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SHORT COMMUNICATION

Chemical constituents and their bioactivities from the fruits of *Vitex negundo* var. *cannabifolia*

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ABSTRACT

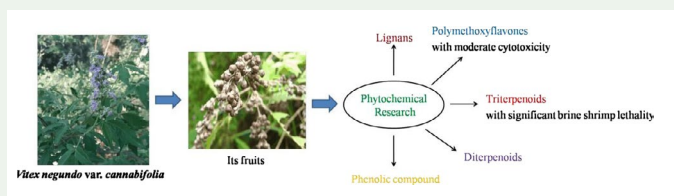
Phytochemical investigation of the fruits of *Vitex negundo* var. *cannabifolia* led to the isolation of 22 compounds (**1–22**). Their structures were elucidated mainly by spectroscopic analysis and comparison with the literature data. Among them, compounds **1** and **2** were two new artificial lignans. Primary bioassay showed that the polymethoxyflavones **9–12** displayed moderate-to-weak cytotoxicity against human HepG2 and rat C6 cell lines, while the triterpenoids **13–17** exhibited significant brine shrimp lethality with LC₅₀ values of 7.5–29.4 μM.

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Vitex negundo var. *cannabifolia*; chemical constituent; cytotoxicity; brine shrimp lethality



1. Introduction

The genus *Vitex* belonging to the family Verbenaceae, comprises about 250 species of shrubs to small trees, which is distributed in tropical to temperate regions (The Editorial Board of Flora of China 1982). Some species (such as *V. trifolia*, *V. agnus-castus*, *V. negundo*, etc.) have been used as traditional medicinal plants for the treatment of anemopyretic cold, headache, rheumatism, cancer and premenstrual disorder (Li et al. 2005; Haq et al. 2012; Mozdianfar et al. 2012; Huang et al. 2013). About 30 species had been investigated on their chemical constituents and showed the presence of diterpenoids, flavonoids, lignans, iridoids, ecdysteroids, triterpenoids and polyphenols (Li et al. 2005; Sharma et al. 2009; Lataoui et al. 2014).

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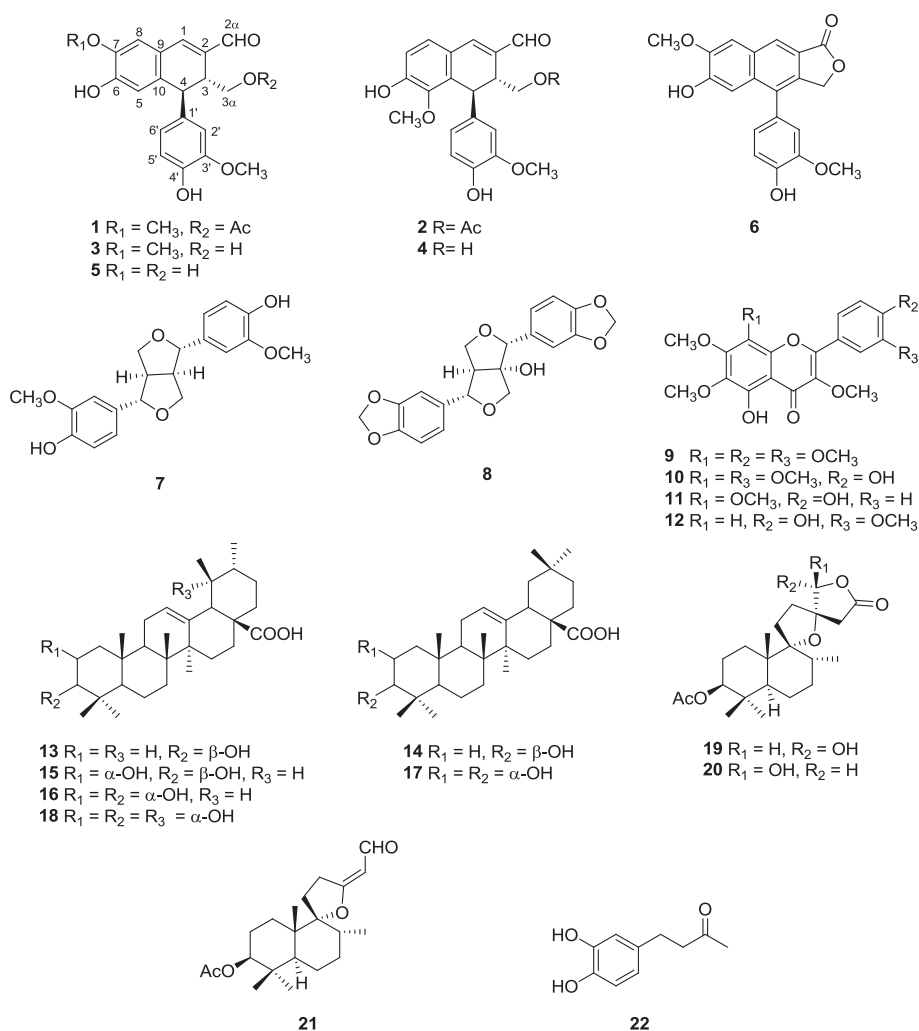


Figure 1. Structures of compounds (1–22) from *V. negundo* var. *cannabifolia*.

Vitex negundo var. *cannabifolia* is an aromatic shrub which grows extensively throughout China, Japan, South Asia, East Africa and South America (Lou et al. 2014). The fresh leaves of this plant were used in traditional Chinese medicine for the treatment of asthma, influenza, analgesia and gastralgia (The State Pharmacopoeia Commission of People's Republic of China's 2010). Its fruits, called 'Mu Jing Zi' in China, were also used in the treatments of asthma, malaria, gastrohelcosis, chronic tracheitis and premenstrual syndrome as a folk medicine (Huang et al. 2013). Considering insufficient phytochemical studies about *V. negundo* var. *cannabifolia* (Li et al. 2014; Lou et al. 2014), and our continuing search for bioactive constituents of the medicinal plants, the chemical constituents of the fruits of *V. negundo* var. *cannabifolia* had been investigated. Twenty-two compounds (1–22) were isolated (Figure 1), and the cytotoxicity against human HepG2 and rat C6 cell lines and brine shrimp lethality of some isolated compounds had been evaluated in this paper.

2. Results and discussion

Twenty-two compounds were isolated from the EtOAc fraction of the MeOH extract of the fruits of *V. negundo* var. *cannabifolia* using extensive column chromatography over Sephadex LH-20, reverse-phase ODS gel and silica gel (Supplementary). Their structures were identified by spectroscopic analysis (1D, 2D NMR and HRMS) and comparison with the literature data. Among them, compounds **1** and **2** were two new artefacts.

Compound **1** was isolated as yellowish powder. The positive HRESIMS indicated the molecular formula of **1** to be $C_{22}H_{22}O_7$ (m/z 421.1264 $[M + Na]^+$, calculated for 421.1263). Detailed comparison of the NMR spectral data of **1** with those of **3** (Supplementary) indicated that they were very similar, except for the extra signals of an acetoxy group [δ_H 2.00 (3H, s); δ_H 171.1 (s), 20.9 (s)] and with the signals due to C-3 α and C-3 slightly shifted in **1**. From these data, compound **1** was considered to be a 3 α -O-acetyl derivative of **3**. This was confirmed by the HMBC correlation of H-3 α with the carbonyl carbon of acetoxy group (Supplementary Figure S1). Thus, the structure of **1** was defined as 6-hydroxy-4-(4-hydroxy-3-methoxyphenyl)-3-acetoxymethyl-7-methoxy-3,4-dihydro-2-naphthaldehyde. Similarly, from comparison of the 1H and ^{13}C NMR spectra data of **2** with those of **4** (Supplementary), it was also apparent that **2** contained one more acetoxy group than **4** at C-3 α . All proton and carbon signals of **2** were completely assigned by the 2D NMR experiments. Therefore, the structure of **2** was established as 3 α -O-acetylvitedoin A. To the best of our knowledge, compounds **1** and **2** had never been isolated previously neither from the genus *Vitex* species nor from any other natural resources. Due to the known compounds, **3** and **4** are the main and characteristic constituents in genus *Vitex* species (Ono et al. 2004; Zheng et al. 2009), compounds **1** and **2** were assumed to be artefacts resulting from the treatment with EtOAc during the process of fractionation and purification rather than be biogenetic precursors of **3** and **4**, respectively. This was also confirmed by HPLC and HPLC-MS analysis, and neither **1** nor **2** was detected in the MeOH extract of the dried fruits of *V. negundo* var. *cannabifolia* (Supplementary Figures S2 and S3).

Compounds **3–8** are five known lignans. According to the literature, compound **3** was previously isolated from the seeds of *V. negundo* (Chawla et al. 1992) and showed anti-inflammatory (Chawla et al. 1992) and antioxidative (Ono et al. 2004) activities. Compounds **4–8** were also reported from the seeds of *V. negundo* (Ono et al. 2004; Zheng et al. 2009, 2011). Compounds **9–12** are four polymethoxyflavones and were isolated from *V. negundo* var. *cannabifolia* for the first time. The triterpenoids including **13** and **15–18** were also reported from the leaves of *V. negundo* var. *cannabifolia* (Li et al. 2014). Compounds **19–21** are three labdane diterpenoids, which were previously isolated from the *V. negundo* seeds in the literature (Zheng et al. 2010, 2012). The structures of these known compounds were identified mainly by comparison with their physical and spectral data with reported values (Supplementary).

Since the constituents from *Vitex* genus species exhibit various pharmacological effects, some isolated compounds were selected to test for cytotoxicity and brine shrimp lethality in this study. The polymethoxyflavones (**9–12**) were evaluated for the inhibitory effect on the proliferation on three cancer cell lines, the human gastric carcinoma cell line (BGC-823), the human hepatoma cell line (HepG2) and the rat glioblastoma cell line (C6), with DMSO used as a negative reference. Primary bioassays showed that compounds **9–12** exhibited moderate-to-weak cytotoxic activities against HepG2 (with IC_{50} values of 10.2, 3.9, 57.7 and

8.7 μM , respectively) and rat C6 (with IC_{50} values of 14.5, 4.8, 15.6 and 26.5 μM , respectively) cell lines and were inactive against BGC-823 cell line. In addition, some isolated compounds were selected to test brine shrimp lethality, and the triterpenoids **13–15** and a mixture of **16** and **17** exhibited significant toxicity against the nauplii of brine shrimp (*Artemia salina* Leach) with LC_{50} values of 7.7, 7.5, 14.8 and 29.4 μM , respectively.

3. Conclusion

Twenty-two compounds (**1–22**) were isolated from the fruits of *Vitex negundo* var. *cannabifolia*, including two new minor lignans (**1** and **2**) as the artefacts of **3** and **4** produced during fractionation and purification procedure. Compounds **9–12**, **14** and **19–22** were isolated from this plant for the first time. In addition, the polymethoxyflavones (**9–12**) displayed moderate-to-weak cytotoxicity against human HepG2 and rat C6 cell lines, while the triterpenoids **13–15** and a mixture of **16** and **17** exhibited significant brine shrimp lethality.

Supplemental material

Supplementary material relating to this article is available online, alongside Figures S1–S11.

Disclosure statement

No potential conflict of interest was reported by the authors.

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