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CHEMICAL CONSTITUENTS AND TYROSINASE INHIBITORY ACTIVITY OF AQUEOUS FRACTION OF THE LEAVES OF *MORUS ALBA* LINN. FROM VIETNAM

Loi Vu Duc [*1], Tung Bui Thanh [1], Huong Le Thi Thu [1] and Bach Nguyen Van [2]

School of Medicine and Pharmacy [1], Vietnam National University, Hanoi, Vietnam.
Vietnam Military Medical University [2], Vietnam.

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Correspondence to Author:
Loi Vu Duc

School of Medicine and Pharmacy, Vietnam National University, No.144 Xuan Thuy Street, Cau Giay, Hanoi, Vietnam.

E-mail: ducloi.smpvnu@gmail.com

ABSTRACT: The mulberry has been widely cultivated to feed silkworms. The leaves of mulberry have been used in traditional medicine as an analgesic, antitussive, cathartic, diuretic. In this study, we have isolated three compounds (LC1-3) by chromatographic methods from the mulberry leaves (*Morus alba* L.) collected in Thai Nguyen province, Vietnam. These compounds were identified as Kaempferol-3, 7-di-O-α-L-rhamnopyranoside (LC1), 7, 4'- dihydroxy-5, 3'- dimethoxyflavone (LC2), (S)-5, 5', 7-trihydroxy-2', 4'-dimethoxy-6-methylflavanone (LC3). Their structures were elucidated by spectroscopic methods, including MS and NMR. Compound LC3 was isolated from mulberry leaves for the first time. These compounds were evaluated the tyrosinase inhibitory activity *in-vitro*. Our data showed that compound LC3 has potential tyrosinase inhibitory effects with IC_{50} values of 15.48 ± 2.96 µg/mL.

INTRODUCTION: In East Asia, whitening skin and protection against skin darkening are considered desirable by some for cosmetic purposes. Because tyrosinase plays a critical regulatory role in melanin biosynthesis, many tyrosinase inhibitors that suppress melanogenesis have been actively studied to develop preparations for skin whitening by many cosmetic companies. Plant extracts having an inhibitory effect on enzyme tyrosinase may be a good choice for this purpose because of their relatively lower side effects. In cosmetic preparations, many plant extracts such as Mulberry (*Morus alba* Linn.) leaves have been used as whitening agent [1].

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Mulberry (*Morus alba* L., a family of Moraceae) is a native plant in Vietnam. It leaves have long been used in traditional medicine for the treatment of several diseases such as fever, protect the liver, improve eyesight, strengthen joints, facilitate discharge of urine and lower blood pressure [2]. Leaves of mulberry species have been widely consumed as antihyperglycemic nutraceutical foods for patients with diabetes mellitus [3].

Previous studies reported that *Morus alba* L. had many pharmacological activities, including anti-hyperglycemic [4], anti-oxidant and antiglycation activities [5]. Phytochemical studies of this plant mainly showed the presence of flavonoids, anthocyanins, anthroquinones, triterpenes, tannins, phytosterols, sitosterols, benzofuran derivatives, morusimic acid, oleanolic acid, alkaloids, steroids, saponins and phenolic compounds [6, 7]. However, in Vietnam, there have been very few studies on this species. Therefore, this paper reports on the phytochemical investigation of the leaves of *Morus*

alba Linn. and the evaluation of the tyrosinase inhibitory activity of isolated compounds.

MATERIALS AND METHODS:

Plant Material: The leaves of *Morus alba* L. were collected in Thai Nguyen province during 6/2016 and authenticated by Dr. Vu Duc Loi, Department of Pharmacognosy and Traditional Medicine, School of Medicine and Pharmacy, Vietnam National University, Hanoi (SMP-VNU). A voucher specimen has been (No. SMP-2017-0016) deposited at the Herbarium of SMP-VNU.

General Experimental Procedures: General experimental procedures were performed as the previous study with some modifications 8. Melting points were measured on Mikroskopheiztisch PHMK-50 (VEB Waegetechnik Rapido, Germany). The FT-IR spectra were recorded on an IMPACT-410 FT-IR spectrometer (CARL ZEISS JENA). The NMR [1H (500 MHz), 13C (125 MHz), and DEPT-90 and 135 MHz)] spectra were recorded on an AVANCE spectrometer AV 500 (Brucker, Germany) in the Institute of Chemistry, Vietnam Academy of Science and Technology (VAST). Chemical shifts were reported in ppm downfield from TMS with J in Hz.

Electrospray Ionization Mass Spectra (ESI-MS) were recorded on a Varian Agilent 1100 LCMSD mass spectrometer. Optical rotation was measured on WXG-4 disc polarimeter. Analytical TLC was performed on Kieselgel 60 F254 (Merck) plates (silica gel, 0.25 mm layer thickness) and RP-18 F254 (Merck) plates (0.25 mm layer thickness). Spots were visualized using ultraviolet radiation (at 254 and 365 nm) and by spraying with 10% H2SO4, followed by heating with a heat gun. Column chromatography was performed on silica gel (70-230 and 230 - 400 mesh, Merck). Organic solvents were of analytical grade. Optical densities were read on an ELISA plate reader (Bio-rad)

Extraction and Isolation: The extraction and isolation procedure was performed as the previous study with some modifications 9. Mulberry leaves (6.0 kg) was dried, powdered and then extracted with methanol (48 h x 4 times). The resulting extract was concentrated under reduced pressure using rotary vacuum evaporator to get crude extract (520 g). The methanol extract was dissolved in water and subjected to liquid-liquid partitioning (3 times) using n-hexane, ethyl acetate, yielding 60.0 g (A) and 75.0 g (B) of residue, respectively. The aqueous fraction was concentrated to yield 42.0 g of residue (C). The aqueous residue (30 g) was suspended in H2O and poured into a Diaion HP-20 column which was stabilized with H2O. The column was eluted with methanol/H2O (1/4 → 1/1, v/v) to obtain 4 fractions (C1 → C4). Fraction C3 (9.5 g) was further separated over YMC column and eluted with Methanol/H2O (2:1, v:v), to yield four sub-fractions (C3.1→C3.3).

Fraction C3.1 (1.2 g) was chromatographed on revert phase column (acetone/H2O, 3/5, v/v), yielding LC1 (30 mg). Fraction C3.2 (1.6 g) purified by silica gel column and eluted with n-hexane/acetone (5/1, v/v) to yield LC2 (21 mg). Fraction C3.3 (1.4 g) was submitted to chromatography on YMC-RP-18 column, eluted with acetone/H2O (1/1, v/v), yielding LC3 (19 mg).

Assay of the Tyrosinase Activity: The assay was performed as described by Kubo with slight modifications [17]. Pre-incubation mixtures consisted of 1.0 ml of 1/15 M phosphate buffer (pH 6.8), 10 µL of the sample solution and 10 µL of the aqueous solution of the enzyme tyrosinase (1 mg/mL). The mixture was pre-incubated at 25 °C for 5 min. Then, 1.0 ml of 1.5 mM L-DOPA was added, and the reaction was monitored at 475 nm for 5 min. The percent inhibition was calculated manually using the following equation:

$$\% \text{ Inhibition} = \quad Ac - At \,/\, Ac - Ao \times 100$$

Where, Ac represents the difference in the absorbance of the control sample between an incubation time of 0.5 and 1.0 min and At represents the difference in the absorbance of the test sample between the incubation time of 0.5 and 1.0 min, and Ao represents the absorbance of the blanks. Each result is the mean of three concurrent readings. Kojic acid was used as a positive standard. The effects of compounds were expressed by IC_{50} values. IC_{50} is defined as the concentration of inhibitor that reduces enzyme activity by 50%.

RESULTS AND DISCUSSION:

Chemical Structure Elucidation:

LC1: Kaempferol-3,7-di-*O*-α-L-rhamnopyranoside: Light yellow powder. UV λ_{max} (MeOH): 265, 328, 343 nm. ESI-MS *m/z*: 577.5 $[M-H]^-$. ^{1}H-NMR

(500 MHz, CD_3OD): δ 6.45 (1H, d, *J* = 2.0 Hz, H-6), 6.77 (1H, d, *J* = 2.0 Hz, H-8), 7.79 (1H, d, *J* = 9.0 Hz, H-2'), 6.92 (1H, d, *J* = 8.5 Hz, H-3'), 6.92 (1H, d, *J* = 8.5 Hz, H-5'), 7.79 (1H, d, *J* = 9.0 Hz, H-6'), 5.30 (1H, s, H-1"), 3.16 (1H, m, H-2"), 3.43 (1H, m, H-3"), 3.31 (1H, m, H-4"), 3.31 (1H, m, H-5"), 0.81(3H, d, *J*= 5.5 Hz, H-6"), 5.54 (1H, s, H-1'''), 3.16 (1H, m, H-2'''), 3.16 (1H, m, H-3'''), 3.31 (1H, m, H-4'''), 3.63 (1H, m, H-5'''), 1.13 (3H, d, *J* = 6,5Hz, H-6'''). ^{13}C-NMR (125 MHz, CD_3OD): δ 157.89 (C-2), 134.66 (C-3), 178.02 (C-4), 161.80 (C-5), 99.52 (C-6), 161.80 (C-7), 94.70 (C-8), 156.22 (C-9), 105.88 (C-10), 120.48 (C-1'), 130.79 (C-2'), 115.48 (C-3'), 160.19 (C-4'), 115.48 (C-5'), 130.49 (C-6'), 101.96 (C-1''), 70.76 (C-2''), 70.31 (C-3''), 71.23 (C-4''), 71.23 (C-5''), 17.50 (C-6''), 98.53 (C-1'''), 70.76 (C-2'''), 70.76 (C-3'''), 71.23 (C-4'''), 70.31 (C-5'''), 17.94 (C-6''').

The ESI-MS data showed the ion peak $[M-H]^-$ at *m/z* 577.5, which matched with the molecular formula of LC1 as $C_{27}H_{30}O_{14}$. The ^{1}H-NMR spectrum of LC1 showed *meta*-coupled aromatic protons (A-ring) at δ_H 6.45 (1H, d, *J* = 2.0 Hz, H-6) and δ_H 6.77 (1H, d, *J* = 2.0 Hz, H-8),; *ortho*-coupled aromatic protons (B-ring) at δ_H 7.79 (2H, d, *J* = 9.0 Hz, H-2', 6') and δ_H 6.92 (2H, d, *J* = 8.5 Hz, H-3', 5'), suggesting the structure of kaempferol aglycone to LC1. The presence of two rhamnose moieties was also suggested by two anomer proton signals at δ_H 5.30 (1H, s, H-1") and δ_H 5.54 (1H, s, H-1'''), two methyl group at δ_H 0.81(3H, d, *J*= 5.5 Hz, H-6") and 1.13 (3H, d, *J* = 6,5Hz, H-6'''). The ^{13}C-NMR and DEPT spectra together with ESI-MS supported the presence of one flavonoid nucleus and two hexose units in LC1. An HMBC experiment performed with LC1, showed correlations between the anomeric proton at δ_H 5.30 (1H, s, H-1") and the quaternary carbon atom at δ_C 134.66 (C_3); the proton at δ_H 5.54 (1H, s, H-1''') and the carbon atom at δ_C 161.80 (C_7), indicating the sites of glycosidation. By comparison with previously reported literature [10, 11], the structure of LC1 was deduced as Kaempferol-3, 7-di-O-α-L-rhamnopyranoside.

LC2: 7,4'-dihydroxy-5,3'-dimethoxyflavone: Yellow powder. R_f = 0.45 (chloroform / methanol / H_2O, 10 / 1.5 / 0.01, *v/v*), ESI-MS (positive) *m/z:* 315 $[M+H]^+$ ^{1}H-NMR (500MHz, CD_3OD) :δ 7.48 (1H, dd, *J* = 2.0, 8.5 Hz, H-6'), 7.45 (1H, d, *J* = 2.0 Hz, H-2'), 6.94 (1H, d, *J* = 8.0 Hz, H-5'), 6.58 (1H, d, *J* = 2.0 Hz, H-8), 6.57 (1H, s, H-3), 6.43 (1H, d, *J* = 2.0 Hz, H-6), 3.97 (3H, s, 3'-OCH_3), 3.91 (3H, s, 5-OCH_3).

LC2 was also obtained as a yellow powder, and its molecular formula was established as $C_{17}H_{14}O_6$ from its MS spectral data that showed $[M+H]^+$ ion at *m/z* 315. The ^{1}H NMR spectrum of LC2 showed the presence of three *meta* coupled aromatic doublets at δ 6.43 (1H, d, *J* = 2.0 Hz, H-6), 6.58 (1H, d, *J* = 2.0 Hz, H-8) and 7.45 (1H, d, *J* = 2.0 Hz, H-2'), one *ortho* coupled aromatic doublet at δ 6.94 (1H, d, *J* = 8.0 Hz, H-5'), one doublet of doublets at δ 7.48 (1H, dd, *J* = 2.0, 8.5 Hz, H-6') corresponding to a *ortho* and *meta* coupled aromatic proton, and a singlet at 6.57 (1H, s, H-3); characteristic for a 5,7,3',4'-tetrasubstituted flavone.

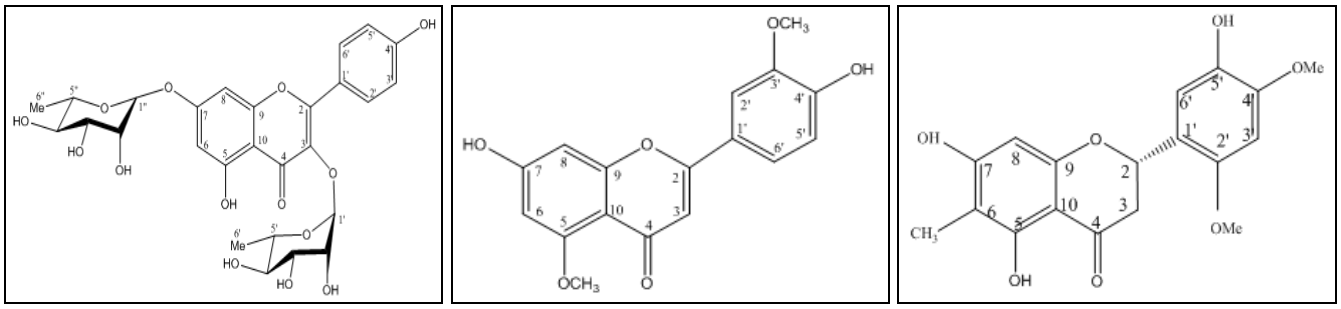
Also, the ^{1}H-NMR showed the presence of two methoxy groups at δ 3.97 (3H, s, OCH_3), 3.91 (3H, s, OCH_3). The NOESY correlations between 3'-OCH_3 (δ_H3.97) / H-2' (δ_H7.46) and between 5-OCH_3(δ_H 3.91)/H-6(δ_H 6.37) indicated the position of two methoxy groups. Based on the spectroscopic evidence and comparison with literature values [12, 13, 14] LC2 was determined to be 7,4'-dihydroxy-5,3'-dimethoxyflavone.

LC3: (S)-5,5',7-trihydroxy-2',4'-dimethoxy-6-methylflavanone: Yellow powder. R_f = 0.5 (chloroform/methanol/H_2O, 5/ 1/ 0.05, *v*/v), $[\alpha]_D^{25}$=–88.0(*c* 0.1, MeOH). CD(*c* 1.4×10^{-3} M, MeOH): λ_{max} (Δe) nm 295(–13.7), 345(+2.1). IRn$_{max}$ (KBr): 3393, 1637, 1516, 1303, 1158 cm^{-1}. HR-ESI-MS *m/z:* 347.1109 $[M+H]^+$ (calcd.347.1130 for $C_{18}H_{19}O_7$). ^{1}H-NMR (500 MHz, CD_3OD): δ 7.00 (1H, s, H-6'), 6.69 (1H, s, H-3'), 5.97 (1H, s, H-8), 5.60 (1H, dd, *J* = 3.0, 13.0 Hz, H-2), 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 2.95 (1H, dd, *J* = 13.0, 17.0 Hz, H_b-4), 2.68 (1H, dd, *J* = 3.5, 17.5 Hz, H_a-4), 1.97 (3H, s, CH_3). ^{13}C-NMR (125 MHz, CD_3OD): δ 75.2 (C-2), 43.4 (C-3), 198.0 (C-4), 162.6 (C-5), 105.3 (C-6), 166.1 (C-7), 95.2 (C-8), 162.6 (C-9), 103.0 (C-10), 120.5 (C-1'), 151.2 (C-2'), 98.7 (C-3'), 149.5 (C-4'), 141.4 (C-5'), 114.5 (C-6'), 6.9 (6-CH_3), 56.9(2'-OMe), 56.6 (4'-OMe).

LC3 was isolated as a yellow powder. LC3 was assigned the molecular formula, $C_{18}H_{18}O_7$, based

on the HR-ESI-MS spectra of the compound obtained in the positive ion mode (*m/z* 307,0810 $[M+H]^+$.calcd for $C_{18}H_{19}O_7$). The ^{13}C-NMR and DEPT spectrum showed 18 carbon signals including twelve aromatic carbons (δ_C 103.0-166.1), one ketone group (δ_C 198.0), one oxygenated methine group (δ_C 75.2), one methylene group (δ_C 43.4), two methoxy groups (δ_C 56.9, 56.6), one methyl group (δ_C 6.9).

The ^{1}H-NMR spectrum showed two methoxy group signals [δ_H 3.90, 3.83 (each 3H, s)], three singlet aromatic proton signals [δ_H 7.00, 6.69, 5.97 (s)], and one methyl singlet signal (δ_H 1.97). Two geminal protons at δ_H 2.95 (1H, dd, *J* = 13.0, 17.0 Hz, H_b-4), 2.68 (1H, dd, *J* = 3.5, 17.5 Hz, H_a-4) together with proton δ_H 5.60 (1H, dd, *J* = 3.0, 13.0 Hz, H-2) suggested LC3 was a flavanone.



LC1 **LC2** **LC3**

FIG. 1: STRUCTURE OF COMPOUND LC1-LC3

The HMBC correlations between H-6' [δ_H 7.00 (s)] and C-2 (δ_C 75.2), C-1' (δ_C 120.5), C-5' (δ_C 141.4), C-2' (δ_C 151.2), C-4' (δ_C 149.5), and between H-3' [δ_H 6.69 (s)] and C-1' (δ_C 120.5), C-5' (δ_C 141.4), C-2' (δ_C 149.5), C-4' (δ_C 151.2) indicated B-ring was 1,2,4,5-tetrasubstituted benzene. The HMBC correlation between two proton signals of methoxy groups δ_H 3.90 (3H, s, OCH_3), 3.83 (3H, s, OCH_3) and carbon C-2' (δ_C 149.5), C-4' (δ_C 151.2) revealed the location of methoxy groups at C-2' and C-4'. The other substituted group was hydroxy at C-5'. The position of a methyl group at C-6 was suggested by the HMBC correlations between methyl singlet signal [1.97 (3H, s)] and two oxygenated aromatic carbons C-5 (δ_C 162.6), C-7 (δ_C 166.1).

The absolute configuration of the asymmetric center C-2 was confirmed as 2*S* by comparison of its circular dichroism data with previous literature [15]. Based on the above deductions and comparing spectral data to reference [15, 16]. LC3 was deduced as (S)-5, 5', 7-trihydroxy-2', 4'-dime- thoxy-6-methylflavanone.

Tyrosinase Inhibitory Activities of Isolated Compounds: The IC50 value of acid kojic was close to that from previous studies [17, 18]. Among three isolated compounds, only (*S*)-5, 5', 7-trihydroxy-2', 4'-dimethoxy-6 -methylflavanone (LC3) showed potential tyrosinase inhibitory effects. Therefore, (*S*)-5, 5', 7-trihydroxy-2', 4'-dimethoxy-6-methylflav -anone is worthy of further studies as potential tyrosinase inhibitors.

TABLE 1: INHIBITORY EFFECTS OF ISOLATED COMPOUNDS (LC1, LC2, LC3) ON TYROSINASE

Concentration (µg/mL)	% Inhibition		
	LC1	LC2	LC3
1.95	11.2 ± 2.4	11.8 ± 1.2	11.8 ± 2.6
3.91	15.6 ± 1.5	19.7 ± 1.5	27.2 ± 2.3
7.81	21.3 ± 1.6	23.1 ± 1.7	36.4 ± 1.9
15.63	31.5 ± 2.1	30.9 ± 1.8	49.2 ± 1.8
31.25	36.1 ± 1.7	40.9 ± 1.3	63.8 ± 2.7
62.50	47.2 ± 1.6	55.1 ± 2.8	72.4 ± 2.4
125.00	58.1 ± 2.9	66.7 ± 1.6	79.1 ± 1.2
250.00	64.4 ± 2.3	78.1 ± 2.5	91.3 ± 1.7
500.00	76.9 ± 1.4	86.9 ± 1.9	96.3 ± 1.8
1000.00	86.2 ± 1.5	90.2 ± 1.7	98.6 ± 1.8

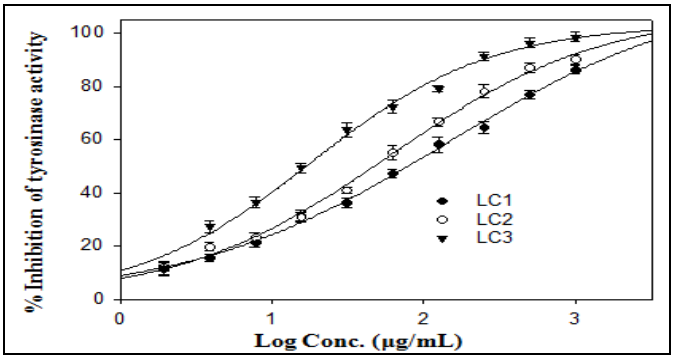


FIG. 2: GRAPH SHOWING TYROSINASE INHIBITION (%) PLOTTED AGAINST LOG CONCENTRATIONS OF ISOLATED COMPOUNDS. The IC_{50} values of isolated compounds were calculated on a graph and converted from log [µg/mL] to µg/mL.

TABLE 2: IC_{50} OF ISOLATED COMPOUNDS ON TYROSINASE

Sample	Log IC_{50}	IC_{50} (µg/mL)
Acid kojic	0.81	6.45 ± 0.42
LC1	1.85	70.79 ± 4.58
LC2	1.67	46.77 ± 3.51
LC3	1.19	15.48 ± 2.96

CONCLUSION: From the mulberry leaves (*Morus alba* Linn.) collected in Thai Nguyen province, three compounds (LC1-3) were isolated by chromatographic methods. Based on spectroscopic analyses and by spectral comparison with published literature, the isolated compounds were identified as Kaempferol-3, 7-di-O-α-L-rhamnopyranoside (LC1), 7, 4'-dihydroxy-5,3'-di-methoxyflavone (LC2), (*S*)-5,5',7-trihydroxy-2', 4'-dimethoxy-6-methylflavanone (LC3). This is the first report on the isolation of LC3 from Mulberry leaves. Among three isolated compounds, LC3 also showed significant tyrosinase inhibitory effects, with IC_{50} values of 15.48 ± 2.96 µg/mL.

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CONFLICT OF INTEREST: These authors have declared that there is no conflict of interest.

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