Monoterpenoid indole alkaloids with potential neuroprotective activities from the stems and leaves of *Melodinus cochinchinensis*

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**ABSTRACT**

A chemical study on the stems and leaves of *Melodinus cochinchinensis* resulted in the isolation and identification of a new monoterpenoid indole alkaloid, melodicochine A (1), together with seven known monoterpenoid indole alkaloids (2–8). The chemical structure of 1 was elucidated on the basis of extensive spectral data analyses and the known compounds were identified by comparing their experimental spectral data with the reported data in the literature. All isolated indole alkaloids were evaluated for their neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells *in vitro*. Monoterpenoid indole alkaloids 1–8 exhibited notable neuroprotective effects with EC50 values in range of 0.72 ± 0.06 to 17.89 ± 0.16 μM.

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1. Introduction

Parkinson’s disease is the second most common neurodegenerative disorder, which is characterized by the selective degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy bodies, leading to a clinical syndrome characterized by slowness of movement, postural instability, stiffness and tremors (Sveinbjornsdottir 2016). Lots of chemical neurotoxins have been associated with the pathological development of Parkinson’s disease. Among these chemical neurotoxins, 6-hydroxydopamine has been widely utilized as a dopaminergic neuron degenerative agent to investigate neurotoxicity in the experimental models for Parkinson’s disease that can selectively damage dopaminergic neurons in vivo and in vitro (Blum et al. 2001; Zhang et al. 2012). Therefore, 6-hydroxydopamine is a surely effective useful tool in building the experimental models for Parkinson’s disease, which is widely applied for studying the effectiveness and mechanism of action of potential therapeutic agents for the prevention and treatment of Parkinson’s disease.

The genus Melodinus in the family of Apocynaceae comprising about 53 species grows widely in tropical and subtropical regions of Asia and Oceania. There are approximately 11 species in China, mainly distributed in Southern China, Southwestern China and Taiwan provinces (Editorial Committee of Flora of China 1977). Most plants of the genus Melodinus have been used as folk medicines, which are commonly used to treat abdominal pain, indigestion, infantile hernia, infantile malnutrition, infantile meningitis, orchitis, rheumatic heart disease, fractures, and so on. Previous phytochemical investigations on the genus Melodinus have resulted in the isolation and characterization of a series of compounds, including monoterpenoid indole alkaloids, triterpenes, lignans and phenolic acids, which displayed an array of anti-tumor, anti-inflammatory, antibacterial, anti-tuberculosis, vasodilator and neuroprotective activities (Cheng et al. 2016; Fang et al. 2018; Feng et al. 2010; Gao et al. 2019; Li et al. 2015; Liu et al. 2012; Li et al. 2016; Wu et al. 2020; Zhang et al. 2020; Zhou et al. 2019). Our preliminary experimental results displayed that the 90% EtOH extract of the stems and leaves of M. cochinchinensis showed notable neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells with the EC50 value of 21.37 ± 0.18 μg/mL in vitro. As a part of our ongoing research into monoterpenoid indole alkaloids with diverse chemical structures and significant biological activities from tropical medicinal plants (Fu et al. 2012a, 2012b, 2014a, 2014b; Liu et al. 2017, 2018, 2019c; Chen et al. 2017a, 2017b), a phytochemical study on the stems and leaves of M. cochinchinensis was therefore implemented and had caused the isolation and identification of a new monoterpenoid indole alkaloid, melodicochine A (1), as well as seven known monoterpenoid indole alkaloids (2–8). Their chemical structures were elucidated by extensive spectral analyses. Furthermore, all isolated monoterpenoid indole alkaloids were assessed for their neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells in vitro. Herein, the isolation, structure elucidation as well as neuroprotective effects of these isolated monoterpenoid indole alkaloids will be reported.

2. Results and discussion

The 90% EtOH extract of the stems and leaves of M. cochinchinensis was suspended in distilled water and extracted successively with petroleum ether (PE) as well as ethyl
acetate (EtOAc). The EtOAc extract fraction was repeatedly subjected to silica gel CC, ODS silica gel CC, Sephadex LH-20 gel CC as well as preparative HPLC, to afford eight monoterpenoid indole alkaloids (1–8), including a new monoterpenoid indole alkaloid, as shown in Figure 1.

Melodicochine A (1) was obtained as a light yellow amorphous powder with a specific rotation of \([\alpha]_{20D} +15.8\) (c 0.11, CH₃OH). Its molecular formula, C₂₁H₂₄N₂O₄, was established on the basis of HRESIMS (\(m/z\) 369.1812 [M + H]+, calcd: 369.1809), with 11 degrees of unsaturation, which could also be confirmed by \(^1\)H, \(^{13}\)C-NMR and DEPT data. Its IR spectrum exhibited the IR absorption peaks indicating the existence of hydroxyl group (3439 cm\(^{-1}\)), ester carbonyl (1728 cm\(^{-1}\)), amide carbonyl (1678 cm\(^{-1}\)) and phenyl group (1628, 1518 and 1437 cm\(^{-1}\)). Its UV spectrum displayed the UV absorption bands at 205, 223 and 283 nm which were characteristic of a monoterpenoid indole alkaloid (Shao et al. 2015; Zhou et al. 2019). The \(^{13}\)C NMR and DEPT data suggested the existence of 21 carbons, including 12 sp\(^2\) carbons, one sp\(^3\) quaternary carbon, two sp\(^3\) methines, four sp\(^3\) methylenes as well as two methyls. In addition, the 12 sp\(^2\) carbons were attributable to one indole ring group, one double bond group, one ester carbonyl group and one amide carbonyl group. The above data revealed that the chemical structure of 1 was similar to that of melosine F (2) (Shao et al. 2015). Further comparisons of \(^1\)H-NMR, \(^{13}\)C-NMR and DEPT data of 1 with melosine F (2) indicated that there were two major differences between their structures. Firstly, the amide carbonyl group of C-3 in melosine F (2) was replaced with a methylene group in 1, which were confirmed by the HMBC correlations of H-3\(\alpha\) and H-3\(\beta\) to C-5 (\(\delta_C\) 46.0) and C-21 (\(\delta_C\) 173.3), H-5\(\alpha\) and H-5\(\beta\) to C-3 (\(\delta_C\) 50.8) and C-21, as well as the \(^1\)H-\(^1\)H COSY correlations of H-14 with H-15, H-3\(\alpha\) and H-3\(\beta\). Secondly, the hydrogen atom at C-19 in melosine F (2) was replaced with a hydroxyl group in 1, which was verified by the existence of the hydroxyl group resonating at \(\delta_H\) 4.88 (1H, d, \(J = 10.0\) Hz, 19-OH) which was supported by the \(^1\)H-\(^1\)H COSY correlation of H-19 with 19-OH and H₃-18. All above inference were also supported by the HMBC correlations of H-15, H-17\(\alpha\), H-17\(\beta\), 19-OH to C-19 (\(\delta_C\) 73.2), H-19 to C-15 (\(\delta_C\) 129.8), C-17 (\(\delta_C\) 44.1), C-20 (\(\delta_C\) 47.4) and C-21. The chemical structure of 1 was further confirmed by detailed analyses of 2D NMR (HSQC, HMBC, \(^1\)H-\(^1\)H COSY and ROSEY) spectra as displayed in
Figure S1. The relative configurations of 1 were assigned on the basis of the typical coupling constant and the ROESY correlations, which were almost identical to those of melosine F (2) (Shao et al. 2015), except for the configuration of C-19. The relative configuration of H-16 was assigned as β-oriented in the light of the large coupling constant (J = 12.1 Hz) between H-16 and H-17α by the comparison of the J-value between H-16 and H-17α with that of (16S)-14,15-didehydro-cleavamine (The relative configuration of H-16 was β-oriented, J = 10.0 and 1.1 Hz) and (16R)-14,15-didehydro-cleavamine (The relative configuration of H-16 was α-oriented, J = 5.5 and 2.4 Hz) (Eles et al. 2002), which was also supported by the ROESY correlations of 16-COOCH3 with H-19, 19-OH and H3-18. However, the absolute configuration of C-19 could not be assigned based on currently available data. Thus, the chemical structure of melodicochine A (1) was determined as shown in Figure 1.

In addition to the new monoterpenoid indole alkaloid, melodicochine A (1), seven known monoterpenoid indole alkaloids were isolated and identified as melosine F (2) (Shao et al. 2015), 6, 7-epoxy-8-oxo-vincadifformine (3) (Zhang et al. 2014), melosine C (4) (Shao et al. 2015), jerantinine C (5) (Lim et al. 2008), fusiformine A (6) (Li et al. 2016), melodinine N (7) (Liu et al. 2012) and melodinine P (8) (Liu et al. 2012), by comparing their experimental and reported spectral data.

All isolated monoterpenoid indole alkaloids 1–8 were assessed for their neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells by means of the MTT method in vitro, in which curcumin was used as a positive control. All isolated monoterpenoid indole alkaloids 1–8 displayed notable neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells with EC50 values in range of 0.72 ± 0.06 to 17.89 ± 0.16 µM (as shown in Table 1). It’s worth noting that monoterpenoid indole alkaloids 1–8 showed obviously neuroprotective effects with EC50 values similar to that of the positive control (curcumin), even more significant neuroprotective effects than that of the positive control (curcumin).

3. Experimental
3.1. General experimental procedures
UV spectrum of new monoterpenoid indole alkaloid 1 was measured using a Beckman DU 640 spectrophotometer. IR spectrum of new monoterpenoid indole alkaloid 1 was recorded by means of a Nicolet Nexus 470 spectrophotometer in KBr discs. Optical
rotations of monoterpenoid indole alkaloid 1–8 were measured on a Perkin Elmer 241 polarimeter. HRESIMS spectra of monoterpenoid indole alkaloid 1–8 were measured on a VG Auto Spec-3000 spectrometer. NMR spectra of monoterpenoid indole alkaloid 1–8 were recorded on Bruker 400 MHz spectrometers using TMS as an internal standard, with chemical shifts recorded as δ values. Preparative HPLC was performed on a Thermo Fisher UltiMate 3000 LC series equipped with a MWD detector using a Waters XBridge C18 column (5 μm, 250 × 20 mm). Silica gel H (10–40 μm, Qingdao Marine Chemical Inc., China), Silica gel (100–200 mesh, 200–300 mesh, Qingdao Marine Chemical Inc., China), Sephadex LH-20 (40–70 μm, Amersham Biosciences, Sweden) and ODS silica gel (50 μm, Merck, Darmstadt, Germany) were used for performing column chromatography (CC).

3.2. Plant material

The stems and leaves of *M. cochinchinensis* were collected from Bawangling National Forest Park, Hainan Province, China, in June 2019, which identified by Prof. Yan-Hui Fu, the director of the Engineering Research Center for Industrialization of Southern Medicinal Plants Resources of Hainan Province, Hainan Normal University. A voucher specimen (No. HNMESU20190618) has been deposited at the Herbarium of the Engineering Research Center for Industrialization of Southern Medicinal Plants Resources of Hainan Province, Hainan Normal University.

3.3. Extraction and isolation

The air-dried stems and leaves of *M. cochinchinensis* (14.9 kg) were powdered and then extracted by means of 90% EtOH at room temperature for three times, each for seven days. The solvent were combined and condensed under reduced pressure to afford a crude extract (1.56 kg). After suspended in distilled water (12.0 L), the crude extract was extracted successively with PE (12.0 L × 7) and EtOAc (12.0 L × 7), to gain the PE extract (216.8 g) as well as the EtOAc extract (486.3 g). The EtOAc extract (485.0 g) was subjected to silica gel CC, eluted with chloroform/methanol (100:0 to 40:60, v/v), affording seven fractions (Fr. 1–Fr. 7). Fr. 2 (42.9 g) was further chromatographed using an ODS silica gel medium-pressure CC (methanol/distilled water, 25:75 to 100:0) to yield eight fractions (Fr. 2A–Fr. 2H). Fr. 2B (3.2 g) was then subjected to a Sephadex LH-20 gel CC eluted with methanol, and was further purified and prepared using preparative HPLC using a Waters XBridge C18 column with 36% methanol/distilled water as mobile phase to obtain 1 (12.8 mg), 2 (26.3 mg), 4 (42.1 mg) and 7 (52.1 mg). Fr. 2 C (4.1 g) was purified by means of a Sephadex LH-20 CC gel CC eluted with methanol, followed by preparative HPLC by a Waters XBridge C18 column with 22% acetonitrile/distilled water as mobile phase to yield 3 (32.1 mg), 5 (23.3 mg), 6 (9.6 mg) and 8 (15.8 mg).

Melodicochine A (1): Light yellow amorphous powder; [α]20D +15.8 (c 0.11, CH3OH); IR (KBr) νmax 3439, 2968, 2923, 1728, 1678, 1628, 1518, 1437, 1381, 1297, 1278, 1171, 1083 and 1049 cm⁻¹; UV (CH3OH) λmax (log ε) 205 (4.28), 223 (4.36) and 283 (3.48) nm; ESIMS m/z 369.18 [M + H]+; HRESIMS m/z 369.1812 (M + H; calcd for C21H25N2O4,
3.4. Neuroprotective activities bioassays

The SH-SY5Y human neuroblastoma cell lines were used as experimental cell lines to evaluate neuroprotective activities of all isolated compounds, which were obtained from American Type Culture Collection (ATCC, Manassas, VA, USA). The SH-SY5Y cells were routinely cultured in complete DMEM medium supplemented with 10% FBS, 10.0 µg/mL streptomycin, 100.0 U/mL penicillin and maintained at 37.0 °C with 5% CO₂ at a humidified atmosphere. The neuroprotective activity assay was conducted in 96-well microplates by the MTT method according to the protocol described in our previously published papers (Liu et al. 2019a, 2019b). Briefly, SHSY5Y cells were cultured in 96-well plates at a density of 2 × 10⁴ cells/well in 200.0 µL for 24.0 h. The cells were treated with 100.0 µM 6-hydroxydopamine and various concentrations (0.0625, 0.32, 1.6, 8.0 and 40.0 µM) of extracts and compounds for an additional 24.0 h. Cell viability was determined by treatment with MTT dissolved in 0.5 mg/mL of phosphate-buffered saline (PBS) at 37.0 °C for 4.0 h. The PBS was then carefully removed, and formazan crystals were dissolved using dimethyl sulfoxide. The absorbance of this solution was then measured at 540.0 nm using a microplate reader. Samples were tested in triplicate and the mean values with standard deviation were used. Neuroprotection against 6-hydroxydopamine induced cell death was calculated using a semilogarithmic graph depicting the relationship between at least four different concentrations of compounds and their percentage effects. All results were typically expressed as EC₅₀. In this neuroprotective activity assay, curcumin was used as a positive control.

4. Conclusions

In current investigation, a chemical study on the stems and leaves of *M. cochinchinesis* resulted in the isolation and characterization of a new monoterpenoid indole alkaloid, melodicochine A (1), along with seven known indole alkaloids (2–8). Furthermore, all isolated monoterpenoid indole alkaloids (1–8) were also investigated for their neuroprotective effects against 6-hydroxydopamine induced cell death in human neuroblastoma SH-SY5Y cells, which were proved to be extremely significant. These discoveries may be used as an interpretation of the folk application of *M.*
cochinichinensis, which is generally believed to play an important role in preventing or reducing the occurrence of Parkinson’s disease. These findings also indicate that these isolated monoterpenoid indole alkaloids showing notable neuroprotective effects from the stems and leaves of *M. cochinichinensis* could be is applied as candidates for further research and development for therapeutic purposes in neural degenerative disease including Parkinson’s disease.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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