolfo Juliani, J. E. Simon, & C.-T. Ho (Eds.), *African natural plant products. Discoveries and challenges in chemistry, health and nutrition* (pp. 263–278). Washington, DC: ACS Publications. <https://doi.org/10.1021/bk-2013-6151127.ch1005>
- Hake, I., Schoenenberger, S., Neumann, J., Franke, K., Paulsen-Merker, K., Reymann, K., ... Latiff, A. (2009). Neuroprotection and enhanced neurogenesis by extract from the tropical plant *Knema laurina* after inflammatory damage in living brain tissue. *Journal of Neuroimmunology*, 206, 91–99.
- Hasheminejad, G., & Caldwell, J. (1994). Genotoxicity of the alkenylbenzenes alpha and beta asarone, myristicin and elemicin as determined by the UDS assay in cultured rat hepatocytes. *Food and Chemical Toxicology*, 32, 223–231.
- Henkin, J. M., Sydara, K., Xayvue, M., Souliya, O., Kinghorn, A. D., Burdette, J. E., ... Soejarto, D. D. (2017). Revisiting the linkage between ethnomedical use and development of new medicines: A novel plant collection strategy towards the discovery of anticancer agents. *Journal of Medicinal Plant Research*, 11, 621–627.
- Hima Sai Bindu, N., Rubesh Kumar, S., Duganath, N., & Devanna, N. (2013). Extraction and screening of trimyristin in the seeds of *Myristica fragrans* and in poly herbal formulations by spectroscopic and chromatographic techniques. *International Journal of Universal Pharmacy and Bio Sciences*, 2, 569–581.
- Hiruma-Lima, C. A., Batista, L., de Almeida, A. B. A., de Pietro Magri, L., dos Santos, L. C., Vilegas, W., & Brito, A. R. M. S. (2009). Anticarcinogenic action of ethanolic extract of the resin from *Virola surinamensis* Warb. (*Myristicaceae*). *Journal of Ethnopharmacology*, 122, 406–409.
- Holmstedt, B., Lindgren, J. E., Plowman, T., River, L., Schultes, R. E., & Tovar, O. (1980). Indole alkaloids in Amazonian *Myristicaceae*: Field and laboratory research. *Botanical Museum Leaflets, Harvard University*, 28, 215–234.
- Hooker, J. D. (1890). *Myristicaceae*. In *Flora of British India* (Vol. 5, pp. 101–114). Kent: Reeve & Co., Ltd.
- Houttuyn, M. (1774). *Natuurlyke historie of uitvoerige beschryving der dieren, planten en mineraalen, volgens het samenstel van den heer Linnaeus*. De boomten.
- Howe, H. F., & Vande Kerckhove, G. A. (1981). Removal of Wild Nutmeg (*Virola surinamensis*) crops by Birds. *Cological Society of America*, 62(4), 1093–1106.
- Hu, J.-F., Garo, E., Yoo, H.-D., Cremin, P. A., Goering, M. G., O'Neil-Johnson, M., & Eldridge, G. R. (2005). Cycloolignans from *Scyphocephalum ochocoea* via high-throughput natural product chemistry methods. *Phytochemistry*, 66, 1077–1082.
- Izzo, A. A., Hoon-Kim, S., Radhakrishnan, R., & Williamson, E. M. (2016). A critical approach to evaluating clinical efficacy, adverse events and drug interactions of herbal remedies. *Phytotherapy Research*, 30(5), 691–700. <https://doi.org/10.1002/ptr.5591>
- Izzo, A. A., Teixeira, M., Alexander, S. P. H., Cirino, G., Docherty, J. R., George, C. H., & Ahluwalia, A. (2020). A practical guide for transparent reporting of research on natural products in the British Journal of Pharmacology: Reproducibility of natural product research. *British Journal of Pharmacology*, 177(10), 2169–2178. <https://doi.org/10.1111/bph.15054>
- Jeong, H. G., & Yun, C.-H. (1995). Induction of rat hepatic cytochrome P450 enzymes by myristicin. *Biochemical and Biophysical Research Communications*, 217, 966–971.
- Jossang, A., Jossang, P., Hadi, H. A., Sevenet, T., & Bodo, B. (1991). Horsfiline, an oxindole alkaloid from *Horsfieldia superba*. *The Journal of Organic Chemistry*, 56, 6527–6530.
- Kalbhen, D. A. (1971). Nutmeg as a Narcotic. A contribution to the chemistry and pharmacology of nutmeg (*Myristica fragrans*). *Angewandte Chemie International Edition in English*, 10, 370–374.
- Kam, T.-S. (1999). Alkaloids from Malaysian flora. In P. S. William (Ed.), *Alkaloids: Chemical and biological perspectives* (Vol. 14, pp. 285–435). Amsterdam, Netherlands: Elsevier.
- Khare, C. P. (2008). *Indian medicinal plants: An illustrated dictionary*. Berlin/Heidelberg, Germany: Springer Science & Business Media.
- Kobelnik, M., Fontanari, G. G., Soares, R. A. M., Figueiredo, A. G., & Ribeiro, C. A. (2013). Study of the thermal behavior of Bicuba Oil (*Virola bicuhyba*). *Journal of Thermal Analysis and Calorimetry*, 115, 2107–2113.
- Koperuncholan, M., & John, S. A. (2011). Antimicrobial and phytochemical screening in *Myristica dactyloides* Gaertn. *Journal of Pharmacy Research*, 4, 398–400.
- Lapoint, J., Dargan, P. I., & Hoffman, R. S. (2013). Synthetic amphetamine derivatives. In *Novel psychoactive substances* (pp. 161–178). Amsterdam, Netherlands: Elsevier.

- Latha, P. G., Sindhu, P. G., Suja, S. R., Geetha, B. S., Pushpangadan, P., & Rajasekharan, S. (2005). Pharmacology and chemistry of *Myristica fragrans* Houtt.-A review. *Journal of Spices and Aromatic Crops*, 14, 94–101.
- Li, B., & Wilson, T. K. (2008). Myristicaceae. In Z. Y. Wu, P. H. Raven, & D. Y. Hong (Eds.), 675 *Flora of China* (pp. 96–101). Beijing, Missouri Botanical Garden Press, St. Louis, MO: Science Press.
- Liu, B., Chen, Y. G., Tian, X. J., & Zhan, R. (2019). Diarylpropanes from *Horsfieldia kingii*. *Natural Product Research*, 1–7. <https://doi.org/10.1080/14786419.2019.1643858>.
- Liu, B., Du, S.-Z., Kuang, F., Liu, Y., Tian, X.-J., Chen, Y.-G., & Zhan, R. (2019). Two new lignans from *Horsfieldia kingii*. *Natural Product Research*, 33, 95–100.
- Liu, Q., Meng, X., Li, Y., Zhao, C. N., Tang, G. Y., & Li, H. B. (2017). Antibacterial and antifungal activities of spices. *International Journal of Molecular Sciences*, 18, 1283. <https://doi.org/10.3390/ijms18061283>
- Lopes, N. P., Kato, M. J., Andrade, E. H. D. A., Maia, J. G. S., Yoshida, M., Planchart, A. R., & Katzin, A. M. (1999). Antimalarial use of volatile oil from leaves of *Viola surinamensis* (Rol.) Warb. by Waiapi Amazon Indians. *Journal of Ethnopharmacology*, 67, 313–319.
- Lu, Z., Van Wagoner, R. M., Pond, C. D., Pole, A. R., Jensen, J. B., Blankenship, D. A., ... Barrows, L. R. (2014). Myristicyclins A and B: Antimalarial procyanidins from *Horsfieldia spicata* from Papua New Guinea. *Organic Letters*, 16, 346–349.
- Marcelle, G. B. (1995). Production, handling and processing of nutmeg and mace and their culinary uses. Food and Agriculture Organization of the United Nations. Retrieved from <http://www.fao.org/3/x5047E/x5047E00.htm#Contents>.
- Martinez, V. J. C., & Cuca, S. (1995). Chemical studies of Myristicaceae species of the Colombian Amazon. In P. R. Seidl, O. R. Gottlieb, & M. A. C. Kaplan (Eds.), *Chemistry of the Amazon* (pp. 116–123). Brazil: ACS Publications.
- Mary, H., Tina, A. V., Jeeja, K. J., & Abiramy, M. R. (2012). Phytochemical analysis and anticancer activity of essential oil from *Myristica fragrans*. *International Journal of Current Pharmaceutical Review and Research*, 2 (4), 188–198.
- Maya, K. M. (2005). Biochemical variability in nutmeg *Myristica fragrans* and related taxa. Ph.D. Thesis. Department of Botany, University of Calicut, India.
- Maya, K. M., Zachariah, T. J., & Krishnamoorthy, B. (2004). Chemical composition of essential oil of nutmeg (*Myristica fragrans* Houtt.) accessions. *Journal of Spices and Aromatic Crops*, 13, 135–139.
- Maya, K. M., Zachariah, T. J., Krishnamurthy, K. S., Rema, J., & Krishnamoorthy, B. (2015). Fatty acids and leaf amino acids in *Myristica fragrans* and its wild taxa. 1–9. Retrieved 8 June 2020 from <http://www.spices.res.in/oldmail/studycircle/myristica.pdf>.
- McKenna, D., & Riba, J. (2016). New world tryptamine hallucinogens and the neuroscience of ayahuasca. In A. L. Halberstadt, F. X. Vollenweider, & D. E. Nichols (Eds.), *Current topics in behavioral neurosciences* (pp. 283–311). Berlin, Heidelberg: Springer.
- McKenna, D. J. (1984). Monoamine oxidase inhibitors in Amazonian hallucinogenic plants: Ethnobotanical, phytochemical, and pharmacological investigations. Ph.D. Thesis. Department of Botany, University of British Columbia, Canada.
- McKenna, D. J., Towers, G. H. N., & Abbott, F. (1984a). Monoamine oxidase inhibitors in South American hallucinogenic plants: Tryptamine and beta-carboline constituents of ayahuasca. *Journal of Ethnopharmacology*, 10, 195–223.
- McKenna, D. J., Towers, G. H. N., & Abbott, F. S. (1984b). Monoamine oxidase inhibitors in South American hallucinogenic plants Part 2: Constituents of orally-active Myristicaceous hallucinogens. *Journal of Ethnopharmacology*, 12, 179–211.
- Megawati, M., & Darmawan, A. (2017). Resorcinol compounds isolated from the Bark of *Myristica fatua* Houtt. *Indonesian Journal of Pharmacy*, 28, 82–90.
- Morais, S. K. R., Teixeira, A. F., Torres, Z. E. D. S., Nunomura, S. M., Yamashiro-Kanashiro, E. H., Lindoso, J. A. L., & Yoshida, M. (2009). Biological activities of lignoids from Amazon *Myristicaceae* Species: *Viola michelii*, *V. mollissima*, *V. pavonis* and *Iryanthera juruensis*. *Journal of the Brazilian Chemical Society*, 20, 1110–1118.
- Morsy, N. F. S. (2016). A comparative study of nutmeg (*Myristica fragrans* Houtt.) oleoresins obtained by conventional and green extraction techniques. *Journal of Food Science and Technology*, 53, 3770–3777.
- Motilal, S., & Maharaj, R. G. (2013). Nutmeg extracts for diabetic neuropathy: A randomized, double-blind, controlled study. *The Journal of Alternative and Complementary Medicine*, 19, 347–352.
- Muchtaridi, S. A., Apriyanton, A., & Mustarichie, R. (2010). Identification of compounds in the essential oil of nutmeg seeds (*Myristica fragrans* Houtt.) that inhibit locomotor activity in mice. *International Journal of Molecular Sciences*, 11, 4771–4781.
- Murray, A. P., Faraoni, M. B., Castro, M. J., Alza, N. P., & Cavallaro, V. (2013). Natural AChE inhibitors from plants and their contribution to Alzheimer's disease therapy. *Current Neuropharmacology*, 11, 388–413.
- Musuyu, M. D., Fruth, B. I., Nzunzu, L. J., Mesia, G. K., Kambu, O. K., Tona, G. L., ... Pieters, L. (2012). In vitro antiprotozoal and cytotoxic activity of 33 ethonopharmacologically selected medicinal plants from Democratic Republic of Congo. *Journal of Ethnopharmacology*, 141, 301–308.
- Nagano, I. (2009). *Myristica fragrans*: An exploration of the narcotic spice. *The Etheogen Review*, 16, 15–24.
- Nagaraju, B., Sahar, S. H., Ali, B., Neha, K. Z., Zahra, A., Zothanmawia, C., & Surendranatha, A. (2013). Anxiolytic effect of *Myristica fragrans*. *International Journal of Phytotherapy Research*, 3, 1–7.
- Narasimhan, B., & Dhake, A. S. (2006). Antibacterial principles from *Myristica fragrans* seeds. *Journal of Medicinal Food*, 9(3), 395–399.
- Ngoua-Meye-Misso, R.-L., Ndong, J. D. L. C., Sima-Obiang, C., Ondo, J. P., Ndong-Atome, G. R., OvonoAbessolo, F., & Obame-Engonga, L.-C. (2018). Phytochemical studies, antiangiogenic, anti-inflammatory and antioxidant activities of *Scyphocephalum ochocoa* Warb. (*Myristicaceae*), medical plant from Gabon. *Clinical Phytoscience*, 4, 1–13.
- Ogunwande, I. A., Olawore, N. O., Adeleke, K. A., & Ekundayo, O. (2003). Chemical composition of essential oil of *Myristica fragrans* Houtt (Nutmeg) From Nigeria. *Journal of Essential Oil-Bearing Plants*, 6(1), 21–26.
- Olajide, O. A., Ajayi, F. F., Ekhelar, A. I., Awe, S. O., Makinde, J. M., & Alada, A. R. A. (1999). Biological effects of *Myristica fragrans* (nutmeg) extract. *Phytotherapy Research*, 13, 344–345.
- Olajide, O. A., Makinde, J. M., & Awe, S. O. (2000). Evaluation of the pharmacological properties of nutmeg oil in rats and mice. *Pharmaceutical Biology*, 38, 385–390.
- Oliveira, M. N., Santos, L. S., Guilhon, G., Santos, A. S., Ferreira, I. C. S., Lopes-Junior, M. L., ... Rodrigues-Filho, E. (2011). Novel anthraquinone derivatives produced by *Pestalotiopsis guepinii*, an endophytic of the medicinal plant *Viola michelii* (*Myristicaceae*). *Journal of the Brazilian Chemical Society*, 22, 993–996.
- Panayotopoulos, D. J., & Chisholm, D. D. (1970). Hallucinogenic effect of Nutmeg. *British Medical Journal*, 1, 754.
- Pavlovskaya, T. L., Redkin, R. G., Lipson, V. V., & Atamanuk, D. V. (2015). Molecular diversity of spirooxindoles. Synthesis & Biological Activity. *Molecular Diversity*, 20, 299–344.
- Phadungkit, M., Rattarom, R., & Rattana, S. (2010). Phytochemical screening, antioxidant, antibacterial and cytotoxic activities of *Knema angustifolia* extracts. *Journal of Medicinal Plant Research*, 4, 1269–1272.
- Piaru, S. P., Mahmud, R., & Perumal, P. (2012). Determination of Antibacterial Activity of Essential oil of *Myristica fragrans* Houtt. using Tetrazolium Microplate Assay and its Cytotoxic activity against Vero Cell Line. *International Journal of Pharmacology*, 8(6), 572–576.
- Pinto, M. M. M., & Kijjoa, A. (1990). Chemical study of *Knema* species from Thailand. *Quim Nova*, 13, 243–244.

- Piras, A., Rosa, A., Marongiu, B., Atzeri, A., Dessi, M. A., Falconieri, D., & Porcedda, S. (2012). Extraction and separation of volatile and fixed oils from seeds of *Myristica fragrans* by supercritical CO₂: Chemical composition and cytotoxic activity on Caco-2 cancer cells. *Journal of Food Science*, 77, C448–C453.
- Prabha, B., Neethu, S., Krishnan, S. L., Sherin, D. R., Madhukrishnan, M., Ananthakrishnan, R., ... Radhakrishnan, K. V. (2018). Antidiabetic potential of phytochemicals isolated from the stem bark of *Myristica fatua* Houtt. var. *magnifica* (Bedd.) Sinclair. *Bioorganic & Medicinal Chemistry*, 26, 3461–3467.
- Prabha, B., Sini, S., Sherin, D. R., Neethu, S., Rameshkumar, K. B., Manojkumar, T. K., ... Radhakrishnan, K. V. (2019). Promalabaricone B from *Myristica fatua* Houtt. seeds demonstrate antidiabetic potential by modulating glucose uptake via the upregulation of AMPK in L6 myotubes. *Natural Product Research*, 35, 1–6.
- Quiroz, D. (2015). Do not fear the supernatural!: The relevance of ritual plant use for traditional culture, nature conservation, and human health in Western Africa. Ph.D. Thesis. Wageningen University, NL.
- Rahman, N. A. A., Fazilah, A., & Effarizah, M. E. (2015). Toxicity of nutmeg (myristicin): A review. *International Journal on Advanced Science, Engineering and Information Technology*, 5, 212–215.
- Rajasekharan, P. E., & Rao, V. R. (2019). *Conservation and utilization of horticultural genetic resources*. Singapore: Springer.
- Ramadhan, R., & Phuwapraisirisan, P. (2015). Arylalkanonones from *Horsfieldia macrobotrys* are Effective Antidiabetic Agents Achieved by a-Glucosidase Inhibition and Radical Scavenging. *Natural Product Communications*, 10(2), 325–328.
- Rangkaew, N., Suttisri, R., Moriyasu, M., & Kawanishi, K. (2009). A new acyclic diterpene acid and bioactive compounds from *Knema glauca*. *Archives of Pharmacol Research*, 32, 685–692.
- Reiche, S., Hermle, L., Gutwinski, S., Jungaberle, H., Gasser, P., & Majic, T. (2018). Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 81, 1–10.
- Rheede tot Drakestein, H. V., & Caserius, J. (1683). *Horti Indici Malabarici*, Pars quarta. Sumptibus Viduae Joannis van Someren, Amstelodamum.
- Rucker, J. J. H., Iliff, J., & Nutt, D. J. (2018). Psychiatry & the psychedelic drugs. Past, present & future. *Neuropharmacology*, 142, 200–218.
- Salleh, W. M. N. H. W., & Farediah, A. (2017). Phytochemistry and Biological Activities of the Genus *Knema* (Myristicaceae). *Pharmaceutical Sciences*, 23, 249–255.
- Saputro, M. A., Andarwulan, N., & Faridah, D. N. (2016). Physical characterization and essential oil properties of West Sumatra mace and nutmeg seed (*Myristica fragrans* Houtt) at different ages at harvest. *Journal of Pharmacognosy and Phytochemistry*, 5, 371–376.
- Saraiva, M. E. V. (2012). Atividades antimicrobiana e antipromastigota de extratos e fracos de *Virola surinamensis* (Rol. ex Rottb.) Warb. (Myristicaceae) Ph.D. Thesis. Universidade Federal do Para and Instituto de Ciencias da Saude Belem, Para, Brazil: 73.
- Schultes, R. E. (1969a). De Plantis Toxicariis E Mundo Novo Tropicale Commentationes V: *Virola* as an orally administered hallucinogen. *Botanical Museum Leaflets, Harvard University*, 22, 229–240.
- Schultes, R. E. (1969b). Hallucinogens of plant origin. *Science*, 163, 245–254.
- Schultes, R. E. (1976). Indole alkaloids in plant hallucinogens. *Journal of Psychedelic Drugs*, 8, 7–25.
- Schultes, R. E. (1977). The botanical and chemical distribution of hallucinogens. *Journal of Psychedelic Drugs*, 9(3), 247–263.
- Schultes, R. E. (1980). De plantis toxicariis e mundo novo tropicale commentationes 26. *Botanical Museum Leaflets, Harvard University*, 28, 1–45.
- Schultes, R. E. (1982). The beta-carboline hallucinogens of South America. *Journal of Psychoactive Drugs*, 14, 205–220.
- Schultes, R. E. (1988). Ethnopharmacological conservation: A key to progress in medicine. *Acta Amazonica*, 18(1–2), 393–406.
- Schultes, R. E., & Farnsworth, N. R. (1980). Ethnomedical, botanical and phytochemical aspects of natural hallucinogens. *Botanical Museum Leaflets, Harvard University*, 28, 123–214.
- Schultes, R. E., Swain, T., & Plowman, T. C. (1977). De Plantis Toxicariis E Mundo Novo Tropicale Commentationes XVII: *Virola* as an oral hallucinogen among the Boras of Peru. *Botanical Museum Leaflets, Harvard University*, 25, 259–272.
- Shafiei, Z., Shuhairi, N. N., Yap, N. M. F. S., Sibungkil, C. A. H., & Latip, J. (2012). Antibacterial activity of *Myristica fragrans* against oral pathogens. *Evidence-based Complementary and Alternative Medicine*, 2012, 825362. <https://doi.org/10.1155/2012/825362>
- Sharma, T., Abirami, K., & Chander, M. P. (2018). Medicinal plants used by tribes of andaman and nicobar Islands: A conservation appraisal. *Indian Journal of Plant Genetic Resources*, 31, 125–133.
- Sheeja, T. E., Rosana, O. B., Swetha, V. P., Shalini, R. S., Siju, S., Dhanya, R., ... Krishnamoorthy, B. (2014). The 18S rDNA gene discriminates between red-listed and unexplored ethnomedicinal species of Myristicaceae restricted to humid tropics of India. *Genetic Resources and Crop Evolution*, 61, 523–535.
- Shulgin, A. T., Sargent, T., & Naranjo, C. (1967). The chemistry and psychopharmacology of nutmeg and of several related phenylisopropylamines. *Psychopharmacology Bulletin*, 4, 202–214.
- Silva Dulce, H. S., Zhang, Y., Santos, L. A., Bolzani, V. S., & Nair, M. G. (2007). Lipoperoxidation and Cyclooxygenase 1 and 2 inhibitory compounds from *Iryanthera juruensis*. *Agricultural and Food Chemistry*, 55, 2569–2574.
- Sinclair, J. (1969). The genus *Myristica* in Malesia and outside Malesia. *The Garden's Bulletin Singapore*, 23, 1–540.
- Sinclair, J. (1975). The genus *Horsfieldia* (Myristicaceae) in and outside Malesia II. *The Gardens' Bulletin (Singapore)*, 28, 1–181.
- Sinclair, J. (1958). A revision of the Malaysian Myristicaceae. *The Gardens' Bulletin Singapore*, 16, 205–472.
- Sinclair, J. (1961). The Genus *Knema* (Myristicaceae) in Malaysia and outside Malaysia. *The Gardens' Bulletin Singapore*, 18, 102–327.
- Singh, G., Marimuthu, P., De Heluani, C. S., & Catalan, C. (2005). Antimicrobial and antioxidant potentials of essential oil and acetone extract of *Myristica fragrans* Houtt. (Aril Part). *Journal of Food Science*, 70, M141–M148.
- Singh, R. H., Sankat, C. K., & Mujaffar, S. (2003). The nutmeg and spice industry in Grenada: Innovations and competitiveness – A case study. Presented at workshop on the role of science, technology and innovation in increasing competitiveness in the productive sector, The University of West Indies, Trinidad, organized by the Office of Science and Technology of the Organization of American States and the Secretariat of Science, Technology and Productive Innovation.
- Sklerov, J., Levine, B., Moore, K. A., King, T., & Fowler, D. (2005). A fatal intoxication following the ingestion of 5-methoxy-N, N-dimethyltryptamine in an ayahuasca preparation. *Journal of Analytical Toxicology*, 29, 838–841.
- Sriphana, U., Yenjai, C., & Koatthada, M. (2016). Cytotoxicity of chemical constituents from the roots of *Knema globularia*. *Phytochemistry Letters*, 16, 129–133.
- Strassman, R. J. (1996). Human psychopharmacology of N, N-dimethyltryptamine. *Behavioural Brain Research*, 73, 121–124.
- Strassman, R. J., Qualls, C. R., Uhlenhuth, E. H., & Kellner, R. (1994). Dose-response study of N, N-dimethyltryptamine in humans: II. Subjective effects and preliminary results of a new rating scale. *Archives of General Psychiatry*, 51, 98–108.
- Subha, S., Vijayakumar, B., Prudhvairaj, K., Anandhi, M. V., Shankar, M., & Nishanthi, M. (2013). Pharmacognostic and preliminary phytochemical investigation on leaf extracts of *Myristica dactyloides* Gaertn. *International Journal of Phytopharmacology*, 4, 18–23.

- Takeda, N., Ikeda, R., Ohba, K., & Kondo, M. (1995). Bufotenine reconsidered as a diagnostic indicator of psychiatric disorders. *Neuroreport*, 6, 2378–2380.
- Talukdar, A. C., Jain, N., De, S., & Krishnamurty, H. G. (2000). An isoflavone from *Myristica malabarica*. *Phytochemistry*, 53, 155–157.
- Thuong, P. T., Hung, T. M., Khoi, N. M., Nhung, H. T. M., Chinh, N. T., Quy, N. T., ... Na, M. (2014). Cytotoxic and anti-tumor activities of lignans from the seeds of Vietnamese nutmeg *Myristica fragrans*. *Archives of Pharmacol Research*, 37, 399–403.
- Tittarelli, R., Mannocchi, G., Pantano, F., & Saverio Romolo, F. (2015). Recreational use, analysis and toxicity of tryptamines. *Current Neuropsychopharmacology*, 13, 26–46.
- TKDL. (2001). Traditional Knowledge Digital Library - Representative database of TKDL. CSIR & AYUSH. Retrieved 3 July 2020 from <http://www.tkdil.res.in/tkdil/langdefault/common/Home.asp?GL=Eng>.
- Truitt, E. B., Jr., Duritz, G., & Ebersber, E. M. (1963). Evidence of monoamine oxidase inhibition by myristicin and nutmeg (21828). *Experimental Biology and Medicine*, 112, 647–650.
- Tupper, K. W., Wood, E., Yensen, R., & Johnson, M. W. (2015). Psychedelic medicine: A re-emerging therapeutic paradigm. *Canadian Medical Association Journal*, 187, 1054–1059.
- Usha Rani, P., Naidu, M. U., Kumar, T. R., & Shobha, J. C. (1997). Evaluation of the efficacy and safety of a new herbal revitalizer revivin. *Ancient Science of Life*, 16, 190–195.
- Valente, V. M. M., Jham, G. N., Dhingra, O. D., & Ghiviriga, I. (2011). Composition and antifungal activity of the Brazilian *Myristica fragrans* Houtt. essential oil. *Journal of Food Safety*, 31, 197–202.
- Van den Berg, S. J. P. L., Punt, A., Soffers, A. E. M. F., Vervoort, J., Ngeleja, S., Spenkelink, B., & Rietjens, I. M. C. M. (2012). Physiologically based kinetic models for the alkenylbenzene elemicin in rat and human and possible implications for risk assessment. *Chemical Research in Toxicology*, 25, 2352–2367.
- Vidhya, B., Venkatesh, P. T., Vishnubharath, A., Tejaashwine, M., Eganathan, P., Saranya, J., & Sujanal, P. (2015). Essential oil composition, antioxidant and nutritional properties of fruit pericarp of *Myristica beddomei* King ssp. *ustulata* de Wilde-an endangered tree species. *Analytical Chemistry Letters*, 5, 21–30.
- Vinayachandra, & Chandrashekar K. R. (2014). Phenolic contents of knema attenuata fruits and their bioactive potentials. *Journal of Herbs, Spices & Medicinal Plants*, 20(2), 183–195. <http://dx.doi.org/10.1080/10496475.2013.848390>.
- Wahab, S. M. A., Sivasothy, Y., Liew, S. Y., Litaudon, M., Mohamad, J., & Awang, K. (2016). Natural cholinesterase inhibitors from *Myristica cinnamomea* King. *Bioorganic & Medicinal Chemistry Letters*, 26, 3785–3792.
- Waller, D. G., & Sampson, T. (2018). *Medical pharmacology and therapeutics E-Book*. Edinburgh: Elsevier Health Sciences.
- Warburg, O. (1897). Monographie der Myristicaceen. In *Nova acta Academiae Caesareae Leopoldino-Carolinae Germanicae Naturae Curiosorum*. (pp. 1873–1932). Dresden: E. Blochmanni et Filii.
- Weiss, G. (1960). Hallucinogenic and narcotic-like effects of powdered *Myristica* (Nutmeg). *Psychiatric Quarterly*, 34, 345–356. <https://doi.org/10.1007/BF01562114>
- Weiss, J. (2019). Herb-drug interaction potential of anti-borreliae effective extracts from *Uncaria tomentosa* (Samento) and *Otoba parvifolia* (Banderol) assessed in vitro. *Molecules*, 24, 137.
- Weiss, E. A. (2002). *Spices Crops*. (pp. 86–103). New York: CABI Publishing.
- Wiert, C. (2007). *Ethnopharmacology of medicinal plants: Asia and the Pacific*. Berlin, Germany: Springer Science & Business Media.
- Williams, L. O. (1960). Ucuuba and related wax-like vegetable tallows. *Qualitas Plantarum et Materiae Vegetabiles*, 7(3), 295–296.
- Williamson, E. M., Liu, X., & Izzo, A. A. (2020). Trends in use, pharmacology, and clinical applications of emerging herbal nutraceuticals. *British Journal of Pharmacology*, 177, 1227–1240.
- Wimalasena, S., & Karunawansa, E. (1994). Characterization of a new aryl alkanone and other compounds present in *Horsfieldia irya* seeds. *Journal of the National Science Foundation of Sri Lanka*, 22, 301.
- Winkelman, M. (2001). Psychointegrators: Multidisciplinary perspectives on the therapeutic effects of hallucinogens. *Complementary Health Practice Review*, 6, 219–237.
- Zachariah, T. J., Leela, N. K., Maya, K. M., Rema, J., Mathew, P. A., Vipin, T. M., & Krishnamoorthy, B. (2008). Chemical composition of leaf oils of *Myristica beddomei* (King), *Myristica fragrans* (Houtt.) and *Myristica malabarica* (Lamk.). *Journal of Spices and Aromatic Crops*, 17, 10–15.
- Zhou, J., & Xie, G. Y. (2011). *Encyclopedia of traditional Chinese medicines-molecular structures, pharmacological activities, natural sources and applications*. Berlin Heidelberg: Springer-Verlag.
- Zucchi, R., Chiellini, G., Scanlan, T. S., & Grandy, D. K. (2006). Trace amine-associated receptors and their ligands. *British Journal of Pharmacology*, 149, 967–978.

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How to cite this article: Barman R, Bora PK, Saikia J, et al. Nutmegs and wild nutmegs: An update on ethnomedicines, phytochemicals, pharmacology, and toxicity of the *Myristicaceae* species. *Phytotherapy Research*. 2021;1–28. <https://doi.org/10.1002/ptr.7098>