Two new methoxylated flavones isolated from *Casimiroa edulis* La Llave and their MMP-9 inhibitory activity

Manami Haba\(^a\), Naohito Abe\(^a\), Tetsuro Kamiya\(^b\), Nagisa Mizuno\(^b\), Satoshi Okubo\(^c\), Takao Yamamura\(^c\), Hirokazu Harab and Masayoshi Oyama\(^a\)

\(^a\)Laboratory of Pharmacognosy, Gifu Pharmaceutical University, Gifu, Japan; \(^b\)Laboratory of Clinical Pharmaceutics, Gifu Pharmaceutical University, Gifu, Japan; \(^c\)The Yamashina Botanical Research Institute, Nippon Shinyaku Co., Ltd., Kyoto, Japan

**ABSTRACT**

*Casimiroa edulis* La Llave is known to contain unusual 5,6-dimethoxyflavones bearing a variously oxygenated B-ring. Phytochemical investigation of the leaves and the roots of *C. edulis* achieved the isolation of two new methoxylated flavones, named casedulones A (1) and B (2), together with 12 known analogues. Their unique structures were established with the aid of spectral analyses and total syntheses. Pre-treatment with 20 µM of 1 and 2 suppressed MMP-9 expression in LPS-mediated THP-1 cells, indicating that the characteristic flavonoids in *C. edulis* could be potential anti-angiogenics for cancer prevention.

1. Introduction

*Casimiroa* La Llave, classified into Zanthoxyloideae of Rutaceae family, consists of 10 species and distributes from Mexico to Central America (Esposito et al. 2011; WFO: World Flora Online 2022). *C. edulis* La Llave, an evergreen tree ranging from 3 to 12 m tall, is well-known to bear edible fruits called ‘white sapote’ that is now harvested in Wakayama and Okinawa prefectures, Japan. Its seeds have been handed down as a Mexican folk medicine for the treatment of insomnia, arthritic pain, and hypertension (Kincl et al. 1956); thus, early phytochemical studies were focused on the seeds to yield a variety of chemical constituents such as alkaloids (Aebi 1956; Meisels and Sondheimer 1957), limonoids (Sondheimer et al. 1959), and flavonoids (Dreyer and Bertelli 1967). The subsequent studies revealed the occurrence of furocoumarins in the...
leaves (Rizvi et al. 1985; Nagai et al. 2014); whereas there have been few reports of the phytochemicals in the roots (Maiti et al. 2007; Tun et al. 2020).

We have unveiled anticarcinogenic natural products from the Zanthoxyloideae as well, e.g. quinolinone-coumarin conjugates (Nakashima et al. 2012a), guaiane-type sesquiterpenes (Nakashima et al. 2012b) and prenylated acetophenone dimers (Oyama et al. 2003) from Melicope denhamii (Seem.) T.G. Hartley and Acronychia trifoliolata Zoll. & Moritzi. Based on subsequent flavonoid research, C. edulis is regarded as a prominent resource containing rare flavones with unique substitution patterns like zapotin (5,6,2’6’-tetramethoxyflavone) that is attracting attention as a potential cancer preventive agent (Maiti et al. 2007). On the other hand, we have pharmacologically examined matrix metalloproteinases (MMPs) that progress the angiogenic process by remodelling the basement membrane in tumour-associated angiogenesis (Weis and Cheresh 2011; Kamiya et al. 2019).

In the current study, we dealt with the isolation of 14 flavonoids including two new methoxylated flavones, named casedulones A (1) and B (2), from the leaves and/or the roots of C. edulis. Herein described are the structure elucidation and the total syntheses of 1 and 2, as well as the evaluation with the lipopolysaccharide (LPS)-mediated MMP-9 expression in human acute monocytic leukaemia (THP-1) cells for finding out anticancer products.

2. Results and discussion

Dried leaves (1.4 kg) and roots (251 g) of C. edulis were pulverized and extracted with CHCl₃-MeOH (1:1, v/v) solution at room temperature to afford 150 g and 32 g of the crude extracts, respectively. Successive chromatographic operations yielded casedulone A (1), 5,6-dimethoxyflavone (3) (Dominguez et al. 1972), 5,6,2’-trimethoxyflavone (4) (Meyer et al. 1985), 5,6,3’-trimethoxyflavone (5) (Dreyer 1968; Mostafa et al. 2018), cerrosillin (5,6,3’5’-tetramethoxyflavone; 6) (Dominguez et al. 1972), zapotin (7) (Dreyer and Bertelli 1967), 5,6,2’3’,6’-pentamethoxyflavone (8) (Heneka et al. 2005; Budzianowski and Wollenweber 2007), 5,6,2’3’,4’-pentamethoxyflavone (9) (Garcia-Argaez et al. 2005), 5,6,2’3’,4’,6’-hexamethoxyflavone (10) (Meyer et al. 1985), 5,6,3’,4’-tetramethoxyflavone (11) (Parveen and Khan 1987), 5-hydroxy-6-methoxyflavone (12) (Wollenweber 1974), 5-hydroxy-6,2’-dimethoxyflavone (13) (Wollenweber et al. 1990) from the leaves extract; whereas casedulone B (2), 3–5, 8, 9 and 5-hydroxyflavone (14) (Matsugi et al. 2010) were identified from the roots extract (Figure 1).

2.1. Structure elucidation of the new compounds

Compound 1 was obtained as a pale-yellow amorphous powder. The molecular formula was established as C₁₇H₁₄O₅ based on HRESIMS (m/z 321.0735 [M + Na]+; calculated for C₁₇H₁₄O₅Na+: 321.0733). Its UV absorption at 270 and 303 nm, as well as the ¹³C-NMR signals at δC 164.3 (C-2), 108.0 (C-3) and 180.6 (C-4), suggested a flavone scaffold (Chirikdjian and Bleier 1971; Fossen and Andersen 2006). The ¹H-NMR spectrum (the chemical shifts are given in Table S1) exhibited an olefinic proton [δH 6.69 (1H, s)], a set of ortho-coupled aromatic protons [δH 7.56, 7.47 (1H each, d, J = 9.2 Hz)], four
mutually coupled aromatic protons assignable to a 3-oxygenated phenyl \([\delta_H 7.44 (1H, \text{br} \text{ d}, J = 7.9 \text{ Hz}), 7.39 (1H, \text{ m}), 7.36 (1H, t, \ J = 7.9 \text{ Hz}), 6.99 (1H, \text{ dd}, J = 7.9, 2.0 \text{ Hz})]\), and two methoxy groups \([\delta_H 3.89, 3.94 (3H \text{ each}, \text{ s})]\). Considering the substructures and the molecular formula, the presence of an additional hydroxy group was expected. The HMBC spectrum narrowed down the possibility of 1 to the following three structures: 3'-hydroxy-5,6-dimethoxyflavone, 3'-hydroxy-5,8-dimethoxyflavone or 3'-hydroxy-7,8-dimethoxyflavone; however, observed were no decisive HMBC correlations to corroborate the A-ring substitution pattern (Figure S1). As far as the previous flavonoids isolated from the *Casimiroa* species are concerned, the 5,6-dioxygenated substitution occurs rather common. Incidentally, we noticed that the NMR spectral data of 5 (5,6,3'-trimethoxyflavone) have never been assigned, and hence its complete assignments with the aid of 2D-NMR experiments were described in the supplementary material. When compared with the A-ring proton signals of 1 and those of 5 (Table S1), both H-7 (1: \(\delta_H 7.56\); 5: \(\delta_H 7.52\)) and H-8 (1: \(\delta_H 7.47\); 5: \(\delta_H 7.44\)) were closely resonated at each other, supporting 1 to be the 3'-demethyl isomer of 5. As there are few reliable NMR spectral data for the other two substitution patterns, it is worthy to note that synthesized isozapotin (5,8,2',6'-tetramethoxyflavone) exhibited the A-ring proton signals at \(\delta_H 6.72\) (H-6) and \(\delta_H 7.12\) (H-7) (Datta et al. 1969; Bouillant et al. 1971); on the other hand, 3'-hydroxy-7,8-dimethoxyflavone, recently isolated from *Galenia africana* L. (Aizoaceae), at \(\delta_H 7.76\) (H-5) and \(\delta_H 7.25\) (H-6) (Du et al. 2015). To the best of our knowledge, 1 is the second flavone in nature with 5,6,3'-trioxygenation pattern except 5. Therefore, we approached the total synthesis of the 3'-hydroxy-5,6-dimethoxyflavone (1j) starting from an acetophenone (1a) and a benzaldehyde (1e) as illustrated in Figure S3. The spectral data of the final product 1j (supplementary material) were identical to those of 1; and consequently, the structure of 1 was confirmed and named casedulone A.

![Figure 1. Chemical structures of the isolated compounds from *Casimiroa edulis*.](image-url)
Compound 2 was obtained as a pale-yellow amorphous powder. The molecular formula was established as C$_{19}$H$_{18}$O$_7$ based on HRESIMS (m/z 381.0937 [M+Na]$^+$; calculated for C$_{19}$H$_{18}$O$_7$Na$^+$: 381.0945). Its UV absorption observed at 244 and 326 nm, and a significantly higher resonance of H-3 [δ$_H$ 6.39 (1H, s)] in the $^1$H-NMR spectrum, indicating a 2',6'-dioxygenated flavone skeleton (Tanaka et al. 1986; Iinuma et al. 1987). The $^1$H-NMR spectrum also exhibited two sets of ortho-coupled aromatic protons [δ$_H$ 7.31, 7.24 (1H each, d, J = 9.2 Hz); δ$_H$ 7.05, 6.67 (1H each, d, J = 9.2 Hz)], four methoxy groups [δ$_H$ 4.00, 3.93, 3.76 and 3.73 (3H each, s)], and a hydroxy group [δ$_H$ 5.46 (1H, br s)] (Table S1). Accordingly, 2 was assumed to be either 5,6,2',3',6'- or 5,8,2',3',6'-pentaoxygenated flavone. A methoxy group substituted at both ortho-positions is empirically observed around δ$_C$ 61 instead of around δ$_C$ 56 in the $^{13}$C-NMR spectrum (Agrawal et al. 1989; Oyama et al. 2013). The methoxy carbon signals resonating at δ$_C$ 61.9, 61.8, 57.2 and 56.4 in 2 suggested that the first two methoxy groups were wedged into the cramped positions of C-5 and C-2' in the 5,6,2',3',6'-pentasubstituted framework. The HMQC spectrum revealed the $^{1}$J$_{HC}$ connection of the methoxy groups as follows: δ$_H$ 4.00/δ$_C$ 61.9, δ$_H$ 3.73/δ$_C$ 61.8, δ$_H$ 3.93/δ$_C$ 57.2 and δ$_H$ 6.67/δ$_C$ 56.4. In the NOE difference experiment, irradiation of the methoxy protons at δ$_H$ 3.93 (6-OMe) and δ$_H$ 3.76 (6'-OMe) enhanced the aromatic protons at δ$_H$ 7.31 (H-7) and δ$_H$ 6.67 (H-5') in the individual ortho-coupled spin systems, respectively. In addition, the HMBC spectrum provided the crucial $^{3}$J$_{HC}$ long-range correlations between δ$_H$ 7.31 (H-7)/δ$_C$ 147.9 (C-5), δ$_H$ 4.00 (MeO-5)/δ$_C$ 147.9 (C-5), δ$_H$ 6.67 (H-5')/δ$_C$ 115.7 (C-1') and δ$_H$ 6.39 (H-3)/δ$_C$ 115.7 (C-1'), indicating that the structure of 2 is a 3'-hydroxy-5,6,2',6'-tetramethoxyflavone (Figure S2). So far, little is known of the naturally occurring flavones with a 2',6',3',6'-tri-oxygenated B-ring aside from viscidulin III (5,7,3',6'-tetrahydroxy-8,2'-dimethoxyflavone) (Tomimori et al. 1984; Iinuma et al. 1985), its 2'-O-β-D-glucoside (Zhang et al. 1994), 5,7,3',6'-tetrahydroxy-6,8,2'-trimethoxyflavone (Zhang et al. 1997) and 8. Hence, we carried out the total synthesis of 2 in accordance with the proven reactions (Figure S4). Comparing the spectral data of 2 and those of the product 2i (supplementary material), 2 was deduced to be the same as 2i and named casedulone B.

On the basis of six plastid markers (atpB, ITS, trnL-trnF, rbcL, rps16 and matK), Appelhans et al. (2021) has proposed new classification in Rutaceae to divide the family into 3 clades and 6 subfamilies: clade A (subfam. Cneoroideae), clade B (subfams. Rutioideae, Amyridoideae, Haplophyloideae and Aurantioideae) and clade C (subfam. Zanthoxyloideae). Casimiroa was placed close to Skimmia Thunb., Orixa Thunb. and Dictamnus L., and they were recognized as an early branched lineage to the rest of clade C. From the chemotaxonomic point of view, Casimiroa and the above-mentioned genera commonly possess quinolone alkaloids; however, the latter contain no or very little polymethoxyflavones (Funayama et al. 2001; Gao et al. 2011; Epifano et al. 2015; Sun et al. 2016). As of now, 5,6-dimethoxygenated zapotin-type flavones are solely discovered from Casimiroa out of 154 rutaceous genera.

### 2.2. MMP-9 inhibitory activity

Anticancer screenings with cultured human promyelocytic leukaemia (HL-60) cells have led to the discovery of zapotin and its analogues identified in *C. edulis* as
cytotoxic principles (Mata-Greenwood et al. 2001; Maiti et al. 2007). According to the successive research, propounded is the idea that the apoptotic effect is associated with protein kinase C (PKC) signalling pathway (Toton et al. 2016). Meanwhile, a recent pharmacological study has demonstrated that nobiletin (5,6,7,8,3′,4′-hexamethoxyflavone), abundantly present in the citrus peels, suppressed MMP-2 and MMP-9 expressions via extracellular signal-regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) pathways in human osteosarcoma cells (Cheng et al. 2016). It is noteworthy that no clinical signs of toxicity were observed after administration of zapotin (40 mg/kg body weight/day) in rats for three days (Strawa et al. 2021). Likewise, the oral intake of nobiletin also did not lead to adverse side effects at the concentration of 40 μM for a period of 3 to 20 weeks (Goh et al. 2019). As far as we surveyed, polymethoxyflavones did not exhibit serious toxicity at the effective concentration.

The efficacy of zapotin-type polymethoxyflavones on the MMPs expression has never been investigated; therefore, we examined the effectiveness of the newly isolated 1 and 2 against mRNA and protein expression, and also enzymatic activity of MMP-9 in THP-1 cells elicited by LPS. As shown in Figure S5, 1 suppressed LPS-induced MMP-9 mRNA (A) and protein (B), and activity (C) by 79%, 77% and 84%, respectively. In addition, 2 suppressed them rather strongly by 97%, 95% and 95%, respectively.

3. Experimental

See supplementary material.

4. Conclusion

Twelve 5,6-dimethoxylated flavones (1 and 3–13) were isolated from the leaves of *Casimiroa edulis*, and seven related compounds (2–5, 8, 9 and 14) were isolated from the roots. The structures of two new zapotin-type flavonoids, named casedulones A (1) and B (2), were elucidated by comparison with the literature values and by means of 2D-NMR experiments. The new flavones were finally synthesized to confirm the structures. Both 1 and 2 inhibited MMP-9 mRNA and protein expression, and enzymatic activity in LPS-mediated THP-1 cells according to their pre-treatment. MMP-9 is involved in metastasis and infiltration of cancer cells; therefore, 1 and 2 could be seed compounds for developing cancer preventive agents.

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