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SHORT COMMUNICATION



# Phytochemical investigation on *Myristica fragrans* stem bark

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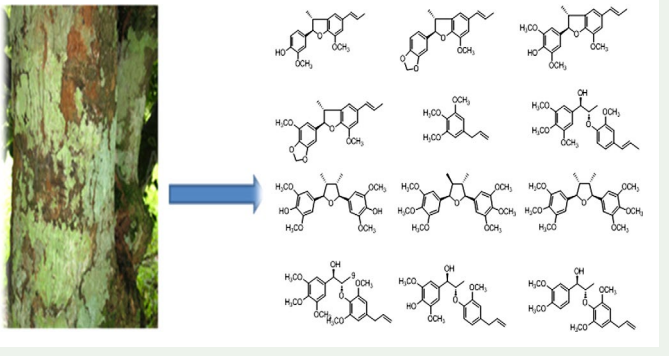
**ABSTRACT**

*Myristica fragran*s Houtt., the source of very important spice 'nutmeg' used world over is native to India, Indonesia, Sri Lanka, South Africa and Southeast Asia. Phytochemical investigation of *M. fragrans* stem bark led to the isolation of bis-aryl dimethyl tetrahydrofuran lignans, such as grandisin [(*7S,8S,7′S,8′S*)-3,3′,4,4′,5,5′-hexamethoxy-7,7′,8,8′-lignan] and (*7S,8S,7′R,8′R*)-3,3′,4,4′,5,5′-hexamethoxy-7,7′,8,8′-lignan along with important lignans and neolignans, licarinA, licarin B, odoratisol A, (*2S, 3R*)-7-methoxy-3-methyl-5-((*E*)-prop-1-enyl)-2-(5-methoxy,3,4-methylenedioxyphenyl)-2,3-dihydrobenzofuran, elemicin, fragransin $B_1$, raphidecursinol B, *erythro*-(*7S,8R*)-$\Delta^{8'}$-4,7-dihydroxy-3,5,3′-trimethoxy-8-*O*-4′-neolignan, *erythro*-(*7S,8R*)-$\Delta^{8'}$-7-hydroxy-3,4,3′,5′-tetramethoxy-8-*O*-4′-neolignan, surinamensin.and β-sitosterol. Structures of the 12 compounds isolated were unambiguously identified by various spectroscopic methods. The former two compounds were isolated from *M. fragrans* for the first time. Furthermore, the X-ray crystal structure of odoratisol A is reported in this paper for the first time.



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## 1. Introduction

*Myristica fragrans* Houtt belonging to Myristicaceae family (Van Gils and Cox 1994) commonly known as nutmeg is extensively used as spice in condiments, perfumery and in traditional medicines. Nutmeg has been described to have tonic (Burkill 1935), stomachic, carminative (Green 1959; Khory and Katrak 1985), nervous stimulant (Ainslie 1979), astringent, hypolipidaemic. The non-volatile part of nutmeg is rich in dimeric phenyl propanoids, lignans and neolignas (Isogai, Murrakoshi, et al. 1973; Janssens and Laekeman 1990). Studies have indicated that the neolignan odoratisol A isolated from *M. fragrans* mace inhibited the activity of human cytochrome CYP3A4 and CYP2C9 (Kimura et al. 2010). Raphidecursinol B, a lignan isolated from *M. fragrans* mace has been found to have antimalarial activity (Kumar Parai et al. 2008; Kumar et al. 2008). Chemical constituents of nutmeg fruit pericarp has been explored earlier by our group (Francis et al. 2014). However, the stem bark of *M. fragrans* tree has not been studied earlier. Herein, we report the isolation of ten known compounds viz., licarinA, licarin B, odoratisol A, (*2S, 3R*)-7-methoxy-3-methyl-5-((*E*)-prop-1-enyl)-2-(5-methoxy,3,4-methylenedioxyphenyl)-2,3-dihydrobenzofuran, elemicin, fragransin $B_1$, raphidecursinol B, *erythro*-(*7S,8R*)-$\Delta^{8'}$-4,7-dihydroxy-3,5,3′-trimethoxy-8-*O*-4′-neolignan, *erythro*-(*7S,8R*)-$\Delta^{8'}$-7-hydroxy-3,4,3′,5′-tetramethoxy-8-*O*-4′-neolignan and surinamensin from the stem bark of *M. fragrans*. In addition, grandisin and *(7S,8S, 7′R,8′R)*-3,3′,4,4′,5,5′-hexamethoxy-7,7′, 8,8′-lignan have also been isolated from *M. fragrans* for the first time.

## 2. Results and discussion

Dichloromethane extract of *M. fragrans* stem bark was subjected to column chromatography on silica gel and neutral alumina which afforded licarin A (**1**) (Aiba et al. 1973), licarin B (**2**) (Aiba et al. 1973), odoratisol A (**3**) (Giang et al. 2006), (*2S,3R*)-7-methoxy-3-methyl-5-((*E*)-prop-1-enyl)-2-(5-methoxy,3,4-methylenedioxy phenyl)-2,3-dihydrobenzofuran (**4**), (Isogai, Suzuki, et al. 1973), elemicin (**5**) (Tommy et al. 1998), *β*-sitosterol, fragransin $B_1$ (**6**) (Hattori et al. 1987), grandisin (**7**) (David and Feoixr 1974), (*7S,8S,7′R,8′R*)-3,3′,4,4′,5,5′-hexamethoxy-7,7′,8,8′-lignan (**8**) (Kraft et al. 2002), raphidecursinol B (**9**) (Isogai, Murrakoshi, et al. 1973), *erythro*-(*7S,8R*)-$\Delta^{8'}$-4,7-dihydroxy-3,5,3′-trimethoxy-8-*O*-4′-neolignan (**10**) (Isogai, Murrakoshi, et al. 1973), *erythro*-(*7S,8R*)-$\Delta^{8'}$-7-hydroxy-3,4,3′,5′-tetramethoxy-8-*O*-4′-neolignan (**11**) (Isogai, Suzuki, et al. 1973) and surinamensin (**12**) (Barata et al. 1978) as well as palmitic acid (Figure 1). To the best of our knowledge this is the first report on the isolation and identification of compounds **7** and **8** from any part of *M. fragrans*. All the compounds were identified by the comparison of their spectral data with that in literature. Stereochemistry of **3** was unambiguously confirmed by single crystal X-ray structure determination (Figure 2).

Molecular formula of compound **7** was found to be $C_{24}H_{32}O_7$ from HRMS (455.2049 $[M + Na]^+$). The $^1H$ NMR spectrum showed the presence of two sec-methyls (1.09, d), six methoxy groups (3.84, 6H s; 3.86, 3H, s and 3.89, 9H, s), two methines (1.80 m), two highly deshielded benzylic methines (4.66, d; $J = 8.5$ Hz) and four magnetically equivalent aromatic protons (6.63, s). The protons at $\delta$ 1.80 showed a correlation with protons appearing at $\delta$ 1.09 in $^1H$-$^1H$ correlation spectrum and also with $\delta$ 4.65 which indicated that the compound **7** contains a tetrahydrofuran moiety. The stereochemistry of the compound **7** has been established from its chemical shifts of the methyl, methine and benzylic methine protons. The stereochemistry of compound **7** is the same as in galbelgin. (Birch et al.1958). The

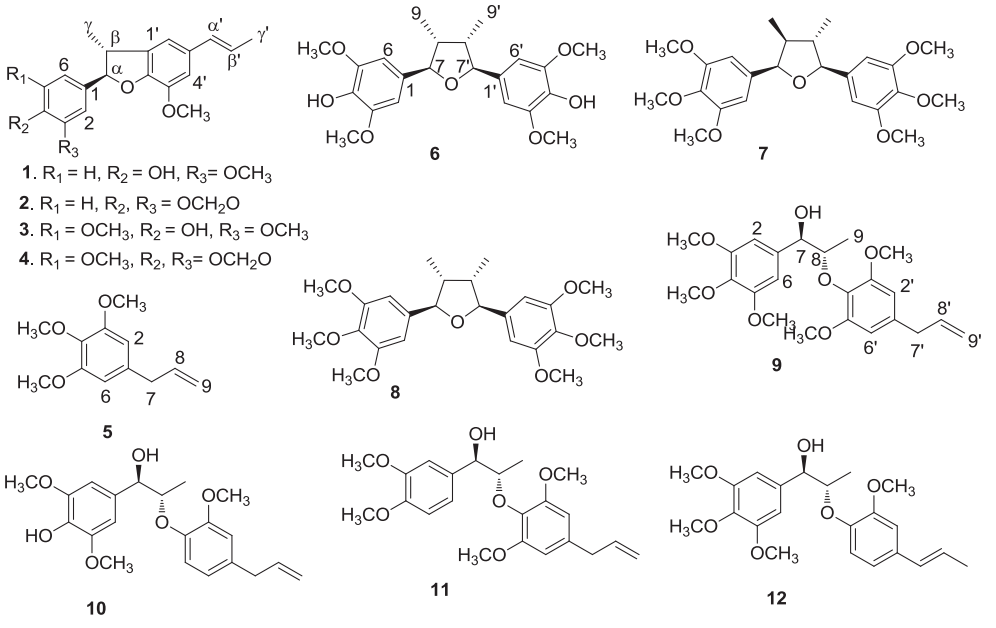


**Figure 1.** Structures of isolated compounds.

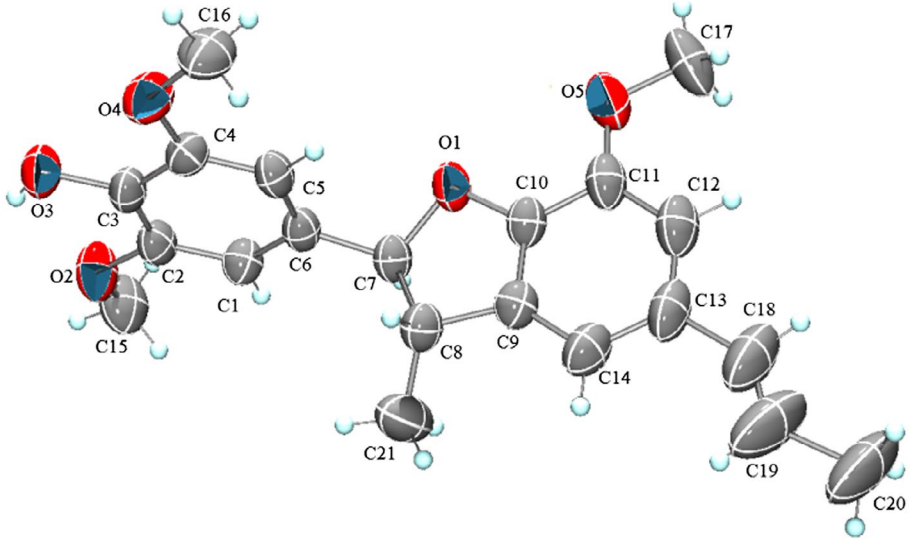


**Figure 2.** ORTEP diagram of compound **3** (odoratisol A).

$^{13}$C NMR and DEPT spectra suggested the presence of 24 carbons, which include eight methyl, eight methine, and eight quaternary carbons. Among them, the signals at $\delta$ 56.0, 56.1 and 60.8 could be attributed to the methoxy carbons. The structure of **7** was thus arrived at as grandisin first isolated from *Litsea grandis* (David and Feoixr 1974) on comparison with spectral data reported in literature.

Molecular formula of the compound **8** ($C_{24}H_{32}O$) (a stereoisomeric form of **7**) was established from HRMS (455.2049 $[M + Na]^+$). The $^1$HNMR spectrum suggested the presence of magnetically equivalent protons in the molecule, as in **7**; signals due to two sec-methyls ($\delta$ 1.09), two methines ($\delta$ 2.36, m), two highly deshielded benzylic methines ($\delta$ 4.54, d, $J$ = 6 Hz), six methoxy groups ($\delta$ 3.85, 6H, s; $\delta$ 3.86, 9H, s and $\delta$ 3.90, 3H, s) and four aromatic protons ($\delta$ 6.64) were seen. The protons at $\delta$ 2.36 showed correlations with protons appearing at $\delta$ 1.09 and $\delta$ 4.54 in $^1$H-$^1$H correlation spectrum which indicated that the compound 8 is a tetrahydrofuran system. The stereochemistry of the compound 8 has been established from its chemical shifts of the methyl, methine and benzylic methine protons and they were essentially similar in chemical shifts and coupling constants to those of a galgravin-type lignan (Blears and Haworth 1968). The $^{13}$C NMR and DEPT spectra suggested the presence of 24 carbons, which include eight methyl, eight methine, and eight quaternary carbons. Among them, the signals at $\delta$ 56.0 and 60.8 could be attributed to the methoxy carbons. Thus, the structure of the compound was confirmed as (*7S,8S, 7′R,8′R*)-3,3′,4,4′,5,5′-hexamethoxy-7,7′, 8,8′-lignan first reported from *Bonamia spectadills* (Kraft et al. 2002) by comparing with the reported data.

## 3. X-ray crystallography of compound 3

The X-ray diffraction data were collected on a Rigaku AFC-12 Saturn 724 + CCD diffractometer equipped with a graphite-monochromated Mo $K_\alpha$ radiation source ($\lambda$ = 0.71073 Å) and an Oxford low temperature device cooled to 150 K. Corrections were applied for Lorentz and polarization effects. The structure was solved by direct methods and refined by full-matrix least-squares cycles on $F^2$ using SHELXL2013 software (Sheldrick 2008). All non-hydrogen atoms were refined anisotropically and the hydrogen atoms were placed in fixed, calculated positions using a riding model.

Crystal data for compound **3**: Molecular Formula: $C_{21}H_{24}O_5$, Formula weight : 356.40, Crystal system : Orthorhombic, space group: $P2_12_12_1$, $a$ = 4.850(6), $b$ = 17.23(2), $c$ = 23.12(4) Å, $V$ = 1932(4)Å$^3$, $Z$ = 4, Density $Dx$ = 1.225 Mg m$^3$, Absorption Coefficient ($\mu$) = 0.087 mm$^{-1}$, Reflections collected = 15,480, Independent reflections = 3889, $R_{int}$ = 0.0706, Number of Parameters = 235, Goodness-of-fit on $F^2$ = 0.855. The crystal structure data of Compound **3** has been deposited with the Cambridge Crystallographic Data Centre with deposition number CCDC 1014391.

## 4. Conclusions

Non-volatile chemical constituents (**1–12**) were isolated from *M. fragrans* stem bark for the first time. Stereochemistry of compound **3** was unambiguously established by single crystal X-ray data. Compounds **7** and **8** are reported from this plant for the firsttime. Studies indicated that *M. fragrans* stem bark is a very good source of the antimalarial compound raphidecursinol B. The structures of these compounds were established on the basis of spectroscopic techniques and X-ray crystallographic data.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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