Paulownia C-geranylated flavonoids: their structural variety, biological activity and application prospects

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Abstract  Paulownia species, especially their flowers and fruits, are traditionally used in Chinese herbal medicines for the treatment of infectious diseases. C-geranylated flavonoids were found to be the major special metabolites in Paulownia flowers and fruits, and 76 C-geranylated flavonoids had been isolated and characterized thus far. Structural variations in Paulownia C-geranylated flavonoids are mainly due to the complicated structural modifications in their geranyl substituents. These natural compounds have attracted much attention because of their various biological activities, including antioxidation, anti-inflammation, cytotoxic activity and various enzymatic inhibitions, etc. Among them, diplacone, a major Paulownia component, was considered to have promise for applications in medicine. This paper summarizes the information from current publications on Paulownia C-geranylated flavonoids, with a focus on their structural variety, key spectroscopic characteristics, biological activity with structure–activity relationships and application prospects. We hope that this paper will stimulate further investigations of Paulownia species and this kind of natural product.

Keywords  Paulownia species · C-geranylated flavonoids · Phytochemistry · Biological properties

Introduction

C-geranylated flavonoids, a small group of flavonoid derivatives consisting of a flavonoid skeleton joined with a terpenoid side-chain (C<sub>10</sub>, geranyl substituent) via a direct carbon–carbon bond directly, are considered as the members of the prenylated flavonoids (Barron and Ibrahim 1996). Among these compounds, the geranyl has been revealed to have the potential to occur as a substituent possibly at the C-3, C-6, C-8, C-2<sup>′</sup> or C-3<sup>′</sup> positions of the flavonoid skeleton (Fig. 1). C-geranylated flavonoids, as secondary metabolic products, are biosynthesized via the mevalonate pathway (for the geranyl skeleton) and the shikimic acid pathway with cinnamoyl CoA (for the flavonoid skeleton), and the connection is
provided by the prenyltransferases, the key biosynthetic enzymes for prenylated polyphenols in plants (Šmejkal 2014; Andersen and Markham 2006; Kuzuyama et al. 2005). Recently, an aromatic prenyltransferase was discovered in *Aspergillus terreus* and exhibited unprecedented promiscuity towards flavonoid acceptors to produce C-geranylated flavonoids (Chen et al. 2017a). C-geranylated flavonoids occur in relatively few plant families, such as Leguminosae, Moraceae, Rutaceae, and Ophioglossaceae (Yazaki et al. 2009). Among them, the *Paulownia* genus (Paulowniaceae family) is a rich natural source of this kind of compound.

The *Paulownia* genus was previously categorized as part of the Scrophulariaceae family, but now, it has now been categorized as a monotypic family of its own, Paulowniaceae, based on the latest molecular phylogenetic data (Erbar and Gülden 2011). Now, only nine species are accepted as part of the *Paulownia* genus by Flora of China as shown in Table 1 (Chinese Flora Editorial Committee 1998). *Paulownia* species are fast-growing shade trees native to China and Southeast Asia and are mainly grown as ornamental trees or commercially for the production of hardwood timber (Zhu et al. 1986; Bergmann 1998). Moreover, their leaves, flowers, fruits and root barks are also traditionally used as Chinese herbal folk medicines for the treatment of enteritis, tonsillitis, bronchitis, dysentery, etc. (He et al. 2016). Phytochemical research has indicated that *Paulownia* plants contain quinones, lignans, triterpenes, phenylpropanoid glycosides, and flavonoids (Xing et al. 2013; He et al. 2016). However, C-geranylated flavonoids, as the main constituents, have attracted much attention due to their structural variation and assorted biological properties.

Among *Paulownia* species, *P. tomentosa* has been the most extensively investigated, and 39 C-geranylated flavanones have been isolated from its flowers and fruits (Schneiderová and Šmejkal 2014). Subsequently, another 37 C-geranylated flavonoids (including C-geranylated flavanones and C-geranylated flavones) were further obtained from *P. tomentosa* and other *Paulownia* species. However, no systematic review of various aspects related to *Paulownia* C-geranylated flavonoids has yet been

Fig. 1 Structural skeleton of C-geranylated flavonoids obtained from *Paulownia* species

| No. | Chinese name | Plant Latin name |
|-----|--------------|-----------------|
| 1   | 楸叶泡桐     | *Paulownia catalpifolia* T. Gong ex D. Y. Hong |
| 2   | 兰考泡桐     | *Paulownia elongata* S. Y. Hu |
| 3   | 川泡桐       | *Paulownia fargesii* Franchet |
| 4   | 白花泡桐     | *Paulownia fortunei* (Seem.) Hemsl. |
| 5   | 台湾泡桐     | *Paulownia kawakamii* T. Ito |
| 6   | 毛泡桐       | *Paulownia tomentosa* Steud. |
| 7   | 南方泡桐     | *Paulownia australis* T. Gong |
| 8   | 毛泡桐（原变种） | *Paulownia tomentosa var. Tomentosa*<sup>a</sup> |
| 9   | 光泡桐       | *Paulownia tomentosa var. tsiningensis* (Pai [Bai]) T. Gong |
| 10  |             | *Paulownia coreana* Uyeki<sup>b</sup> |

The plant Latin names are presented according to the new classification (http://www.theplantlist.org), even though older classifications are presented in the references

<sup>a</sup> Status as “Synonym”

<sup>b</sup> The *Paulownia* species, *Paulownia coreana* Uyeki, investigated by Jin et al. is an unresolved name and is not accepted in Flora of China (1998) by the Chinese Flora Editorial Committee.
reported. The present paper summarizes existing publications associated with *Paulownia* C-geranylated flavonoids and their chemical structures, key spectroscopic characteristics, biological activities and application prospects. We hope that the provided information in this paper can provide an overview of research on *Paulownia* C-geranylated flavonoids and stimulate further investigations on this kind of compound.

**Structural variations in *Paulownia* C-geranylated flavonoids**

Seventy-six C-geranylated flavonoids (1–76, Figs. 2, 3, 4, 5, 6) were isolated and identified from *Paulownia* species and are the main bioactive constituents. Among them, C-geranylated flavanones represented the overwhelming majority (1–72, Figs. 2, 3, 4, 5) and only four C-geranylated flavones (73–76, Fig. 6) were obtained so far. Except for compounds 19 and 27, which were C-8 substituted, all the other *Paulownia* C-geranylated flavonoids possessed a C-6 geranyl-mono-substituted structure pattern. Pau-catalinone A (19) was also the first sample as a natural dimeric C-geranylated flavanone derivative (Gao et al. 2015). In *Paulownia* C-geranylated flavonones, C-2 in ring C is a chiral carbon, and most of them possess an S configuration at the stereogenic centre C-2, except for compounds 19, 25, 27, 37, 41, 43, 46, 60, and 67, which were obtained as racemic mixtures of 2R and 2S enantiomers. Moreover, all the stereogenic centres of C-2 and C-3 in *Paulownia* C-geranylated flavanols 13, 14, 15, 16, 17, 18, 32, 36, 51, 52, and 58 were 2R, 3R configurations, although 17 was a racemic mixture of 2R,3R and 2S,3S enantiomers.

Basically, *Paulownia* C-geranylated flavonoids originally occurred with an unmodified geranyl substituent, and their structural variation occurred due only to phenolic hydroxyl groups or methoxy groups in the flavonoid skeleton, such as those in compounds 1–19 (Fig. 2) and 73 (Fig. 6).

However, the geranyl substituent in *Paulownia* C-geranylated flavonoids could undergo further oxidation (mainly hydroxylation or carbonylation) at different positions to give rise to various modified geranyl substituents as the linear C10 side chain (Fig. 4). It could be hydroxylated at C-7″ to produce a common 7-hydroxy-3,7-dimethyl-2(5E)-octenyl substituent (20–27) or a rare (2E,5E)-7-hydroxy-3,7-dimethyl-octa-2,5-dien-1-yl substituent (40); at C-6″ to achieve a 6-hydroxy-3,7-dimethyl-2(5E)-7-octadienyl-substituent (28–37), which could be further oxidized.

![Unmodified C-geranylated flavanones isolated from the *Paulownia* genus](image-url)
to yield an unusual 3,7-dimethyl-6-oxoocta-2,7-dien-1-yl substituent (41); or at C-2″ to obtain a rare 2-hydroxy-7-methyl-3-methyleneoct-6-en-1-yl substituent (38 and 39). The oxidation could also occur at C-7″ and C-8″ simultaneously to form 6,7-dihydroxy-3,7-dimethyloct-2-en-1-yl (42 and 43) or 6-hydroxy-7-methoxy-3,7-dimethyloct-2-en-1-yl (44–46) substituents.

Interestingly, on the foundation of hydroxylation, further cyclic modifications could occur in the geranyl substituent to yield more attractive *Paulownia* C-geranyllflavonoids (Fig. 4). The pyran or furan moiety could be generated in *Paulownia* C-geranyllflavonoids by a further cyclization between the geranyl substituent and C-7 in ring A via an oxygen atom or between two carbon atoms in the geranyl via an oxygen atom. Compounds 47–56, containing a 2,3,7,8-tetrahydropyran moiety, and compounds 57–62, containing a 2,3-dihydropyran moiety with a double bond assigned to C-1″ and C-2″, were provided by cyclization between C-3″ of the geranyl substituent and C-7 in ring A of the flavanone skeleton via an oxygen atom. Meanwhile, some other carbon atoms in these modified geranyl substituents, such as C-2″ (56), C-6″ (61) or C-7″ (62), could be further hydroxylated to yield more complex geranylated flavonoid derivatives. Similarly, cyclization occurring between C-2″ of the geranyl substituent and C-7 in ring A of the flavanone skeleton via an oxygen atom could produce a 2H-furo unit (63 and 64), but this structural modification was not universal in natural C-geranylated flavonoid derivatives. Cyclization could also occur between two carbon atoms in the geranyl chain via an oxygen atom to

### Fig. 3 Noncyclic modified C-geranyllflavanones isolated from the *Paulownia* genus

![Diagram of noncyclic modified C-geranyllflavanones](image-url)
yield furan (between C-3″ and C-6″, 65) or pyran (between C-3″ and C-7″, 66) moieties in *Paulownia* C-geranylflavonoids. Compound 67 was, to date, a unique C-geranylflavanone with a monocyclic monoterpen side-chain isolated from *Paulownia* plants up to mow (Wang et al. 2019), and its oxygenated cyclogeranyl substituent was similar to that (without the hydroxyl) in some ugonins isolated from *Helminthostachys zeylanica* (Huang et al. 2003; 2010).

In addition, five C-geranylflavanones with different degraded geranyl side chains (68–72, Fig. 5) were isolated from *P. tomentosa* fruits in small amounts. Their side chains all consisted of C7 units with the decomposition of a terminational propenyl group from their geranyl substituents. These compounds were proven not to be artefacts formed during the extraction and separation procedures (Navrátilová et al. 2013).

Compared with C-geranylflavanones, fewer C-geranylated flavones were isolated from *Paulownia* plants. To date, only four C-geranylated flavones (73–76, Fig. 6) were obtained from the fruits of *P. catalpifolia* (Wang et al. 2017, 2019). The variety of their geranyl substituents was minimal, with only hydroxylation at C-7″ to form a 7-hydroxy-3,7-dimethyl-2(α)-octenyl substituent (74–76).
Occurrence of C-geranylated flavonoids in Paulownia

To date, only four Paulownia species, including P. tomentosa, P. catalpifolia, P. coreana and P. fortunei, have been found to contain C-geranyllflavonoids based on different phytochemical investigations. Their flowers, leaves, and especially fruits, are an excellent source of this kind of constituent (Table 2). It has also been discovered that the glandular hairs on its young reproductive organs contain flavonoids at concentrations over 1000 times greater than those on the surfaces of its young leaves (Kobayashi et al. 2008). Asai et al. (2008) isolated a number of C-geranyllflavonanes from the viscous secretion on the surface of immature P. tomentosa fruits and presumed that these flavonoids were biosynthesized in the microstructures glandular trichomes on the fruit surface (Asai et al. 2008; Gang et al. 2002). In addition, the correlation between the seasonal variations and changes in the content of C-geranyllflavonoids in P. tomentosa fruits has also been described, and the late autumn was considered as the appropriate harvesting time to obtain high concentrations of C-geranyllflavonoids in P. tomentosa fruits (Holubová and Šmejkal 2011).

Spectroscopic and structural characteristics of Paulownia C-geranyllflavonoids

Two structural subtypes of Paulownia C-geranyllflavonoids were isolated, C-geranylated flavanone and C-geranylated flavone. Their UV features, a main maximum absorption at approximately $\lambda$ 290 nm with a shoulder peak at approximately $\lambda$ 230 nm and a weak absorption at approximately $\lambda$ 340 nm for C-geranyllflavanone and two main maximum UV absorption at approximately $\lambda$ 220–280 nm and $\lambda$ 300–400 nm for C-geranyllflavone (Fig. 7), were similar to those of their respective parent flavonoid skeletons (Mabry et al. 1969). However, if the geranyl side chain was modified by the formation of a pyran ring with a double bond between C-1″ and C-2″, as in the structures of compounds 62 and 57–61, the conjugated chromophoric system between the pyran ring, the ring A and the C-4 carbonyl group in the flavonoid skeleton caused an unusual UV spectrum with two main maximum absorptions at approximately $\lambda$ 230 and 275 nm, and a shoulder peak at approximately $\lambda$ 290 and 360 nm. This kind of modified geranyl substituent could clearly influence
### Table 2 The distribution of C-geranylated flavonoids in *Paulownia* species

| Compounds               | Name                  | Species       | Part                | References                          |
|-------------------------|-----------------------|---------------|---------------------|-------------------------------------|
| 1                       | Mimulone              | *P. tomentosa* | Fruit               | Navrátilová et al. (2013)           |
|                         |                       |               |                     | Cho et al. (2013)                   |
|                         |                       |               |                     | Hanáková et al. (2015)              |
|                         |                       |               | Flower              | Chen et al. (2009)                  |
|                         |                       |               |                     | Jiang et al. (2004)                 |
|                         |                       | *P. fortunei* | Flower              | Duan et al. (2007)                  |
|                         |                       |               | Leaf                | Li et al. (2008)                    |
| 2                       | Diplacone             | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Navrátilová et al. (2013)           |
|                         |                       |               |                     | Cho et al. (2013)                   |
|                         |                       |               |                     | Ryu et al. (2017)                   |
|                         |                       |               | Flower              | Chen et al. (2009)                  |
|                         |                       |               |                     | Jiang et al. (2004)                 |
|                         |                       | *P. fortunei* | Flower              | Duan et al. (2007)                  |
|                         |                       |               |                     | Wang et al. (2017)                  |
|                         |                       | *P. catalpifolia* | Fruit            | Jin et al. (2015)                   |
|                         |                       | *P. coreana*  | Flower              |                                       |
| 3                       | Schizolaenone C       | *P. tomentosa* | Fruit               | Šmejkal et al. (2010)               |
| 4                       | 3′-O-methyl diplacone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Šmejkal et al. (2007)               |
|                         |                       |               |                     | Cho et al. (2013)                   |
|                         |                       |               |                     | Hanáková et al. (2015)              |
|                         |                       |               |                     | Ryu et al. (2017)                   |
| 5                       | 3′-O-methyl-5′-hydroxydiplacone | *P. tomentosa* | Fruit               | Šmejkal et al. (2008a)              |
|                         |                       |               | Flower              | Jin et al. (2015)                   |
| 6                       | 3′-O-methyl-5′-O-methyl diplacone | *P. tomentosa* | Fruit               | Šmejkal et al. (2008a)              |
| 7                       | 4′-O-methyl diplacone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Cho et al. (2013)                   |
| 8                       | 3′,4′-O-dimethyl-5′-hydroxydiplacone | *P. tomentosa* | Fruit               | Hanáková et al. (2015)              |
| 9                       | 6-Geranyl-5,7,3′,5′-tetrahydroxy-4′-methoxyflavanone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Hanáková et al. (2015)              |
| 10                      | 6-Geranyl-5,7-dihydroxy-3′,4′-dimethoxyflavanone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Hanáková et al. (2015)              |
| 11                      | 6-Geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxyflavanone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Hanáková et al. (2015)              |
|                         |                       |               |                     | Ryu et al. (2017)                   |
|                         |                       | *P. coreana*  | Flower              | Jin et al. (2015)                   |
| 12                      | 6-Geranyl-4′,5,5′,7-tetrahydroxy-3′-methoxyflavanone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Navrátilová et al. (2013)           |
| 13                      | 6-Geranyl-3′,3′,5,7-tetrahydroxy-4′-methoxyflavanone | *P. tomentosa* | Fruit secretion     | Asai et al. (2008)                  |
|                         |                       |               | Fruit               | Cho et al. (2013)                   |
|                         |                       | *P. fortunei* | Flower              | Zhang and Li (2008)                 |
| Compounds | Name | Species | Part | References |
|-----------|------|---------|------|------------|
| 14        | Diplacol | P. tomentosa | Fruit secretion | Asai et al. (2008) |
|           |       | P. coreana | Flower | Jin et al. (2015) |
| 15        | 3′-O-methyldiplacol | P. tomentosa | Fruit secretion | Asai et al. (2008) |
|           |       | P. coreana | Flower | Kobayashi et al. (2008) |
|           |       |           | Fruit | Navrátilová et al. (2013) |
|           |       |           |       | Cho et al. (2013) |
|           |       |           |       | Hanáková et al. (2015) |
|           |       |           |       | Šmejkal et al. (2008a) |
| 16        | 6-Geranyl-3,3′,5′,7-pentahydroxy-4′-methoxyflavane | P. tomentosa | Fruit | Zhang and Li (2008) |
|           |       |           |       | Cho et al. (2012) |
| 17        | 3′-O-methyl-5′-methoxydiplacol | P. tomentosa | Fruit | Šmejkal et al. (2007) |
| 18        | 3′-O-methyl-5′-hydroxydiplacol | P. coreana | Flower | Jin et al. (2015) |
| 19        | Paucatalinone A | P. catalpifolia | Fruit | Gao et al. (2015) |
| 20        | 5,7-Dihydroxy-6-(7-hydroxy-3,7-dimethyl-2-en-1-yl)-2S-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one | P. tomentosa | Fruit | Ryu et al. (2017) |
|           |       | P. catalpifolia | Fruit peel | Wang et al. (2019) |
| 21        | Prokinawan | P. tomentosa | Flower | Kobayashi et al. (2008) |
|           |       |           | Fruit secretion | Asai et al. (2008) |
|           |       |           | Fruit | Ryu et al. (2017) |
|           |       |           |       | Tang et al. (2017) |
| 22        | 3,3′,4′,5,7-Pentahydroxy-6-[7-hydroxy-3,7-dimethyl-2(E)-octenyl]flavone | P. tomentosa | Fruit secretion | Asai et al. (2008) |
| 23        | Tomentin J | P. tomentosa | Fruit | Ryu et al. (2017) |
| 24        | Paucatalinone J | P. catalpifolia | Fruit | Wang et al. (2019) |
| 25        | Isopaucatalinone B | P. catalpifolia | Fruit | Gao et al. (2015) |
| 26        | Tomentin K | P. tomentosa | Fruit | Ryu et al. (2017) |
|           |       | P. catalpifolia | Fruit peel | Wang et al. (2019) |
| 27        | Paucatalinone B | P. catalpifolia | Fruit | Gao et al. (2015) |
| 28        | Mimulone B | P. tomentosa | Fruit | Schneiderová et al. (2013) |
|           |       | P. coreana | Flower | Jin et al. (2015) |
| 29        | Tomentomimulol | P. tomentosa | Fruit | Schneiderová et al. (2013) |
| 30        | Tanariflavanone D | P. tomentosa | Fruit secretion | Asai et al. (2008) |
|           |       |           | Fruit | Schneiderová et al. (2013) |
|           |       |           |       | Ryu et al. (2017) |
| 31        | Tanariflavanone | P. tomentosa | Fruit secretion | Asai et al. (2008) |
|           | (2R,3R)-3,3′,4′,5,7-pentahydroxy-6-[6-hydroxy-3,7-dimethyl-2(E),7-octadienyl]flavone | P. tomentosa | Fruit secretion | Asai et al. (2008) |
| 33        | Tomentodiaplatone | P. tomentosa | Fruit | Šmejkal et al. (2008a) |
| 34        | (2R,3R)-4′,5,5′,7-tetrahydroxy-3′-methoxy-6-[6-hydroxy-3,7-dimethyl-2(E),7-octadienyl]flavone | P. tomentosa | Fruit secretion | Asai et al. (2008) |
|           |       | P. catalpifolia | Fruit peel | Wang et al. (2019) |
| 35        | Tomentin I | P. tomentosa | Fruit | Ryu et al. (2017) |
Table 2 continued

| Compounds | Name               | Species     | Part          | References                                |
|-----------|--------------------|-------------|---------------|-------------------------------------------|
| 36        | Tomentodiplacol    | *P. tomentosa* | Fruit         | Šmejkal et al. (2007)                     |
| 37        | Paucatalinone I    | *P. catalpifolia* | Fruit peel   | Wang et al. (2019)                        |
| 38        | Minulone H         | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 39        | Tomentodiplacone M | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 40        | Tomentodiplacone B | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 41        | Tomentodiplacone I | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 42        | Minulone F         | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 43        | Paulownione A      | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 44        | Minulone G         | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 45        | Tomentodiplacone G | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 46        | Paulownione B      | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 47        | Tomentin A         | *P. tomentosa* | Fruit         | Cho et al. (2013)                        |
| 48        | Tomentin B         | *P. tomentosa* | Fruit         | Cho et al. (2013)                        |
| 49        | Tomentin C         | *P. tomentosa* | Fruit         | Cho et al. (2013)                        |
| 50        | Tomentin D         | *P. tomentosa* | Fruit         | Cho et al. (2013)                        |
| 51        | Tomentin E         | *P. tomentosa* | Fruit         | Cho et al. (2013)                        |
| 52        | Tomentin F         | *P. tomentosa* | Fruit         | Ryu et al. (2017)                        |
| 53        | Tomentin G         | *P. tomentosa* | Fruit         | Ryu et al. (2017)                        |
| 54        | Tomentin H         | *P. tomentosa* | Fruit         | Ryu et al. (2017)                        |
| 55        | Paucatalinone G    | *P. catalpifolia* | Fruit peel | Wang et al. (2019)                       |
| 56        | Tomentodiplacone N | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 57        | Tomentinone        | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 58        | Tomentodiplacol B  | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 59        | Tomentodiplacone O | *P. tomentosa* | Fruit         | Hanáková et al. (2017)                   |
| 60        | Paulownione C      | *P. tomentosa* | Fruit         | Hanáková et al. (2017)                   |
| 61        | Minulone C         | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 62        | Minulone D         | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 63        | Bonannione B       | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 64        | Tomentodiplacone L | *P. tomentosa* | Fruit         | Hanáková et al. (2015)                   |
| 65        | Tomentodiplacone H | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 66        | Paucatalinone H    | *P. catalpifolia* | Fruit peel | Wang et al. (2019)                       |
| 67        | Paucatalinone F    | *P. catalpifolia* | Fruit peel | Wang et al. (2019)                       |
| 68        | Tomentodiplacone C | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
| 69        | Tomentodiplacone D | *P. tomentosa* | Fruit         | Navrátilová et al. (2013)                |
the UV spectrum obviously (Hanáková et al. 2015, 2017).

In C-geranylated flavanone, the chiral carbon of C-2 in ring C produces different Cotton effects in its CD spectrum at $\lambda$ 320–360 nm and $\lambda$ 280–310 nm (Slade et al. 2005). Most of the Paulownia C-geranylated flavanones possessed a 2$S$ absolute configuration, which could be deduced by a positive effect at approximately 330 nm and a negative effect at approximately 290 nm. However, no obvious Cotton effects were found in their CD spectra of some racemic mixtures of 2$R$ and 2$S$ enantiomers (Fig. 8).

In addition, the key ESI–MS/MS characteristic of Paulownia C-geranylated flavonoids under the positive ion model was different from that under the negative ion model. In the positive ESI–MS/MS test, quasi-molecular ion peaks such as [M+H]$^+$ and/or [M+Na]$^+$ appeared in the ESI–MS$^1$ spectrum. The quasi-molecular ion peak was subjected to MS$^2$ (ESI–MS/MS) analysis, and the main positive fragment ion peak of the parent flavonoid structure with a methylene was generated by the neutral loss of a C$_9$ unit from the C$_{10}$ side chain in the C-geranylated flavonoid by further fragmentation (Hsu et al. 2011; Lin et al. 2012). However, as measured by the negative ESI–MS/MS, the quasi-molecular ion peak as [M–H]$^-$ was generated in the ESI–MS$^1$ spectrum, and the main negative ion peak of the parent flavonoid structure fragment was generated in the ESI–MS$^2$ spectrum by the neutral loss of the whole C$_{10}$ side chain in further fragmentation. The positive and negative ESI-MS/MS assays of diplacone (2), a major Paulownia C-geranyllflavanone, corroborated the above difference (Fig. 9). Furthermore, the UV and ESI-MS/MS features of C-geranylated flavonoids could be used to distinguish this kind of natural constituent. Tang et al. (2017) attempted to detect C-geranylated flavonoids in the fruits of P. catalpifolia by HPLC–DAD–ESI–MS/MS coupling techniques, unfortunately, accurate structures for each detected HPLC signal could not be demonstrated definitively only by UV and MS experiments alone because of the above uncertainties.

**Biological activities of Paulownia C-geranylated flavonoids**

**Antioxidant effects**

Paulownia C-geranylated flavonoids are natural polyphenols, and antioxidant activity is their most basic biological activity, involved in ageing, inflammation, cancer, diabetes, and neurodegenerative diseases, is very important for human health protection.

In general, Paulownia C-geranylated flavonoids possessed very good free radical quenching activity, such as scavenging DPPH (Table 3), due to their ortho-dihydroxy functionality in the B ring. The geranyl side chain did not affect activity significantly, but it could modify the solubility of Paulownia C-geranylated flavonoids, such as diplacone (2), and eventually affected their reaction kinetics (Smékal et al. 2007; Zima et al. 2010; Asai et al. 2008; Wang et al. 2017). However, Paulownia C-geranylated flavonoids revealed different cellular cytoprotective effects on different cell lines damaged by diverse oxidants in vitro (Table 3). Interestingly, diplacone (2) and its unmodified C-geranylated flavanone analogues, 3’-$O$-methyl-5’-hydroxydiplacone (5), 3’-$...
-methyl-5′-O-methyldiplacone (6) and 3′-O-methylidiplacol (15), could significantly decrease the levels of reactive oxygen species and cellular DNA damage in 2 Gy-irradiated AHH-1 cells (Moon et al. 2014). Diplacone (2), paucatalinone A (19) and paucatalinone C (73) also obviously protected premature senescent human embryonic lung diploid fibroblast cells at 10 μM from ageing induced by \( \text{H}_2\text{O}_2 \) (Tang et al. 2017; Wang et al. 2017). Thirteen C-geranylated flavonoids isolated from \( P. \text{catalpifolia} \) had been evaluated for their antioxidant activity on HUVEC injury induced by homocysteine or \( \text{H}_2\text{O}_2 \).
and compounds 2, 25, 26, 34 and 67 caused improved proliferative activity at 10 µM, however, at 20 µM or higher, diplacone (2) expressed cytotoxic activity to HUVECs and reduced its proliferative activity (Chen et al. 2017b; Wang et al. 2019).

Anti-inflammatory effects

For Paulownia C-geranylated flavonoids, only mimulone (1) and diplacone (2) were evaluated in vivo in a colitis model in Wistar rats. When orally administered at a bolus dose of 25 mg/kg, they all exhibited greater effects than the positive control of sulfasalazine, reducing the level of COX-2 and increasing the ratio of pro-MMP2/MMP2 by prophylactic/therapeutic administration (Vochyánová et al. 2015). In addition, the effects of 21 Paulownia C-geranylated flavonoids on the secretion of the typical pro-inflammatory cytokine TNF-α in LPS-stimulated THP-1 cell from were evaluated. Compounds 2, 4, 8, 38 and 56 could affect the secretion of TNF-α at 2.0 µM more than prednisone as the positive control, and mimulone H (38) and tomentodiplacone N (56) significantly increased the level of reactive oxygen species (ROS) in the THP-1 cells without LPS stimulation (Hanákova et al. 2015). In another biological activity assay on human alveolar basal epithelial cells (A549 cells), compounds 23, 26, 35, 52–54 significantly inhibited TNF-α-induced IL-8 levels at a concentration of 2.5 µM without detectable cell toxicity (Ryu et al. 2017).

Fig. 9 Key ESI–MS/MS characteristics of Paulownia C-geranylated flavonoids in positive ion mode and negative ion mode. Key ESI–MS/MS characteristics of Paulownia C-geranylated flavonoids could be described with diplacone (2) as an example. a: Main ESI–MS/MS characteristics of 2 in the positive ion mode. m/z 425.1 is the quasi-molecular ion peak as [M+H]+, and m/z 300.8 is the fragment ion peak of the parent flavonoid structure with a methylene, which was produced by a neutral loss of a C9 unit from the C10 side chain in 2 by further fragmentation. b: Main ESI–MS/MS characteristics of 2 in the negative ion mode. m/z 423.0 is the quasi-molecular ion peak as [M–H]−, and m/z 285.7 is the fragment ion peak of the parent flavonoid structure, which was produced by the neutral loss of the whole C10 side chain in 2 by further fragmentation.
Table 3  Antioxidant activity of different *Paulownia* C-geranylated flavonoids in comparison to standard antioxidants

| Compounds | DPPH quenching activity | Cytoprotective effect (cell viability % at 10 µM) | Activity of the positive control | References |
|-----------|-------------------------|---------------------------------------------|----------------------------------|------------|
| 1         | TEAC 0.4±0.004 at 10 µM<sup>a</sup> | NP<sup>b</sup>                           | NP                               | Šmejkal et al. (2007) |
|           | TEAC 0.02±0.01 at 50 µM |                               |                                  | Zima et al. (2010) |
| 2         | TEAC 5.2±0.001 at 10 µM | NP                           | NP                               | Šmejkal et al. (2007) |
|           | TEAC 1.06±0.04 at 50 µM |                               |                                  | Zima et al. (2010) |
|           | SC<sub>50</sub> 3.2 µg/mL<sup>c</sup> |                               | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) | Asai et al. (2008) |
|           | HUVECs (72.7%)<sup>e</sup> |                               |                                  | Wang et al. (2019) |
| 4         | TEAC 0.8±0.006 at 10 µM | NP                           | NP                               | Šmejkal et al. (2007) |
|           | SC<sub>50</sub> 3.2 µg/mL |                               | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) | Asai et al. (2008) |
| 5         | TEAC 0.98±0.03 at 50 µM | NP                           | NP                               | Zima et al. (2010) |
| 6         | TEAC 0.29±0.02 at 50 µM |                               |                                  | Zima et al. (2010) |
| 10        | SC<sub>50</sub> > 50 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 11        | SC<sub>50</sub> > 50 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 12        | SC<sub>50</sub> 4.5 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 14        | SC<sub>50</sub> 1.9 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 15        | TEAC 0.10±0.00 at 50 µM | NP                           | NP                               | Zima et al. (2010) |
| 20        | HUVECs (56.8%)                  |                               |                                  | Wang et al. (2019) |
| 21        | SC<sub>50</sub> 1.9 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 22        | SC<sub>50</sub> 1.8 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 24        | HUVECs (56.9%)                  |                               |                                  | Wang et al. (2019) |
| 25        | HUVECs (69.1%)                  |                               |                                  | Wang et al. (2019) |
| 26        | HUVECs (70.0%)                  |                               |                                  | Wang et al. (2019) |
| 32        | SC<sub>50</sub> 2.9 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 33        | TEAC 0.14±0.04 at 50 µM | NP                           | NP                               | Zima et al. (2010) |
| 34        | SC<sub>50</sub> 1.8 µg/mL | α-Tocopherol (SC<sub>50</sub> 4.7 µg/mL) |                                  | Asai et al. (2008) |
| 36        | TEAC 2.0±0.007 at 10 µM | NP                           | NP                               | Šmejkal et al. (2007) |
| 37        | HUVECs (70.3%)                  |                               |                                  | Wang et al. (2019) |
| 40        | TEAC 0.12±0.00 at 50 µM | NP                           | NP                               | Zima et al. (2010) |
| 51        | HUVECs (55.4%)                  |                               |                                  | Wang et al. (2019) |
| 54        | HUVECs (56.1%)                  |                               |                                  | Wang et al. (2019) |
| 55        | HUVECs (69.6%)                  |                               |                                  | Wang et al. (2019) |
| 66        | HUVECs (59.1%)                  |                               |                                  | Wang et al. (2019) |
| 67        | HUVECs (78.4%)                  |                               |                                  | Wang et al. (2019) |
| 73        | IC<sub>50</sub> 4.82 µM<sup>d</sup> | α-Tocopherol (IC<sub>50</sub> 12.11 µM) |                                  | Wang et al. (2017) |
| 74        | IC<sub>50</sub> 5.15 µM | 2BS cells (83.26%)<sup>f</sup> | α-Tocopherol (74.55%)            | Wang et al. (2017) |
| 75        | IC<sub>50</sub> 15.22 µM | 2BS cells (61.04%)            | α-Tocopherol (74.55%)            | Wang et al. (2017) |

<sup>a</sup> Determined by the TEAC method.
<sup>b</sup> NP: Not yet published.
<sup>c</sup> SC<sub>50</sub>: 50% Survival concentration.
<sup>d</sup> IC<sub>50</sub>: 50% Inhibitory concentration.
<sup>e</sup> HUVECs: Human Umbilical Vein Endothelial Cells.
<sup>f</sup> 2BS cells: 2B cells.

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Cytotoxic activities

The cytotoxic activities of some Paulownia C-geranylated flavonoids were tested in different cell lines (Table 5). Compounds 2–5 were all active (EC50 < 10 µM) against breast carcinoma (MCF-7), T-lymphoblastic leukaemia (CEM), multiple myeloma (RPMI 8226 and U266), cervical cancer cells (HeLa), monocytic leukaemia cell line THP-1, and the normal BJ fibroblast cell line (Šmejkal et al. 2010). Moreover, compounds 1, 6, 8, 10, 15, 39, 56, and 64 also showed potential cytotoxic effects all with IC50 values < 10 µM on the viability of THP-1 cells (Hana´ková et al. 2015). In addition, paucatalinone A (19) displayed good antiproliferative effects on human lung cancer cells A549 (IC50 8.9 µM) with a clear increase in the percentage of cells in G1 phase and a decrease in the percentage of cells in S and G2/M phases in comparison with the control cells (Gao et al. 2015). Tomentodiplacone B (40) could inhibit human monocytic leukaemia (THP-1) cell growth in a dose-dependent manner at concentrations of 5 µM or higher by directly inhibiting the cyclin-dependent kinase 2 signal pathway as a possible mechanisms (Kollár et al. 2011).

Antimicrobial effects

Antimicrobial assays for some Paulownia C-geranylated flavonoids were carried out, and the results indicated that Gram-positive bacteria were susceptible to this kind of natural product, however, none of the compounds was able to inhibit the growth of gram-negative bacteria or the yeast. Compounds 1, 2, 4, 5, 6, 15 and 33 exhibited positive activity in the range of the concentrations tested for Bacillus, Enterococcus, Listeria, Staphylococcus strains and 15 was the most active in MICs of 2–4 µg mL−1 (Šmejkal et al. 2008a, b). Furthermore, compounds 1 and 15 were also active to various methicillin resistant strains of S. aureus (MRSA) with promising anti-MRSA activity (Ríos and Recio 2005). Compound 40 inhibited the growth of different MRSA bacteria with MICs in the range of 8–16 µg mL−1 (Navrátilová et al. 2013; 2016).

Antiparasitic activities

The antiparasitic activities of Paulownia C-geranylated flavonoids mainly involved the effects of seven unmodified C-geranylfavanones on Leishmania species, including mimulone (1), diplacone (2), 3′-O-methyl diplacone (4), 3′-O-methyl-5′-hydroxydiplacone (5), 3′-O-methyl-5′-O-methyl diplacone (6), 4′-O-methyl diplacone (7), and 3′-O-methyl diplacol (15). Compounds 4 and 6 achieved significant antileishmanial activity with IC50 values of 10.4 and 12.7 µM against L. donovani, and 11.3 and 8.0 µM against L. braziliensis, respectively, compared with 9.5 and 6.7 µM of miltefosine as the positive control (Navrátilová et al. 2016). Furthermore, diplacone (2) was also active (IC50 1.4 µg mL−1) against the related kinetoplastid parasite Trypanosoma brucei brucei (Salem et al. 2011).

Enzymatic inhibitory effects

Different kinds of enzymatic assays in vitro were explored for the biological screening of Paulownia C-geranylated flavonoids (Table 6).
| Compounds | Anti-inflammatory effects\(^{a,b}\) | Positive control | References |
|-----------|-------------------------------------|------------------|------------|
| 1         | Colitismodel induced in Wistar rats (ameliorated the symptoms of colitis; reduced the levels of COX-2; increased the ratio of pro-MMP2/MMP2) | Sulfasalazine | Vochýánová et al. (2015) |
| 2         | Colitismodel induced in Wistar rats (ameliorated the symptoms of colitis; reduced the levels of COX-2; increased the ratio of pro-MMP2/MMP2) LPS-induced NO production in RAW264.7 cells (IC\(_{50}\) 5.02 µM) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 3         | LPS-induced murine macrophage cell lineJ774.A1 (ROS level; 1xB-α degradation; COX-2 expression) | NP | Hošek et al. (2013) |
| 4         | LPS-induced THP-1 cells (TNF-α expression; MCP-1 expression; ZFP36 expression) | Indomethacin | Hošek et al. (2010) |
| 5         | LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS) | Prednisone | Hanáková et al. (2015) |
| 6         | LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 7         | LPS-induced NO production in RAW264.7 cells (IC\(_{50}\) 6.44 µM) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 8         | LPS-induced NO production in RAW264.7 cells (IC\(_{50}\) 4.53 µM) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 9         | LPS-induced NO production in RAW264.7 cells (IC\(_{50}\) 5.94 µM) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 10        | LPS-induced NO production in RAW264.7 cells (IC\(_{50}\) 1.48 µM) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 11        | LPS-induced NO production in RAW264.7 cells (IC\(_{50}\) 23.49 µM) | Aminoguanidine (IC\(_{50}\) 16.60 µM) | Jin et al. (2015) |
| 12        | LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS) | Prednisone | Hanáková et al. (2017) |
| 13        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 14        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 15        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 16        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 17        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 18        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 19        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 20        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 21        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 22        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 23        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 24        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 25        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 26        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 27        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 28        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 29        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 30        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 31        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 32        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 33        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 34        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 35        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 36        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 37        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 38        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 39        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 40        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 41        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 42        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 43        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 44        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 45        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 46        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 47        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 48        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 49        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 50        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 51        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 52        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 53        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 54        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 55        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |
| 56        | TNF-α-stimulated A549 cells (IL-8 expression) | NP | Ryu et al. (2017) |

\(^{a}\) Individual cell models, including RAW264.7 cells: murine macrophage cell line; J774.A1 cells: murine macrophage cell line; THP-1 cells: monocytic leukaemia cell line; A549 cells: human alveolar basal epithelial adenocarcinoma cell line

\(^{b}\) Individual enzymes and inflammatory cytokines, including COX-2: cyclooxygenase-2; MMP2: matrix metalloproteinase-2; ZFP36: zinc finger protein 36; NF-κB: nuclear factor κB; ROS: reactive oxygen species; IL-8: interleukin 8; TNF-α: pro-inflammatory cytokine

\(^{c}\) LPS: Lipopolysaccharide
The cholinesterase inhibitory effects of nine Paulownia C-geranylated flavonoids (1, 2, 4, 7, 9, 11, 13, 15 and 16) were estimated and all of them apart from 11 exhibited cholinesterase inhibition with IC\(_{50}\) values ranging from 7.2 to 316 \(\mu\)M for human acetylcholinesterase (hAChE) and 1.4–80.0 \(\mu\)M for butyrylcholinesterase (BChE). Diplacone (2) was the most effective inhibitor (IC\(_{50}\) 7.2 and 1.4 \(\mu\)M), compared with IC\(_{50}\) 0.15 and 3.7 \(\mu\)M for the positive control, eserine (Cho et al. 2012).

Twelve Paulownia C-geranylated flavanones (1, 2, 4, 7, 11, 13, 15, 47–51) were selected to examine their inhibition of severe acute respiratory syndrome-CoV papain-like protease (SARS-CoV PLpro) and all were active in a dose-dependent manner with IC\(_{50}\) values ranging between 5.0 and 14.4 \(\mu\)M. Those C-geranylated flavanones with a 3,4-dihydro-2\(H\)-pyran moiety (47–51) showed better inhibition than their parent compounds, and 48 was considered as a reversible inhibitor with a y axis intercept of 0 and IC\(_{50}\) of 6.1 \(\mu\)M (Cho et al. 2013).

Moreover, the antiparasitic activities of some Paulownia C-geranylated flavonoids were further evaluated by molecular docking energy analysis to

### Table 5 Cytotoxic activity of different Paulownia C-geranylated flavonoids against human cancer cell lines in comparison to the standard cytotoxic agents

| Compounds | Cytotoxic effect\(^a\) | Positive control | References |
|-----------|------------------------|------------------|------------|
| 1         | WB 344 (NE)\(^b\)      | NP               | Šmejkal et al. (2007) |
|           | THP-1 (IC\(_{50}\) 6.6 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 2         | WB 344 (IC\(_{50}\) 14.3 \(\mu\)M) | NP               | Šmejkal et al. (2007) |
|           | MCF (EC\(_{50}\) < 10 \(\mu\)M); CEM (EC\(_{50}\) 3.2 \(\mu\)M); RPMI8226 (EC\(_{50}\) 2.4 \(\mu\)M); HeLa (EC\(_{50}\) < 10 \(\mu\)M); BJ (EC\(_{50}\) 5.9 \(\mu\)M); THP-1 (EC\(_{50}\) < 10 \(\mu\)M) | Olomoucine II, Diaziquone, Oxaliplatin, Camptothecin (Data in reference) |
| 3         | MCF (EC\(_{50}\) < 10 \(\mu\)M); CEM (EC\(_{50}\) < 10 \(\mu\)M); RPMI8226 (EC\(_{50}\) 7.1 \(\mu\)M); U266 (EC\(_{50}\) 1.9 \(\mu\)M); HeLa (EC\(_{50}\) 6.3 \(\mu\)M); BJ (EC\(_{50}\) 7.5 \(\mu\)M); THP-1 (EC\(_{50}\) 8.5 \(\mu\)M) | Olomoucine II, Diaziquone, Oxaliplatin, Camptothecin (Data in reference) |
| 4         | WB 344 (IC\(_{50}\) 30.2 \(\mu\)M) | NP               | Šmejkal et al. (2007) |
|           | MCF (EC\(_{50}\) < 10 \(\mu\)M); CEM (EC\(_{50}\) < 10 \(\mu\)M); RPMI8226 (EC\(_{50}\) 7.3 \(\mu\)M); U266 (EC\(_{50}\) 5.5 \(\mu\)M); HeLa (EC\(_{50}\) 7.4 \(\mu\)M); BJ (EC\(_{50}\) 7.5 \(\mu\)M); THP-1 (EC\(_{50}\) < 10 \(\mu\)M) | Olomoucine II, Diaziquone, Oxaliplatin, Camptothecin (Data in reference) |
| 5         | THP-1 (EC\(_{50}\) 7.1 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 6         | THP-1 (IC\(_{50}\) 7.9 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 8         | THP-1 (IC\(_{50}\) 6.4 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 10        | THP-1 (IC\(_{50}\) 8.0 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 15        | THP-1 (IC\(_{50}\) 7.2 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 19        | A549 (IC\(_{50}\) 8.9 \(\mu\)M) | Oridonin (IC\(_{50}\) 18.7 \(\mu\)M) | Gao et al. (2015) |
| 27        | A549 (IC\(_{50}\) 23.7 \(\mu\)M) | Oridonin (IC\(_{50}\) 18.7 \(\mu\)M) | Gao et al. (2015) |
| 39        | THP-1 (IC\(_{50}\) 6.5 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 40        | THP-1 (IC\(_{50}\) > 5 \(\mu\)M) | NP               | Kollár et al. (2011) |
| 56        | THP-1 (IC\(_{50}\) 6.7 \(\mu\)M) | NP               | Hanáková et al. (2015) |
| 60        | A549 (IC\(_{50}\) 22.1 \(\mu\)M) | Oridonin (IC\(_{50}\) 18.7 \(\mu\)M) | Gao et al. (2015) |
| 64        | THP-1 (IC\(_{50}\) 6.7 \(\mu\)M) | NP               | Hanáková et al. (2015) |

\(^a\) Individual cell models, including WB 344: epithelioid cell line; A549: lung cancer cell line; MCF-7: breast carcinoma cell line; CEM: T-lymphoblastic leukaemia cell line; RPMI 8226 and U266: multiple myeloma cell line; HeLa: cervical cancer cell line; THP-1: monocytic leukemia cell line; BJ: fibroblast cell line

\(^b\) NE: The IC\(_{50}\) could not be estimated because the cytotoxicity was less than 50% of that of the control
Table 6 Enzymatic inhibitory effects of different *Paulownia* C-geranylated flavonoids in comparison to the positive controls

| Compounds | Enzymatic inhibitory effects\(^a\) (IC\(_{50}\), \(\mu\)M) | Positive control | References |
|-----------|--------------------------------------------------------|-----------------|------------|
| 1         | COX-1 (3.7); COX-2 (6.0)                               | Ibuprofen (IC\(_{50}\) 6.3, 4.2 \(\mu\)M) | Hanáková et al. (2017) |
|           | SARS-CoV PLpro (14.4)                                  | NP              | Cho et al. (2013) |
|           | PTP1B (1.9); \(\alpha\)-Glucosidase (30.7)             | NaVO\(_4\) (IC\(_{50}\) 32.6 \(\mu\)M); Voglibose (IC\(_{50}\) 24.5 \(\mu\)M) | Song et al. (2017) |
| 2         | COX-1 (1.8), COX-2 (4.2); 5-LOX (0.05)                 | Ibuprofen (6.3, 4.2); Zileuton (0.35) | Hanáková et al. (2017) |
|           | AChE (7.2), BChE (1.4)                                 | Eserine (0.15, 3.7) | Cho et al. (2012) |
| 3         | HNE (7.8)                                              | Luteolin (12.7)  | Ryu et al. (2017) |
|           | SARS-CoV PLpro (13.2)                                  | NP              | Cho et al. (2013) |
|           | PTP1B (3.9); \(\alpha\)-Glucosidase (18.4)             | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 4         | COX-1 (3.3), COX-2 (10.6); 5-LOX (0.06)                | Ibuprofen (6.3, 4.2); Zileuton (0.35) | Hanáková et al. (2017) |
| 5         | SARS-CoV PLpro (12.7)                                  | NP              | Cho et al. (2013) |
|           | PTP1B (8.2); \(\alpha\)-Glucosidase (25.8)             | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 6         | COX-1 (4.2), COX-2 (6.4)                               | Eserine (0.15, 3.7) | Cho et al. (2012) |
| 7         | PTP1B (3.8); \(\alpha\)-Glucosidase (78.9)             | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 8         | HNE (3.3)                                              | Luteolin (12.7)  | Ryu et al. (2017) |
|           | SARS-CoV PLpro (9.2)                                   | NP              | Cho et al. (2013) |
|           | PTP1B (5.9); \(\alpha\)-Glucosidase (6.5)              | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 11        | SARS-CoV PLpro (13.9)                                  | NP              | Cho et al. (2013) |
| 12        | AChE (22.9), BChE (6.4)                                | Eserine (0.15, 3.7) | Cho et al. (2012) |
| 13        | AChE (31.9), BChE (12.7)                               | Eserine (0.15, 3.7) | Cho et al. (2012) |
|           | SARS-CoV PLpro (9.2)                                   | NP              | Cho et al. (2013) |
|           | PTP1B (12.7); \(\alpha\)-Glucosidase (25.8)            | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 15        | PTP1B (5.9); \(\alpha\)-Glucosidase (78.9)             | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 16        | AChE (15.6), BChE (3.8)                                | Eserine (0.15, 3.7) | Cho et al. (2012) |
|           | PTP1B (6.6); \(\alpha\)-Glucosidase (2.2)              | NaVO\(_4\) (32.6); Voglibose (24.5) | Song et al. (2017) |
| 21        | HNE (6.7)                                              | Luteolin (12.7)  | Ryu et al. (2017) |
| 22        | HNE (6.3)                                              | Luteolin (12.7)  | Ryu et al. (2017) |
| 23        | HNE (2.4)                                              | Luteolin (12.7)  | Ryu et al. (2017) |
| 24        | HNE (15.4)                                             | Luteolin (12.7)  | Ryu et al. (2017) |
| 25        | HNE (13.6)                                             | Luteolin (12.7)  | Ryu et al. (2017) |
| 26        | HNE (8.4)                                              | Luteolin (12.7)  | Ryu et al. (2017) |
| 27        | SARS-CoV PLpro (6.2)                                   | NP              | Cho et al. (2013) |
| 28        | SARS-CoV PLpro (6.1)                                   | NP              | Cho et al. (2013) |
| 29        | SARS-CoV PLpro (11.6)                                  | NP              | Cho et al. (2013) |
| 30        | SARS-CoV PLpro (5.0)                                   | NP              | Cho et al. (2013) |
| 31        | 5-LOX (0.35)                                           | Zileuton (0.35)  | Hanáková et al. (2017) |
| 32        | 5-LOX (0.37)                                           | Zileuton (0.35)  | Hanáková et al. (2017) |

\(^a\) Individual enzyme models, including COX-1 and COX-2: cyclooxygenase-1 and 2; 5-LOX: 5-lipoxygenase; SARS-CoV PLpro: severe acute respiratory syndrome-CoV papain-like protease; PTP1B: protein tyrosine phosphatase 1B; hAChE: human acetylcholinesterase; BChE: butyrylcholinesterase; HNE: human neutrophil elastase
identify potential protein targets of *Leishmania* enzymes. Docking energies (value of Edock) for diplacone (2) to *L. major* *N*-myristoyltransferase (−135.7 kJ/mol); 3′-O-methyl diplacone (4) to *L. pteridin reductase* 1 (−142.2 kJ/mol), to *L. glycerol-3-phosphate dehydrogenase* (−148.3 kJ/mol) and to *L. cyclophilin* (−126.5 kJ/mol); 4′-*O*-methyl diplacone (7) to *L. glycerol-3-phosphate dehydrogenase* (−143.1 kJ/mol); and 3′-*O*-methyl diplacone (16) displayed potent inhibition against an α-glucosidase with IC$_{50}$ 2.2 µM compared with IC$_{50}$ 24.5 µM for the reference inhibitor, Voglibose (Song et al. 2017).

**Neuroprotective effects**

The neuroprotective effects of mimulone (1) and diplacone (2) against glutamate-induced neurotoxicity were studied in primary cultured rat cortical cells. It was found that only diplacone (2) weakly attenuated glutamate-induced toxicity at 10 µM (Kim et al. 2010).

**Structure–activity relationship (SAR) of *Paulownia* C-geranylated flavonoids**

Possible SARs involved in the radical scavenging of flavonoids have been discussed carefully (Cao et al. 1997; Dugas et al. 2000; Sekher et al. 2001; Heim et al. 2002; Zheng et al. 2019), however, it could be considered that the substitution of a geranyl group or its oxidized congeners did not significantly alter the radical scavenging activity of *Paulownia* C-geranylated flavonoids (Smejkal et al. 2007; Asai et al. 2008; Wang et al. 2017). Regarding cellular biological activities (anti-inflammatory and cytotoxic effects), antibacterial and antiparasitic activities, and enzymatic inhibitions, an ortho-dihydroxy arrangement at C-3′,4′ of the B-ring was considered an essential group but also enhanced the cytotoxic risk. Hydroxylation at C-3 in ring C and 4′-methoxy substitution of ring B might cause a loss of bioactive potency (Šmejkal et al. 2008a; Wang et al. 2019). In addition, the unmodified geranyl group at the C-6 position seemed to be crucial for these various biological effects in vitro and in vivo (Vochyánová et al. 2015) of C-geranylated flavonoids, however, hydroxylation on the distal end of the geranyl substituent decreased the biological activities revealed by different research (Alcaráz et al. 2000; Šmejkal et al. 2010; Hanáková et al. 2017; Ryu et al. 2017). The presence of a β-carbon (proximal) OH group on the geranyl chain did not affect the cytotoxicity (Hanáková et al. 2015). In addition, the 3,4-dihydro-2*H*-pyran moiety in some *Paulownia*...
C-geranylated flavonoids seemed to be positive for their SARS-CoV PLpro enzyme inhibition (Cho et al. 2013).

**Research and application prospects of Paulownia C-geranylated flavonoids**

Phytochemical research demonstrated that *Paulownia* species are natural resources of C-geranylated flavonoids with varied geranyl substituents. There might be another C-geranylated flavonoid constituent with more attractive geranyl variations, such as the cyclic monoterpenic side-chain in paucatalinone F (67, Wang et al. 2019), metabolized in *Paulownia* species. Therefore, it is worthwhile to carry out further investigations on *Paulownia* species for more novel C-geranylated flavonoids on the phytochemical view.

Moreover, it was reported that the C-isoprenoid chain could increase the affinity of flavonoids towards P-glycoprotein (P-gp) located at the cell membrane because of the increased hydrophobicity (Barron et al. 2002). Some *Paulownia* C-geranylated flavonoids were supposed to have a greater ability to penetrate the membranes of cells than a lipophilic substituent (Tsuchiya and Iinuma 2000; Šmejkal 2014). We considered the possibility that different modifications of geranyls in C-geranylated flavonoids could influence their transmembrane absorption or intracellular distribution. Unfortunately, almost none of the *Paulownia* C-geranylated flavonoids had been assayed to evaluate these correlative physiological effects. The role of diverse geranyl variations in *Paulownia* C-geranylated flavonoids in these physiological effects should be worth evaluating in the further studies.

Among the *Paulownia* C-geranylated flavonoids, diplacone (2), first isolated from *Diplacus aurantiacus* (Lincoln 1980), was a main component with a high content in the flower and fruit of *P. tomentosa* (Jiang et al. 2004; Chen et al. 2009; Holubová and Šmejkal 2011). Recently, a series of biological activities such as those mentioned above were evaluated for this compound. The results indicated that it possessed excellent antioxidant and anti-inflammatory effects, and it was considered as a potential antioxidant therapy agent for the treatment of inflammatory bowel disease (Moura et al. 2015) and as a potential novel 5-lipoxygenase inhibitor for the treatment of asthma (Bruno et al. 2018). At present, diplacone and its isomers have been protected by patent application as a pharmaceutical composition for treating an ocular disease (Liao 2016). Diplacone may be used as a lead compound for new drug design.

**Conclusions**

The article presents an overview of C-geranylated flavonoids from *Paulownia* species focusing on their structural variety, key spectroscopic characteristics, biological activity with structure–activity relationships and application prospects. To date, 76 naturally occurring *Paulownia* C-geranylated flavonoids have been reported in the phytochemical literature. Among them, C-geranylflavanones were predominant constituents with a single geranyl substituent mainly attached to the C-6 position of the flavonoid skeleton. Furthermore, the geranyl substituent could suffer different modifications, such as oxidation (hydroxylation and carbonylation), dehydration, cyclization, or special reduction, to result in the structural variety and novelty of *Paulownia* C-geranylflavonoids. As a natural resource, fruits of *P. tomentosa* were explored more abundantly and *P. catalpifolia* gave rise to some unusual C-geranylflavonoids. Unfortunately, other *Paulownia* species were with poor attention by researchers and need further phytochemical and pharmacological investigations.

Meanwhile, *Paulownia* C-geranylflavonoids displayed a wide spectrum of biological activities associated with their structural varieties and their antioxidant and anti-inflammatory activities were the focus of pharmacological research. Given the traditional medicinal use of *Paulownia* plants, it is worthwhile to evaluate some *Paulownia* C-geranylflavonoids on some airway inflammation diseases, such as chronic bronchitis and asthma.

In brief, structural variations in *Paulownia* C-geranylflavonoids with excellent biological activities suggested this kind of constituent might be worthy of further study and may be valuable for the development of new drug candidates.

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