Fitoterapia xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Fitoterapia

journal homepage: www.elsevier.com/locate/fitote

Monoamine oxidases inhibitors from *Colvillea racemosa*: Isolation, biological evaluation, and computational study

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ARTICLE INFO

Keywords:
Colvillea
Dihydrochalcones
Colveol
Monoamine oxidase
Docking

ABSTRACT

Bioassay-guided fractionation and chemical investigation of *Colvillea racemosa* stems led to identification of two new *α, β*-dihydroxydihydrochalcones, colveol A (**1**) and colveol B (**2**) along with fifteen known compounds. The structures were elucidated via interpretation of spectroscopic data. The absolute configurations of the dihydrochalcones **1** and **2** were assigned by a combination of chemical modification and electronic circular dichroism data. The isolated compounds were evaluated for their inhibition activity toward recombinant human monoamine oxidases (rhMAO-A and -B). Compound **1** demonstrated preferential inhibition against hMAO-A isoenzyme (IC_{50} 0.62 μM, $SI_{A/B}$ 0.02) while *S*-naringenin (**13**) and isoliquiritigein (**15**) demonstrated preferential hMAO-B inhibition (IC_{50} 0.27 and 0.51 μM, $SI_{A/B}$ 31.77 and 44.69, respectively). Fisetin (**11**) showed inhibition against hMAO-A with IC_{50} value of 4.62 μM and no inhibitory activity toward hMAO-B up to 100 μM. Molecular docking studies for the most active compounds were conducted to demonstrate the putative binding modes. It suggested that **1** interacts with Gln215, Ala111, Phe352, and Phe208 amino acid residues which have a role in the orientation and stabilization of the inhibitor binding to hMAO-A, while *S*-naringenin (**13**) occupies both entrance and substrate cavities and interacts with Tyr326, a critical residue in inhibitor recognition in hMAO-B.

1. Introduction

Monoamine oxidases (MAOs) are mitochondrial flavoenzymes that catalyze oxidative deamination of monoaminergic neurotransmitters and dietary monoamines [1]. In mammalian cells, gene coded biosynthesis results in two separate MAO isoforms. Serotonin, adrenaline, and noradrenaline are metabolized by MAO-A isoenzyme, while *β*-phenylethylamine and benzylamine are metabolized by MAO-B isoenzyme, whereas, dopamine and *p*-tyramine are common nonselective substrates for both isoenzymes. Hence the MAO-A isoform is a pharmacological target for the treatment of depression, anxiety, and major depressive disorders, while the MAO-B isoform is a target for the therapy of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases [1]. A plethora of natural products have been reported to inhibit MAOs, such as flavonoids which exhibit desired pharmacological effects on central nervous system due to their potential to pass the blood brain barrier [2].

Colvillea racemosa Bojer ex Hook (Colville's glory tree, whip tree) belongs to a monotypic genus of the family Leguminosae and is native to Madagascar [3]. The plant is cultivated as an ornamental in some tropical countries and is used locally as a decorative shade tree. Its wood is used for construction purposes and its trunks are hollowed out to make canoes [4]. Previous chemical and biological studies on the plant are quite limited. The antibacterial potentials of the acetone extract of *C. racemosa* plant were reported [5], while 6-methoxy-7-hydroxy bis-coumarin has been reported from the plant seeds [6]. Our preliminary pharmacological evaluation revealed that the ethanol extract of *C. racemosa* stems displayed significant human MAO-A and -B (hMAO-A and -B) inhibition (Table 2). Therefore, a series of extraction, separation, and purification procedures were performed on *C. racemosa* stems, which resulted in the isolation and characterization of two new *α,β*-dihydroxydihydrochalcones (**1** and **2**) and fifteen known

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https://doi.org/10.1016/j.fitote.2017.11.009
Received 11 October 2017; Received in revised form 9 November 2017; Accepted 13 November 2017

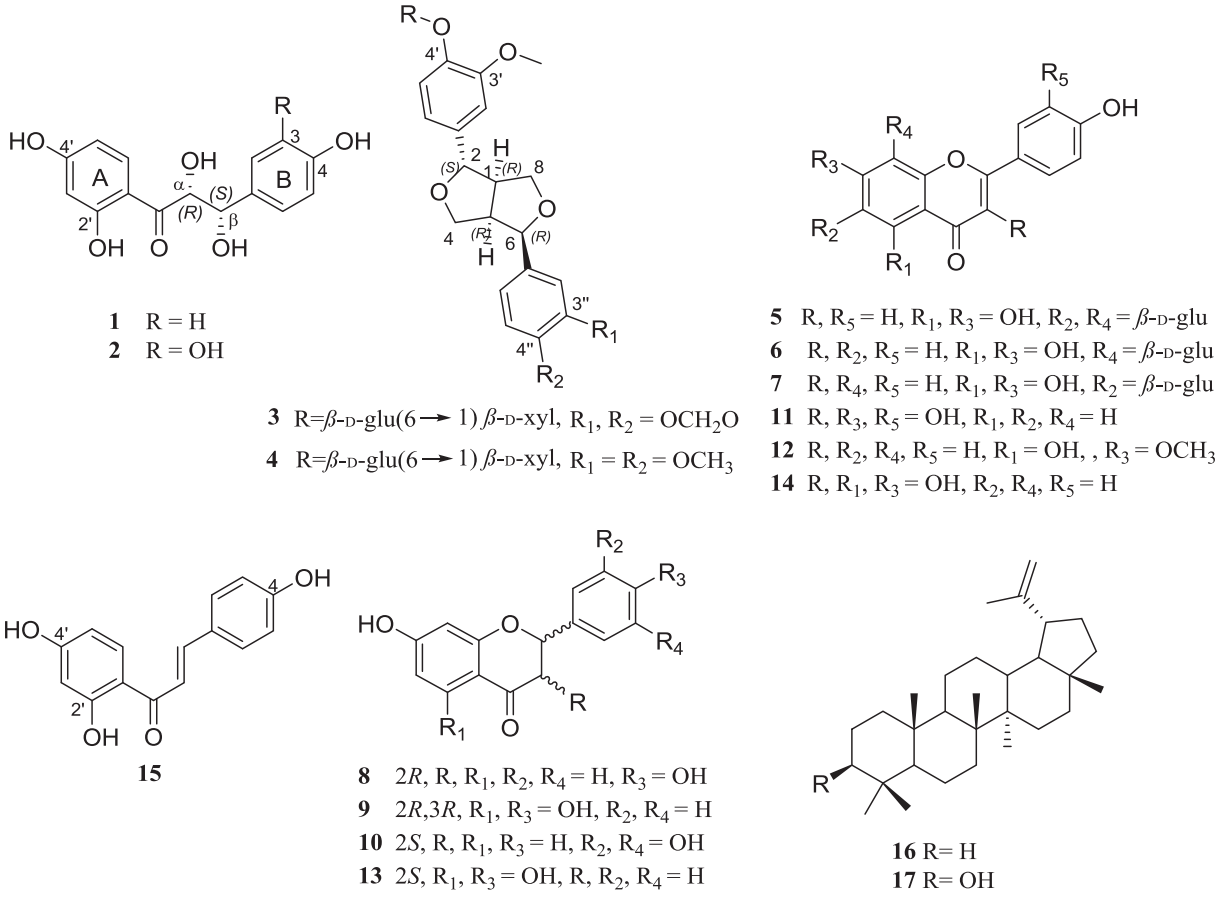

Fig. 1. Chemical structures of isolated compounds (1–17) from *Colvillea racemosa* stems.

compounds, including lantibeside C (**3**) [7], lantibeside (**4**) [7], vicenin-2 (**5**) [8], vitexin (**6**) [9], isovitexin (**7**) [10], *R*-liquiritigenin (**8**) [11,12], *R,R*-aromadendrin (**9**) [13,14], 2*S*-7,3′,5′-trihydroxyflavanone (**10**) [12,15], fisetin (**11**) [16], genkwanin (**12**) [17], *S*-naringenin (**13**) [12,18], kaempferol (**14**) [19], isoliquiritigenin (**15**) [19–21], lup-20(29)-ene (**16**) [22], and lupeol (**17**) [23] (Fig. 1). Herein, we describe the isolation, structural elucidation and hMAOs inhibition activity of the isolated compounds. The study was further extended to molecular docking analysis and determination of the putative mode of binding of the active compounds to hMAO-A and -B isoenzymes.

2. Results and discussion

A bioassay guided fractionation procedure of the EtOH extract of *C. racemosa* stems using various chromatographic techniques (see Experimental Section), afforded compounds **1–17**. The structures of compounds **3–17** were established by comparison of their observed and reported data (S1, Supplementary data). Compound **1**, obtained as yellow amorphous powder, was assigned the molecular formula $C_{15}H_{14}O_6$ based on HRESIMS data *m/z* 273.0762 $[M + H - H_2O]^+$, calcd for $C_{15}H_{13}O_5$, 273.0763. The ^1H and ^{13}C NMR spectroscopic data (Table 1) of **1** showed two doublets for two aliphatic oxygenated methines of AB spin system at δ_H 4.51 and 4.99 (J_{AB} = 11.8 Hz) and a carbonyl carbon at δ_C 194.4, suggesting the presence of a –COCH(OH)-CH(OH)- subunit [24], which confirmed by HMBC ^3J correlations between δ_H 4.99 (H-*β*) and δ_C 194.4 (CO) and ^2J correlations between δ_H 4.51 (H-*α*) and both δ_C 194.4 (CO) and δ_C 85.4 (C-*β*) and between δ_H 4.99 (H-*β*) and δ_C 74.5 (C-*α*), whereas the ABX spin system of three mutually coupled aromatic protons at δ_H 6.31 (1H, d, *J* = 2.0 Hz, H-3′), δ_H 6.52 (1H, dd, *J* = 2.0, 8.7 Hz, H-5′), and δ_H 7.72 (1H, d, *J* = 8.7 Hz, H-6′) and signals of two oxygenated sp^2-hybridized carbons at δ_C 165.2 (C-2′) and δ_C 167.6 (C-4′) indicate a dioxygenated A-ring, where the coupling pattern is compatible with a 2′,4′-dioxygenation of this ring and this is corroborated by the HMBC cross peak pattern of H-6′ at δ_H 7.72 with the carbonyl carbon at δ_C 194.4, and the oxygenated carbons at δ_C 165.2 (C-2′) and δ_C 167.6 (C-4′) (Table 1). The AA′XX′ spin system [δ_H 6.84 (2H, d, *J* = 8.5 Hz, H-3/H-5) and δ_H 7.37 (2H, d, *J* = 8.5 Hz, H-2/H-6)] of the B-ring and oxygenated sp^2-hybridized carbon at δ_C

Table 1
^1H and ^{13}C NMR data for (*αR,βS*)-*α,β*,4,2′,4′-pentahydroxydihydrochalcone (1) and (*αR,βS*)-*α,β*,3,4,2′,4′-hexaahydroxydihydrochalcone (2).[a]

	1			2	
No.	δ_C, type	δ_H (*J* in Hz)	HMBC[b]	δ_C, type	δ_H (*J* in Hz)
1	129.5, C	–	–	130.4, C	–
2	130.4, CH	7.37, d (8.5)	4,6, *β*	115.8, CH	6.99, d (1.6)
3	116.1, CH	6.84, d (8.5)	1, 4, 5	146.3, C	–
4	159.1, C	–	–	147.0, C	–
5	116.1, CH	6.84, d (8.5)	1, 3, 4	116.0, CH	6.80, d (8.0)
6	130.4, CH	7.37, d (8.5)	2, 4, *β*	120.9, CH	6.85, dd (1.6,8.0)
α	74.5, CH	4.51, d (11.8)	1, *β*, CO	74.4, CH	4.42, d (11.6)
β	85.4, CH	4.99, d (11.8)	2, 6,*α*, CO	85.4, CH	4.94, d (11.9)
1′	113.1, C	–	–	114.8, C	–
2′	165.2, C	–	–	165.6, C	–
3′	103.8, CH	6.31, d (2.0)	1′, 2′, 4′	104.5, CH	6.16, d (2.1)
4′	167.6, C	–	–	165.6, C	
5′	112.4, CH	6.52, dd(2.0, 8.7)	1′, 3′	110.9, CH	6.41, dd (2.2, 8.9)
6′	130.0, CH	7.72, d (8.7)	2′, 4′, CO	129.8, CH	7.64, d (8.7)
C = O	194.4	–	–	193.8	–

[a] Spectra run at 400 MHz, (^1H) and 100 MHz (^{13}C) in CD_3OD.
[b] HMBC correlations are from proton (s) stated to the indicated carbon.