Review Article

Chemically Diverse Secondary Metabolites from *Davidia involucrata* (Dove Tree)

Li-Yan Song,^{1,2} Ran Lin,^{1,2} Zu-Jian Wu,¹ and Ming-An Ouyang¹

¹Key Laboratory of Plant Virology of Fujian Province, Institute of Plant Virology, Fujian Agriculture and Forestry University, Fuzhou, Fujian 350002, China

²Key Laboratory of Biopesticide and Chemical Biology, Fujian Agriculture and Forestry University, Ministry of Education, Fuzhou, Fujian 350002, China

Correspondence should be addressed to Ming-An Ouyang; minganouyang@163.com

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Dove tree, *Davidia involucrata* Baill. which is endemic in western China, is not only one of the best known relict species of the tertiary, but also a famous ornamental plant with dove-shaped flowers. A diverse array of secondary metabolites have been isolated and identified from *Davidia involucrata*. The 58 structures of the secondary metabolites were presented and classified as triterpenoids, tannins, phenolic compounds, lignans, flavonoids, alkaloids, and sterol. In addition, the biosynthetic route of some triterpenoids was proposed. Moreover, the advances in the discovery of unprecedented compounds and uncovering of notable bioactivities were highlighted in this review.

1. Introduction

Dove tree (*Davidia involucrata* Baill.), as the sole member of the genera *Davidia*, is listed as one of the “first-grade” nationally protected plants in China. It is a tertiary paleotropical kingdom relict species rare to China and usually regarded as a “botanic living fossil” [1–3]. Dove tree is not only an endangered and rare relict species, but also famous as an ornamental plant by virtue of the pair of large white bracts that surround the small flowers and create the appearance of doves perching among its branches to give the tree its common name (Figure 1). Its distribution is limited to the subtropical mountains of central to southwestern China. Natural populations are often found in deciduous or evergreen broad-leaf forests at elevations of 700–2400 m [4]. Additionally, as an ornamental plant, *Davidia involucrata* has been introduced from China to many countries since 1904. The ecological, scientific, and horticultural values of *Davidia involucrata* have been illustrated and well recognized [5–7].

Davidia, *Camptotheca*, and *Nyssa* belong to Cornaceae family, which is distributed in Asia and North America. In 1966, Wall et al. discovered camptothecin, a cytotoxic quinoline alkaloid which inhibits the DNA enzyme topoisomerase

I (topo I), from the bark and stem of *Camptotheca acuminata* (*Camptotheca*, tree of joy) [8]. Encouraged by the potent anti-tumor agent secured from the plants under Cornaceae family, the phytochemical community have published a number of reports since then and addressed the structures and biological activities of chemical constituents from Cornaceae family [9].

The investigation on phytochemical analysis of *Davidia involucrata* could be traced back to 1982. Haddock and coworkers isolated two phenolic esters from the leaves of *Davidia involucrata* (dove tree) [10]. One of the phenolic esters was firstly named as davidiin [11] in 1990 by the same group. In the middle of the 1990s, davidiin was found to selectively inhibit the binding of a ligand to a μ -opioid receptor by Zhu et al. [12]. Since then, the antitumor activity of davidiin has been well elucidated by several research groups [13–15]. However, due to the scarcity of *Davidia involucrata*, little has been done [16] to develop the phytochemical research of the monotypic genus of *Davidia*. The important bioactivities and structural complexity coupled with the interesting chemical diversity prompted Ouyang to initiate the phytochemical investigations of this genus in 2002. Owing to their continuing efforts, 15 novel compounds

FIGURE 1: The flowers of *Davidia involucrata* that tremble in a slight breeze.

combined with 35 known compounds have been isolated and characterized, comprising more than 80% of the reports in this field. Moreover, biological evaluations have been carried out and compounds exhibiting cytotoxicities have been picked out for further investigations. Given the fact that no extensive review in the field has been published, herein, the metabolites from *Davidia involucrata* that have been documented in the literature from 1982 to 2014 were summarized, concerning the isolation, structural elucidation, and biological evaluation. In fact, every endeavor was made to thoroughly search the literature. Compounds that have novel carbon skeletons and/or biological activities will be discussed in greater detail.

2. Chemical Structures and Biological Activities

Different kinds of secondary metabolites had been isolated from *Davidia involucrata*. For clarity, they would be introduced sequentially according to their structural features.

2.1. Triterpenoids

2.1.1. Taraxerane-Type and Ursane-Type Triterpenoids. The carbon skeletons of taraxerane triterpene (1) and ursane triterpene (2) have been presented as follows (Figure 2).

The first reported example of triterpenoids from *Davidia involucrata* was taraxerone 3 and taraxerol 4 isolated by Xiang and Lu [16] in 1989, although 3 and 4 were not new at the time of publication [17, 18]. 3 and 4 were isolated from the petroleum ether fraction of the branch of *Davidia involucrata*. They were characterized by IR and NMR spectra.

A number of oxygenation patterns around a basic taraxerane skeleton were observed (Figure 3). The dihydroxylated compound myricadiol (5) was isolated from the methanolic extract of the branch bark of *Davidia involucrata* [19] and the compound had been reported before [20–22]. Taraxerane-type triterpenoids containing carbonyl moieties at positions 3, 16, and 21 of the taraxerane-type skeleton are observed, such as davinvolunone B (6) and davinvolunone C (7). Both of these compounds, which were highly oxidized, were isolated from the same sample of *Davidia involucrata*

TABLE 1: Cytotoxicity of compounds 5–19 against three human tumor cell lines (IC₅₀, μ M)^a.

Compounds	Cell lines		
	SGC-7901	MCF-7	BEL-7404
5	>100	>100	>100
6	30.57 $\pm$ 1.63	41.34 $\pm$ 1.24	37.29 $\pm$ 1.64
7	32.22 $\pm$ 1.22	42.54 $\pm$ 1.67	39.26 $\pm$ 1.14
8	>100	>100	>100
9	>100	>100	>100
10	35.47 $\pm$ 1.55	55.24 $\pm$ 2.28	53.82 $\pm$ 2.11
11	>100	>100	>100
12	37.65 $\pm$ 1.85	58.93 $\pm$ 2.58	54.77 $\pm$ 2.05
13	>100	>100	>100
14	36.30 $\pm$ 2.00	37.40 $\pm$ 1.57	47.41 $\pm$ 2.04
15	>100	>100	>100
17	>100	>100	>100
18	>100	>100	>100
19	58.23 $\pm$ 2.36	65.35 $\pm$ 3.12	70.26 $\pm$ 4.21
20	42.35 $\pm$ 1.79	45.80 $\pm$ 2.15	38.24 $\pm$ 1.57
21	39.25 $\pm$ 1.83	21.24 $\pm$ 1.15	24.59 $\pm$ 1.51
22	7.26 $\pm$ 0.08	12.37 $\pm$ 0.18	8.15 $\pm$ 0.13
23	10.26 $\pm$ 0.52	15.21 $\pm$ 0.28	18.14 $\pm$ 0.30
Doxorubicin ^b	0.19 $\pm$ 0.032	0.08 $\pm$ 0.007	0.12 $\pm$ 0.011

^aThe error was presented as standard deviation (SD).

^bPositive control.

and unequivocally determined by extensive spectroscopic analysis [19].

Oxidation of the methyl group at C-28 in the ursane-type skeleton is also observed. Methanolic extraction of the branch bark of *Davidia involucrata* yielded six examples euscaphic acid (8) [23], myrianthic acid (9) [24], 3 β -O-*trans*-p-coumaroyl-2 α -hydroxy-urs-12-en-28-oic acid (10) [25–27], 3 β -O-*cis*-p-coumaroyl-2 α -hydroxy-urs-12-en-28-oic acid (11), 3 β -O-*trans*-p-feruloyl-2 α -hydroxy-urs-12-en-28-oic acid (12), and 3 β -O-*cis*-p-feruloyl-2 α -hydroxy-urs-12-en-28-oic acid (13) [27] where C-28 had been oxidized to a carboxylic acid functionality [19, 28]. Compounds 8–13, which had been previously documented, were characterized by comparison of various spectra including NMR, IR, mass, and specific rotation. Compounds 5–13 were subjected to evaluation for cytotoxic activities against SGC-7901 human gastric cancer cells, MCF-7 human breast cancer cells, and BEL-7404 human hepatoma cells (Table 1). Gratifyingly, compounds 6–7, 10, and 12 showed moderate cytotoxic activities against all the three cell lines [19].

2.1.2. Rearranged Taraxerane-Type and Ursane-Type Triterpenoids. Triterpenes may rearrange to form a 2-nor-pentacyclic triterpenoid carbon skeleton with 29 carbons and a five-membered A-ring, which was unprecedented to the best of one's knowledge [19, 28]. A plausible biosynthetic pathway was proposed and depicted in Scheme 1. Epoxidation followed by epoxide opening led to the dihydroxylation of the ursane framework. Further oxidative cleavage gave the ring

FIGURE 2: The carbon skeleton of taraxerane and ursane.

FIGURE 3: Taraxerane- and ursane-type triterpenoids.

SCHEME 1: Proposed biosynthesis of compounds 8–16.

opening product, 2,3-seco-ursane triterpene. Five-member A-ring was generated by ring-contraction rearrangement followed by decarboxylation of the C-3 carboxylic acid moiety (resulting from the selective oxidation of aldehyde functionality).

One example of ring-A modified ursane-type triterpene was davinvolunic acid C (**14**), a tetracyclic triterpenoid isolated from the methanolic fraction of the branch bark of *Davidia involucrata*. A rearranged skeleton with a five-member A-ring was also secured from the same source, for example, davinvolunic acid A (**15**) and davinvolunic acid B (**16**). The structures of davinvolunic acids A–C were established via exhaustive 1D and 2D NMR spectroscopy. It was noted that davinvolunic acid C (**14**) showed moderate cytotoxicities against the cell proliferation of SGC-7901, MCF-7, and BEL-7404 with IC_{50} ranging from 36.3 to 76.4 μ M (Table 1) [28].

Davinvolunol A (**17**), davinvolunol B (**18**), and davinvolunone A (**19**) were identified from the water insoluble fraction of the branch bark of *Davidia involucrata* [19]. Davinvolunone A (**19**) exhibited moderate cytotoxicities

against human tumor cell lines (Table 1). Their carbon skeleton connection and stereochemistry were established through extensive spectral analysis. Interestingly, they all possessed a 5/6/6/6/6 nortriterpenoid framework rearranged from taraxerane-type triterpene (Figure 4). It is postulated that the biosynthetic route of **17–19** was very similar to the pathway presented in Scheme 1.

2.1.3. Lupane-Type Triterpenoids. The third collection of pentacyclic triterpenoids from the MeOH fraction of the branch bark of *Davidia involucrata* are the lupane-type compounds, including lupeol (**20**) [29], betulin (**21**) [30], betulinic acid (**22**) [31], and platanic acid (**23**) [32] (Figure 5). The four compounds were not new; however, they exhibited moderate cytotoxic activities against three tumor cell lines (Table 1) [28]. It is noteworthy that betulinic acid (**22**) not only possessed the most potent antitumor cytotoxicity with IC_{50} value of 7.26–12.37 μ M, but also shows antitumor activity against a broad panel of cancers. In addition, betulinic acid (**22**) is also found to exhibit antimalarial, antimicrobial, and anti-HIV bioactivities by several research groups [33–36].

FIGURE 4: Rearranged triterpenoids.

FIGURE 5: Lupane-type triterpenoids.

2.2. Tannins

2.2.1. Ellagic Acid. 3'-O-Methyl-3,4-O,O-methylidene ellagic acid (**24**), 3,3',4-5-trimethylellagic acid (**25**), and ellagic acid (**26**) were firstly obtained from the ethanolic extraction of the branch of *Davidia involucrata* by Xiang and Lu [16] in 1989

(Figure 6). The structures were not novel and characterized by comparison of IR and NMR spectra [37–39].

2.2.2. Ellagitannins. Ellagitannins are a structurally and biologically diverse class of hydrolysable tannins [40]. Haddock [10] and coworkers conducted the pioneer work of phytochemical investigation of *Davidia involucrata*. The first reported examples were β -1,6-(S)-hexahydroxydiphenoyl-2,4-dehydrohexahydroxy-diphenoyl-D-glucopyranose (**27**) and davidiin (**28**) from the phenolic extract of the leaves of *Davidia involucrata* (Figure 6). The relative configurations of **27** and **28** were determined by NMR spectroscopy and the axial chiralities of **27** and **28** were established through circular dichroism spectrum. Recently, a total synthesis of davidiin (**27**) has been published by Kasai et al. [41] and the chemical structure of davidiin (**28**) was further confirmed. Davidiin (**28**) showed anticancer activity against hepatocellular carcinoma cells and DU-145 cells by Chen and Ito [14, 15]. It is noteworthy that davidiin (**28**) is the strongest nature-derived small ubiquitin-related modification inhibitor reported so far (IC_{50} value $0.15 \mu\text{M}$) [15], which is very promising for drug discovery.

2.3. Phenolic Compounds

2.3.1. Caffeoyl Derivatives. Ouyang's group also conducted the phytochemical investigation of the leaves of *Davidia*

FIGURE 6: Tannins.

involutrata. The methanolic extract yielded three novel caffeoyl galactonic acid derivatives, davidiosides A–C (29–31) [42], and the chemical structures of 29–39 were determined by spectroscopic data and chemical evidence. No biological activities were reported for any of the metabolites (Figure 7).

Four known caffeoyl derivatives, such as caffeic acid (32), methyl caffeate (33), chlorogenic acid (34), and methyl chlorogenate (35) [43], were obtained from the same source and characterized by comparison of NMR and mass spectra (Figure 7).

2.3.2. Miscellaneous Phenolic Compounds. The phytochemical research on the methanolic extract of the branch bark of *Davidia involutrata* also led to the discovery of two new phenolic water-soluble metabolites, involcranoside A (36) and involcranoside B (37) [44] (Figure 7). Identification of their structures was achieved by 1D and 2D NMR experiments. Little is known about their bioactivity profiles.

Five known phenolic compounds, 3,4-dimethoxyphenyl- O - β -D-glucopyranoside (38), picein (29) [45], 1,4-dihydroxy-3-methoxy-phenyl-4- O - β -D-glucopyranoside (40) [46], leonuriside A (41) [47], and 4-hydroxy-3-methoxybenzoic acid (42), were identified along with the two new phenolic

glycosides (36–37) and NMR experiments and mass spectroscopy were utilized to secure the structures of 38–42 (Figure 7).

2.4. Neolignans and Lignans. Two new neolignan glycosides, davidioside A (43) and davidioside B (44) [48], were isolated from the methanolic extraction of the branch bark of *Davidia involutrata* (Figure 8) and identified by 1D and 2D NMR experiments.

In addition, six known compounds, such as dihydrodehydrodiconiferyl alcohol-9- O - β -D-xylopyranoside (45) [49], dihydrodehydrodiconiferyl alcohol-4'- O - β -D-glucopyranoside (46) [50], dihydrodehydrodiconiferyl alcohol-9- O - β -D-glucopyranoside (47) [51], glochidioboside (48) [52], dihydrodehydrodiconiferyl alcohol (49) [53], and isolariciresinol-9- O - β -D-glucopyranoside (50) [54], were coisolated and characterized by comparison of NMR spectroscopy and mass spectral data (Figure 8).

2.5. Flavonoids. Six known flavones and their glycosides were isolated from the methanolic extraction of the leaves of *Davidia involutrata* [55] (Figure 9). Their structures were

FIGURE 7: Phenolic compounds.

FIGURE 8: Neolignans and lignans.

FIGURE 9: Flavonoids.

established as kaempferol (51), kaempferol-3-*O*- β -D-glucopyranoside (52), kaempferol-3-*O*- β -D-galactopyranoside (53), quercetin (54), quercetin-3-*O*- β -D-arabinopyranoside (55), and quercetin-3-*O*- β -D-galactopyranoside (56) [56]. The structures of all these compounds were identified by comparison of the spectra data.

The isolated tannins, phenolic compounds, lignans, and flavonoids demonstrated the potential to serve as radical

scavengers and antioxidant reagents in light of their structural features [57–62].

2.6. Alkaloid Glycosides. Three known compounds (Figure 10), one quinoline alkaloid glycoside pumiloside (57) [63] and two closely related indole alkaloid glycosides vincosamide (58) [64] and strictosidinic acid (59) [65], were

FIGURE 10: Alkaloids and sterol.

isolated from the MeOH extract of the branch bark of *Davidia involucrata* and determined through careful analysis of the spectroscopic data [66, 67]. It is noted that the structure of pumiloside (57) is similar to camptothecin [68–70], a remarkable anticancer lead compound. In fact, pumiloside (57) serves as a biosynthetic precursor of camptothecin [71].

Chemical transformations were performed to hydrolyze compounds 36–59. The sugars were verified by comparison with authentic samples to provide chemical evidences.

2.7. Sterol. β -Sitosterol (60) is the only compound in this group (Figure 10). Although it existed as a widely distributed known plant sterol [72], β -sitosterol was firstly reported to be isolated from the petroleum ether extract of the branch of *Davidia involucrata* and identified by spectroscopic analysis by Xiang and Lu [16] in 1989.

3. Conclusions

A literature review of constituents from *Davidia involucrata* has been done and several conclusions could be drawn. Firstly, the new and unique structures isolated reflect the chemical diversity of *Davidia involucrata*. The novel phytochemistry presented in this review provides important evolutionary and chemotaxonomic knowledge of the monotypic genus *Davidia*. Secondly, these compounds constitute an interesting type of natural products, for some of them, as davidiin, have shown important biological activities. However, the bioactivity profiles of many of them are still not fully demonstrated. Finally, *Davidia involucrata* is one of the least studied groups of plants and therefore represents great potential for the discovery of new pharmacologically active metabolites.

Competing Interests

The authors declare no conflict of interests.

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