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FULL PAPER

CHEMISTRY & BIODIVERSITY

Anti-Food Allergic Alkaloids from the Lotus Seed Pot

Tuan-Wu Cao[+],[a] Chun-Lan Xie[+],[b] Chao-Qun Chen[+],[c] Zhi-Hui He,[b] Qing-Xiang Yan,[b] Gang Xu,*[c] and Xian-Wen Yang*[b]

[a] Laboratory of Natural Medicine Research and Development in Wuling Mountain, School of Chemistry and Chemical Engineering, Yangtze Normal University, Fuling 408100, China

[b] Key Laboratory of Marine Biogenetic Resources, Third Institute of Oceanography, Ministry of Natural Resources, 184 Daxue Road, Xiamen 361005, China, e-mail: yangxw76@163.com

[c] State Key Laboratory of Phytochemistry and Plant Resources in West China, and Yunnan Key Laboratory of Natural Medicinal Chemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China, e-mail: xugang008@mail.kib.ac.cn

Lotus seed pod (LSP) has been used as traditional herbal cuisine to modulate immunity. From the AcOEt-soluble extract of LSP, one new aporphine alkaloid, *N*-[2-(2*H*-phenanthro[3,4-*d*][1,3]dioxol-5-yl)ethyl]acetamide (nelunucine A, **1**) was obtained along with 19 known ones. Their structures were established by detailed analysis of the 1D-, 2D-NMR, and HR-ESI-MS data. *N*-Nornuciferine (**9**) and lirinidine (**10**) showed potent *in vitro* anti-food allergic activity with IC_{50} values of 40.0 and 55.4 μM, respectively, compared to 91.4 μM for loratadine, the positive control.

Keywords: *Nelumbo nucifera*, lotus seed pod, alkaloids, anti-food allergy.

Introduction

Lotus (*Nelumbo nucifera* Gaertn, *Nymphaeaceae*), a well-known agricultural crop, is widely cultivated in many countries, almost all parts of this plant and their processing by-products, being as health food that are widely consumed in many countries.[1] More importantly, lotus has been considered as food-medicine herbs approved by The Chinese Food and Drug Administration, and its seeds, stamens, seedpods, leaves and other parts were recorded in the 'Chinese Pharmacopeia',[2] Many aporphine alkaloids have been isolated from leaves and flowers of *Nelumbo nucifera*, which based on the nucleus structure, are divided into three categories i.e., single benzyl isoquinoline, aporphine and dehydrogenase aporphine,[3] and exhibited antioxidant and anticancer,[4] hyaluronidase inhibitory activity,[5] acetylcholinesterase inhibiting activity,[6] accelerative effects on neurite outgrowth in PC-12 cells,[7] the glucose consumption-stimulatory activity.[8] Lotus seedpod (LSP) is discarded directly during the lotus seed processing which is used as traditional medicines with hemostasis function and for eliminating bruises in China.[9] LPS has been reported to be rich in procyanidins which exhibited some great biological activities, including antioxidant, anticancer, antiobesity, hypolipidemic, improving learning and memory properties.[10–12]

Food allergy, a global health concern, was rapidly growing and life-threatening.[13] Up to now, adverse reactions to food were divided into immune-mediated food allergies and non-immune-mediated intolerances, whereas nutritional regulation based on food displayed a vital treatment.[14] Previous studies on LSP have focused on the large polar ingredient such as procyanidins and flavonoids,[12,15,16] while the alkaloids of LSP has been no further study to date. Our previous research showed that the extract of LSP exhibited potent anti-food allergic effect. In order to find the effective ingredients of anti-food allergy from LSP, a systematically chemical examination was performed,

[+] Tuan-Wu Cao, Chun-Lan Xie, and Chao-Qun Chen contributed equally to this work.

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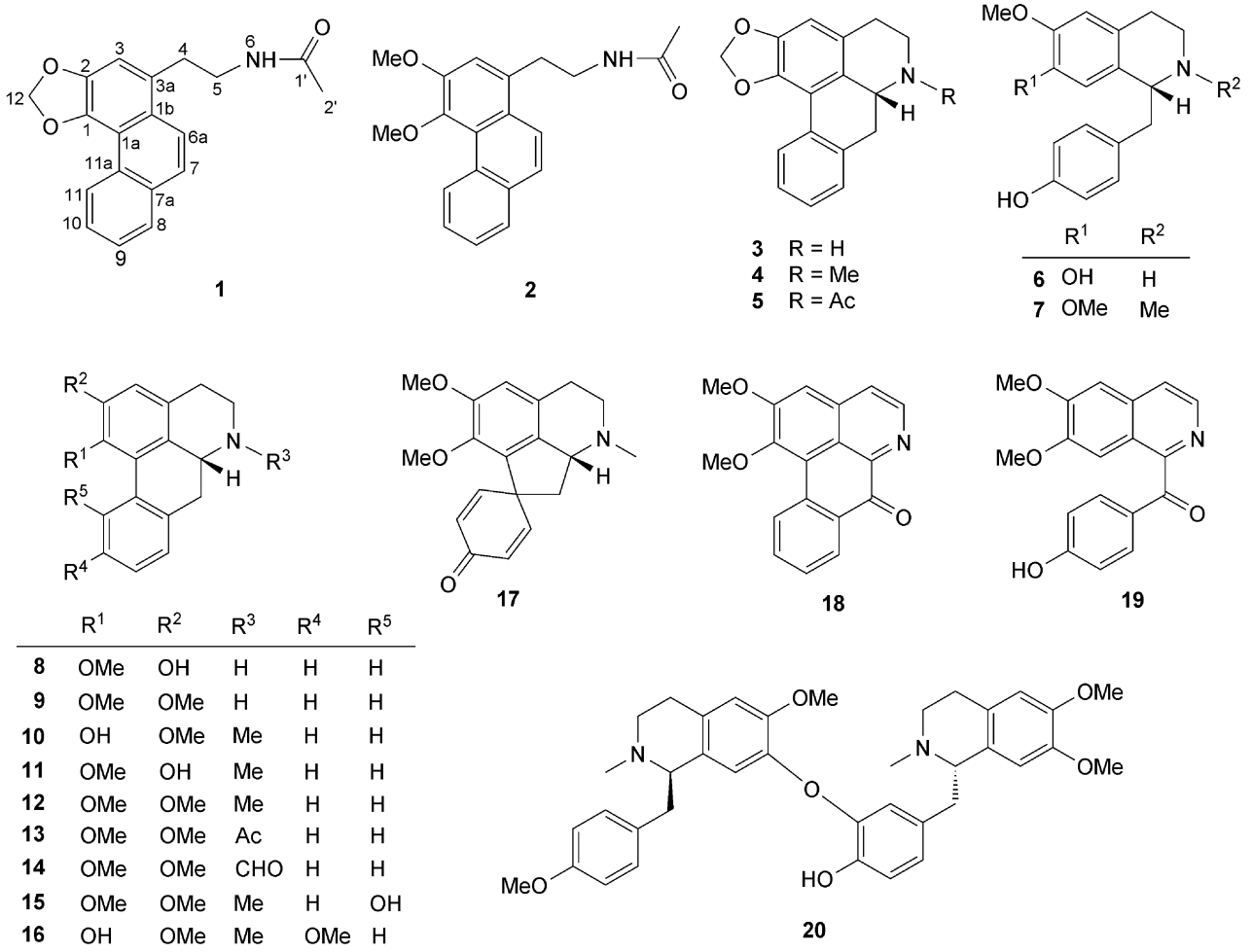
which resulted in the isolation of 20 aporphine alkaloids (**1**–**20**, *Figure 1*). Interestingly, compound **1** was the first natural acyclic aporphine alkaloid. Herein, we report the isolation, structure, and anti-food allergic activities of these compounds.

Results and Discussion

The alkaline extract of LSP was subjected to repeated column chromatography (CC) over silica gel, Sephadex LH-20, and MCI gel CC to give 20 alkaloids. By comparison of NMR data with those reported in literature, 19 known compounds were identified as *N*-[2-(3,4-dimethoxyphenanthren-1-yl)ethyl]acetamide (**2**),[17] anonaine (**3**),[18] roemerine (**4**),[8] (−)-*N*-acetylanonaine (**5**),[19] coclaurine (**6**),[20] armepavine (**7**),[21] asimilobine (**8**),[18] *N*-nornuciferine (**9**),[22] lirinidine (**10**),[23] *O*-nornuciferine (**11**),[24] nuciferine (**12**),[8] *N*-acetylnornuciferine (**13**),[25] (−)-*N*-formylnornuciferine (**14**),[25] 1,2-dimethoxy-11-hydroxyaporphine (**15**),[26] (±)-1-hydroxy-2,10-dimethoxyaporphine (**16**),[27] pronuciferine (**17**),[8] lysicamine (**18**),[21] (6,7-dimethoxy-1-isoquinolinyl)(4′-hydroxyphenyl)methanone (**19**),[28] and neferine (**20**).[29]

Compound **1** was obtained as a brownish amorphous powder. The molecular formula $C_{19}H_{17}NO_3$ was deduced from its positive HR-ESI-MS mass spectrum at *m/z* 330.1104 $[M+Na]^+$, corresponding to twelve degrees of unsaturation. The UV spectrum of **1** showed absorptions at 203, 248, 282, 312 and 350 nm, suggesting the presence of a phenanthryl group. Its IR spectrum revealed absorption bands characteristics of –NH (3428 cm^{-1}), –C=O (1636 cm^{-1}), and aromatic rings (1597, 1506, 1451 cm^{-1}). The ^{1}H-NMR spectrum showed seven aromatic protons [δ_H 7.28 (1H, s, H-3), 7.65 (1H, td, J=7.1, 1.1, H-9), 7.69 (1H, d, J=9.1, H-7), 7.70 (1H, ddd, J=8.2, 7.1, 1.1, H-10), 7.94 (1H, dd, J=



	R^1	R^2	R^3	R^4	R^5
8	OMe	OH	H	H	H
9	OMe	OMe	H	H	H
10	OH	OMe	Me	H	H
11	OMe	OH	Me	H	H
12	OMe	OMe	Me	H	H
13	OMe	OMe	Ac	H	H
14	OMe	OMe	CHO	H	H
15	OMe	OMe	Me	H	OH
16	OH	OMe	Me	OMe	H

Figure 1. Chemical structures of compounds **1**–**20**.

7.1, 1.0, H-8), 8.22 (1H, d, $J=9.2$, H-6a), 9.26 (1H, d, $J=8.2$, H-11)], one oxygenated methylene which is typical of a 1,2-methylenedioxy group [δ_H 6.21 (2H, s, H-12)], two aliphatic methylene groups [δ_H 3.43 (2H, t, $J=7.3$, H-4), 3.81 (2H, td, $J=7.3$, 5.4, H-5)], one acylated nitrogen proton [δ_H 8.79 (1H, t, $J=5.4$, H-6)], and one methyl [δ_H 2.10 (3H, s, H-2′)]. Analysis of the ^{13}C and DEPT NMR spectra revealed 19 carbons, including one methyl [δ_C 23.5 (q, C-2′)], one acetal [δ_C 101.9 (t, C-12)] and two aliphatic [δ_C 34.3 (t, C-4), 41.8 (t, C-5)] methylene groups, seven sp^2 methine groups [δ_C 111.7 (d, C-3), 128.5 (d, C-8), 127.1 (d, C-10), 127.8 (d, C-9), 125.8 (d, C-7), 128.2 (d, C-11), 124.2 (d, C-6a)], as well as one carbonyl [δ_C 170.6 (s, C-1′)] and seven sp^2 quaternary carbons [δ_C 129.5 (s, C-11a), 127.01 (s, C-1b), 117.6 (s, C-1a), 131.6 (s, C-3a), 132.9 (s, C-7a), 142.9 (s, C-1), 145.9 (s, C-2)]. These NMR spectroscopic data (*Table 1*) were very similar to those of *N*-[2-(3,4-dimethoxyphenanthren-1-yl)ethyl]acetamide (**2**),[17] except that an 1,2-methylenedioxy group instead of a dimethoxy moiety was found in **1**. In the ^1H-^1H COSY spectrum, correlations were found of H-4/H-5/H-6, H-6a/H-7, and H-8/H-9/H-10/H-11, indicating three fragments of **1**, which could be connected by the HMBC cross peaks of H-6a to C-1/C-1a/C-1b/C-3a/C-7a, H-7 to C-8/C-11a, H-11 to C-1a/C-7a/C-9, H-12 to C-1/C-2, H-5 to C-1′/C-3a, H-3 to C-1/C-1b/C-2/C-4, and H-4 to C-1b/C-3/C-3a (*Figure 2*).

Table 1. ^1H (600 MHz) and ^{13}C (150 MHz) NMR spectroscopic data of **1** in C_5D_5N (δ in ppm, J in Hz).

Position	δ_H	δ_C
1		142.9 C
1a		117.6 C
1b		127.01 C
2		145.9 C
3	7.28 s	111.7 CH
3a		131.6 C
4	3.43 (t, 7.3)	34.3 CH_2
5	3.81 (td, 7.3, 5.4)	41.8 CH_2
6	8.79 (t, 5.4)	
6a	8.22 (d, 9.2)	124.2 CH
7	7.69 (d, 9.1)	125.8 CH
7a		132.9 C
8	7.94 (dd, 7.1, 1.0)	128.5 CH
9	7.65 (td, 7.1, 1.1)	127.8 CH
10	7.70 (ddd, 8.2, 7.1, 1.4)	126.98 CH
11	9.26 (d, 8.2)	128.2 CH
11a		129.5 C
12	6.21 s	101.9 CH_2
1′		170.6 C
2′	2.10 s	23.5 CH_3

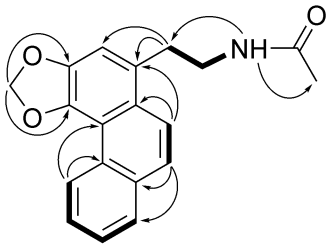


Figure 2. The key COSY (bold) and HMBC (arrows) correlations of **1**.

Table 2. Inhibitory effects of compounds **1**–**20** on RBL-2H3 cell degranulation ($n=3$, means ± SD).

Compound	Inhibition rate (%)	IC_{50} (μM)
9	83.3	40.0 ± 2.5
10	56.1	55.4 ± 3.9
Others[a]	< 50	–
Loratadine [b]	39.5	91.4 ± 3.4

[a] Other compounds, including **1**–**8** and **11**–**20**. [b] Loratadine was a commercially available anti-food allergic medicine.

Further by exhaustively analysis of its HSQC, COSY, HMBC, and ROESY spectra, the structure of **1** was then established as *N*-[2-(2*H*-phenanthro[3,4-*d*][1,3]dioxol-5-yl)ethyl]acetamide, and named nelunucine A.

All isolated compounds (**1**–**20**) were evaluated for their cytotoxic and anti-food allergic bioactivities. However, none showed cytotoxicity against the BIU-87, 7402, ECA-109, HeLa-S3, PANC-1 cell lines (IC_{50} > 10 μM). While *N*-nornuciferine (**9**) and lirinidine (**10**) showed potent anti-food allergic effects with IC_{50} values of 40.0 and 55.4 μM, respectively, which was about 2-fold stronger than that of the positive control, loratadine with an IC_{50} value of 91.4 μM (*Table 2*).

Conclusions

From the lotus seed pot, 20 aporphine alkaloids were isolated. The structure of the new compound **1** was named as nelunucine A. *N*-Nornuciferine (**9**) and lirinidine (**10**) showed potent *in vitro* anti-food allergic activity with IC_{50} values of 40.0 and 55.4 μM, respectively. While loratadine, a commercially available antiallergic medicine used as the positive control, showed its IC_{50} value of 91.4 μM. These data demonstrates that LSP could exert anti-food allergic effects with alkaloids as the bioactive components.

Experimental Section

General

Optical rotations were measured on a JASCO P-1020 polarimeter. UV spectra were detected on a Shamashim UV 2401 spectrometer. IR spectra were determined on a Bruker Tensor-27 infrared spectrophotometer with KBr disks. 1D and 2D NMR spectra were recorded on Bruker DRX-600 spectrometers using TMS as an internal standard. Unless otherwise specified, chemical shifts (δ) were expressed in ppm with reference to the solvent signals. ESI-MS analysis and HR-EI-MS were determined carried out on a Waters Autospec Premier P776 mass spectrometer. Preparative HPLC were performed on LC50 system equipped with ODS column. Silica gel, Amphichroic RP-18 gel and MCI gel were used for column chromatography.

Plant Material

The seed pot of *Nelumbo nucifera* Gaertn were collected in Bozhou Medicinal Market, Anhui Province, China, in October 2016. It was identified by Dr. Li-Xin Yang of the Kunming Institute of Botany, Chinese Academy of Sciences. A voucher specimen (201610N01) was deposited at Kunming Institute of Botany, Chinese Academy of Sciences.

Extraction and Isolation

An air-dried sample of LSP (100 kg) was extracted by MeOH at 80 °C for 10 h. The solvent was concentrated to a small volume and partitioned between AcOEt and HCl (1.5 %). Then the water was adjusted to pH 9–10 with ammonia solution. Further extraction by AcOEt got a crude extract (1000 g).

The extract was subjected to column chromatography (CC) over silica gel eluting with gradient petroleum ether (PE)-acetone (Me_2CO) (9:1→1:1) to afford seven fractions Frs. A-G. Fraction Fr. E (20.0 g) was separated by CC over silica gel (PE-AcOEt, 10:1) and Sephadex LH-20 (MeOH), followed by prep-HPLC (20→80 % MeOH) to afford compounds **2** (6.8 mg), **11** (30.0 mg), **14** (3.0 mg), **16** (17.3 mg). Fraction Fr. F (60.0 g) was CC over MCI-gel (MeOH-H_2O from 4:6 to 10:0), followed by CC over silica gel using gradient PE-Me_2CO. Final purification by prep-HPLC (40→100 % MeOH) and crystallization afforded compounds **1** (22.9 mg), **5** (4.0 mg), **4** (8.5 mg), **13** (4.0 mg), **18** (8.8 mg), and Compound **20** (36.0 mg). Fraction Fr. G (428.2 g) was subjected to CC over MCI-gel (MeOH-H_2O, 3:7→10:0) to yield 17 fractions (Frs. G1–G17). Fraction Fr. G6 was separated by CC over silica gel (PE-AcOEt, 10:1) to get **3** (2.0 mg) and fraction G7 was purified by CC over silica gel ($CHCl_3$-MeOH, 1:1) to give **12** (125.8 mg). Fraction Fr. G8 was subjected to semi-prep. HPLC (20→100 % MeOH) to give compounds **9** (6.9 mg) and **10** (3.2 mg). Fraction Fr. G9 was separated into two subfractions (Fr. G9.1–G9.2) by CC on Sephadex LH-20 (MeOH). Subfraction Fr. G 9.1 was purified by semi-prep. HPLC (40→100 % MeOH) to afford **7** (4.8 mg), **8** (10.2 mg), and **15** (16.1 mg). Similarly, **6** (26.0 mg), **17** (10.5 mg), and **19** (4.0 mg) were obtained from subfraction Fr. G9.2 using semi-prep. HPLC (45→100 % MeOH).

***N*-[2-(2*H*-Phenanthro[3,4-*d*][1,3]dioxol-5-yl) ethyl]acetamide** (**nelunucine A**, **1**). Brownish amorphous powder. UV (MeOH) λ_{max} (log ε): 203 (4.10), 248 (3.88), 283 (3.57), 312 (3.29), 350 (2.86) nm, IR (KBr): ν_{max} 3428, 3295, 1636, 1597, 1552, 1506, 1451, 1391, 1280, 1113, 1049, 812, 752 cm^{-1}, ^{1}H- and ^{13}C-NMR: *Table 1*, (+) HR-ESI-MS *m/z* 330.1104 $[M+Na]^+$ (calc. for $C_{19}H_{17}NO_3Na^+$, 330.1101).

Bioassays

In vitro anti-food allergic experiment was carried out using an IgE-mediated mast cell allergic reaction as previously reported.[30] In brief, RBL-2H3 cells were treated with antidinitrophenyl (DNP)-IgE overnight. Then cells were washed with Tyrode's buffer and the tested compounds were added for 1 h. After stimulated with DNP-BSA for 1 h, cells were measured the total β-hexosaminidase activity. The activity was quantified by detecting the fluorescence intensity (360 nm excitation and 450 nm emission).

While cytotoxic assay was conducted against five tumor cell lines of BIU-87, Bel-7402, ECA-109, HeLa-S3, and PANC-1 by MTT method.[31]

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Author Contribution Statement

X.-W.Y. and G.X. designed and coordinated the project; T.-W.C., C.-L.X., and C.-Q.C. conducted experiments. C.-L.X, Z.-H.H., and Q.-X.Y. analyzed the data. T.-W.C. and C.-L.X. wrote the article, while critical revision of the publication was performed by all authors.

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