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

Chun-lei Cheng · Xian-hui Jia · Cheng-mei Xiao · Wen-zhao Tang

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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 (C₁₀, 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' or C-3' 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

C. Cheng
Shandong Institute for Food and Drug Control, Jinan
250101, Shandong, People's Republic of China

X. Jia · C. Xiao · W. Tang (✉)
Institute of Materia Medica, Shandong Academy of
Medical Sciences, No. 18877, Jingshi Road, Jinan
250062, Shandong, People's Republic of China
e-mail: twzsd@sina.com

X. Jia · C. Xiao · W. Tang
Key Laboratory for Biotech-Drugs Ministry of Health,
Jinan 250062, Shandong, People's Republic of China

X. Jia · C. Xiao · W. Tang
Key Laboratory for Rare and Uncommon Diseases of
Shandong Province, Jinan 250062, Shandong, People's
Republic of China

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,

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

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

Table 1 *Paulownia* plants in China

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

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

^a Status as “Synonym”

^b 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-geranylfavonoids

Seventy-six C-geranylfavonoids (**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. Paucatalinone A (**19**) was also the first sample as a natural dimeric C-geranylated flavanone derivative (Gao et al. 2015). In *Paulownia* C-geranylated

flavanones, 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 2*R* and 2*S* enantiomers. Moreover, all the stereogenic centres of C-2 and C-3 in *Paulownia* C-geranylated flavanones **13**, **14**, **15**, **22**, **24**, **32**, **36**, **51**, **52**, and **58** were 2*R*, 3*R* configurations, although **17** was a racemic mixture of 2*R*, 3*R* and 2*S*, 3*S* 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-geranylfavonoids 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(*E*)-octenyl substituent (**20–27**) or a rare (2*E*,5*E*)-7-hydroxy-3,7-dimethylocta-2,5-dien-1-yl substituent (**40**); at C-6'' to achieve a 6-hydroxy-3,7-dimethyl-2(*E*)-7-octadienyl-substituent (**28–37**), which could be further oxidized

Fig. 2 Unmodified C-geranylfavonones isolated from the *Paulownia* genus

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

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-geranylflavanoids (Fig. 4). The pyran or furan moiety could be generated in *Paulownia* C-geranylflavanoids 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-tetrahydropyrano moiety, and compounds **57–62**, containing a 2,3-dihydropyrano 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. 4 Cyclic modified *C*-geranylflavanones isolated from the *Paulownia* genus

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 monoterpene side-chain isolated from *Paulownia* plants up to now (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 C_7 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(*E*)-octenyl substituent (**74–76**).

Fig. 5 Degraded C-geranylflavanones isolated from the *Paulownia* genus

Fig. 6 C-geranylated flavones isolated from the *Paulownia* genus

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-geranylflavonoids 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-geranylflavanones 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-geranylflavonoids 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-geranylflavonoids in *P. tomentosa* fruits (Holubová and Šmejkal 2011).

Spectroscopic and structural characteristics of *Paulownia* C-geranylflavonoids

Two structural subtypes of *Paulownia* C-geranylflavonoids were isolated, C-geranylated flavanone and C-geranylated flavone. Their UV features, a main maximum absorption at approximately λ 290 nm with a shoulder peak at approximately λ 230 nm and a weak absorption at approximately λ 340 nm for C-geranylflavanone and two main maximum UV absorption at approximately λ 220–280 nm and λ 300–400 nm for C-geranylflavone (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 λ 230 and 275 nm, and a shoulder peak at approximately λ 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	<i>P. tomentosa</i>	Fruit	Navrátilová et al. (2013)
				Cho et al. (2013)
		<i>P. fortunei</i>	Flower	Hanáková et al. (2015)
				Chen et al. (2009)
2	Diplacone	<i>P. tomentosa</i>	Jiang et al. (2004)	
			Flower	Duan et al. (2007)
			Leaf	Li et al. (2008)
			Fruit secretion	Asai et al. (2008)
		<i>P. fortunei</i>	Fruit	Navrátilová et al. (2013)
				Cho et al. (2013)
				Ryu et al. (2017)
			Flower	Chen et al. (2009)
				Jiang et al. (2004)
			Flower	Duan et al. (2007)
3	Schizolaenone C	<i>P. catalpifolia</i>	Fruit	Wang et al. (2017)
		<i>P. coreana</i>	Flower	Jin et al. (2015)
4	3'- <i>O</i> -methyl diplacone	<i>P. tomentosa</i>	Fruit	Šmejkal et al. (2010)
5	3'- <i>O</i> -methyl-5'-hydroxydiplacone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Fruit	Šmejkal et al. (2007)
		<i>P. fortunei</i>		Cho et al. (2013)
				Hanáková et al. (2015)
				Ryu et al. (2017)
			Flower	Duan et al. (2007)
			Fruit	Šmejkal et al. (2008a)
			Flower	Jin et al. (2015)
			Fruit	Šmejkal et al. (2008a)
			Fruit secretion	Asai et al. (2008)
			Fruit	Cho et al. (2013)
6	3'- <i>O</i> -methyl-5'- <i>O</i> -methyl diplacone	<i>P. tomentosa</i>	Fruit	Hanáková et al. (2015)
7	4'- <i>O</i> -methyl diplacone	<i>P. tomentosa</i>	Fruit	Ryu et al. (2017)
8	3',4'- <i>O</i> -dimethyl-5'-hydroxydiplacone	<i>P. tomentosa</i>	Fruit	Asai et al. (2008)
9	6-Geranyl-5,7,3',5'-tetrahydroxy-4'-methoxyflavanone	<i>P. tomentosa</i>	Fruit secretion	Hanáková et al. (2015)
			Fruit	
10	6-Geranyl-5,7-dihydroxy-3',4'-dimethoxyflavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Fruit	Hanáková et al. (2015)
11	6-Geranyl-4',5,7-trihydroxy-3',5'-dimethoxyflavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Fruit	Navrátilová et al. (2013)
				Cho et al. (2013)
				Hanáková et al. (2015)
		<i>P. coreana</i>	Flower	Ryu et al. (2017)
				Jin et al. (2015)
12	6-Geranyl-4',5,5',7-tetrahydroxy-3'-methoxyflavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Fruit	Navrátilová et al. (2013)
13	6-Geranyl-3,3',5,7-tetrahydroxy-4'-methoxyflavanone (4'- <i>O</i> -methyl diplacol)	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Fruit	Cho et al. (2013)
		<i>P. fortunei</i>	Flower	Ryu et al. (2017)
				Zhang and Li (2008)

Table 2 continued

Compounds	Name	Species	Part	References
14	Diplacol	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
		<i>P. coreana</i>	Flower	Jin et al. (2015)
15	3'- <i>O</i> -methyl diplacol	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Flower	Kobayashi et al. (2008)
			Fruit	Navrátilová et al. (2013)
				Cho et al. (2013)
				Hanáková et al. (2015)
				Šmejkal et al. (2008a)
		<i>P. fortunei</i>	Flower	Zhang and Li (2008)
		<i>P. coreana</i>	Flower	Jin et al. (2015)
16	6-Geranyl-3,3',5,5',7-pentahydroxy-4'-methoxyflavane	<i>P. tomentosa</i>	Fruit	Cho et al. (2012)
17	3'- <i>O</i> -methyl-5'-methoxydiplacol	<i>P. tomentosa</i>	Fruit	Šmejkal et al. (2007)
18	3'- <i>O</i> -methyl-5'-hydroxydiplacol	<i>P. coreana</i>	Flower	Jin et al. (2015)
19	Paucatalinone A	<i>P. catalpifolia</i>	Fruit	Gao et al. (2015)
20	5,7-Dihydroxy-6-(7-hydroxy-3,7-dimethyloct-2-en-1-yl)-2S-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one	<i>P. tomentosa</i>	Fruit	Ryu et al. (2017)
		<i>P. catalpifolia</i>	Fruit peel	Wang et al. (2019)
21	Prokinawan	<i>P. tomentosa</i>	Flower	Kobayashi et al. (2008)
			Fruit secretion	Asai et al. (2008)
			Fruit	Ryu et al. (2017)
		<i>P. catalpifolia</i>	Fruit	Tang et al. (2017)
22	3,3',4',5,7-Pentahydroxy-6-[7-hydroxy-3,7-dimethyl-2(<i>E</i>)-octenyl]flavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
23	Tomentin J	<i>P. tomentosa</i>	Fruit	Ryu et al. (2017)
24	Paucatalinone J	<i>P. catalpifolia</i>	Fruit	Wang et al. (2019)
25	Isopaucatalinone B	<i>P. catalpifolia</i>	Fruit	Gao et al. (2015)
		<i>P. tomentosa</i>	Fruit	Ryu et al. (2017)
26	Tomentin K	<i>P. tomentosa</i>	Fruit	Ryu et al. (2017)
		<i>P. catalpifolia</i>	Fruit peel	Wang et al. (2019)
27	Paucatalinone B	<i>P. catalpifolia</i>	Fruit	Gao et al. (2015)
28	Mimulone B	<i>P. tomentosa</i>	Fruit	Schneiderová et al. (2013)
		<i>P. coreana</i>	Flower	Jin et al. (2015)
29	Tomentomimulol	<i>P. tomentosa</i>	Fruit	Schneiderová et al. (2013)
30	Tanariflavanone D	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
			Fruit	Schneiderová et al. (2013)
				Ryu et al. (2017)
31	Tanariflavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
32	(2 <i>R</i> ,3 <i>R</i>)-3,3',4',5,7-pentahydroxy-6-[6-hydroxy-3,7-dimethyl-2(<i>E</i>),7-octadienyl]flavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
33	Tomentodiplacone	<i>P. tomentosa</i>	Fruit	Šmejkal et al. (2008a)
34	(2 <i>R</i> ,3 <i>R</i>)-4',5,5',7-tetrahydroxy-3'-methoxy-6-[6-hydroxy-3,7-dimethyl-2(<i>E</i>),7-octadienyl]flavanone	<i>P. tomentosa</i>	Fruit secretion	Asai et al. (2008)
		<i>P. catalpifolia</i>	Fruit peel	Wang et al. (2019)
35	Tomentin I	<i>P. tomentosa</i>	Fruit	Ryu et al. (2017)

Table 2 continued

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

Table 2 continued

Compounds	Name	Species	Part	References
70	Tomentodiplacone E	<i>P. tomentosa</i>	Fruit	Navrátilová et al. (2013)
71	Tomentodiplacone F	<i>P. tomentosa</i>	Fruit	Navrátilová et al. (2013)
72	Mimulone E	<i>P. tomentosa</i>	Fruit	Navrátilová et al. (2013)
73	Paucatalinone C	<i>P. catalpifolia</i>	Fruit	Wang et al. (2017)
74	Paucatalinone D	<i>P. catalpifolia</i>	Fruit	Wang et al. (2017)
75	Paucatalinone E	<i>P. catalpifolia</i>	Fruit	Wang et al. (2017)
76	Paucatalinone K	<i>P. catalpifolia</i>	Fruit peel	Wang et al. (2019)

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 λ 320–360 nm and λ 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–MS¹ spectrum. The quasi-molecular ion peak was subjected to MS² (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 C₉ unit from the C₁₀ 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–MS¹ spectrum, and the main negative ion peak of the parent flavonoid structure fragment was generated in the ESI–MS² spectrum by the neutral loss of the whole C₁₀ side chain in further fragmentation. The positive and negative ESI–MS/MS assays of diplacone (2), a major *Paulownia* *C*-geranylfavanone, 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 (Smejkal 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'-

Fig. 7 UV spectra for *C*-geranylated flavanone and *C*-geranylated flavone. The UV spectra of *C*-geranylated flavanone and *C*-geranylated flavone could be described by diplacone (**2**) and paucatalinone C (**73**) as samples, respectively. **a** UV spectrum of diplacone (**2**) as a *C*-geranylated flavanone with a main maximum absorption at approximately

λ 290 nm, a shoulder peak at approximately λ 230 nm and a weak absorption at approximately λ 340 nm. **b** UV spectrum of paucatalinone C (**73**) as a *C*-geranylated flavone with two main maximum UV absorption at approximately λ 270 nm and λ 350 nm

Fig. 8 Typical CD spectrum of 2*S* configurational isomer and racemic mixtures of 2*R* and 2*S* enantiomers. The typical CD spectrum of 2*S* configurational isomer and racemic mixtures of 2*R* and 2*S* enantiomers could be described by paucatalinone H (**66**) and paucatalinone F (**67**) as samples, respectively. **a** CD

spectrum of paucatalinone H (**66**) as a 2*S* configurational isomer with a positive Cotton effect at approximately 328 nm and a negative effect at approximately 285 nm. **b** CD spectrum of paucatalinone F (**67**) as a racemic mixtures of 2*R* and 2*S* enantiomers with no obvious Cotton effects

O-methyl-5'-*O*-methyldiplacone (**6**) and 3'-*O*-methyldiplacol (**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 μ M from ageing induced by H_2O_2 (Tang et al. 2017; Wang et al. 2017). Thirteen *C*-geranylated flavonoids isolated from *P. catalpifolia* had been evaluated for their antioxidant activity on HUVEC injury induced by homocysteine or H_2O_2 ,

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 C_9 unit from the C_{10} 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 C_{10} side chain in **2** by further fragmentation

and compounds **2**, **25**, **26**, **34** and **67** caused improved proliferative activity at 10 μ M, however, at 20 μ M 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 (Vočhyánová et al. 2015).

Moreover, different pro-inflammatory and anti-inflammatory cytokines produced by various inflammatory cell models were detected in vitro to evaluate the anti-inflammatory effects of *Paulownia* C-geranylated flavonoids (Table 4). Diplacone (**2**) significantly downregulated the expression of tumour necrosis factor α (TNF- α) and monocyte chemoattractant protein 1 (MCP-1) and upregulated the expression of zinc finger protein 36 (ZFP36) at

10 μ M, with effects even better than those of the positive control of indomethacin (Hošek et al. 2010), which also inhibited I κ B- α degradation and COX-2 expression at 1.25 μ M in the murine macrophage cell line J774.A1 (Hošek et al. 2013). Compounds **2**, **5**, **11**, **14**, **15**, and **17** exhibited significant inhibition of LPS-induced NO production in murine macrophage RAW264.7 cells with IC₅₀ values from 1.48 to 16.66 μ M, compared with IC₅₀ 16.60 μ M of aminoguanidine as the positive control (Jin 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 μ M 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 (Hanáková 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 μ M without detectable cell toxicity (Ryu et al. 2017).

Table 3 Antioxidant activity of different *Paulownia* C-geranylated flavonoids in comparison to standard antioxidants

Compounds	DPPHquenchingactivity	Cytoprotective effect (cell viability % at 10 μ M)	Activity of the positive control	References
1	TEAC 0.4 ± 0.004 at 10 μ M ^a		NP ^b	Šmejkal et al. (2007)
	TEAC 0.02 ± 0.01 at 50 μ M		NP	Zima et al. (2010)
2	TEAC 5.2 ± 0.001 at 10 μ M		NP	Šmejkal et al. (2007)
	TEAC 1.06 ± 0.04 at 50 μ M		NP	Zima et al. (2010)
	SC ₅₀ 3.2 μ g/mL ^c	HUVECs (72.7%) ^c	α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
			NP	Wang et al. (2019)
4	TEAC 0.8 ± 0.006 at 10 μ M		NP	Šmejkal et al. (2007)
	TEAC 0.12 ± 0.02 at 50 μ M		NP	Zima et al. (2010)
	SC ₅₀ 3.2 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
5	TEAC 0.98 ± 0.03 at 50 μ M		NP	Zima et al. (2010)
6	TEAC 0.29 ± 0.02 at 50 μ M		NP	Zima et al. (2010)
10	SC ₅₀ > 50 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
11	SC ₅₀ > 50 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
12	SC ₅₀ 4.5 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
14	SC ₅₀ 1.9 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
15	TEAC 0.10 ± 0.00 at 50 μ M		NP	Zima et al. (2010)
20		HUVECs (56.8%)	NP	Wang et al. (2019)
21	SC ₅₀ 1.9 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
22	SC ₅₀ 1.8 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
24		HUVECs (56.9%)	NP	Wang et al. (2019)
25		HUVECs (69.1%)	NP	Wang et al. (2019)
26		HUVECs (70.0%)	NP	Wang et al. (2019)
32	SC ₅₀ 2.9 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
33	TEAC 0.14 ± 0.04 at 50 μ M		NP	Zima et al. (2010)
34	SC ₅₀ 1.8 μ g/mL		α -Tocopherol (SC ₅₀ 4.7 μ g/mL)	Asai et al. (2008)
		HUVECs (80.6%)	NP	Wang et al. (2019)
36	TEAC 2.0 ± 0.007 at 10 μ M		NP	Šmejkal et al. (2007)
37		HUVECs (70.3%)	NP	Wang et al. (2019)
40	TEAC 0.12 ± 0.00 at 50 μ M		NP	Zima et al. (2010)
51		HUVECs (55.4%)	NP	Wang et al. (2019)
54		HUVECs (56.1%)	NP	Wang et al. (2019)
55		HUVECs (69.6%)	NP	Wang et al. (2019)
66		HUVECs (59.1%)	NP	Wang et al. (2019)
67		HUVECs (78.4%)	NP	Wang et al. (2019)
73	IC ₅₀ 4.82 μ M ^d		α -Tocopherol (IC ₅₀ 12.11 μ M)	Wang et al. (2017)
		2BS cells (83.26%) ^f	α -Tocopherol (74.55%)	Wang et al. (2017)
74	IC ₅₀ 5.15 μ M		α -Tocopherol (IC ₅₀ 12.11 μ M)	Wang et al. (2017)
		2BS cells (61.04%)	α -Tocopherol (74.55%)	Wang et al. (2017)
75	IC ₅₀ 15.22 μ M		α -Tocopherol (IC ₅₀ 12.11 μ M)	Wang et al. (2017)
		2BS cells (58.13%)	α -Tocopherol (74.55%)	Wang et al. (2017)

Table 3 continued

Compounds	DPPHquenchingactivity	Cytoprotective effect (cell viability % at 10 μ M)	Activity of the positive control	References
76		HUVECs (58.2%)	NP	Wang et al. (2019)

^a TEAC: Trolox equivalent antioxidant capacity

^b NP: data are not provided

^c EC₅₀: half maximal effective concentration

^d IC₅₀: inhibitory concentration

^e HUVECs: human umbilical vein endothelial cells

^f 2BS cells: senescent human embryonic lung diploid fibroblasts cells

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 μ M) 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 μ M on the viability of THP-1 cells (Hanáková et al. 2015). In addition, paucatalinone A (**19**) displayed good antiproliferative effects on human lung cancer cells A549 (IC₅₀ 8.9 μ M) 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 μ M or higher by directly inhibiting the cyclin-dependent kinase 2 signal pathway as a possible mechanisms (Kollár et al. 2011).

Antibacterial 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 μ g 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 μ g 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-methyldiplacone (**4**), 3'-O-methyl-5'-hydroxydiplacone (**5**), 3'-O-methyl-5'-O-methyldiplacone (**6**), 4'-O-methyldiplacone (**7**), and 3'-O-methyldiplacol (**15**). Compounds **4** and **6** achieved significant antileishmanial activity with IC₅₀ values of 10.4 and 12.7 μ M against *L. donovani*, and 11.3 and 8.0 μ M against *L. braziliensis*, respectively, compared with 9.5 and 6.7 μ M of miltefosine as the positive control (Navrátilová et al. 2016). Furthermore, diplacone (**2**) was also active (IC₅₀ 1.4 μ g 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).

Table 4 Anti-inflammatory effects of different *Paulownia* C-geranylated flavonoids in comparison to the positive controls

Compounds	Anti-inflammatory effects ^{a,b}	Positive control	References
1	Colitis model induced in Wistar rats (ameliorated the symptoms of colitis; reduced the levels of COX-2; increased the ratio of pro-MMP2/MMP2)	Sulfasalazine	Vochyánová et al. (2015)
2	Colitis model induced in Wistar rats (ameliorated the symptoms of colitis; reduced the levels of COX-2; increased the ratio of pro-MMP2/MMP2)	Sulfasalazine	Vochyánová et al. (2015)
	^c LPS-induced NO production in RAW264.7 cells (IC ₅₀ 5.02 μM)	Aminoguanidine (IC ₅₀ 16.60 μM)	Jin et al. (2015)
	LPS-induced murine macrophage cell line J774.A1 (ROS level; IκB-α degradation; COX-2 expression)	NP	Hošek et al. (2013)
	LPS-induced THP-1 cells (TNF-α expression; MCP-1 expression; ZFP36 expression)	Indomethacin	Hošek et al. (2010)
	LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS)	Prednisone	Hanáková et al. (2015)
4	LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS)	Prednisone	Hanáková et al. (2015)
5	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 6.44 μM)	Aminoguanidine (IC ₅₀ 16.60 μM)	Jin et al. (2015)
14	LPS-induced NO production in RAW264.7 cells (IC ₅₀ 4.53 μM)	Aminoguanidine (IC ₅₀ 16.60 μM)	Jin et al. (2015)
15	LPS-induced NO production in RAW264.7 cells (IC ₅₀ 5.94 μM)	Aminoguanidine (IC ₅₀ 16.60 μM)	Jin et al. (2015)
18	LPS-induced NO production in RAW264.7 cells (IC ₅₀ 16.66 μM)	Aminoguanidine (IC ₅₀ 16.60 μM)	Jin et al. (2015)
23	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)
28	LPS-induced NO production in RAW264.7 cells (IC ₅₀ 23.49 μM)	Aminoguanidine (IC ₅₀ 16.60 μM)	Jin et al. (2015)
35	TNF-α-stimulated A549 cells (IL-8 expression)	NP	Ryu et al. (2017)
38	LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS)	Prednisone	Hanáková et al. (2015)
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)
56	LPS-induced THP-1 cells (TNF-α expression; nuclear translocation of NF-κB; generation of ROS)	Prednisone	Hanáková et al. (2015)

^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

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 µM)	NP	Hanáková et al. (2015)
2	WB 344 (IC ₅₀ 14.3 µM)	NP	Šmejkal et al. (2007)
	MCF (EC ₅₀ < 10 µM); CEM (EC ₅₀ 3.2 µM); RPMI8226 (EC ₅₀ < 10 µM); U266 (EC ₅₀ 2.4 µM); HeLa (EC ₅₀ < 10 µM); BJ (EC ₅₀ 5.9 µM); THP-1 (EC ₅₀ < 10 µM)	Olomoucine II, Diaziquone, Oxaliplatin, Camptothecin (Data in reference)	Šmejkal et al. (2010)
3	MCF (EC ₅₀ < 10 µM); CEM (EC ₅₀ < 10 µM); RPMI8226 (EC ₅₀ 7.1 µM); U266 (EC ₅₀ 1.9 µM); HeLa (EC ₅₀ 6.3 µM); BJ (EC ₅₀ 7.5 µM); THP-1 (EC ₅₀ 8.5 µM)	Olomoucine II, Diaziquone, Oxaliplatin, Camptothecin (Data in reference)	Šmejkal et al. (2010)
4	WB 344 (IC ₅₀ 30.2 µM)	NP	Šmejkal et al. (2007)
	MCF (EC ₅₀ < 10 µM); CEM (EC ₅₀ < 10 µM); RPMI8226 (EC ₅₀ 7.3 µM); U266 (EC ₅₀ 5.5 µM); HeLa (EC ₅₀ 7.4 µM); BJ (EC ₅₀ 4.7 µM); THP-1 (EC ₅₀ < 10 µM)	Olomoucine II, Diaziquone, Oxaliplatin, Camptothecin (Data in reference)	Šmejkal et al. (2010)
	THP-1 (EC ₅₀ 7.1 µM)	NP	Hanáková et al. (2015)
6	THP-1 (IC ₅₀ 7.9 µM)	NP	Hanáková et al. (2015)
8	THP-1 (IC ₅₀ 6.4 µM)	NP	Hanáková et al. (2015)
10	THP-1 (IC ₅₀ 8.0 µM)	NP	Hanáková et al. (2015)
15	THP-1 (IC ₅₀ 7.2 µM)	NP	Hanáková et al. (2015)
19	A549 (IC ₅₀ 8.9 µM)	Oridonin (IC ₅₀ 18.7 µM)	Gao et al. (2015)
27	A549 (IC ₅₀ 23.7 µM)	Oridonin (IC ₅₀ 18.7 µM)	Gao et al. (2015)
39	THP-1 (IC ₅₀ 6.5 µM)	NP	Hanáková et al. (2015)
40	THP-1 (IC ₅₀ > 5 µM)	NP	Kollár et al. (2011)
56	THP-1 (IC ₅₀ 6.7 µM)	NP	Hanáková et al. (2015)
60	A549 (IC ₅₀ 22.1 µM)	Oridonin (IC ₅₀ 18.7 µM)	Gao et al. (2015)
64	THP-1 (IC ₅₀ 6.7 µM)	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 IC₅₀ could not be estimated because the cytotoxicity was less than 50% of that of the control

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 IC₅₀ values ranging from 7.2 to 316 µM for human acetylcholinesterase (hAChE) and 1.4–80.0 µM for butyrylcholinesterase (BChE). Diplacone (**2**) was the most effective inhibitor (IC₅₀ 7.2 and 1.4 µM), compared with IC₅₀ 0.15 and 3.7 µM 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 IC₅₀ values ranging between 5.0 and 14.4 µM. Those C-geranylated flavanones with a 3,4-dihydro-2H-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 IC₅₀ of 6.1 µM (Cho et al. 2013).

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

Table 6 Enzymatic inhibitory effects of different *Paulownia* C-geranylated flavonoids in comparison to the positive controls

Compounds	Enzymatic inhibitory effects ^a (IC ₅₀ , μM)	Positive control	References
1	COX-1 (3.7); COX-2 (6.0)	Ibuprofen (IC ₅₀ 6.3, 4.2 μM)	Hanáková et al. (2017)
	SARS-CoV PLpro (14.4)	NP	Cho et al. (2013)
	PTP1B (1.9); α-Glucosidase (30.7)	NaVO ₄ (IC ₅₀ 32.6 μM); Voglibose (IC ₅₀ 24.5 μM)	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)
	SARS-CoV PLpro (10.4)	NP	Cho et al. (2013)
4	HNE (7.8)	Luteolin (12.7)	Ryu et al. (2017)
	SARS-CoV PLpro (13.2)	NP	Cho et al. (2013)
	PTP1B (3.9); α-Glucosidase (18.4)	NaVO ₄ (32.6); Voglibose (24.5)	Song et al. (2017)
5	COX-1 (3.3), COX-2 (10.6); 5-LOX (0.06)	Ibuprofen (6.3, 4.2); Zileuton (0.35)	Hanáková et al. (2017)
6	5-LOX (0.38)	Zileuton (0.35)	Hanáková et al. (2017)
7	SARS-CoV PLpro (12.7)	NP	Cho et al. (2013)
	PTP1B (7.8); α-Glucosidase (19.6)	NaVO ₄ (32.6); Voglibose (24.5)	Song et al. (2017)
8	COX-1 (4.2), COX-2 (6.4)	Ibuprofen (6.3, 4.2)	Hanáková et al. (2017)
	PTP1B (3.8); α-Glucosidase (78.9)	NaVO ₄ (32.6); Voglibose (24.5)	Song et al. (2017)
9	HNE (3.3)	Luteolin (12.7)	Ryu et al. (2017)
	AChE (22.9), BChE (6.4)	Eserine (0.15, 3.7)	Cho et al. (2012)
	PTP1B (5.9); α-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)
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 (8.2); α-Glucosidase (25.8)	NaVO ₄ (32.6); Voglibose (24.5)	Song et al. (2017)
15	AChE (48.5), BChE (11.2)	Eserine (0.15, 3.7)	Cho et al. (2012)
	SARS-CoV PLpro (9.2)	NP	Cho et al. (2013)
	PTP1B (4.9); α-Glucosidase (17.8)	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); α-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)
23	HNE (6.3)	Luteolin (12.7)	Ryu et al. (2017)
25	HNE (2.4)	Luteolin (12.7)	Ryu et al. (2017)
30	HNE (15.4)	Luteolin (12.7)	Ryu et al. (2017)
35	HNE (13.6)	Luteolin (12.7)	Ryu et al. (2017)
47	HNE (8.4)	Luteolin (12.7)	Ryu et al. (2017)
48	SARS-CoV PLpro (6.2)	NP	Cho et al. (2013)
49	SARS-CoV PLpro (6.1)	NP	Cho et al. (2013)
50	SARS-CoV PLpro (11.6)	NP	Cho et al. (2013)
51	SARS-CoV PLpro (5.0)	NP	Cho et al. (2013)
57	5-LOX (0.35)	Zileuton (0.35)	Hanáková et al. (2017)
60	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. pteridine* 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 diplacol (**15**) to *L. methionyl*-tRNA synthetase (−145.9 kJ/mol), have demonstrated their antiparasitic activities against both *L. donovani* and *T. b. brucei* (Ogungbe et al. 2014).

In addition, the inhibition of cyclooxygenases (COX-1 and COX-2) and 5-lipoxygenase (5-LOX) for nine *Paulownia* *C*-geranylated flavonoids was performed to test their anti-inflammatory effects. Compounds **1**, **2**, **5**, **8** and **59** showed significant effects with IC₅₀ values ranging from 1.8 to 26.3 μM for COX-1 and from 4.2 to 10.6 μM for COX-2, which were better than the reference inhibitor ibuprofen (IC₅₀ 6.3 and 4.2 μM). Diplacone (**2**) was the best inhibitor (IC₅₀ 1.8 and 4.2 μM) but with no selectivity for COX-1 and COX-2 (the COX-1/COX-2 selectivity ratio was 0.43). Although **59** showed weaker inhibition (IC₅₀ 26.3 and 9.5 μM), it possessed greater selectivity against COX-2 (COX-1/COX-2 selectivity ratio was 2.8). Meanwhile, compounds **2**, **5**, **6**, **57**, and **60** were selected for determination of their effect on 5-LOX. Compound **2** (IC₅₀ 0.05 μM) and **5** (IC₅₀ 0.06 μM) showed activities almost 10 times greater than that of zileuton (IC₅₀ 0.35 μM) as the positive control (Hanáková et al. 2017). Furthermore, compounds **4**, **9**, **21**, **23**, **25** and **47** were found to greatly inhibit human neutrophil elastase (HNE) activity with IC₅₀ values ranging from 2.4 to 8.4 μM and compound **9** was selected as the best potential inhibitor by kinetic enzymatic assays with the HNE substrate MeOSuc-AAPV-pNA (Ryu et al. 2017).

The methanol extract of *P. tomentosa* fruits was characterized as a source of PTP1B and α-glucosidase inhibitors and eight isolated *C*-geranylated flavonoids (**1**, **4**, **6**, **7**, **9**, **13**, **15** and **16**) displayed dual inhibition of PTP1B and α-glucosidase. The inhibitory potency of these compounds varied accordingly, but most of the compounds were more effective against PTP1B than α-glucosidase. Mimulone (**1**) was the most effective against PTP1B with

IC₅₀ 1.9 μM (NaVO₄ as the positive control, IC₅₀ 32.6 μM), whereas 6-geranyl-3,3',5,5',7-pentahydroxy-4'-methoxyflavane (**16**) displayed potent inhibition against an α-glucosidase with IC₅₀ 2.2 μM compared with IC₅₀ 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 monoterpene 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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