Arch. Pharm. Res. (2020) 43:1067–1092
https://doi.org/10.1007/s12272-020-01285-4

Online ISSN 1976-3786
Print ISSN 0253-6269

Archives of Pharmacal Research
www.springer.com/12272

REVIEW

Phytochemical and pharmacological properties of *Myristica fragrans* Houtt.: an updated review

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Received: 8 September 2020 / Accepted: 4 November 2020 / Published online: 18 November 2020

Abstract *Myristica fragrans* Houtt. (Myristicaceae), an aromatic evergreen tree, is well known as a commercial source of mace (aril) and nutmeg (seed), which have long been widely used as spices in the culinary field. In addition, various parts of *M. fragrans* have been used in folk medicine for treating several diseases. Since its extensive uses in the culinary sector and folk medicine, *M. fragrans* has long attracted a great deal of attention from pharmacologists and chemists. Numerous studies have indicated that *M. fragrans* contains diverse phytochemicals such as lignans, neolignans, diphenylalkanes, phenylpropanoids, and terpenoids, which exhibit many of pharmacological activities. Among them, macelignan (**1**), *meso*-dihydroguaiaretic acid (**2**), myristicin (**111**), and malabaricone C (Mal C, **104**) are the most active compounds. The aim of this review is to comprehensively summarize the phytochemical and pharmacological properties of *M. fragrans* that have reported to date.

Keywords *Myristica fragrans* · Myristicaceae · Lignan · Neolignan · Diphenylalkane · Malabaricone C

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Introduction

Myristica fragrans Houtt. (more commonly known as the nutmeg tree) is an evergreen tropical tree possessing a pleasant aroma and taste, widely cultivated for commercial purposes in many countries, including Indonesia, Thailand, Japan, China, South Africa, and India. This plant belongs to the Myristicaceae family in the order Magnoliales which also comprises about 150 genera and more than 3000 species. The genus *Myristica* contains about 72 tropical species native to Moluccas, indigenous to Indonesia, India, and Sri Lanka, and which are now cultivated in many tropical countries of both hemispheres as well as in South Africa (Periasamy et al. 2016).

Myristica fragrans usually grows about 5–13 m high, and occasionally up to 20 m. The bark contains watery pink or red sap. The leaves (5–15 cm × 2–7 cm) are alternately arranged along the branches, pointed, dark green-colored, the stems of which are approximately 1 cm long. The *M. fragrans* flowers are pale yellow, fleshy, waxy, and bell-shaped, and usually single sexed, occasionally, both male and female flowers are found on the same tree (Gupta and Rajpurohit 2011). Fruits of *M. fragrans* are yellow, globose, with fleshy pericarp, and 6 to 9 cm long with a longitudinal ridge. Nutmeg is the dried kernel of the ripe seed and mace is the red lacy covering (aril) surrounding the seed. Nutmeg has a distinctive, pungent fragrance and a warm, slightly sweet taste. The seeds (nutmegs) are broadly ovoid (2 to 3 cm long), firm, fleshy, whitish and transversed by red-brown veins (Arumugam et al. 2019). *M. fragrans* is indigenous native to Indonesia, and is exotic to Grenada, India, Mauritius, Singapore, Sri Lanka, United States of America, South Africa, as well as the majority of African countries. This plant needs a warm and humid tropical climate and

usually grows wild on rich volcanic soils in lowland tropical rain forests (Orwa et al. 2009).

There are three major commercial products of *M. fragrans*: mace, nutmeg, and essential oils, which are widely used as spices and flavoring ingredients in food products, with possible beneficial health effects (Damien Dorman et al. 1995; Adjene and Igbigbi 2010). In addition to their use in the culinary sector, various parts of the *M. fragrans* plant have been used in folk medicine for treating several diseases. In traditional Chinese medicine, *M. fragrans* mace has been used as a remedy for strengthening the stomach and expelling "wind-evil", and as an alleged abortifacient and narcotic (Hattori et al. 1988). In Ayurvedic medicine (a healthy-lifestyle system of medicine in India), mace is used to treat humoral asthma, low-grade fever, and to alleviate gastrointestinal complaints when mixed with aromatics (Hattori et al. 1993). For a long time, nutmeg has been used medicinally to treat diarrhea, rheumatism, headaches, psychosis, fever, bad breath, nausea, stomach cramps, chronic vomiting, hemorrhoids, and to stimulate appetite, and to control flatulence (Arumugam et al. 2019). It also used in some medicines as an aphrodisiac, an abortifacient, a narcotic, and as a tonic after child birth (Gupta and Rajpurohit 2011). In the form of an ointment, nutmeg butter is used as a mild external stimulant to treat sprains and paralysis (Arumugam et al. 2019). In addition, nutmeg seeds are known to have hallucinogenic properties. Their effect on the central nervous system was first observed in the early nineteenth century (Orwa et al. 2009). With antiseptic and analgesic properties, nutmeg oil is used for the treatment of rheumatism, diarrhea, cholera, intestinal disorders, stomach cramps, and flatulence, and to dissolve kidney stones and alleviate infections of the kidney (Sanghai-Vaijwade et al. 2011; Periasamy et al. 2016). Owing to its extensive uses in the culinary sector and folk medicine, *M. fragrans* has long attracted attention from pharmacologists and chemists. The present review comprehensively summarizes the chemical constituents, pharmacological properties, and toxicology of *M. fragrans* that have been reported to date.

Phytochemistry of *M. fragrans*

Myristica fragrans is characterized by a number of phytochemicals, including lignans, neolignans, diphenylalkanes, phenylpropanoids, terpenoids, alkanes, fatty acids, fatty acid esters, and a few minor constituents such as steroids, saponins, triterpenoids, and flavonoids. The majority of investigations in *M. fragrans* are focused on the isolation and structural elucidation of lignans from the aril (mace) or nutmeg (seed) of the *M. fragrans* fruit. However, several studies on the leaves (Zachariah et al. 2008), stem bark (Francis et al. 2019), and fruit pericarp (Francis et al. 2014; Zhang et al. 2015) have also been published.

Lignans

Lignans are dimers of phenylpropanoid (C_6C_3) units linked by the central carbons (β–β linkage) of their side chains (C_3), while naturally occurring dimers that exhibit linkages other than this type of bond are known as neolignans. Many of the major bioactive secondary metabolites of *M. fragrans* are lignan derivatives; to date, a total of 35 lignans have been identified in *M. fragrans*. These lignans were classified into three structural classes, including 2,3-dimethyl-1,4-diaryl-butane type lignans (**1–10**), aryltetralin lignans (**11–13**), and tetrahydrofuran lignans (**14–35**) (Figs. 1 and 2). In the present review, all secondary metabolite lignans of *M. fragrans* from the literature have been shown in Table 1. In 1987, Woo et al. reported the first isolation of two 2,3-dimethyl-1,4-diaryl-butane type lignans, (2*R*,3*S*)-1-(3,4-melhylenedioxyphenyl)-2,3-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-butane (macelignan, **1**) and *meso*-dihydroguaiaretic acid (**2**), from the arils of *M. fragrans* (Woo et al. 1987). Among them, the absolute configuration of macelignan (**1**) was established as 2*R*,3*S* by using X-ray crystallographic analysis. Macelignan (**1**) also includes *erythro*-austrobailignan-6, a diastereoisomer of austrobailignan-6 isolated previously from *Austrobaileya scandens* (Woo et al. 1987). In addition, another *A. scandens* lignan (*threo*-austrobailignan-5, **9**) was also identified in methanol (95%) extracts of *M. fragrans* seeds (Kwon et al. 2008). A monomethyl ether derivative (**8**) of myristargenol (**4**) was also isolated from *M. fragrans* seeds by Kwon et al. (2008); however, its absolute configuration has not been determined. The absolute configuration of compound **5** was determined as (8*R*,8′*S*) by the same positive optical rotation as macelignan (**1**) and similar ^{13}C NMR data as secoisolariciresinol in the literature (Min et al. 2011). There are three aryltetralin lignans (**11–13**) isolated to date from the nutmeg including otobaphenol (**11**) (Yang et al. 2006), isootobaphenol (**12**) (Kwon et al. 2014), and (+)-guaiacin (**13**) (Min et al. 2011). The structures of 21 tetrahydrofuran lignans (**14–35**) are shown in Fig. 2. The relative configuration of tetrahydrofuran ring in compounds **14–28** was determined based on a comparison of the published NMR spectral data (Hattori et al. 1987a; Hada et al. 1988). Recently, according to a phytochemical investigation of *M. fragrans* stem bark, Francis et al. (2019) have reported the first isolation of grandisin (**34**) and (7S,8S,7′R,8′R)-3,3′,4,4′,5,5′-hexamethoxy-7,7′,8,8′-lignan (**35**).

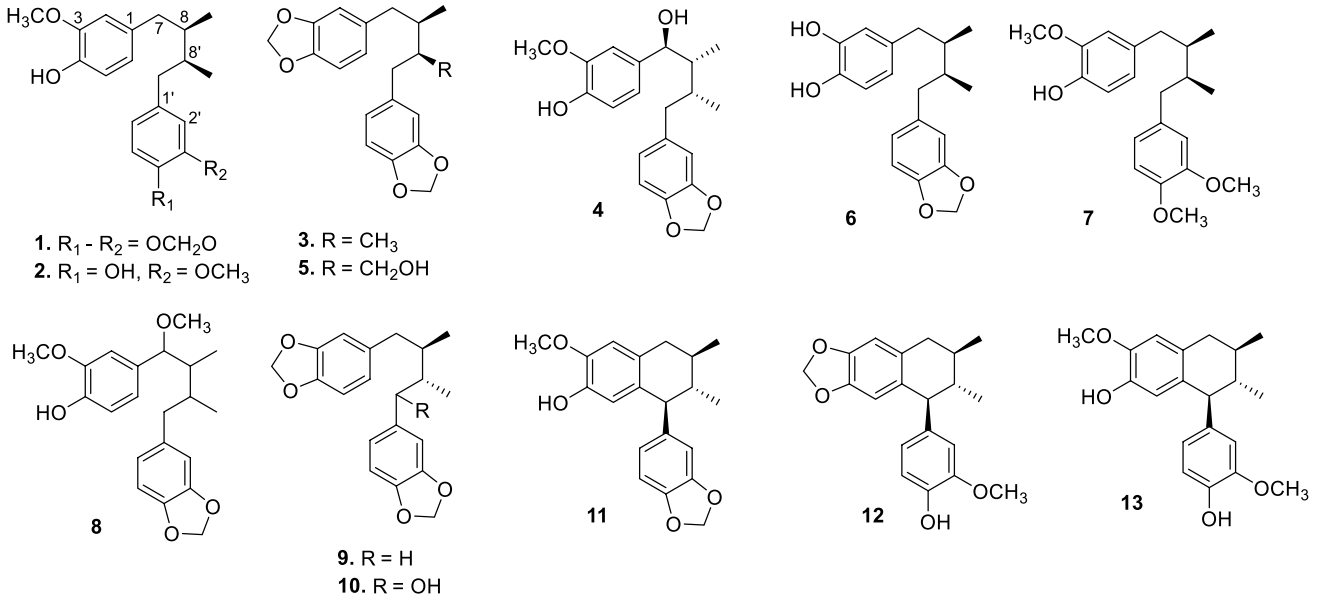


Fig. 1 Structures of 2,3-dimethyl-1,4-diaryl-butane type lignans **1–10** and aryltetralin lignans **11–13**

Neolignans

In addition to lignans, neolignans are also major constituents of *M. fragrans*. About 91 neolignan compounds have been isolated from the aril, seed, fruit, fruit pericarp, or stem bark of *M. fragrans*, of which approximately 35.1% are benzofuranoid neolignans, 61.5% are 8.*O*.4′ neolignans (8-*O*-4′ type diarylpropanoid ethers), and 3.4% are diphenylpropanoid neolignans (Table 2). The chemical structures of the mentioned compounds are shown in Figs. 3 and 4, of which some structures have been reported lacking absolute configuration. For the benzofuranoid neolignans (32 compounds, **36–59**), the relative and absolute configurations of the benzofuran skeleton at positions 2 and 3 were determined by various methods. While Morikawa et al. (2016) determined the relative configuration using nuclear Overhauser effect spectroscopy (NOESY), Hattori et al. (1988) identified structures based on the chemical shifts of CH_3-3 and H-2 [*cis* isomer: δ_H 0.7–0.8 (CH_3-3) and δ_H 5.7–5.8 (H-2); *trans* isomer: δ_H 1.3–1.4 (CH_3-3) and δ_H ~ 5.1 (H-2)]. In addition, the *trans*-vicinal coupling of the dihydrobenzofuran ring in **52–56** was determined by a large coupling constant $J_{2,3}$ = 8.8–9.2 Hz between H-2 and H-3, and confirmed by NOESY experiment (Cao et al. 2013; Chumkaew and Srisawat 2019). The absolute configuration of fragransol C (**50**, 2*S*,3*S*) and fragransol D (**51**, 2*R*,3*R*) was determined based on their optical rotation value: [α] **–**44 and [α] + 47.6, respectively (Hattori et al. 1988). In another way, Kimura et al. (2010) determined the absolute configuration of compounds **36b**, **38b**, **39b**, and **40b** based on the aromatic quadrant and the P/M helicity rules, in which, all showed negative signs at the ^1L_a band (around 230 nm) and positive signs at the ^1L_b band (around 280 nm), establishing the 2*S*,3*S* configurations for all compounds. In addition, the absolute configuration of compounds **37**, **38a**, **40a**, **42**, **45**, **46**, and **57** were elucidated by the analysis of their ECD spectrum and optical rotation value in comparison with reported values in the literature (Li and Yang 2007; Morikawa et al. 2016). For example, the absolute configuration of **38a**, **40a**, and **57** were determined as 2*R*,3*R* based on their positive optical rotation values and positive Cotton effects at 260–285 nm (Li and Yang 2007; Morikawa et al. 2016). However, in a recent study (Chumkaew and Srisawat 2019), three new benzofuranoid neolignans (myticaganals A**–**C, **54–56**) were also characterized by the positive optical rotation and positive Cotton effects at 260–285 nm, but their absolute configuration were reported as 2*S*,3*S*. This inconsistency can be further observed when comparing the optical rotation of **54–56** (positive) with those other compounds with the same absolute configuration such as: fragransol C (**50**, 2*S*,3*S*, [α] **–** 44) (Hattori et al. 1988) and dihydrocarinatidin (**50**, 2*S*,3*S*, [α] **–** 12.7) (Li and Yang 2007). A new benzofuranoid neolignane, [3-(4-Allyl-2,6-dimethoxy-phenyloxy)-2-methyl-5-methoxy-2,3-dihydrobenzofuran, **59**], different from all those previously described (**36–58**) with a phenoxy moiety and a methyl group attached to positions 3 and 2, respectively, has been isolated from the seeds of *M. fragrans*.

The chemical structures of 8.*O*.4′ neolignans (56 compounds, **60–99**), together with their stereochemistry (absolute configuration or only relative configuration) are shown in Fig. 4. Of these, the reported compounds with *erythro* configurations were more abundant than compounds with

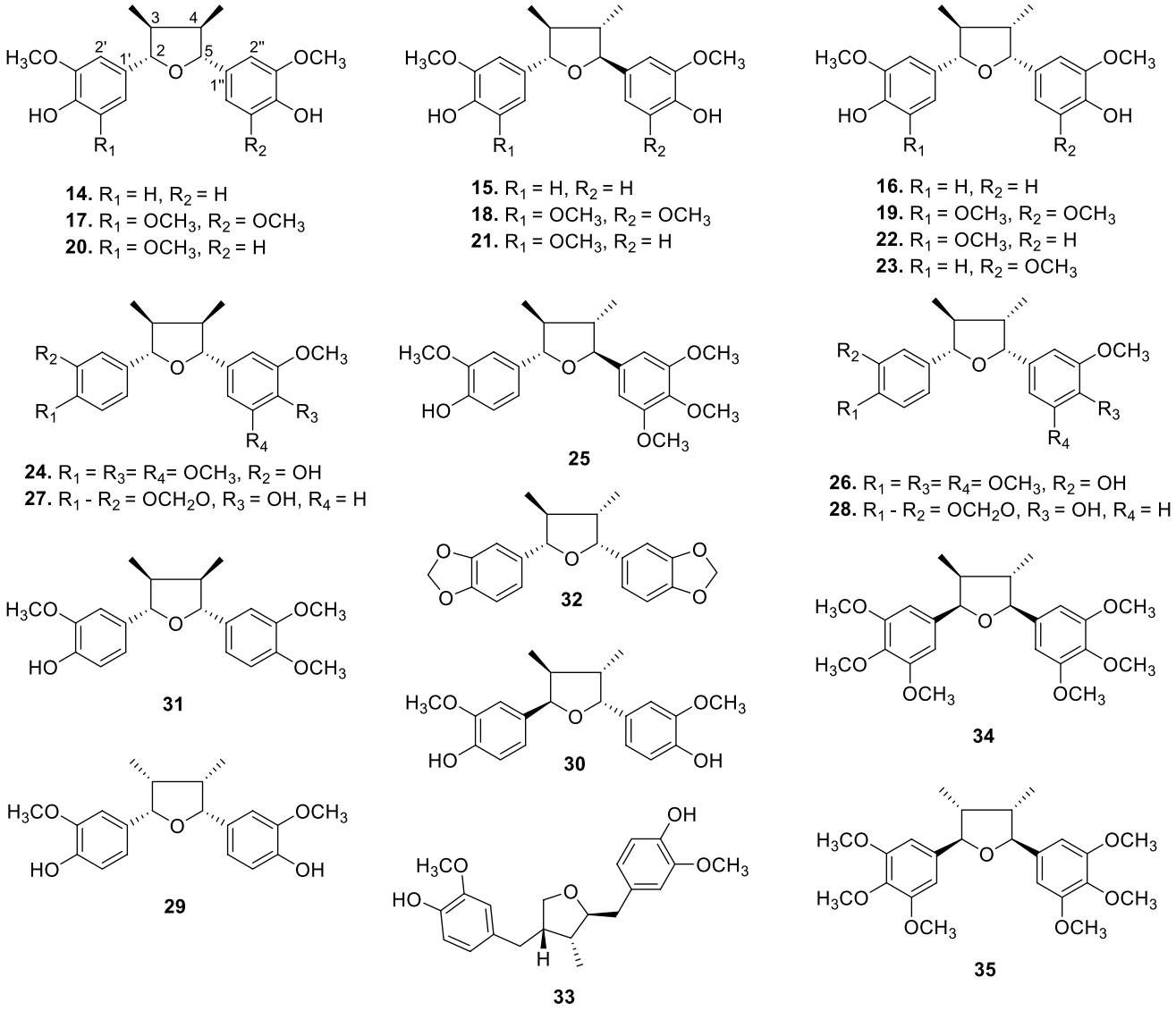


Fig. 2 Structures of tetrahydrofuran lignans **14–35**

threo configurations (Table 2). The *erythro* relative configuration of 8-*O*-4′ type diarylpropanoid ethers from *M. fragrans* was determined by a small coupling constant ($J_{7,8}$ = 2.3**–**3.5 Hz) observed between two methine protons H-7 and H-8 (Isogai et al. 1973b; Forrest et al. 1974; Hattori et al. 1987b), while the *threo* configuration of 8.*O*.4′ neolignans, evident in **63**, **65**, **74b**, **81**, **83**, and **85–87**, was characterized by a larger coupling constant ($J_{7,8}$ = 8.0**–**8.6 Hz). Occasionally, the H-7 methine proton did not appear in a simple doublet because of overlap with the H-8 proton signal or spin–spin coupling with the 7-hydroxyl proton. The difficulty in determining $J_{7,8}$ values could be generally overcome by using CD_3COOD as an NMR solvent instead of $CDCl_3$ (Hattori et al. 1987b). In another way, these diastereomers (*erythro* and *threo*) can be simply distinguished based on the basis of the methyl signal (CH_3-8) in the ^{13}C NMR spectrum, appearing at δ_H 16.5–17.4 for the *threo* derivatives and at δ_H 12 0.6–13.9 for the *erythro* derivatives (Hattori et al. 1987b). Currently, there are only a few reports on the absolute configuration of the 8.*O*.4′ neolignans isolated from *M. fragrans* (Kimura et al. 2010; Cao et al. 2015; Morikawa et al. 2016, 2018). The absolute configuration of the *erythro* derivatives **67a** and **68** was determined as (1*S*,2*R*) based on the negative Cotton effects at 244 and 280 nm in their CD spectra (Kimura et al. 2010). While Cao et al. (2015) have elucidated the absolute configuration (1*R*,2*S*) of the *erythro* 8.*O*.4′ neolignans (**88–91**) based on their negative optical rotation and positive Cotton effect at 237 nm, however, there is inconsistency within this paper itself and with the report of Kimura et al. (2010).

Table 1 Lignan constituent of *M. fragrans*

No.	Compound name	Plant part	References
2,3-Dimethyl-1,4-diaryl-butane lignans			
1	Macelignan [(2*R*,3*S*)-1-(3,4-melhylenedioxyphenyl)-2,3-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-butane]	Aril, seed	Woo et al. (1987), Lee et al. (2009), Thuong et al. (2014)
2	*Meso*-dihydroguaiaretic acid	Aril, seed	Woo et al. (1987), Yang et al. (2006), Lee et al. (2009), Thuong et al. (2014)
3	Machilin A	Seed	Lee et al. (2009)
4	Myristargenol	Seed	Lee et al. (2009), Kwon et al. (2008)
5	(8*R*,8′*S*)-7-(3,4-Methylenedioxyphenyl)-8-methyl-8′-hydroxymethyl-7′-(3′,4′-methylenedioxyphenyl)-butanol	Seed	Min et al. (2011)
6	(8*R*,8′*S*)-7′-(3′,4′-Methylenedioxyphenyl)-8,8′-dimethyl-7-(3,4-dihydroxyphenyl)-butane	Seed	Min et al. (2011)
7	*Meso*-monomethyldihydroguaiaretic acid	Seed	Min et al. (2011)
8	7-(4-Hydroxy-3-methoxyphenyl)-7-(3,4-methylenedioxyphenyl)-8,8-lignan-7-methyl ether	Seed	Kwon et al. (2008), Min et al. (2011)
9	*Threo*-austrobailignan-5	Seed	Kwon et al. (2008)
10	2,3-Dimethyl-1,4-bis-(3,4-methylenedioxyphenyl)butan-1-ol	Aril	Hattori et al. (1988)
Aryltetralin lignans			
11	Otobaphenol	Seed	Yang et al. (2006)
12	Isootobaphenol	Seed	Kwon et al. (2014)
13	(+)-Guaiacin	Seed	Min et al. (2011)
Tetrahydrofuran lignans			
14	Nectandrin B	Aril, seed	Hattori et al. (1987a), Thuong et al. (2014), Lee et al. (2009), Nguyen et al. (2010)
15	Fragransin A_2	Aril, seed	Hattori et al. (1987a), Thuong et al. (2014)
16	Verrucosin [7S,8S,7′R,8′S)-4,4′-dihydroxy-3,3′-dimethoxy-7,7′-epoxylignan]	Aril	Hattori et al. (1987a), Duan et al. (2009)
17	Fragransin B_1	Aril, stem bark	Hattori et al. (1987a), Francis et al. (2019)
18	Fragransin B_2	Aril	Hattori et al. (1987a)
19	Fragransin B_3	Aril	Hattori et al. (1987a)
20	Fragransin C_1	Aril	Hattori et al. (1987a)
21	Fragransin C_2	Aril	Hattori et al. (1987a)
22	Fragransin C_{3a}	Aril	Hattori et al. (1987a)
23	Fragransin C_{3b}	Aril	Hattori et al. (1987a)
24	Fragransin D_1	Aril	Hada et al. (1988)
25	Fragransin D_2	Aril	Hada et al. (1988)
26	Fragransin D_3	Aril	Hada et al. (1988)
27	Fragransin E_1 or machilin F	Aril, seed	Hada et al. (1988), Lee et al. (2009)
28	Austrobailignan-7	Aril	Hada et al. (1988)
29	Tetrahydrofuroguaiacin B	Seed	Nguyen et al. (2010)
30	Saucernetindiol	Seed	Nguyen et al. (2010)
31	Nectandrin A	Seed	Nguyen et al. (2010)
32	Galbacin	Seed	Nguyen et al. (2010)
33	(7S,8′R,7′R)-4,4′-Dihydroxy-3,3′-dimethoxy-7′,9-epoxylignan	Seed	Min et al. (2011)
34	Grandisin	Stem bark	Francis et al. (2019)
35	(7S,8S,7′R,8′R)-3,3′,4,4′,5,5′-Hexamethoxy-7,7′,8,8′-lignan	Stem bark	Francis et al. (2019)

Table 2 Neolignan constituent of *M. fragrans*

No.	Compound name	Plant part	References
Benzofuranoid neolignans			
36	Licarin A or dehydrodiisoeugenol	Aril, fruit pericarp, seed, stem bark	Isogai et al. (1973b), Hattori et al. (1986), Francis et al. (2019); Zhang et al. (2015)
36a	(+)-Licarin A	Aril	Morikawa et al. (2016)
36b	(2*S*,3*S*)-2,3-Dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-7-methoxy-3-methyl-5-(*E*-propenyl) benzofuran	Aril, seed	Kimura et al. (2010)
37	Isolicarin A	Aril	Li and Yang (2007)
38	Odoratisol A [3′-methoxy-licarin A]	Aril, seed, stem bark	Hattori et al. (1986), Chiu et al. (2016), Acuña et al. (2016), Francis et al. (2019)
38a	Maceneolignan A [(2*R*,3*R*)-2,3-Dihydro-2-(4-hydroxy-3,5-dimethoxyphenyl)-7-methoxy-3-methyl-5-(*E*-propenyl) benzofuran]	Aril	Morikawa et al. (2016)
38b	(2*S*,3*S*)-2,3-Dihydro-2-(4-hydroy-3,5-dimethoxyphenyl)-7-methoxy-3-methyl-5-(*E*-propenyl) benzofuran	Aril, seed	Kimura et al. (2010)
39	Licarin B	Aril, fruit pericarp, seed, stem bark	Isogai et al. (1973b), Hattori et al. (1986), CaoCao et al. (2013), Morikawa et al. (2016), Francis et al. (2019), Zhang et al. (2015), Kim et al. (1991b)
39a	Licarin E	Seed	Kapoor et al. (2013)
39b	(2*S*,3*S*)-2,3-Dihydro-2-(3,4-methylenedioxyphenyl)-7-methoxy-3-methyl-5-(*E*-propenyl) benzofuran	Aril, seed	Kimura et al. (2010)
40	3′-Methoxy-licarin B	Aril, fruit pericarp, seed, stem bark	Isogai et al. (1973b), Hattori et al. (1986), Cao et al. (2013), Zhang et al. (2015), Morikawa et al. (2016), Francis et al. (2019)
40a	Maceneolignan B [(2*R*,3*R*)-3′-methoxy-licarin B]	Aril	Morikawa et al. (2016)
40b	(2*S*,3*S*)-2,3-Dihydro-2-(5-methoxy-3,4-methylenedioxyphenyl)-7-methoxy-3-methyl-5-(*E*-propenyl) benzofuran	Aril, seed	Kimura et al. (2010)
41	Licarin C	Aril, seed	Chiu et al. (2016), Acuña et al. (2016)
42	Maceneolignan C	Aril	Morikawa et al. (2016)
43	Acuminatin	Fruit pericarp	Francis et al. (2014)
44	(2*R*,3*R*)-2,3-Dihydro-2-(3,4-dihydroxyphenyl)-7-methoxy-3-methyl-5-(*E*-propenyl) benzofuran	Fruit	Duan et al. (2009)
45	Maceneolignan D	Aril	Morikawa et al. (2016)
46	Maceneolignan E	Aril	Morikawa et al. (2016)
47	(2S,3S)-2-(4-Hydroxy-3-methoxyphenyl)-5-formyl-7-methoxy-3-methyldihydrobenzofuran	Aril	Morikawa et al. (2016)

Table 2 (continued)

No.	Compound name	Plant part	References
48	Fragransol A	Aril	Hada et al. (1988)
49	Fragransol B	Aril	Hada et al. (1988)
50	Fragransol C	Aril	Hattori et al. (1988)
51	Fragransol D	Aril	Hattori et al. (1988)
52	Myrisfrageal A	Seed	Cao et al. (2013), Chumkaew and Srisawat (2019)
53	Myrisfrageal B	Seed	Cao et al. (2013), Chumkaew and Srisawat (2019)
54	Myticaganal A	Seed	Chumkaew and Srisawat (2019)
55	Myticaganal B	Seed	Chumkaew and Srisawat (2019)
56	Myticaganal C	Seed	Chumkaew and Srisawat (2019)
57	Isodihydrocarinatidin	Aril, seed	Li and Yang (2007), Cao et al. (2013)
58	Dihydrocarinatidin	Aril	Morikawa et al. (2016)
59	3-(4-Allyl-2,6-dimethoxy-phenyloxy)-2-methyl-5-methoxy-2,3-dihydrobenzofuran	Seed	Chiu et al. (2016)
8.O.4′ Neolignans (8-*O*-4′ type diarylpropanoid ethers)			
60	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-methylenedioxyphenyl) propan-1-ol	Aril, seed	Forrest et al. (1974)
60a	(+)-*Erythro*-(1*S*,2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-methylenedioxyphenyl) propan-1-ol	Aril	Morikawa et al. (2016)
61	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl) propan-1-ol	Fruit, fruit pericarp, aril, seed, stem bark	Forrest et al. (1974), Hattori et al. (1993), Isogai et al. (1973b), Duan et al. (2009), Francis et al. (2019), Zhang et al. (2015)
61a	(+)-*Erythro*-(1*S*,2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl) propan-1-ol	Aril, seed	Cao et al. (2015), Morikawa et al. (2016)
62	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	Fruit, fruit pericarp, aril, seed	Forrest et al. (1974), Isogai et al. (1973b), Duan et al. (2009), Zhang et al. (2015), Kim et al. (1991a)
62a	(+)-*Erythro*-(1*S*,2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	Aril	Morikawa et al. (2016)
62b	Myrislignan [(−)-*erythro*-(1*R*,2*S*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol]	Aril, seed	Cao et al. (2015), Morikawa et al. (2016)
63	*Threo*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	Aril	Hattori et al. (1987b)
64	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol	Fruit, fruit pericarp, seed, stem bark	Yang et al. (2008), Francis et al. (2014), Francis et al. (2019), Zhang et al. (2015)
64b	(−)-*Erythro*-(1*R*,2*S*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol	Aril	Morikawa et al. (2016)
65	*Threo*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol	Fruit pericarp	Zhang et al. (2015)

Table 2 (continued)

No.	Compound name	Plant part	References
66	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-methylenedioxyphenyl) propan-1-ol acetate	Aril, seed	Forrest et al. (1974) Acuña et al. (2016)
66b	(−)-*Erythro*-(1*R*,2*S*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-methylenedioxyphenyl) propan-1-ol acetate	Aril	Morikawa et al. (2016)
67	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol acetate	Fruit, fruit pericarp, aril, seed	Yang et al. (2008), Francis et al. (2014), Duan et al. (2009), Acuña et al. (2016), Zhang et al. (2015)
67a	(1*S*,2*R*)-2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol acetate	Aril, seed	Kimura et al. (2010), Kang et al. (2013)
67b	Maceneolignan H [(−)-*erythro*-(1*R*,2*S*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol acetate]	Aril	Morikawa et al. (2016)
68	(1*S*,2*R*)-2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol acetate	Aril, seed	Kimura et al. (2010)
69	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(5-acetoxy-3,4-dimethoxyphenyl) propan-1-ol acetate	Aril, seed	Forrest et al. (1974)
70	2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl) propane	Aril, seed	Forrest et al. (1974), Isogai et al. (1973b)
70a	(−)-(2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl) propane	Aril	Morikawa et al. (2016)
71	(−)-(2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-methylenedioxyphenyl) propane	Aril	Morikawa et al. (2016)
72	*Threo*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol methyl ether	Aril	Hattori et al. (1986)
73	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol methyl ether	Aril	Hattori et al. (1987b)
74	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3,5-dimethoxyphenyl) propan-1-ol	Aril, stem bark	Hattori et al. (1987b), Francis et al. (2019)
74a	Maceneolignan F [(+)-*erythro*-(1*S*,2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3,5-dimethoxyphenyl) propan-1-ol]	Aril, seed	Cao et al. (2015), Morikawa et al. (2016)
74b	Myrifralignan D [*threo*-(1*S*,2*S*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3,5-dimethoxyphenyl) propan-1-ol]	Seed	Cao et al. (2015)
75	2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propane	Seed	Yang et al. (2008)
76	2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propane	Aril	Hattori et al. (1987b)
76a	(−)-(2*R*)-2-(4-Allyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propane	Aril	Morikawa et al. (2016)

Table 2 (continued)

No.	Compound name	Plant part	References
77	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3-hydroxy-4,5-dimethoxyphenyl) propan-1-ol	Aril	Hattori et al. (1987b)
78	Myrisisolignan [*threo*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3-hydroxy-5-methoxyphenyl) propan-1-ol]	Seed	Yang et al. (2008)
79	*Erythro*-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl) propan-1,3-diol	Aril	Hada et al. (1988)
80	*Erythro*-2-(4-allyl-2-methoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	Aril	Hattori et al. (1987b)
81	*Threo*-2-(4-allyl-2-methoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol	Aril	Hada et al. (1988)
82	*Erythro*-1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propan-1-ol	Aril	Hada et al. (1988)
83	Machilin D [*threo*-1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propan-1-ol]	Aril, seed	Hada et al. (1988), Cao et al. (2015)
84	*Erythro*-1-(4-hydroxy-3-methoxyphenyl)-1-methoxy-2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propane	Aril	Hada et al. (1988)
85	*Threo*-1-(4-hydroxy-3-methoxyphenyl)-1-methoxy 2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propane	Aril	Hada et al. (1988)
86	*Threo*-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propan-1-ol	Aril	Hattori et al. (1987b)
87	Surinamensin [*threo*-1-(3,4,5-trimethoxyphenyl)-2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propan-1-ol]	Fruit, seed, stem bark	Francis et al. (2014), Cao et al. (2015), Chiu et al. (2016), Francis et al. (2019)
87b	(1*R*,2*S*)-1-(3,4,5-Trimethoxyphenyl)-2-(2-methoxy-4-(1(*E*)-propenyl) phenoxy) propan-1-ol	Seed	Cao et al. (2015)
88	Myrifralignan A [(1*R*,2*S*)-2-(4-(1(*E*)-propenyl)-2,6-dimethoxyphenoxy)-1-(3,4-methylenedioxyphenyl)-propan-1-ol]	Seed	Cao et al. (2015)
89	Myrifralignan C [(1*R*,2*S*)-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-(1(*E*)-propenyl)-2-methoxy phenoxy) propan-1-ol]	Aril, seed	Cao et al. (2015), Morikawa et al. (2016)
90	Myrifralignan B [(1*R*,2*S*)-2-(4-acroloyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol acetate]	Seed	Cao et al. (2015)
91	Myrifralignan E [(1*R*,2*S*)-2-(4-acroloyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3,5-dimethoxyphenyl) propan-1-ol]	Seed	Cao et al. (2015)
92	Maceneolignan G [(+)-*erythro*-(1*S*,2*R*)-2-(4-acroloyl-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol]	Aril	Morikawa et al. (2016)

Table 2 (continued)

No.	Compound name	Plant part	References
93	Myristicanol A [*erythro*-2-(4-(3-hydroxy-1-(*E*)-propenyl)-2,6-dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl) propan-1-ol]	Aril	Hada et al. (1988)
94	Myristicanol B [*erythro*-2-(4-(3-hydroxy-1-(*E*)-propenyl)-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol]	Aril	Hada et al. (1988)
95	Myrislignanometin E [(1*R*,2*S*)-2-(4-(3-hydroxy-1-(*E*)-propenyl)-2,6-dimethoxyphenoxy)-1-(4-hydroxy-3-methoxyphenyl) propan-1-ol]	Aril	Morikawa et al. (2016)
96	Maceneolignan I	Aril	Morikawa et al. (2018)
97	(−)-Miliusfragranol B	Aril	Morikawa et al. (2018)
98	Maceneolignan J	Aril	Morikawa et al. (2018)
99	Maceneolignan K	Aril	Morikawa et al. (2018)
Diphenylpropanoid neolignans			
100	1-Deoxycarinatone [2-[(1*S*)-2-(4-hydroxy-3-methoxyphenyl)-1-methylethyl]-6-methoxy-4-(prop-2-enyl)phenol]	Aril	Li and Yang (2007)
101	Dehydrodieugenol	Seed	Isogai et al. (1973a)
102	(*S*)-1-(3,4,5-Trimethoxyphenyl)-2-(3-methoxy-5-(prop-1-yl) phenyl)-propan-1-ol	Aril	(Acuña et al. 2016)

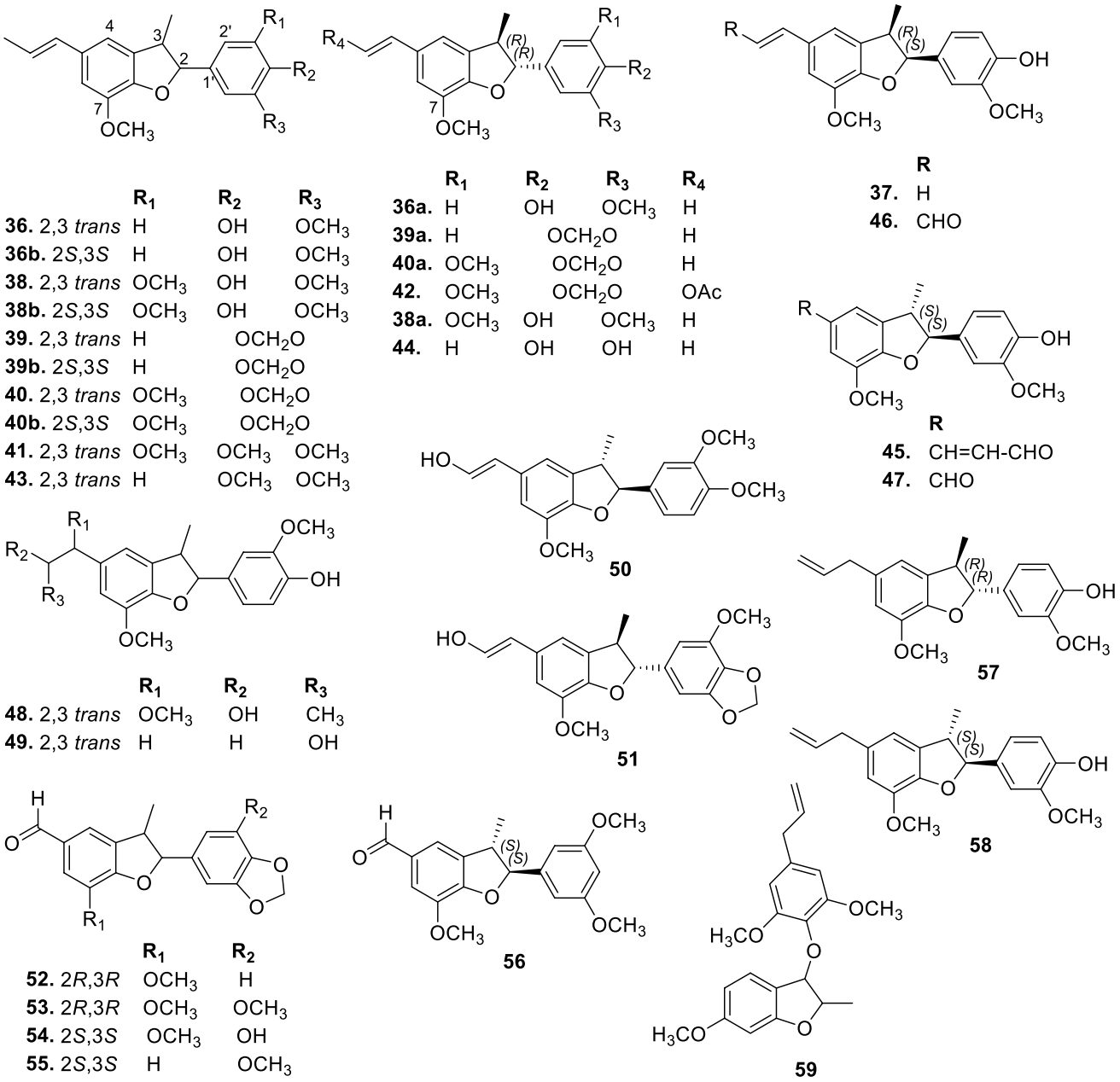
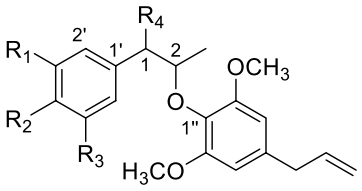
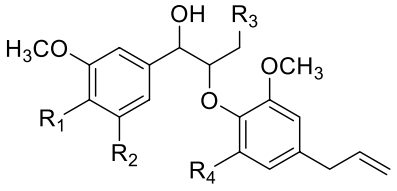


Fig. 3 Structures of benzofuranoid neolignans **36–59**

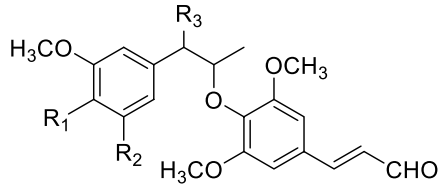
Specifically, in the experiment section of the paper (Cao et al. 2015), the CD data of **88–91** are all negative at around 237 nm, while the *threo* derivative (**74b**, 1*S*,2*S*) also exhibits negative optical rotation and a negative Cotton effect at 237 nm (Cao et al. 2015). In addition, according to the study by Morikawa et al. (2018), the absolute configuration (1*S*,2*R*) of **98** was characterized by its positive optical rotation and positive Cotton effect at 242 nm. Based on the comparison of the optical rotation values with those of similar neolignans, there are two absolute configuration types of the *erythro* 8.*O*.4′ neolignans reported in the study of Morikawa et al. (2016) including (+)-*erythro*-(1*S*,2*R*) for compounds **60a**, **61a**, **62a**, **74a**, and **92** and (−)-*erythro*-(1*R*,2*S*) for compounds **62b**, **64b**, **66b**, **67b**, and **89**. In addition, some 2-phenoxy-1-phenyl-propane derivatives, such as compounds **70**, **70a**, **71**, **75**, **76**, and **76a**, were isolated from arils and seeds of *M. fragrans* (Isogai et al. 1973b; Forrest et al. 1974; Morikawa et al. 2016). The diphenylpropanoid neolignans include 3 compounds: 1-deoxycarinatone (**100**, 2-[(1*S*)-2-(4-hydroxy-3-methoxyphenyl)-1-methylethyl]-6-methoxy-4-(prop-2-enyl)phenol) (Li and Yang 2007), dehydrodieugenol (**101**) (Isogai et al. 1973a),



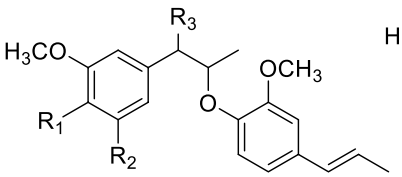
	R_1	R_2	R_3	R_4
60. *erythro*	OCH_2O		H	OH
60a. 1*S*,2*R*	OCH_2O		H	OH
61. *erythro*	OCH_3	OCH_3	OCH_3	OH
61a. 1*S*,2*R*	OCH_3	OCH_3	OCH_3	OH
62. *erythro*	OCH_3	OH	H	OH
62a. 1*S*,2*R*	OCH_3	OH	H	OH
62b. 1*R*,2*S*	OCH_3	OH	H	OH
63. *threo*	OCH_3	OH	H	OH
64. *erythro*	OCH_3	OCH_3	H	OH
64b. 1*R*,2*S*	OCH_3	OCH_3	H	OH
65. *threo*	OCH_3	OCH_3	H	OH
66. *erythro*	OCH_2O		H	OAc
66b. 1*R*,2*S*	OCH_2O		H	OAc
67. *erythro*	OCH_3	OCH_3	H	OAc
67a. 1*S*,2*R*	OCH_3	OCH_3	H	OAc
67b. 1*R*,2*S*	OCH_3	OCH_3	H	OAc
68. 1*S*,2*R*	OCH_3	OH	H	OAc
69. *erythro*	OCH_3	OCH_3	OAc	OAc
70.	OCH_3	OCH_3	OCH_3	H
70a. 2*R*	OCH_3	OCH_3	OCH_3	H
71. 2*R*	OCH_2O		H	H
72. *threo*	OCH_3	OH	H	OCH_3
73. *erythro*	OCH_3	OH	H	OCH_3
74. *erythro*	OCH_3	OH	OCH_3	OH
74a. 1*S*,2*R*	OCH_3	OH	OCH_3	OH
74b. 1*S*,2*S* (*threo*)	OCH_3	OH	OCH_3	OH
75.	OCH_3	OCH_3	H	H
76.	OCH_3	OH	H	H
76a. 2*R*	OCH_3	OH	H	H
77. *erythro*	OH	OCH_3	OCH_3	OH
78. *erythro*	OH	H	OCH_3	OH



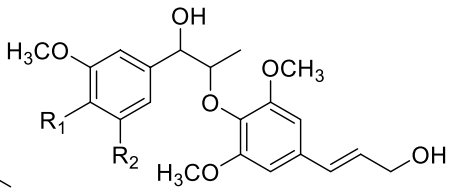
	R_1	R_2	R_3	R_4
79. *erythro*	OCH_3	OCH_3	OH	OCH_3
80. *erythro*	OH	H	H	H
81. *threo*	OH	H	H	H



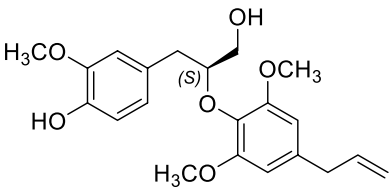
	R_1	R_2	R_3
90. 1*R*,2*S*	OCH_3	H	OAc
91. 1*R*,2*S*	OH	OCH_3	OH
92. 1*S*,2*R*	OH	H	OH



	R_1	R_2	R_3
82. *erythro*	OH	H	OH
83. *threo*	OH	H	OH
84. *erythro*	OH	H	OCH_3
85. *threo*	OH	H	OCH_3
86. *threo*	OH	OCH_3	OH
87. *threo*	OCH_3	OCH_3	OH
87b. 1*R*,2*S*	OCH_3	OCH_3	OH



	R_1	R_2
93. *erythro*	OCH_3	OCH_3
94. *erythro*	OCH_3	H
95. 1*R*,2*S*	OH	H



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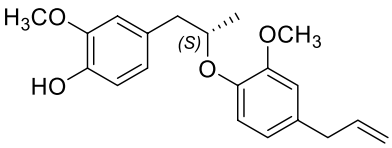

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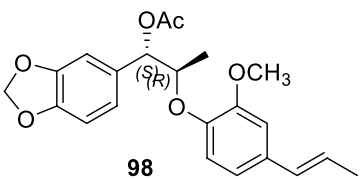

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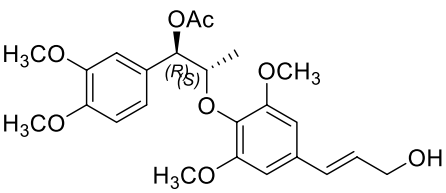

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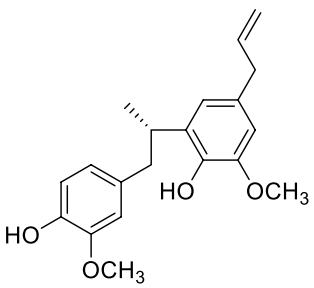

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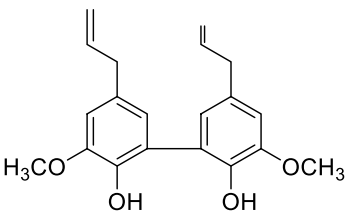

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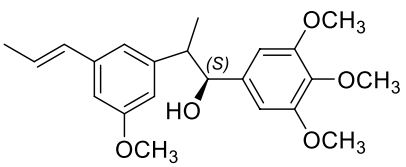


102

Fig. 4 Structures of 8.*O*.4′ neolignans **60–99** and diphenylpropanoid neolignans **100–102**

and (*S*)-1-(3,4,5-trimethoxyphenyl)-2-(3-methoxy-5-(prop-1-yl) phenyl)-propan-1-ol (**102**) (Acuña et al. 2016). The absolute configuration of **100** was determined as 1*S* based on the negative Cotton effect at 260–285 nm in its CD spectrum and positive optical rotation, while the absolute configuration of **102** at position 1 was established as *S* by Mosher's method.

Diphenylalkanes

Eight diphenylalkanes (**103–110**) have been reported to be present in *M. fragrans* (Table 3). Among them, malabaricone C (**104**) is well known as the most active compound. Malabaricones B and C were found in arils, seeds, and whole fruit of *M. fragrans*. Duan et al. (2009) have reported the isolation of a malabaricone C derivative: (−)-1-(2,6-Dihydroxyphenyl)-9-[4-hydroxy-3-(*p*-menth-1-en-8-oxy)-phenyl]-1-nonanone (**105**) from *M. fragrans* fruit. In addition to malabaricone C (**104**), Cuong et al. have isolated more three diphenylalkane derivatives (**106–108**) from the seeds (Cuong et al. 2011). Recently, tetramethylhexestrol (**110**) was isolated from *M. fragrans* seeds (Dzotam et al. 2018). The presence of diphenylalkane (virolane, **109**) in the fruit pericarp of *M. fragrans* was also confirmed by Francis et al. (2014).

Phenylpropanoids

Table 4 and Fig. 5 list the names and structures of 17 phenylpropanoids (**111–127**) isolated from various parts of *M. fragrans*. Phenylpropanoids (**111–119**) are one of the main components (15–20%) of *M. fragrans* seed essential oils, of which myristicin (**111**), elemicin (**112**), eugenol (**113**), and safrole (**114**) are the primary compounds (Jaiswal et al. 2009; Du et al. 2014). In 2009, Duan et al. also reported the isolation of four propanediol derivatives (**123–126**) from *M. fragrans* seeds (Duan et al. 2009). In the phytochemical investigation of mace and nutmeg, Kimura et al. (2010) have isolated eight phenylpropanoids including 5-hydroxyeugenol (**120**) and 2,3-dimethoxy-5-(1-propenyl)-phenol (**121**), together with compounds **111–114**, **116**, and **118**. Recently, elemicin (**112**) and anthriscinol (**127**) have also been found in the stem bark and arils of *M. fragrans*, respectively (Morikawa et al. 2016; Francis et al. 2019).

Terpenes and their derivatives

In addition to phenylpropanoids (**111–119**), terpene hydrocarbons and their derivatives are constituents of essential oils and oleoresins extracted from *M. fragrans* seeds and fruits (Jaiswal et al. 2009; Piaru et al. 2012; Kapoor et al. 2013; Du et al. 2014). Some terpene hydrocarbons (**128–136**), such as α, β-pinenes, sabinene, camphene, terpinen-4-ol, limonene, p-cymene, γ-terpinene, and β-phellandrene, as well as terpene derivatives [α-terpineol (**148**), geraniol (**169**), and linalool (**171**)] are reported as major constituents of *M. fragrans* seed essential oils (10%) (Jaiswal et al. 2009). *M. fragrans* aril oil (up to 12% in the spice) contains the same aroma components, but the total fraction of terpenoids is increased by nearly 90% (Jaiswal et al. 2009). In addition, according to a study by Zachariah et al. (2008), monoterpenes account for 91% of *M. fragrans* leaf oil, in which sabinene (19.07%), α-pinene (18.04%), terpinen-4-ol (11.83%), limonene (8.32%), and β-pinene (7.92%) are main components. The chemical structures of 45 terpene hydrocarbons and their derivatives are shown in Fig. 6.

Alkanes, fatty acid, and fatty acid esters

In total, seven alkanes (**178–184**), seven fatty acids (**185**, **186**, **188**, **190**, and **192–194**), and five fatty acid esters (**187**, **189**, **191**, **195**, and **196**) have been identified in *M. fragrans* (Niyas et al. 2003; Kapoor et al. 2013; Du et al. 2014; Morikawa et al. 2016; Omidpanah et al. 2020) (Fig. 7). Most of these constituents are present in the essential oil and oleoresins of nutmeg seeds or fruits (Kapoor et al. 2013; Du et al. 2014). Five fatty acids, including lauric acid (**185**), myristic acid (**186**), palmitic acid (**188**), stearic acid (**192**), and petroselinic acid (**194**) have been detected in *M. fragrans* seeds by GC–MS (Niyas et al. 2003). In addition, Morikawa et al. (2016) have reported the presence of palmitic acid (**188**), oleic acid (**190**), methyl oleate (**191**), and linoleic acid (**193**) in the arils of *M. fragrans* (Fig. 7).

Steroids, saponins, triterpenoids, and flavonoids

Two steroids [β-sitosterol (**197**) and stigmasterol (**199**)], three saponins [daucosterol (**198**), stigmasteryl-3-*O*-*β*-glucoside (**200**), and sitosterol 3-*O*-[*β*-D-glucopyranos-6′-yl tetradecanoate (**201**)], and one triterpenoid (cycloartenol, **202**) were isolated from the seeds (for **197**, **198**, and **201**) (Hou et al. 2012; Dzotam et al. 2018), stem bark (for **197** and **199**) (Francis et al. 2019), and fruit pericarp (for **202**, a mixture of **197** and **199**, a mixture of **198** and **200**) (Zhang et al. 2015) of *M. fragrans* (Fig. 8). In addition, three flavonoids including quercetin 3-*O*-*α*-L-rhamnopyranosyl-(1 → 6)-*O*-[*α*-L-rhamnopyranosyl-(1 → 2)]-*O*-*β*-D-galactopyranoside (**203**), 5,7-diacetyl chrysin (**204**), and catechin (**205**) have been found in the arils (Morikawa et al. 2016), seeds (Omidpanah et al. 2020), and fruits (Shan et al. 2005) of *M. fragrans*, respectively (Fig. 8). These above reports are in accordance with the previous study (Olaleye et al. 2006), in which saponins and flavonoids were detected in the aqueous extract of *M. fragrans* seeds.

Table 3 Diphenylalkane constituent of *M. fragrans*

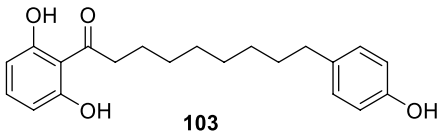
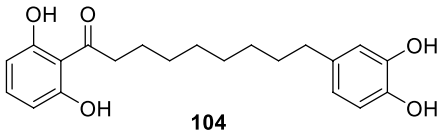
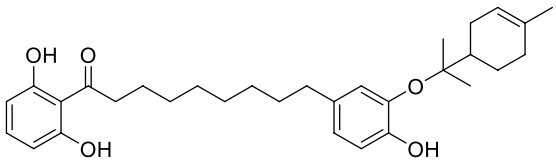
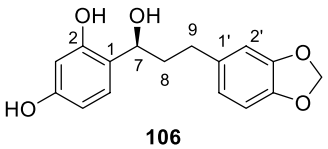
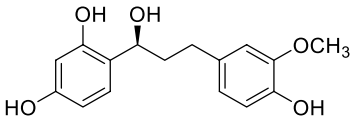
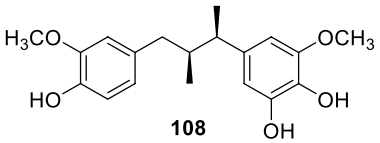
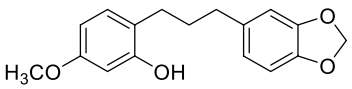
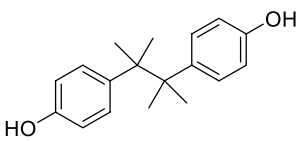
Compound name	Plant part	References
 **103** Malabaricone B	Fruit, aril, seed	Duan et al. (2009), Chiu et al. (2016), Orabi et al. (1991)
 **104** Malabaricone C	Fruit, aril, seed	Duan et al. (2009), Cuong et al. (2011), Chiu et al. (2016), Orabi et al. (1991)
 **105** (−)-1-(2,6-Dihydroxyphenyl)-9-[4-hydroxy-3-(*p*-menth-1-en-8-oxy)-phenyl]-1-nonanone	Fruit	Duan et al. (2009)
 **106** ((7*S*)-9-(Benzo[3′,4′]dioxol-1′-yl)-hydroxypropyl)benzene-2,4-diol	Seed	Cuong et al. (2011)
 **107** ((7*S*)-9-(4′-Hydroxy-3′-methoxyphenyl)-7-hydroxypropyl)benzene-2,4-diol	Seed	Cuong et al. (2011)
 **108** ((8*R*,9*S*)-7-(4-Hydroxy-3-methoxyphenyl)-8′-methylbutan-8-yl)-3′-methoxybenzene-4′,5′-diol	Seed	Cuong et al. (2011)
 **109** Virolane	Fruit pericarp	Francis et al. (2014)
 **110** Tetramethylhexestrol	Seed	Dzotam et al. (2018)

Table 4 Phenylpropanoid constituent of *M. fragrans*

No.	Compound name	Plant part	References
111	Myristicin	Fruit, fruit pericarp, aril, seed,	Kapoor et al. (2013), Du et al. (2014), Zhang et al. (2015), Chiu et al. (2016), Morikawa et al. (2016)
112	Elemicin	Fruit, fruit pericarp, aril, seed, stem bark	Zhang et al. (2015), Chiu et al. (2016), Francis et al. (2019)
113	Eugenol	Fruit, seed	Kapoor et al. (2013)
114	Methyleugenol	Fruit, seed	Kapoor et al. (2013), Du et al. (2014)
115	Methylisoeugenol	Fruit, seed	Kapoor et al. (2013), Du et al. (2014)
116	Safrole	Fruit, aril, seed	Lee et al. (2009), Kapoor et al. (2013), Du et al. (2014)
117	*trans*-Isoeugenol	Fruit	Kapoor et al. (2013)
118	Methoxyeugenol	Fruit	Kapoor et al. (2013)
119	Isoelemicin	Fruit, seed	Chiu et al. (2016), Kapoor et al. (2013)
120	5-Hydroxyeugenol	Aril, seed	Kimura et al. (2010)
121	2,3-Dimethoxy-5-(1-propenyl)-phenol	Aril, seed	Kimura et al. (2010)
122	Caffeic acid	Fruit	Shan et al. (2005)
123	(1*R*,2*R*)-1-(4-Hydroxy-3-methoxyphenyl)-1,2-propanediol	Fruit	Duan et al. (2009)
124	(2*R*)-3-(3,4,5-Trimethoxyphenyl)-1,2-propanediol	Fruit	Duan et al. (2009)
125	(2*R*)-3-(5-Methoxy-3,4-methylenedioxyphenyl)-1,2-propanediol	Fruit	Duan et al. (2009)
126	(2*R*)-3-(3,4-Methylenedioxyphenyl)-1,2-propanediol	Fruit	Duan et al. (2009)
127	Anthriscinol	Aril	Morikawa et al. (2016)

2-alkylcyclobutanones and other constituents

The natural occurrence of 2-alkylcyclobutanones in nutmeg (*M. fragrans*) is still questionable as reports are conflicting. While Variyar et al. (2008) claimed the presence of 2-decylcyclobutanone (**206**) and 2-dodecylcyclobutanone (**207**) (Fig. 9) in non-irradiated nutmeg via supercritical fluid extraction coupled with TLC, GC, and MS analysis, Chen et al. (2012); Leung et al. (2013); Breidbach and Ulberth (2016) did not. Specifically, using GC–MS analysis, Chen et al. (2012) indicated that 2-alkylcyclobutanones were found only in irradiated nutmeg samples, and their amount increased proportionally with an increase in the irradiation dose. Utilizing the newly developed LC–MS/MS method to enhance analytical sensitivity and selectivity, Leung et al. (2013) claimed that 2-dodecylcyclobutanone (**207**) either does exist naturally in non-irradiated nutmeg, or that it may be present at concentrations below the detection limit of the existing method. In addition, Breidbach and Ulberth (2016) have tested for the presence of 2-alkylcyclobutanones in 14 nutmeg samples obtained from retailers in 10 different EU Member States using the optimized HPLC–HRMS method, one of the 14 nutmeg samples contained traces of 2-alkylcyclobutanones (Fig. 9).

Some other constituents were also reported from *M. fragrans* such as 3-methyl-5-pentyl-furylarylic acid (**208**) (Kimura et al. 2010; Sathya et al. 2020) from the seeds and arils and a mixture of succinic (**211**) and fumaric (**212**) acids (Dzotam et al. 2018) from the seeds of *M. fragrans* (Fig. 9). Two phenolic aldehydes including vanillin (**209**) (Morikawa et al. 2016) and 2,3-dihydroxy-5-(hydroxymethyl) benzaldehyde (**210**) (Zhang et al. 2015) have been identified in the arils and fruit pericarp of *M. fragrans*, respectively (Fig. 9). In addition, a phytochemical screening of the aqueous extract of *M. fragrans* seeds led to the detection of alkaloids, anthraquinones, cardiac glycosides, phlobatannins, saponins, and flavonoids while tannins were absent (Olaleye et al. 2006).

Pharmacological properties of *M. fragrans*

Anti-inflammatory and analgesic activities

According to an investigation of the pharmacological properties of nutmeg oil in animal models (Olajide et al. 2000), the oil showed pharmacological activities similar to those of non-steroidal anti-inflammatory drugs. An analgesic effect was produced by the oil in the acetic acid-induced writhing model, and in the late phase of the formalin-induced licking (Olajide et al. 2000). The chloroform extract of *M. fragrans* seeds demonstrated anti-inflammatory activity by inhibiting

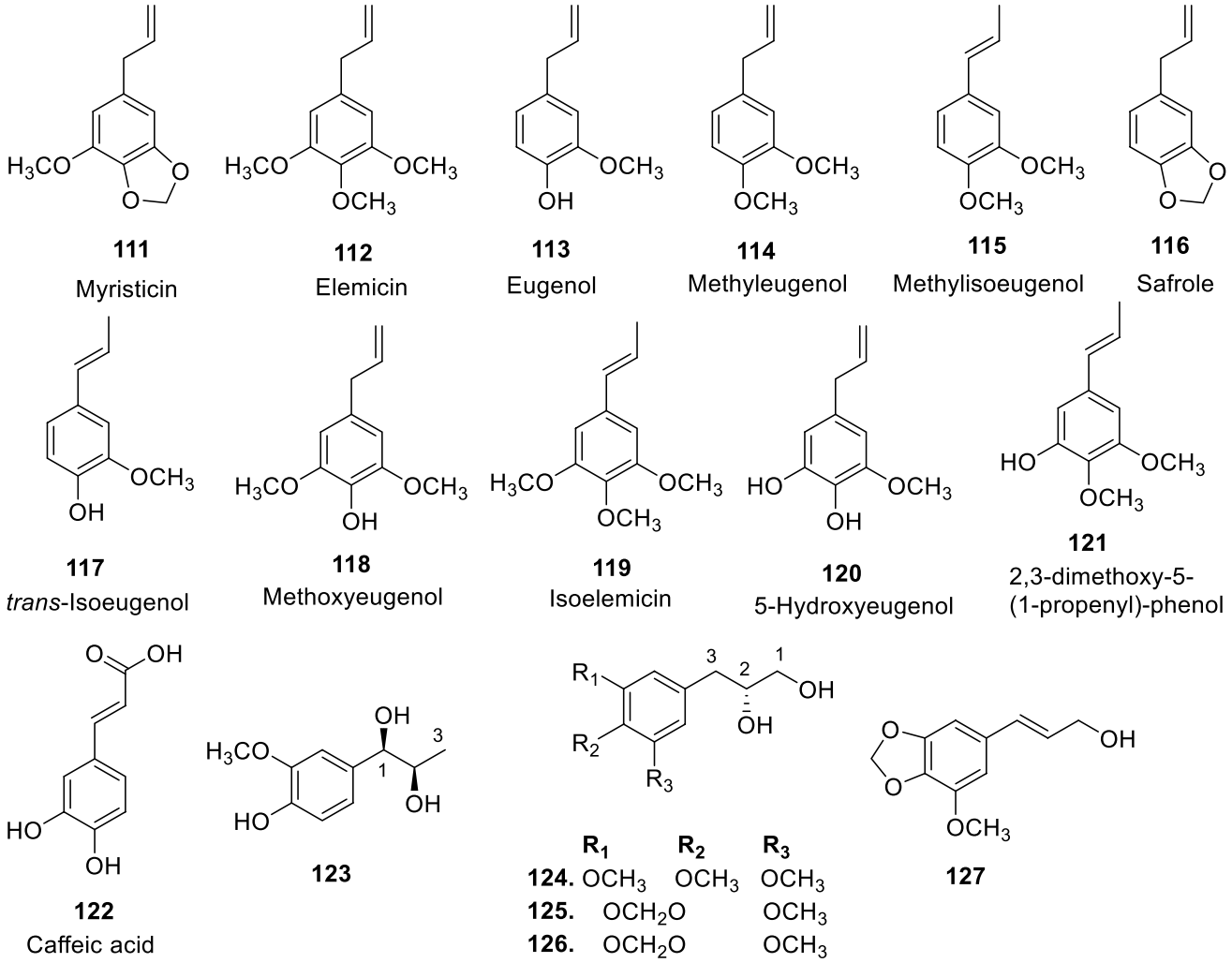


Fig. 5 Structures of phenylpropanoids **111–127**

carrageenan-induced rat paw edema, as well as exhibiting a strong analgesic effect (Olajide et al. 1999). Lignan derivatives are well known for their immense anti-inflammatory potential (Jung et al. 2015, 2019). Macelignan (**1**) potently suppressed the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), which resulted in a reduction of nitric oxide in lipopolysaccharide (LPS)-treated microglial cells. It also significantly suppressed the production of pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Jin et al. 2005). Myrislignan (**62b**) attenuated the LPS-induced inflammatory reaction in macrophages by inhibiting NO and inflammatory cytokines production, as well as the gene and protein expression of iNOS and COX-2. These effects were mediated by inhibiting the activation of NF-κB and P65 nuclear translocation (Jin et al. 2012). In another study by Acuña et al. (2016), compounds **41**, **66**, **67**, and **102** showed strong PARP-1 [Poly (adenosine 50-diphosphate (ADP)-ribose) polymerase 1] inhibitory activity with IC_{50} values of 3.11, 22.07, 0.001, and 3.04 μM, respectively. Furthermore, when tested in the p65 assay, neolignans **67** and **66** displayed potent NF-κB inhibition (IC_{50} = 1.5 nM and 3.4 nM, respectively). 2,3-Dimethyl-1,4-diaryl-butane type lignan (**6**) and diphenylalkane (malabaricone C, **104**) showed strong inhibitory activity on LPS-induced NO production in RAW264.7 macrophages with IC_{50} values of 3.4 and 2.3 μM in comparison with the positive control (celastrol, IC_{50} = 1.0 μM) (Cuong et al. 2011; Min et al. 2011). Malabaricone C (**104**) at a concentration of 0.1–10 μM dose-dependently reduced LPS-induced COX-2 and iNOS expressions, but did not change the α-tubulin expression. Both **6** and **104** inhibited not only iNOS and COX-2 mRNA expressions, but also iNOS and COX-2 promoter activities in LPS stimulated RAW264.7 cells, suggesting that these compounds could suppress LPS-induced iNOS and COX-2 expressions at the transcription level (Cuong et al. 2011; Min et al. 2011). In a

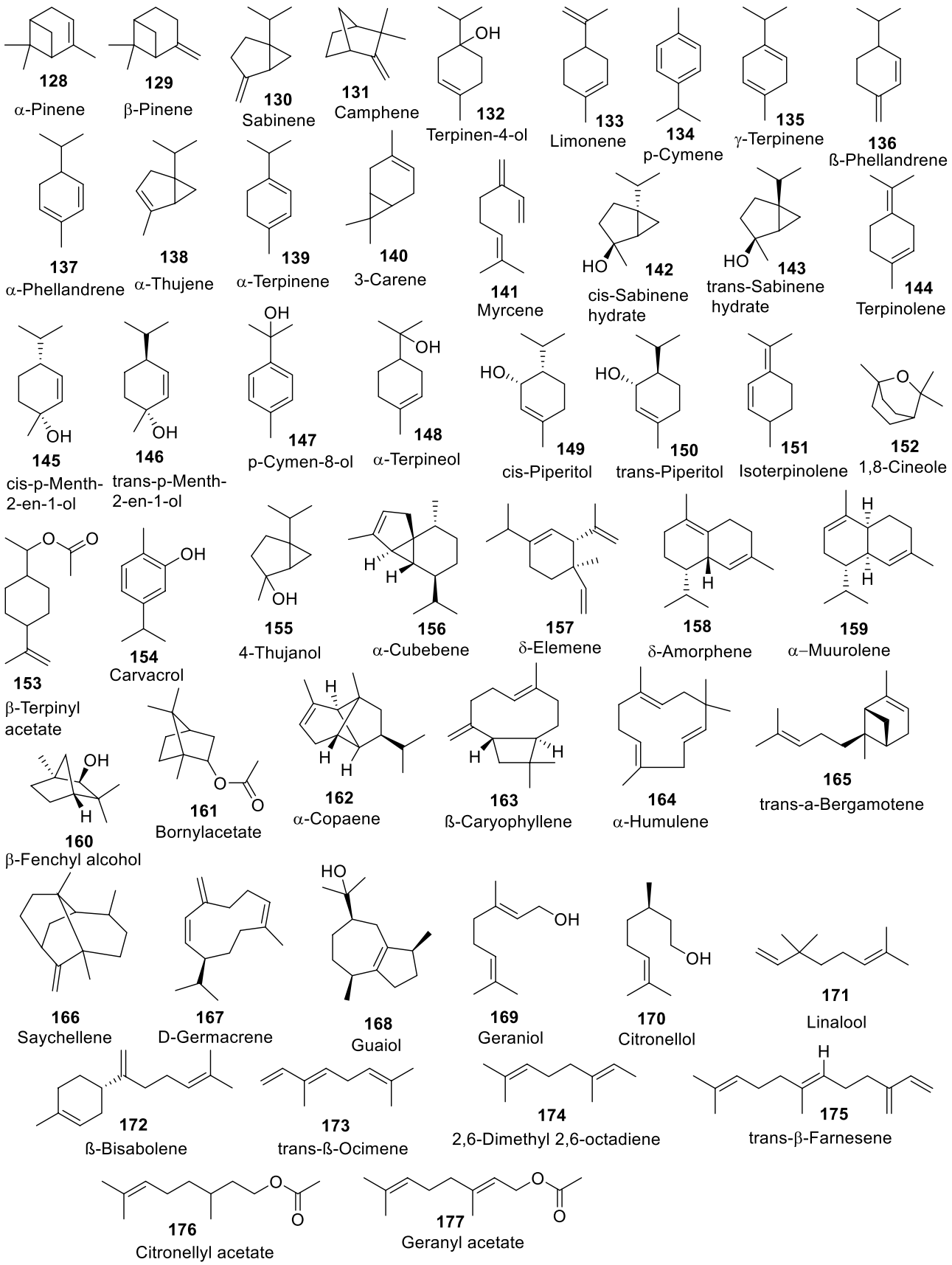


Fig. 6 Structures of terpene hydrocarbons and their derivatives **128–177**

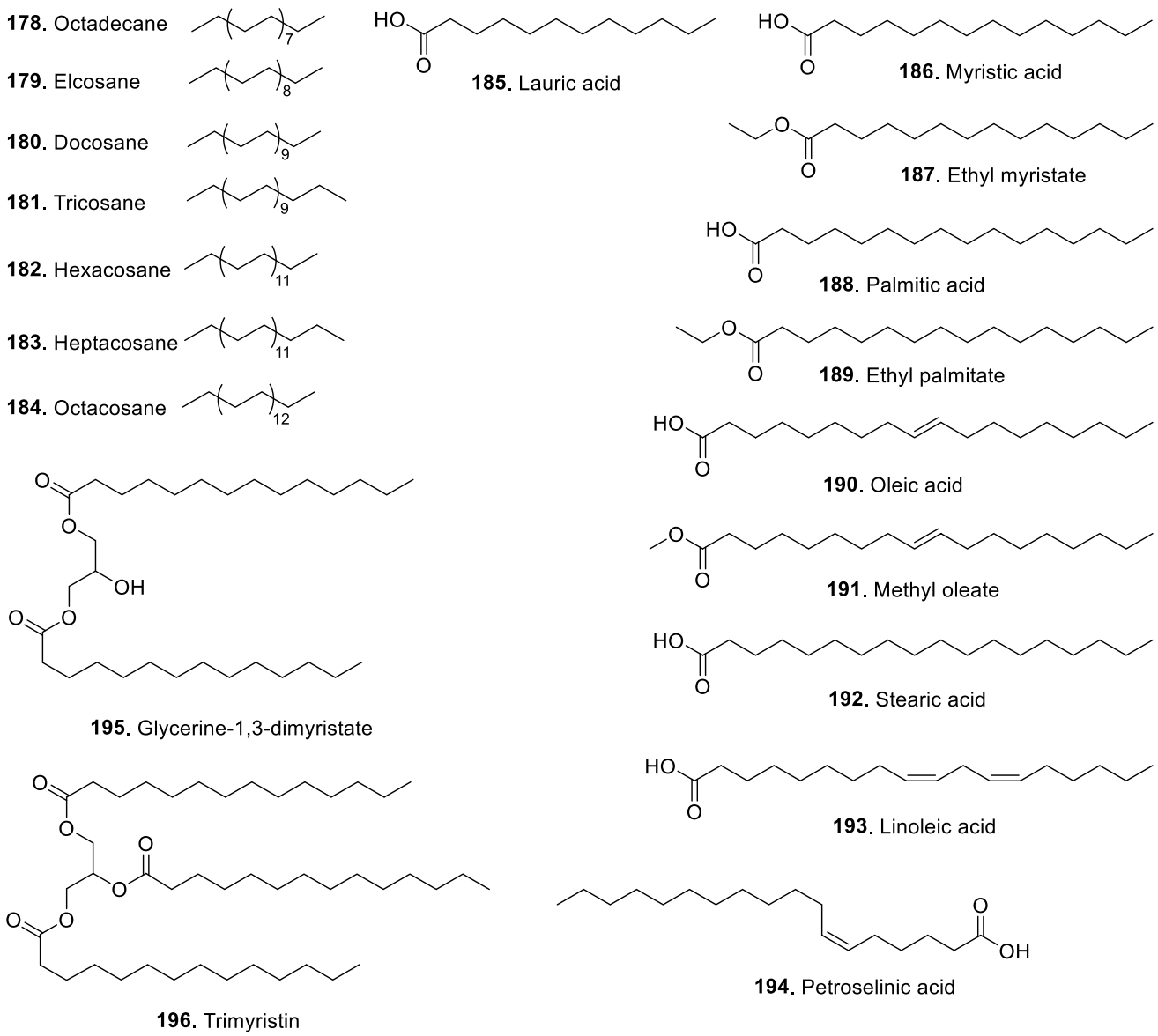


Fig. 7 Structures of alkanes, fatty acids, and fatty acid esters **178–194**

series of studies on anti-inflammatory activity of *M. fragrans* neolignans by Cao et al., six benzofuranoid neolignans (**36**, **39**, **40**, **52**, **53**, and **57**) and eight 8.*O*.4′ neolignans (**61a**, **62b**, **74a**, **74b**, **83**, **87b 89**, and **91**) demonstrated inhibition of nitric oxide production in lipopolysaccharide-activated murine monocyte-macrophage RAW264.7 (Cao et al. 2013, 2015). Among these compounds, **36**, **52**, **53**, **62b**, and **83** significantly suppressed the expression of LPS-induced iNOS mRNA in a dose-dependent manner (Cao et al. 2013, 2015). The hexane, ethyl acetate, and methanol extracts of *M. fragrans* pericarps showed COX-1 enzyme inhibition of 44%, 44%, and 42%, and COX-2 enzyme inhibition of 47%, 41%, and 36%, respectively (Zhang et al. 2015). The compounds isolated from these extracts, including **40, 61**, **62**, **64**, **65**, **67**, **111**, **112**, **199**, and **204** inhibited COX-1 and -2 enzymes by 37–49% (Zhang et al. 2015).

Antioxidant activity

The antioxidant capacity of extracts or pure isolates of *M. fragrans* can be investigated by various chemical assays, such as estimation of total phenolic concentration, capacity to scavenge the stable free radical 2,2-diphenyl-1-picryl-hydrazyl (DPPH), inhibition of lipid peroxidation (LPO), inhibition of β-carotene bleaching, ability to chelate iron (II) ions, ferric reducing/antioxidant power assay (FRAP), and so on (Gupta et al. 2013; Kapoor et al. 2013; Zhang et al. 2015). A study by Kapoor et al. indicated that in vitro

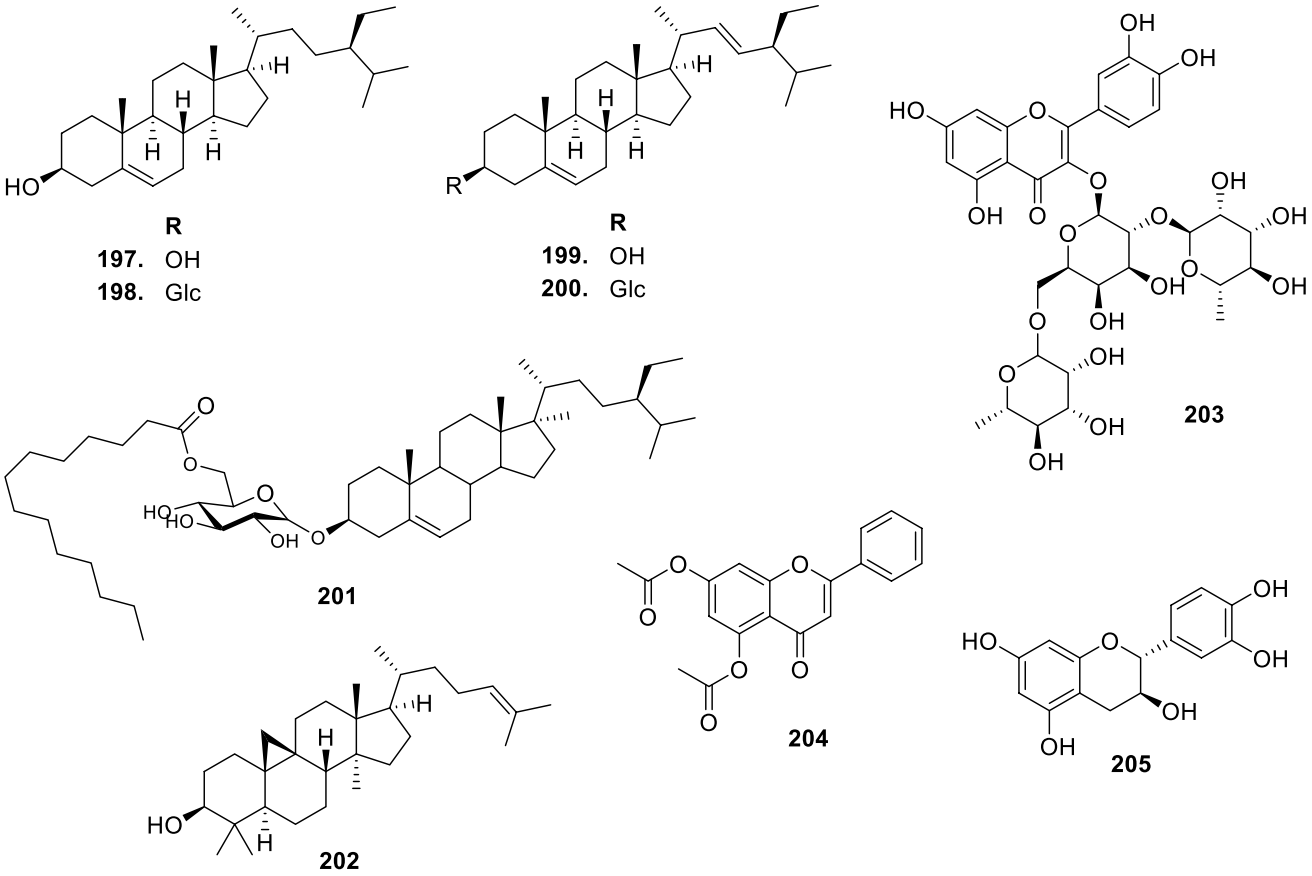


Fig. 8 Structures of steroids, saponins, triterpenoids, and flavonoids **197–205**

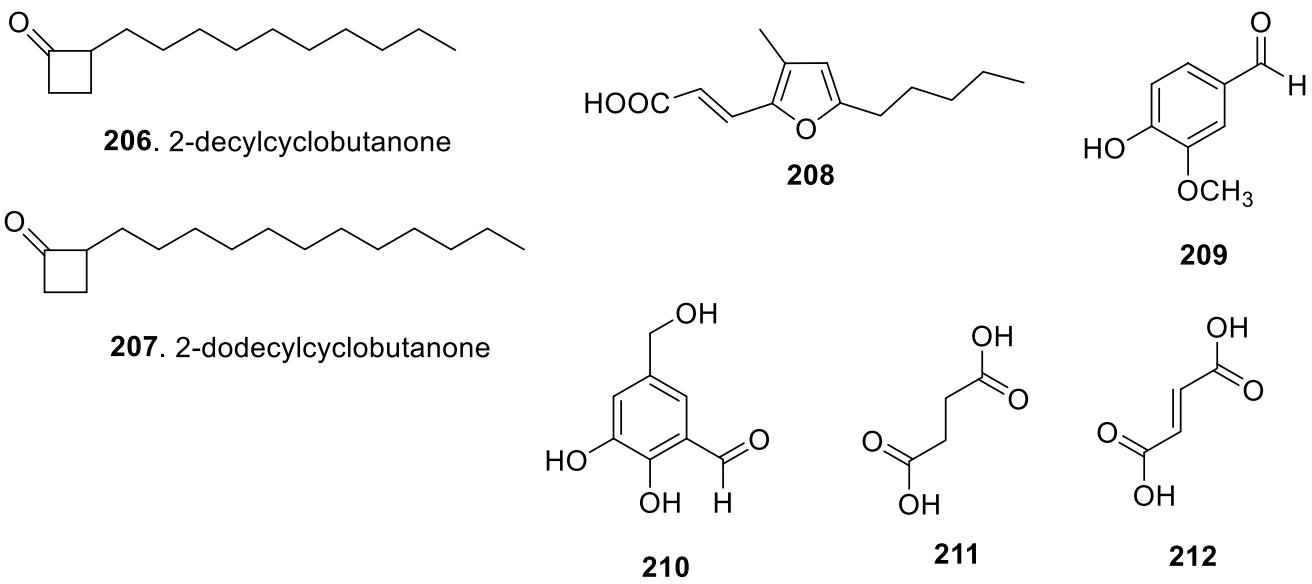


Fig. 9 Structures of 2-alkylcyclobutanones and other constituents **206–212**

antioxidant properties of the essential oil and various oleoresins extracted from *M. fragrans* are as potent as those of known synthetic antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Kapoor et al. 2013). Acetone, ethanol, methanol, butanol, and water extracts of *M. fragrans* seed have all shown significant antioxidant activity against microorganisms (Gupta et al. 2013). Among these five extracts, the acetone extract demonstrated the highest antioxidant activity, with 93.12 mg GAE (gallic acid equivalents)/100 g dry weight total phenolic content, DPPH scavenging activity of 63.04%, chelating activity of 64.11%, and inhibition of β-carotene bleaching by 74.36% at an extract concentration of 1 mg/ml (Gupta et al. 2013). In another study by Duan et al. (2009), one tetrahydrofuran lignan (**16**), one 8.*O*.4′ neolignan (**62**), and one phenylpropanoid (**123**) exhibited strong radical scavenging activity against DPPH in a concentration-dependent manner with IC_{50} values of 39.4, 191.7 and 125.9 μM, respectively, which were more active than or close to the positive control, BHT (IC_{50} = 150.6 μM). Malabaricone C (Mal C, **104**) also showed strong radical scavenging activity against DPPH (IC_{50} = 6.56 μg/ml) in comparison with the positive control, ascorbic acid (IC_{50} = 5.76 μg/ml) (Sathya et al. 2020). In the lipid peroxidation inhibitory (LPO) antioxidant assay, the hexane, ethyl acetate, and methanolic extracts of *M. fragrans* pericarps and neolignans **36**, **39**, **40**, **62**, and **65** at 100 μg/ml also showed good activity with LPO inhibition of 70–99% (Zhang et al. 2015). *Meso*-dihydroguaiaretic acid (**2**) showed potent low-density lipoprotein (LDL)-antioxidant activity with an IC_{50} value of 2.6 μM in TBARS (Thiobarbituric Acid Reactive Substances) assay (Kwon et al. 2008) and strong inhibitory activity against soybean lipoxygenase-1 (IC_{50} = 25.7 μM) (Kwon et al. 2014). In macrophage-mediated LDL oxidation, the TBARS formation was also inhibited by *meso*-dihydroguaiaretic acid (**2**) (Kwon et al. 2008). In addition, Checker et al. (2008) reported that lignan **25** and neolignans **60** and **62a** present in aqueous extract of *M. fragrans* arils possess antioxidant, radioprotective, and immunomodulatory effects in mammalian splenocytes via modulating mitogen-induced splenocyte proliferation and cytokine production. Moreover, the presence of phenolic compounds that belong to hydroxycinnamic acid group such as caffeic acid (**122**) and flavan-3-ol group such as catechin (**205**) in *M. fragrans* might contribute to its higher secondary antioxidant activity (Shan et al. 2005).

Antibacterial and antifungal activities

Among acetone, ethanol, methanol, butanol, and water extracts of *M. fragrans* seed, the acetone extract was able to exert antimicrobial activity against all 4 species of bacteria (*Bacillus subtilis*, *Staphylococcus aureus*, *Pseudomonas putida*, and *Pseudomonas aeruginosa*) and 3 species of fungi (*Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus flavus*) tested. The acetone extract has also shown the strongest antibacterial and antifungal activity against *Staphylococcus aureus* (13.8 ± 0.42 mm) and *A. niger* (14.4 ± 0.37 mm), respectively (Gupta et al. 2013). Smith-Palmer et al. (2002) found that essential oils from *M. fragrans* seeds inhibited the growth of Listeria monocytogenes by suppressing the production of the bacterial extracellular protein, listeriolysin and the bacterial enzyme phospholipase. The crude essential oil of the Brazilian nutmeg at a concentration of 0.1% inhibited radial growth of *Aspergillus glaucus* (60%), *A. niger* (71%), *Fusarium oxysporum* (75%), *F. semitectum* (78%), *Colletotrichum musa* (97%), and *C. gloeosporoides* (98%). At a concentration of 0.3%, the growth inhibition increased from 85 to 100% (Valente et al. 2011). The methanol extract of *M. fragrans* seeds also showed strong antibacterial activity against multi-drug resistant *Salmonella typhi* with MIC (minimum inhibitory concentration) of 12.5 μg/ml (Rani and Khullar 2004), whilst the methanol extract of *M. fragrans* arils inhibited the growth of all human carcinogen *Helicobacter pylori* strains with a MIC value of 12.5 μg/ml (Bhamarapravati et al. 2003). Two diphenylalkanes [malabaricone B (**103**) and malabaricone C (**104**)] isolated from *M. fragrans* arils (mace) exhibited strong antimicrobial activity against *Staphylococcus aureus* and *Candida albicans* (Orabi et al. 1991). Dihydroguaiaretic acid (**2**) has also shown anti-*H. pylori* activity, with a MIC of 100 μg/ml and a MBC (minimum bacteriocidal concentration) of 125 μg/ml, in comparison to a control drug (clarithromycin) with a MIC value of 120 μg/ml (Bhamarapravati et al. 2006). Three lignans, including macelignan (*erythro*-austrobailignan-6, **1**), *meso*-dihydroguaiaretic acid (**2**), and nectandrin-B (**14**), showed in vitro and in vivo antifungal activities against plant pathogenic fungi *Alternaria alternata*, *Magnaporthe grisea*, *Agrobacterium tumefaciens*, *Burkholderia glumae*, *Acidovorax konjaci*, *Colletotrichum coccodes*, and *C. gloeosporioides* (Cho et al. 2007). In addition, licarin A (dehydrodiisoeugenol, **36**) and 3′-methoxy-licarin A (**38**) completely inhibited the bacterial growth of *Streptococcus mutans* at a concentration 12.5 μg/ml of thereby helping to prevent dental caries (Hattori et al. 1986). Recently, a mixture of succinic (**211**) and fumaric (**212**) acids was reported to show strong antibacterial activity against *E. coli* ATCC8739 with a MIC value of 8 μg/ml (Dzotam et al. 2018).

Anti-obesity and antidiabetic activity

AMP-activated protein kinase (AMPK) is a potential therapeutic target for the treatment of metabolic syndrome, including type-2 diabetes and obesity (Nguyen et al. 2010). Three tetrahydrofuran lignans, including nectandrin B (**14**), tetrahydrofuroguaiacin B (**29**), and nectandrin A (**31**) at a concentration of 5 μM produced strong AMPK stimulation

in differentiated C2C12 cells (Nguyen et al. 2010). Macelignan (**1**) downregulated inflammatory gene expression in the liver and increased AMP-activated protein kinase activation in the skeletal muscle of the *db*/*db* obesity mouse model (Han et al. 2008). One well-established therapeutic approache for controlling postprandial hyperglycemia is the inhibition of α-glucosidase (Ha et al. 2018). The petroleum ether extract of *M. fragrans* seeds decreased blood glucose levels in normal, glucose-fed, and alloxan-induced diabetic rats (Somani and Singhai 2008). The ethanolic extract of the *M. fragrans* fruits is documented to moderately lower blood sugar in streptozotocin (STZ)-induced diabetic rats after 3 to 7 h post-treatment (Ahmad et al. 2008). Macelignan (**1**) significantly ameliorated insulin resistance and exerted beneficial effects on fatty acid and glucose metabolism in *db*/*db* mice, similar to troglitazone (Han et al. 2008). In addition, **1** enhanced insulin sensitivity and improved lipid metabolic disorders by activating peroxisome proliferator-activated receptor α/γ and attenuating endoplasmic reticulum stress, suggesting that this lignan has potential as an anti-diabetic agent for the treatment of type 2 diabetes (Han et al. 2008). Compound 3-methyl-5-pentyl-furylarylic acid (**208**) showed strong α-glucosidase inhibitory activity with IC_{50} value of 50.91 μg/ml in comparison with the positive control, acarbose (IC_{50} = 265.3 μg/ml) (Sathya et al. 2020). Protein tyrosine phosphatase 1B (PTP1B) is regarded as an attractive drug target for the treatment of type 2 diabetes and obesity (Ha et al. 2018). Lignans *meso*-dihydroguaiaretic acid (**2**) and otobaphenol (**10**) non-competitively inhibited PTP1B with IC_{50} values of 19.6 ± 0.3 and 48.9 ± 0.5 μM, respectively (Yang et al. 2006). Treatment of 32D cells overexpressing the insulin receptor (IR) with *meso*-dihydroguaiaretic acid (**2**) resulted in a dose-dependent increase in the tyrosine phosphorylation of the IR. These results suggest that *meso*-dihydroguaiaretic acid (**2**) can act as an enhancing agent in intracellular insulin signaling, possibly through the inhibition of PTP1B activity (Yang et al. 2006).

Anticancer and chemopreventive activities

The 80% ethanol extract of nutmeg strongly suppressed the growth of human lymphoid, leukemia Molt 4 B cells (Moteki et al. 2002). Myristicin (**111**) was considered a potential chemopreventive agent after demonstrating the potential to induce an increase in the detoxifying glutathione *S*-transferase enzyme system in the liver and small intestinal mucosa of mice (Zheng et al. 1992). The aqueous suspension of *M. fragrans* arils exhibited the ability to modulate xenobiotic-metabolizing enzymes, to activate and detoxify carcinogens to inhibit tumor formation (Chhabra and Rao 1994). *Meso*-dihydroguaiaretic acid (**2**) suppressed leukemia, lung cancer, and colon cancer in an in vitro bioassay (Park et al. 1998), it was also considered a cancer chemopreventive agents, as it interruptied the activity of fos–jun proteins, which have been implicated in specific oncogenic transformations (Park et al. 1998). The methanol extract of *M. fragrans* bark at concentrations of 50 and 100 μg/ml significantly inhibited Jurkat cell proliferation and induced apoptosis, as detected by annexin V staining (Chintana et al. 2007). Four lignans isolated from Vietnamese *M. fragrans* seeds including macelignan (*erythro*-austrobailignan-6, **1**), *meso*-dihydroguaiaretic acid (**2**), nectandrin-B (**14**), and fragransin A_2 (**15**) were examined for in vitro cytotoxicity against various cancer cell lines H1299 (human non-small cell lung carcinoma), H358 (human bronchiolar lung cancer), H460 (large cell lung cancer), Hela (human cervical cancer), HepG2, KPL4, MCF-7, RD, and MDCK (Multicystic dysplastic kidney) cells (Thuong et al. 2014). As a result, 2,3-dimethyl-1,4-diaryl-butane lignans (**1** and **2**) showed stronger cytotoxic activity than tetrahydrofuran lignans (**14** and **15**). Compound **2** exhibited potent cytotoxic activities against most H358, HepG2, RD, MCF-7, KPL4, H1299, and H460 cancer cells with IC_{50} values ranging from 10.1 to 27.7 μM, compared to the positive control [taxol, IC_{50} = 4.9–6.6 μM]. Macelignan (**1**) also showed potent cytotoxicity against H358 (IC_{50} = 10.2 μM) and Hela (IC_{50} = 25.1 μM) cancer cells. Recently, the new dihydrobenzofuran neolignan (myticaganal C, **56**) showed significant cytotoxicity against two human cancer cell lines: KB (oral cavity; IC_{50} = 5.9 μM) and NCIH187 (small cell lung cancer, IC_{50} = 6.3 μM) (Chumkaew and Srisawat 2019).

Hepatoprotective effects

Nutmeg shows the most potent hepatoprotective activity in comparison with 21 other spices examined when orally administered to rats with liver damage caused by lipopolysaccharide (LPS) and D-galactosamine (D-GalN) (Morita et al. 2003). In that study, Morita et al. also reported the extraordinarily potent hepatoprotective activity of myristicin (**111**), which markedly suppressed LPS/D-GalN-induced enhancement of serum TNF-α concentration and hepatic DNA fragmentation in mice (Morita et al. 2003). The aqueous extract of *M. fragrans* seeds inhibited isoproterenol-induced hepatotoxicity, and protected experimental hepatic injury as revealed by the amelioration of marker enzymes along with hepatoprotective effects, without any clinical complications as shown by oral toxicity studies (Kareem et al. 2013).

Neuropharmacologic effects

Myristica fragrans is documented to have many effects in the central nervous system (CNS). At the cellular level, macelignan (**1**) was confirmed to significantly decrease neurodegenerative disease progression by slowing neuroinflammation

and oxidative damage (Jin et al. 2005). Trimyristin (**196**) and the hexane extract of *M. fragrans* seeds showed anxiogenic activity in mice when tested in elevated plus maze and hole-board paradigms (Sonavane et al. 2002b). The hexane extract also elicited a significant antidepressant-like effect in mice in the forced swim and tail suspension tests (Dhingra and Sharma 2006). Licarin A (dehydrodiisoeugenol, **36**) and licarin B (**39**) showed not only a significant prolongation of hexobarbital (HB)-induced sleeping time but also a significant inhibition of aminopyrine N-demethylase and hexobarbital hydroxylase activities in mice after a single dose treatment (200 mg/kg, i.p.). Myristicin (**111**) and licarin B (**39**) provoked a sleep episode at a sub-hypnotic dose of HB, suggesting that these compounds possess CNS-depressant properties (Shin et al. 1988). In addition, myristicin (**111**) was documented to antagonize the anxiolytic effects of midazolam, increase anxiety, and affect motor movements (Leiter et al. 2011). In addition, the potent of diphenylalkanes (**104** and **107**) and lignan **6** in treatment of Alzheimer's disease was recognized by their acetylcholinesterase (AChE) inhibitory activity with IC_{50} values of 44.0, 35.1, and 42.1 μM, respectively (Cuong et al. 2014). Malabaricone C (Mal C, **104**) also showed AChE inhibitory activity (IC_{50} = 2.06 μg/ml) in comparison with the positive control, donepezil HCl (IC_{50} = 0.03 μg/ml) (Sathya et al. 2020).

Cardioprotective effects

Platelets play a critical role in the pathogenesis of cardiovascular disorders and strokes and the inhibition of platelet function is beneficial for the treatment and prevention of these diseases (Kang et al. 2013). In the study by Kang et al. (2013), neolignan **67a** [(1*S*,2*R*)-2-(4-allyl-2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl) propan-1-ol acetate] preferentially inhibited thrombin- and platelet-activating factor (PAF)-induced platelet aggregation without affecting platelet damage in a concentration-dependent manner with IC_{50} values of 3.2 and 3.4 μM, respectively. In another study by Kareem et al. (2009), the aqueous extract of *M. fragrans* seeds has cardioprotective effect against myocardial infarction (MI). Adult male rats with isoproterenol-induced MI were daily administered aqueous *M. fragrans* extract (100 mg/kg, p.o.) for 30 days. The results show that pretreatment with the aqueous *M. fragrans* extract offered protection against isoproterenol effects on blood glucose, plasma lipids, as well as histological myocardial changes, suggesting a potential cardiovascular protective role of *M. fragrans* seed consumption (Kareem et al. 2009). In addition, one of the most active compounds of *M. fragrans,* malabaricone C (Mal C, **104**), exerted potential anti-hypertensive activity in deoxycorticosterone acetate (DOCA)-salt-induced hypertensive rats by reducing systolic blood pressure, ventricular hypertrophy, and inflammation in the ventricles and aorta. It also improved the vascular endothelial and smooth muscle as well as liver and kidney functions (Rathee et al. 2016). In another in vivo study, the extract of *M. fragrans* fruits exhibited hypolipidemic effect in rabbits (Ram et al. 1996), while the extract of *M. fragrans* seeds also was documented to show significant anti-cholesterolemic and anti-atherosclerotic effects in rabbits (Sharma et al. 1995).

Toxicological effects

The presence of two main phenylpropanoid constituents, myristicin (**111**) and elemicin (**116**) in *M. fragrans* seeds has been believed to be the main cause of its toxic effects (Sonavane et al. 2002a; Ehrenpreis et al. 2014). Myristicin (**111**) was documented to have attributed toxicological effects associated with nutmeg ingestion to the nervous system (drowsiness, paresthesia, delirium, numbness, and reality detachment), gastrointestinal (vomiting and ileus), and cardiovascular system (hypotension and tachycardia) (Hallström and Thuvander 1997; Sangalli et al. 2000; Grover et al. 2002). The hallucinogenic effects *M. fragrans* seeds are believed to be caused by myristicin due to its metabolism structure of 3-methoxy-4,5 methylendioxyamphetamine (MMDA) after the consumption of nutmeg (Rahman et al. 2015). Minimum dosage (toxic dose) of nutmeg that can cause psychogenic effect is 5 g of ground nutmeg, which contains 1 to 2 mg myristicin. At higher dosage of myristicin death may occur (Rahman et al. 2015).

Other pharmacological effects

The hexane extract of *M. fragrans* seeds significantly inhibited hepatic drug-metabolizing enzyme activity (Shin et al. 1988). In addition, the anabolic activity in bone metabolism of *M. fragrans* lignans and neolignans has been reported. Specifically, machilin A (**3**) stimulated osteoblast differentiation via activation of p38 MAP kinase in two in vitro osteoblast differentiation models. While compounds macelignan (**1**), *meso*-dihydroguaiaretic acid (**2**), myristargenol (**4**), nectandrin B (**14**), machilin F (**27**), licarin A (**36**), licarin B (**39**), and safrole (**116**), also stimulated osteoblast differentiation in MC3T3-E1 cells (Lee et al. 2009). The ethanolic extract of *M. fragrans* seeds and its active constituent (myristicin, **111**) are reported to show antihelmintic effects against *Anisakis* simplex (López et al. 2015). The aphrodisiac activity of the 50% ethanolic extract of *M. fragrans* seeds was reported via stimulation of the mounting behavior of male mice, and also significantly increase their mating performance (Tajuddin et al. 2003). *M. fragrans* extract and its constituent have been documented containing skincare properties via several studies (Cho et al. 2008; Chung et al. 2012). Maceligan (**1**) effectively inhibits melanin biosynthesis and thus

could be employed as a new skin-whitening agent (Cho et al. 2008). Whilst the ethanolic extract of *M. fragrans* seeds after removing substances safrole and myristicin was considered as a potential nutraceutical candidate for the treatment of atopic dermatitis (Chung et al. 2012). In addition, some other activities of *M. fragrans* have been reported such as anticonvulsant and behavioural actions (Sonavane et al. 2002a; Wahab et al. 2009); antipyretic (Olajide et al. 2000), antiulcer (Capasso et al. 2000), antidiarrheal (Gupta et al. 1992) activities.

Conclusion

Myristica fragrans, an aromatic evergreen tree, is well known for its commercial products including mace (aril) and nutmeg (seed), which have been used for spice and medicinal purposes. This review has summarized a comprehensive understanding of the phytochemical and pharmacological properties of *M. fragrans* reported to date. The majority of investigations are focused on the isolation and structural elucidation of lignans from the aril (mace) or nutmeg (seed) of the *M. fragrans* fruit. Extensive research has been reported the presence of approximately 250 compounds from this plant, including lignans, neolignans, diphenylalkanes, phenylpropanoids, terpenoids, steroids, triterpenoids, saponin, flavonoids, and other constituents. *M. fragrans* extract and its constituents exert various biological activities, such as anti-inflammatory, antioxidant, antibacterial, antifungal, anti-obesity, antidiabetic, and anticancer activities, together with analgesic, chemopreventive, hepatoprotective, neuropharmacologic, cardioprotective, toxicological, and other pharmacological effects. As the literature has documented, macelignan (**1**), *meso*-dihydroguaiaretic acid (**2**), myristicin (**111**), and malabaricone C (Mal C, **104**) are the most active compounds. However, there are still some scientific gaps in the reported literature on the phytochemistry of *M. fragrans* such as the inconsistency in determination absolute configuration of the *M. fragrans* neolignans and the conflict about the natural occurrence of 2-alkylcyclobutanones in *M. fragrans* seeds. This review provides a practical base for further scientific research on this plant and its favorable clinical application.

Acknowledgements This research was supported by the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (2020R1F1A1072001) and the Ministry of Education (2016R1D1A1B03930246), Korea.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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