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Phytochemical profile of *Paulownia tomentosa* (Thunb). Steud.

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Abstract *Paulownia tomentosa*, a member of the plant family Paulowniaceae and a rich source of biologically active secondary metabolites, is traditionally used in Chinese herbal medicine. Flavonoids, lignans, phenolic glycosides, quinones, terpenoids, glycerides, phenolic acids, and miscellaneous other compounds have been isolated from different parts of *P. tomentosa* plant. Recent interest in this species has focused on isolating and identifying of prenylated flavonoids, that exhibit potent antioxidant, antibacterial, and antiphlogistic activities and inhibit severe acute respiratory syndrome coronavirus papain-like protease. They show cytotoxic activity against various human cancer cell lines and inhibit the effects of human cholinesterase, butyrylcholinesterase, and bacterial neuraminidases. Most of the compounds considered here have never been isolated from any other species of plant. This review summarizes the information about the isolated compounds that are active, their bioactivities, and the structure–activity relationships that have been worked out for them.

Keywords *Bignonia tomentosa* · Flavonoid · Lignan · *Paulownia tomentosa* · Paulowniaceae · Phenolic glycosides

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Introduction

The plant *Paulownia tomentosa* (Thunb.) Siebold & Zucc. ex Steud. is a very adaptable and extremely fast-growing timber tree native to central and western China traditionally used in Chinese Medicine. This deciduous tree is now grown in many areas worldwide, mostly as a decorative ornamental tree (Erbar and Gűlden 2011; Zhu et al. 1986).

Two related varieties of *P. tomentosa* have been described—var. *tsinlingensis* has a round to shallowly cordate leaf base and a glabrous or sparsely hairy lower leaf surface, whereas var. *tomentosa* is characterized by a cordate leaf blade base and an abaxial surface that is densely hairy when mature (Hong et al. 1998).

Paulownia was named *paulownia* in honour of Anna Paulowna (1795–1865), queen consort of The Netherlands and a daughter of Tsar Paul I of Russia. Nowadays, it is commonly known under its synonym *Bignonia tomentosa* (Zhu et al. 1986) or as the princess-tree, empress-tree, foxglove tree, royal paulownia, kiri, or mao pao tong (yuan bian zhong) (Erbar and Gűlden 2011; Hong et al. 1998).

The genus *Paulownia* was first assigned to family Bignoniaceae by Swiss botanist Thunberg (1781). It was then transferred to the Scrophulariaceae family by the Dutch scholars Zuccarini and Siebold (1835) (Zhu et al. 1986). At last, Paulownia has been categorized as a family of its own, Paulowniaceae, based on data from the latest molecular phylogenetic studies. This

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Table 1 Non-prenylated flavonoid aglycones isolated from *P. tomentosa*

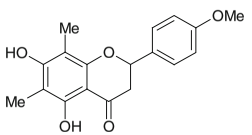
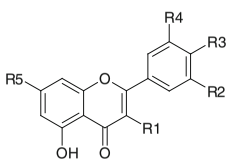
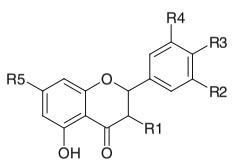
Name of compound and ID	Isolation source	Biological activity	Chemical structure				
Matteucinol (syn. 4′-*O*-methylfarrerol) (**1**) (2*S*)	Leaves (Zhu et al. 1986)	Weak cytotoxic activity in vitro against human leukaemia (HL-60) and human hepatoma (SMMC-7721) cell lines (Zhao et al. 2012); no α-glucosidase inhibitory effect (Zhao et al. 2009); weak aldose-reductase inhibitory activity (Kadota et al. 1994); moderate inhibitory effect on human immunodeficiency virus-1 protease (Lee et al. 2008); no activity against lipopolysaccharide (LPS)-induced NO production in RAW 264.7 macrophages (Li et al. 2011)					
							
			R1	R2	R3	R4	R5
Apigenin (**2**)	Leaves (Zhao et al. 2012), flowers (Chen et al. 2009; Jiang et al. 2004)	Antioxidant (Prince Vijeya Singh et al. 2004); antibacterial, anti-inflammatory, antispasmodic, antidiarrhoic, antiproliferative, vasorelaxant (Jiang et al. 2004); neuroprotective (Losi et al. 2004); cardioprotective (Psotová et al. 2004); chemopreventive activity against skin cancer (Chen et al. 2009); activity reviewed by Shukla and Gupta (2009) and Patel et al. (2007)	H	H	OH	H	OH
Kaempferol (**3**)	Leaves (Si et al. 2008a)	Cytotoxic, pro-apoptic (suppresses cell metastasis via inhibition of the ERK-p38-JNK and AP-1 signaling pathways in U-2 OS human osteosarcoma cells) (Chen et al. 2013); antioxidant (e.g., attenuates bladder hyperactivity caused by potassium chloride after protamine sulphate-induced bladder injury) (Huang et al. 2014); impact on human health and cancer chemoprevention reviewed by Chen and Chen (2013), and Calderon-Montano et al. (2011)	OH	H	OH	H	OH

Table 1 continued

			R1	R2	R3	R4	R5
Luteolin (**4**)	Leaves (Si et al. 2008a; Zhang and Li 2011)	Memory-improving (Yoo et al. 2013); inhibition of α-amylase activity (Funke and Melzig 2005); cytotoxic (BGC-823 gastric carcinoma xenografts in nude mice) (Lu et al. 2013); vascular protective (Si et al. 2013); biological activity reviewed by Lopez-Lazaro (2009)	H	OH	OH	H	OH
Quercetin (**5**)	Bark (Si et al. 2011b), leaves (Si et al. 2008a)	Antifibrotic (Yoon et al. 2012); antioxidant, antiproliferative, anti-inflammatory, cardioprotective (Chen et al. 2013); neuroprotective (Ghosh et al. 2013); anti-diabetic [dose-dependent inhibition of both Na^+/K^+ ATPase and sodium hydrogen exchanger in type 2 diabetic erythrocytes (Mishra and Rizvi 2012); inhibition of PI3K (Koch et al. 2013)]; antiviral [anti HCV (Khachatoorian et al. 2012); HCMV (Cotin et al. 2012)]; no anti-HIV activity in vitro tested on H9 cells in the absence of toxicity (Tang et al. 1994); review of bioactivities by Russo et al. (2012)	OH	H	OH	OH	OH
7,3′-Dimethylquercetin (syn. rhamnazin) (**6**)	Leaves, green immature fruit (Wollenweber et al. 2008)	Antimicrobial activity, poor antifungal effect (Omosa et al. 2014); low antimicrobial activity, low toxicity against human lymphocytes and monocytes, antioxidant/anti-inflammatory activity (Martini et al. 2004; Pelzer et al. 1998); low affinity to acetylcholinesterase (Remya et al. 2012); low inhibitory effect on NO production in RAW264.7 cells (Sudsai et al. 2013); no activity against HSV-1, low toxicity against Vero cells (Tian et al. 2009); no antioxidant activity (Takamatsu et al. 2003); no trypanocidal activity (Grael et al. 2000); activity against lipid peroxidation in rat liver microsomes (Yun et al. 2000); cytotoxicity against TK-10, MCF-7 and UACC-62 cells (Lopez-Lazaro et al. 2000); no inhibition of glycolysis in various tumor cells (Suolinna et al. 1975)	OH	OMe	OH	H	OMe

Table 1 continued

		R1	R2	R3	R4	R5
7,3′,4′-Trimethylquercetin (**7**)	Thrombin inhibition (Shi et al. 2012); inhibition of IL-4 synthesis in basophils (Hirano et al. 2006); weak trypanocidal activity (Jordao et al. 2004); weak inhibition of NO production in LPS-activated mouse peritoneal macrophages (Matsuda et al. 2003); weak inhibition of degranulation of RBL-2H3 cells (Mastuda et al. 2002); inhibition of Pgp activity (Scambia et al. 1994); no inhibition of glycolysis in a variety of tumor cells (Suolinna et al. 1975)	OH	OMe	OMe	H	OMe
7,3′,4′-Trimethylmyricetin (**8**)	Weak inhibition of NO production in LPS-activated mouse peritoneal macrophages (Matsuda et al. 2003); weak inhibition of degranulation of RBL-2H3 cells (Mastuda et al. 2002)	OH	OMe	OMe	OH	OMe
7,3′,4′,5′-Tetramethylmyricetin (**9**)		OH	OMe	OMe	OMe	OMe

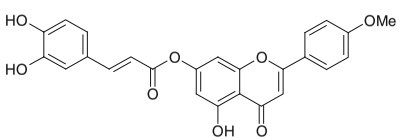


			R_1	R_2	R_3	R_4	R_5
(+)-Catechin (**10**) (2*R*, 3*S*)	Leaves (Si et al. 2008a)	Antiviral (HCV) (Khachatoorian et al. 2012); antimicrobial (Mankovskaia et al. 2013); antioxidant, e.g., adjunctive therapy for the treatment of Parkinson's disease (Teixeira et al. 2013); osteogenic (Wei et al. 2011); anti-proliferative, anti-inflammatory, antifibrotic (GRX cells) (Bragança de Moraes et al. 2012); activity reviewed, for example, by Bansal et al. (2013)	OH	H	OH	OH	OH
Dihydrotricin (**11**) (2*S*)	Fruits (Šmejkal et al. 2007a)	Antioxidant, vasorelaxant, low anti-platelet aggregation activity (Chang et al. 2010)	H	OMe	OH	OMe	OH

Table 1 continued

			R_1	R_2	R_3	R_4	R_5
(−)-Epicatechin (**12**) (2*R*, 3*R*)	Leaves (Si et al. 2008a)	Antifungal (Betts et al. 2013); improves muscle mitochondrial structure (Taub et al. 2012); antioxidant, cardioprotective (Paneerselvam et al. 2010); cytotoxic (HT29 human colon adenocarcinoma cells) (Sánchez-Tena et al. 2013); anti-inflammatory (Fu et al. 2013); activity reviewed, for example, by Fraga and Oteiza (2011)	OH	H	OH	OH	OH
Homoeriodictyol (syn. hesperetin) (**13**) (2*S*)	Leaves (Zhang and Li 2011)	Major flavonoid of citrus, activity reviewed by Khan and Zill-E-Huma (2014)	H	H	OH	OMe	OH
Naringenin (**14**) (2*S*)	Bark (Si et al. 2011b), leaves (Si et al. 2008a)	Anti-diabetic (inhibition of PI3K) (Koch et al. 2013); antiviral [anti HCV (Khachatoorian et al. 2012), HCMV (Cotin et al. 2012)]; antimicrobial (de Aguiar et al. 2013); anti-inflammatory (Jayaraman et al. 2012); antioxidant (Wang et al. 2012); cytotoxic (ERα-transfected HeLA cells, ERα-containing HepG2 cells) (Bulzomi et al. 2010); no antiparasitic activity against *Leishmania* spp. (*major*, *chagasi*, *braziliensis*, *amazonensis*), *Trypanosoma cruzi* (Grecco Sdos et al. 2012); major flavonoid of citrus, activity reviewed by Khan and Zill-E-Huma (2014)	H	H	OH	H	OH
Taxifolin (**15**) (2*R*, 3*R*)	Leaves (Si et al. 2008a)	Inhibition of β-amyloid aggregation (Sato et al. 2013); potential for atopic dermatitis treatment (blocks hERG K^+ channels) (Yun et al. 2013); cytotoxic, pro-apoptotic (DU145 human prostate carcinoma cells) (Zhang and Coultas 2013); hypotensive (ACEI), anti-inflammatory, antioxidant (diminished 5-lipoxygenase and NADPH oxidase activity) (Arutyunyan et al. 2012); activity reviewed by Weidmann (2012)	OH	OH	OH	H	OH

Table 1 continued

			R_1	R_2	R_3	R_4	R_5
5,4′-Dihydroxy-7,3′-dimethoxyflavanone (**16**) (2*S*)	Flowers (Chen et al. 2009; Jiang et al. 2004; Kim et al. 2010a, b)	Inactive against glutamate-induced neurotoxicity studied in primary-cultured rat cortical cells (Kim et al. 2010a, b); no trypanocidal activity (Grael et al. 2000)	H	H	OH	OMe	OMe
5-Hydroxy-7,3′,4′-trimethoxyflavanone (**17**) (2*S*)	Flowers (Kim et al. 2010a, b)	Inactive against glutamate-induced neurotoxicity studied in primary-cultured rat cortical cells (Kim et al. 2010a, b); inhibition of inflammation by induction of synovial apoptosis of fibroblast-like synoviocytes through caspase 3 activation in rats with adjuvant arthritis (Li et al. 2010, 2013); inhibition of JAK2-STAT3 signal pathway in rats (Li et al. 2012); inhibition of phosphodiesterase 4 (Yang et al. 2011); low toxicity on B16F10 and SK-MEL-1 melanoma cells (Rodriguez et al. 2002); antimutagenic activity (Miyazawa et al. 2000)	H	H	OMe	OMe	OMe
7-Caffeoyl-acacetin (syn. 7-caffeoyl-4′-methoxyapigenin) (**18**)	Stem bark (Si et al. 2009)						

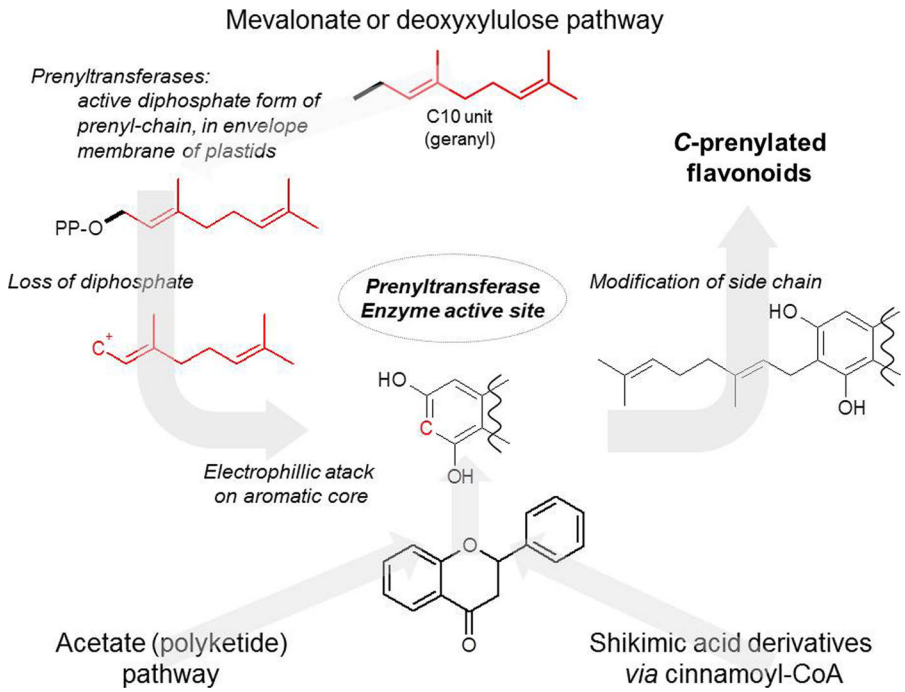


Fig. 1 Schematic of the pathways of the biosynthesis of geranylated flavonoids

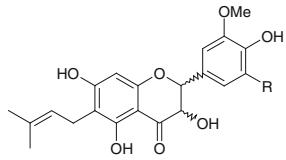
family includes only one genus and between six and ten species. It was originally introduced in 1949 by the research of Nakai (Erbar and Gűlden 2011).

Biological activity and traditional uses of *P. tomentosa* extracts

According to both legends and records, people were already using Paulownia for various purposes about 2,600 years ago. Chinese herbal medicine has used *P. tomentosa* traditionally to relieve bronchitis, especially by reducing coughing, asthma, and phlegm (Zhu et al. 1986). It has also been used to treat conjunctivitis, dysentery, enteritis, erysipelas, gonorrhea, hemorrhoids, parotitis, traumatic bleeding, and tonsillitis (Jiang et al. 2004; Si et al. 2009). Solutions prepared from the leaves and fruit extracted in water have been used in daily applications to promote the healthy growth of hair and turn grey hair dark. An extract prepared from the wood and leaves may relieve swollen feet. Pharmacological experiments have shown that extracts from the fruit can reduce blood pressure. Nowadays, injections and tablets prepared from *Paulownia* flowers and fruit are used for the herbal treatment of chronic bronchitis and other kinds of inflammation (Zhu et al. 1986).

More than 130 physiologically active constituents have been isolated from different parts of the *Paulownia* plant. Their biological activity has been tested using both the isolated compounds and different types of extracts. For example, *n*-butanol, EtOAc, and MeOH extracts obtained from the fruit have displayed antiradical activity in anti-DPPH and peroxynitrite assays, due to mainly the presence of flavonoids and phenolic glycosides, but not of all compounds present in these extracts have been identified) (Šmejkal et al. 2007b). An MeOH extract obtained from the fruit inhibited hAChE ($IC_{50} = 1.44$ mg/ml) and BChE ($IC_{50} = 0.97$ mg/ml) significantly more strongly than $CHCl_3$ and water extracts (possibly due to the content of phenolic glycosides and *C*-prenylated dihydroflavonols and flavanones) (Cho et al. 2012). Significant concentration-dependent anti-inflammatory properties of EtOH extracts of the bark of the tree have also been observed recently using a lipopolysaccharide (LPS)-induced nitric oxide production inhibition model in the murine macrophages cell line RAW264.7 (Si et al. 2011a). Kim et al. (2010a, b) showed potential of aqueous extract of *P. tomentosa* to suppress glutamate

Table 2 *C*-prenylated flavonoids isolated from *P. tomentosa*

Name of compound and ID	Isolation	Biological activity	Chemical structure
			
			R
6-Isopentenyl-3′-*O*-methyltaxifolin (**19**) (2*R*, 3*R*)	Fruit (Šmejkal et al. 2007a)		H
3,4′,5,5′,7-Pentahydroxy-3′-methoxy-6-(3-methyl-2-butenyl) flavanone (**20**) (2*R*, 3*R*)	Fruit (Asai et al. 2008)	Antioxidant (Asai et al. 2008); cytotoxic (A2780 human ovarian cancer cell line) (Murphy et al. 2005, 2006)	OH

induced toxicity in primary cultured rat cortical cells (with possible sesquiterpene lactone as active substance). The bio-activities of individual compounds and, where possible, the structure–activity relationships are in Tables 1, 2, 3 and 4 and discussed in separate chapters.

P. tomentosa flavonoids and their biological activity

Flavonoids represent the most numerous group of secondary metabolites isolated from *P. tomentosa*. They can be divided into simple non-prenylated flavonoids **1–18** (Table 1), *C*-prenylated and *C*-geranylated flavonoids **19–59** (Tables 2, 3, respectively), and flavonoid glycosides **60–65**. Compounds **16**, **17**, **19**, **20**, **25–31**, **33–36**, **38–59** have never been isolated from any other species. Most of the isolated flavanones are characterized by a *2S* configuration in contrast to the dihydroflavonols, for which *2R*, *3R* isomer is often observed.

Some of the flavonoid compounds found in *P. tomentosa* have been categorized as dietary flavonoids. Consuming these compounds is believed to deliver health benefits. The activities of these flavonoids are frequently been reviewed, for example in the papers of Romano et al. (2013), Marzocchella et al. (2011), Ross and Kasum (2002), and Havsteen (2002). Some simple flavonoid substances isolated from fruit of *P. tomentosa* are commonly observed as the lipophilic components of different plant exudates. Flavonoids **1–18** show broad-spectrum pharmacological activities (Table 1). Many papers report their potential role as anticancer compounds for use against human cervical and breast (Bulzomi et al. 2010, 2012), hepatoma, leukemic (Zhao et al. 2012), osteosarcoma (Chen et al. 2013), gastric carcinoma (Lu et al. 2013), colon adenocarcinoma (Sánchez-Tena et al. 2013), or prostatic (Zhang and Coultas 2013) cancer cell lines. Their antioxidant properties could explain their promising cardioprotective (Paneerselvam et al. 2010; Psotová et al. 2004) and neuroprotective effects (Losi et al. 2004). Antimicrobial (Betts et al. 2013; Jiang et al. 2004; Mankovskaia et al. 2013) and antiviral (Khachatoorian et al. 2012) bio-activities against different pathogens have also been discovered. In some cases, no specific biological activity has been observed (Kim et al. 2010a, 2010b; Tang et al. 1994).

Paulownia tomentosa is also a rich source of prenylated and geranylated flavonoids (**19–59**), whose occurrence is limited to relatively a few plant families (Yazaki et al. 2009). There are sometimes misunderstandings in the naming of these compounds. A compound containing both a phenolic skeleton and a terpenoid side chain is often designated as a "prenylated" phenolic substance, even though it contains not a prenyl, but rather a geranyl or other type of terpenoid side-chain. Prenylated flavonoids are biosynthesized by a combination of several pathways: the acetate, shikimate, and mevalonate (Fig. 1). It is now known that the prenyl and geranyl moieties are biosynthesized via mevalonate or deoxyxylulose pathway. The connection of terpenoid and flavonoid biosynthetic

Table 3 *C*-geranylated flavonoids isolated from *P. tomentosa*

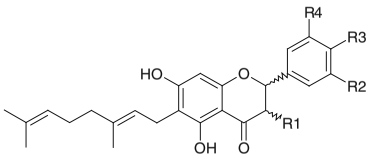
Name of compound and ID	Isolation	Biological activity	Chemical structure			
						
			R_1	R_2	R_3	R_4
Mimulone (syn. 6-geranylnaringenin, bonannione A) (**21**) (2*S*)	Flowers (Chen et al. 2009; Jiang et al. 2004; Kim et al. 2010a, b), fruit (Asai et al. 2008; Cho et al. 2012, 2013; Lee et al. 2014; Šmejkal et al. 2007a, 2008b)	Antioxidant (Šmejkal et al. 2007b; Zima et al. 2010), antioxidant and anti-inflammatory properties in vitro in S100B-induced human monocytes (Lin et al. 2011), anti-inflammatory activity in LPS-activated THP-1 cells (Peluso et al. 2010); antimicrobial against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), antimicrobial against *S. aureus* and various methicillin resistatant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059) (Navrátilová et al. 2013); cytotoxic [epithelioid cell line WB344 (Šmejkal et al. 2007b), human erythro-leukaemia cell line K562 (Šmejkal et al. 2008a), human ovarian cancer cell line A2780 (Murphy et al. 2005, 2006; Yoder et al. 2007), KB, KB-VIN, A549, DU145 (Rosselli et al. 2011), low activity against T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010)]; SARS-CoV PLpro activity (Cho et al. 2013); hAChE, BChE inhibitor (Cho et al. 2012); significant inhibitory effects against *Cp*-NanI (a sialidase from *C. perfringens*) (Lee et al. 2014); weak estrogenic, no progestogenic and androgenic activity (Milligan et al. 2000); inactive against glutamate-induced neurotoxicity studied in primary-cultured rat cortical cells (Kim et al. 2010a, b)	H	H	OH	H

Table 3 continued

			R_1	R_2	R_3	R_4
Diplacone (syn. propolin C, nymphaeol A) (**22**) (2*S*)	Flowers (Chen et al. 2009; Jiang et al. 2004; Kim et al. 2010a, b), fruit (Asai et al. 2008; Cho et al. 2012, 2013; Lee et al. 2014; Šmejkal et al. 2007a, 2008b)	Antioxidant (Kumazawa et al. 2007; Asai et al. 2008; Šmejkal et al. 2007b; Zima et al. 2010; Trusheva et al. 2011), prooxidant and anti-inflammatory (Hošek et al. 2013); antiherbivore (Kobayashi et al. 2008); antimicrobial against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), antimicrobial against *S. aureus*, various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059)—most potent together with **31** (Navrátilová et al. 2013) and methicillin-susceptible *S. aureus* strain. Anti-MRSA, inactive against *P. auruginosa* (Raghukumar et al. 2010); antiphlogistic (TNF-α, similar to indomethacin) (Hošek et al. 2010), but no anti-inflammatory effect was observed in COX-2 inhibition assay (Phommart et al. 2005); cytotoxic (epithelioid cell line WB344 (Šmejkal et al. 2007a), T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010), human erythro-leukaemia cell line K562 (Šmejkal et al. 2008a), KB human oral carcinoma, human breast cancer, human small cell lung cancer NCI-H187 (Phommart et al. 2005), induction of apoptosis via caspase activation, bid and cytochrome c release in human melanoma cells (Chen et al. 2004), human ovarian cancer cell line A2780 (Murphy et al. 2005, 2006; Yoder et al. 2007), PC-3, DU-145, Hep-3B cell line (Chen et al. 2012)); hAChE, BChE inhibitor (Cho et al. 2012), SARS-CoV PLpro activity (Cho et al. 2013); significant inhibitory effects against *Cp*-NanI (a sialidase from *C. perfringens*) (Lee et al. 2014); selective docking to *Leishmania major* N-myristoyltransferase (Ogungbe et al. 2014); antileishmanial activity (*L. donovani* amastigotes) (Salem et al. 2011); inactive against glutamate-induced neurotoxicity studied in primary-cultured rat cortical cells (Kim et al. 2010a, b)	H	OH	OH	H

Table 3 continued

			R_1	R_2	R_3	R_4
Diplacol (**23**) (2*R*, 3*R*)	Fruit (Asai et al. 2008), flowers, leaves (Kobayashi et al. 2008)	Antioxidant (Asai et al. 2008); cytotoxic (human ovarian cancer cell line A2780) (Murphy et al. 2006; Yoder et al. 2007), low activity against T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010)	OH	OH	OH	H
3′-*O*-methyldiplacone (**24**)	Fruit (Asai et al. 2008; Cho et al. 2012, 2013; Lee et al. 2014; Šmejkal et al. 2007a, 2008b), flowers and leaves (Kobayashi et al. 2008)	Antioxidant (Šmejkal et al. 2007a; Yazaki et al. 2009); SARS-CoV PLpro activity (Cho et al. 2013); weak hAChE, BChE inhibitor (Cho et al. 2012); significant inhibitory effects against *Cp*-NanI (a sialidase from *C. perfringens*) (Lee et al. 2014); strong docking energy to *L. major* pteridine reductase 1, selective docking to glycerol-3-phosphate dehydrogenase (Ogungbe et al. 2014), antileishmanial activity (*L. donovani* amastigotes) (Salem et al. 2011); activity against lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010), human erythro-leukaemia cell line K562 (Šmejkal et al. 2008a); weak antimicrobial against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), weak antimicrobial activity against *S. aureus*, various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059) (Navrátilová et al. 2013)	H	OMe	OH	H
3′-*O*-methyldiplacol (syn. diplacol 3′-*O*-methylether) (**25**) (2*R*, 3*R*)	Flowers (Kobayashi et al. 2008), fruit (Asai et al. 2008; Cho et al. 2012, 2013; Šmejkal et al. 2008b)	Antioxidant (Asai et al. 2008; Yazaki et al. 2009), antimicrobial against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059)—most potent together with **27** (Navrátilová et al. 2013); cytotoxic (human erythro-leukaemia cell line K562) (Šmejkal et al. 2008a), low activity against T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010); SARS-CoV PLpro activity (Cho et al. 2013); hAChE, BChE inhibitor (Cho et al. 2012); antileishmanial activity (*L. donovani* amastigotes) (Salem et al. 2011), selective docking to *L. major* methionyl tRNA synthetase (Ogungbe et al. 2014)	OH	OMe	OH	H

Table 3 continued

			R_1	R_2	R_3	R_4
3′-*O*-methyl-5′-*O*-methyldiplacone (syn. 6-geranyl-4′,5,7-trihydroxy-3′,5′-dimethoxyflavanone) (**26**) (2*S*)	Fruit (Asai et al. 2008; Cho et al. 2012, 2013; Šmejkal et al. 2008b)	Antioxidant (Yazaki et al. 2009), antimicrobial against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059) (Navrátilová et al. 2013); cytotoxic (multiple myeloma RPMI 8226 and U266 cell lines, human cervical cancer cells HeLa, BJ human fibroblast cell line (Šmejkal et al. 2010), human erythro-leukaemia cell line K562) (Šmejkal et al. 2008a); SARS-CoV PLpro activity (Cho et al. 2013); hAChE, BChE inhibitor (Cho et al. 2012)	H	OMe	OH	OMe
3′-*O*-methyl-5′-hydroxydiplacone (syn. 6-geranyl-4′,5,5′,7-tetrahydroxy-3′-methoxyflavanone) (**27**) (2*S*)	Immature fruit (Asai et al. 2008), fruit (Šmejkal et al. 2008b), leaves (Kobayashi et al. 2008)	Antioxidant (Asai et al. 2008; Yazaki et al. 2009; Zima et al. 2010); antimicrobial activity against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059) (Navrátilová et al. 2013); cytotoxic (human erythro-leukamia cell line K562) (Šmejkal et al. 2008a), activity against T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010)	H	OMe	OH	OH
3′-*O*-methyl-5′-methoxydiplacol (**28**) (racemic mixture of 2*R*, 3*R* and 2*S*, 3*S*)	Fruit (Šmejkal et al. 2007a)		OH	OMe	OH	OMe
6-Geranyl-5,7-dihydroxy-3′,4′-dimethoxyflavanone (**29**) (2*S*)	Immature fruit (Asai et al. 2008)	Antioxidant (Asai et al. 2008)	H	H	OMe	OMe
6-Geranyl-3′,5,7-tri-hydroxy-4′-methoxyflavanone (syn. 4′-*O*-methyldiplacone) (**30**) (2*S*)	Immature fruit (Asai et al. 2008), fruits (Cho et al. 2012, 2013; Lee et al. 2014)	Antioxidant (Asai et al. 2008); SARS-CoV PLpro activity (Cho et al. 2013); hAChE, BChE inhibitor (Cho et al. 2012); significant inhibitory effects against *Cp*-NanI (a sialidase from *C. perfringens*) (Lee et al. 2014); antileishmanial activity (*L. donovani* amastigotes) (Salem et al. 2011)	H	H	OMe	OH
6-Geranyl-3,3′,5,7-tetrahydroxy-4′-methoxyflavanone (syn. 4′-*O*-methyldiplacol) (**31**) (2*R*, 3*R*)	Immature fruit (Asai et al. 2008), fruit (Cho et al. 2012, 2013)	Antioxidant (Asai et al. 2008), SARS-CoV PLpro activity (Cho et al. 2013); hAChE, BChE inhibitor (Cho et al. 2012)	OH	H	OMe	OH
Schizolaenone C (**32**) (2*S*)	Fruit (Šmejkal et al. 2010)	Cytotoxic (T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, human cervical cancer cells HeLa, BJ human fibroblast cell line) (Šmejkal et al. 2010), cytotoxic (human ovarian cancer cell line A2780) (Murphy et al. 2006; antioxidant (Zima et al. 2010)	H	OH	H	OH

Table 3 continued

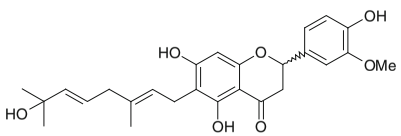
			R_1	R_2	R_3	R_4
6-Geranyl-3,3′,5,5′,7-pentahydroxy-4′-methoxyflavanone (**33**) (2*R*, 3*R*)	Fruit (Cho et al. 2012)	hAChE, BChE inhibitor (Cho et al. 2012)	OH	OH	OMe	OH
6-Geranyl-3′,5,5′,7-tetrahydroxy-4′-methoxyflavanone (**34**) (2*S*)			H	OH	OMe	OH
Tomentodiplacone B (**35**) (2*S*)	Fruits (Šmejkal et al. 2008b)	Antioxidant (Yazaki et al. 2009; Zima et al. 2010); low direct cytotoxicity (human erythro-leukamia cell line K562) (Šmejkal et al. 2008a); low direct activity against T-lymphoblastic leukaemia CEM, multiple myeloma RPMI 8226 and U266 cell lines, BJ human fibroblast cell line (Šmejkal et al. 2010), effect on cell cycle (THP-1 human monocytic leukaemia cells) (Kollár et al. 2011); antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059) (Navrátilová et al. 2013), no antimicrobial activity on Gram-negative bacteria or yeast and on seven Gram-positive bacteria (Navrátilová et al. 2013; Šmejkal et al. 2008b)				
			R			
3,3′,4′, 5,7-Pentahydroxy-6-[7-hydroxy-3,7-dimethyl-2(*E*)octenyl] flavanone (**36**) (2*R*, 3*R*)	Immature fruit (Asai et al. 2008)	Antioxidant (Asai et al. 2008)	OH			
Prokinawan (**37**) (2*S*)	Flowers (Kobayashi et al. 2008), immature fruit (Asai et al. 2008)	Antioxidant (Asai et al. 2008)	H			

Table 3 continued

			R1	R2	R3
Tomentodiplacone (**38**) (2*S*)	Fruit (Šmejkal et al. 2008b)	Antioxidant (Yazaki et al. 2009); antimicrobial against seven Gram-positive bacteria, no antimicrobial activity against three types of Gram-negative bacteria or yeast (Šmejkal et al. 2008b), weak erythroid differentiation activity (Šmejkal et al. 2008a)	H	OMe	H
Tomentodiplacol (**39**) (2*R*, 3*R*)	Fruit (Šmejkal et al. 2007a)	Antioxidant (Šmejkal et al. 2007a)	OH	OMe	H
4′,5,5′,7-Tetrahydroxy-6-[6-hydroxy-3,7-dimethyl-2(*E*),7-octadienyl]-3′-methoxyflavanone (**40**) (2*S*)	Immature fruit (Asai et al. 2008)	Antioxidant (Asai et al. 2008)	H	OMe	OH
3,3′,4′,5,7-Pentahydroxy-6-[6-hydroxy-3,7-dimethyl-2(*E*),7-octadienyl]flavanone (**41**) (2*R*, 3*R*)	Immature fruit (Asai et al. 2008)	Antioxidant (Asai et al. 2008)	OH	OH	H
Tanariflavanone D (**42**) (2*S*)	Immature fruit (Asai et al. 2008), fruit (Schneiderová et al. 2013)	Antioxidant (Asai et al. 2008; Phommart et al. 2005); cytotoxic (human breast cancer cell line BC) (Phommart et al. 2005); no anti-inflammatory effect in COX-2 inhibition assay (Phommart et al. 2005)	H	H	OH
Tomentomimulol (**43**) (*2R*, *3R*)	Fruit (Schneiderová et al. 2013)		OH	H	H
Mimulone B (**44**) (2*S*)	Fruit (Schneiderová et al. 2013)		H	H	H

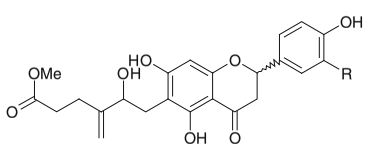


Table 3 continued

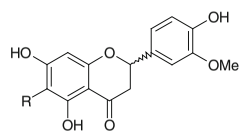
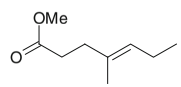
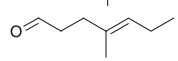
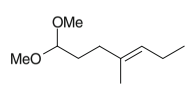
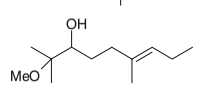
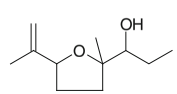
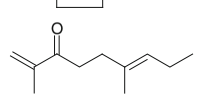
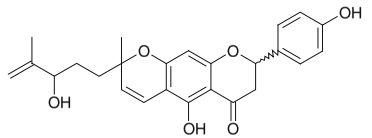
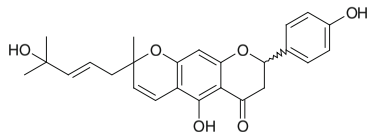
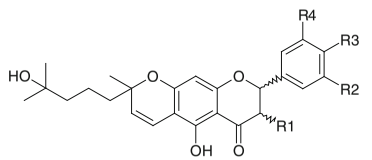
			R
Tomentodiplacone C (**45**) (racemic mixture of 2*R*, 2*S*)	Fruit (Navrátilová et al. 2013)	Antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059), no antimicrobial activity on Gram-negative bacteria, minor ability to affect the initiation of eukaryotic translation via dual-luciferase reported assay (firefly and renilla) in comparison with anisomycin (Navrátilová et al. 2013)	OMe
Mimulone E (**46**) (2*S*)	Fruit (Navrátilová et al. 2013)		H 
Tomentodiplacone D (**47**) (2*S*)	Fruit (Navrátilová et al. 2013)	Antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059), no antimicrobial activity on Gram-negative bacteria, no ability to affect the initiation of eukaryotic translation via dual-luciferase reported assay (firefly and renilla) (Navrátilová et al. 2013)	
Tomentodiplacone E (**48**) (2*S*)	Fruit (Navrátilová et al. 2013)		
Tomentodiplacone F (**49**) (2*S*)	Fruit (Navrátilová et al. 2013)		
Tomentodiplacone G (**50**) (2*S*)	Fruit (Navrátilová et al. 2013)	Antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059), no antimicrobial activity on Gram-negative bacteria, no ability to affect the initiation of eukaryotic translation via dual-luciferase reported assay (firefly and renilla) (Navrátilová et al. 2013)	
Tomentodiplacone H (**51**) (racemic mixture 2*R*, 2*S*)	Fruit (Navrátilová et al. 2013)		
Tomentodiplacone I (**52**) (racemic mixture of 2*R*, 2*S*)	Fruit (Navrátilová et al. 2013)		

Table 3 continued

			R
Mimulone C (**53**) (2*S*)	Fruit (Navrátilová et al. 2013)	Antimicrobial against *S. aureus* and various methicillin resistant strains of *S. aureus* (MRSA 287, MRSA 4211, MRSA, 6975, MRSA 630, MRSA 62059), no antimicrobial activity on Gram-negative bacteria, **53** has no ability to affect the initiation of eukaryotic translation via dual-luciferase reported assay (firefly and renilla) (Navrátilová et al. 2013)	
Mimulone D (**54**) (2*S*)	Fruit (Navrátilová et al. 2013)		
			

			R1	R2	R3	R4
Tomentin A (**55**) (2*S*)	Fruit (Cho et al. 2013)	Activity against Severe acute respiratory syndrome corona virus (SARS-CoV PLpro, a reversible inhibitor **63** was the most potent compound tested (Cho et al. 2013)	H	H	OH	OH
Tomentin B (**56**) (2*S*)			H	H	OMe	OH
Tomentin C (**57**) (2*S*)			H	OH	OMe	OMe
Tomentin D (**58**) (2*S*)			H	OMe	OH	OMe
Tomentin E (**59**) (2*R*, 3*S*)			OH	H	OH	OMe

Table 4 Phenolic glycosides isolated from *P. tomentosa*

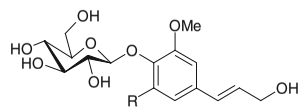
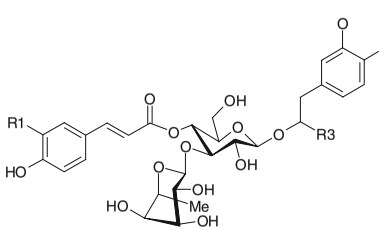
Name of compound and ID	Isolation	Biological activity	Chemical structure
			
			R
Coniferin (syn. abietin, coniferosid, laricin) (**69**)	Bark (Sticher and Lahloub 1982; Zhu et al. 1986)	Antiphlogistic (Choi et al. 2004), low COX-2/1 and 5-LOX inhibition (Wang et al. 2013; Diaz Lanza et al. 2001); low antioxidant activity in vitro (DPPH) (She et al. 2013); stimulation osteoblastic bone formation in vitro (Ding et al. 2010); concentration-dependent contractions in rat aortic rings (Deliorman et al. 2000); inhibition of ADP-induced platelet aggregation (Panossian et al. 1998); hypotensive in rats (Matsubara et al. 1991)	H
Syringin (syn. eleutherosid B) (**70**)	Bark (Sticher and Lahloub 1982; Zhu et al. 1986)	Antidepressant (Kurkin et al. 2006), antiphlogistic, antinociceptive (Choi et al. 2004); peroxyl radical scavenging capacity (Kim et al. 2010a, b), inhibition of NO production in LPS-induced RAW 264.7 cells (Lee et al. 2009); enhances memory in aged rats (Huang et al. 2013a, b); protective effects against Aβ(25–35)-induced atrophies of axons and dendrites (Bai et al. 2011; Tohda et al. 2008); immunomodulatory activity in PMN phagocytic function test (Sharma et al. 2012); hepatoprotective in mice (Gong et al. 2014); adiponectin receptor 2 agonist (Sun et al. 2013); low COX and 5-LOX inhibition (Diaz Lanza et al. 2001); concentration-dependent contractions in rat aortic rings (Deliorman et al. 2000); inhibition of ADP-induced platelet aggregation (Panossian et al. 1998; Iizuka et al. 2005); moderate in vitro cytotoxic activities against A549 and HL-60 (Yang et al. 2012); antitumour activity in sarcoma S180 transplanted mice (Zhang et al. 2007); weak inhibition of snake PDE I (Chai et al. 2009); hypoglycemic effect (Liu et al. 2008; Niu et al. 2008a, b; Niu et al. 2007); adaptogenic activity reviewed by Panossian and Wagner (2005)	OMe
			

Table 4 continued

			R1	R2	R3
Acteoside (syn. verbascoside) (**71**)	Bark (Si et al. 2011b; Sticher and Lahloub 1982; Zhu et al. 1986), wood (Si et al. 2008d), sapwood (Ota et al. 1993), fruit (Šmejkal et al. 2007b), leaves (Schilling et al. 1982), young plant (Damtoft and Jensen 1993)	Antioxidant, anti-inflammatory (Lin et al. 2006; Šmejkal et al. 2007b); antihepatotoxic (Xiong et al. 1998), antimicrobial (Kurkin 2003), antiviral (Kim et al. 2001); immuno-modulatory (Akbay et al. 2002); antihypertensive (Ahmad and Rizwani 1995); neuroprotective (Koo et al. 2005); cytotoxic (e.g., human erythro-leukemia cell line K562 (Šmejkal et al. 2008a), antiestrogen in breast cancer cells MCF7 and osteoblast without any effect on endometrial cancer cells Ishikawa (Papoutsi et al. 2006), bioactivities reviewed by He et al. (2011)	OH	OH	H
β-Oxoacteoside (syn. tomentoside A) (**72**)		Antioxidant (Tozuka et al. 2005)	OH	OH	=O
Martynoside (**73**)	Stem (Kang et al. 1994)	Antioxidant (Jimenéz and Riguera 1994); antihypertensive (Kang et al. 2003); cytotoxic (antiestrogen in breast cancer cells MCF7 via the ER-pathway, osteoblasts KS483, endometrial cancer cells Ishikawa) (Papoutsi et al. 2006)	OMe	OMe	H
Campneoside I (**74**)	Wood (Si et al. 2008d), stem (Kang et al. 1994)	Antibacterial against *Staphylococcus* and *Streptococcus* species (MIC 150 μg/ml) (Kang et al. 1994)	OH	OH	OMe
Campneoside II (syn. *β*-hydroxy-acteoside) (**75**)	Bark (Si et al. 2011b), wood (Si et al. 2008b)	Antibacterial, anti-inflammatory (Jimenéz and Riguera 1994), anticomplement (Si et al. 2008b)	OH	OH	OH
Ilicifolioside A (**76**)	wood (Si et al. 2008b)	Anticomplement (Si et al. 2008b)	OH	OH	OEt

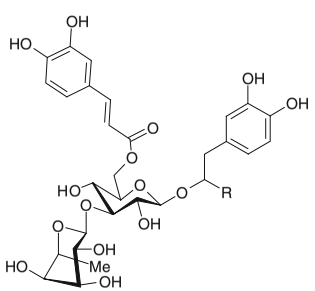
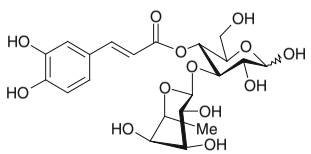
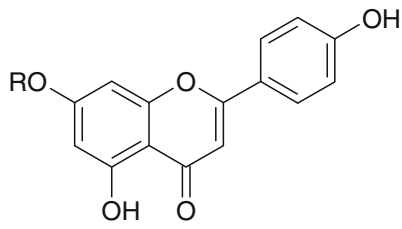


Table 4 continued

			R
Isoacteoside (syn. isoverbascoside) (**77**)	Bark (Si et al. 2011b), wood (Si et al. 2008d), sapwood (Ota et al. 1993), fruit (Šmejkal et al. 2007b), leaves (Schilling et al. 1982), young plant (Damtoft and Jensen 1993)	Antioxidant (Šmejkal et al. 2007b), xanthine oxidase inhibition (Kong et al. 1999); suppression of glutamate induced neurotoxicity (Koo et al. 2005); antioxidant, immunosuppressive (Jimenéz and Riguera 1994); cytotoxic (e.g., human erythro-leukemia cell line K562) (Šmejkal et al. 2008a)	H
Isocampneoside I (**78**)	Wood (mixture of *R*- and *S*-epimers) (Si et al. 2008d)	Inhibition of D-galactosamine induced cytotoxicity in primary cultured mouse hepatocytes (Pan et al. 2010)	OMe
Isocampneoside II (**79**)	Bark (Si et al. 2011b), wood (Si et al. 2008b)	Aldose reductase inhibitor (potential against diabetic complications) (Kim et al. 2011); anticomplement (Si et al. 2008b); antioxidant, neuro-protective on hydrogen peroxide-induced oxidative injury in PC12 cells (Si et al. 2013).	OH
Isoilicifolioside A (**80**)	Wood (Si et al. 2008b)	Anticomplement (Si et al. 2008b)	OEt
Cistanoside F (**81**)	Bark (Si et al. 2011b)	Antioxidant (Xiong et al. 1996); vasorelaxant (Yoshikawa et al. 2006); interaction with bovine serum albumin (Wu et al. 2012)	

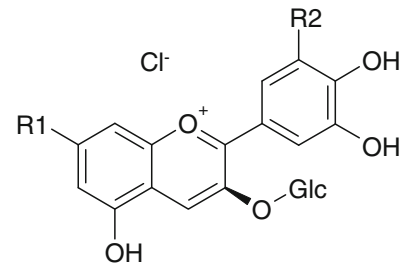


60-62

60 R= β-D-Glc

61 R= β-D-GluA

62 R= β-D-GluA (2→1) β-D-GluA



63-65

63 R1= R2= OH

64 R1= O-β-D-Glc, R2= OH

65 R1= O-β-D-Glc, R2= H

Fig. 2 Flavonoid glycosides

pathways is provided by prenyltransferases (Šmejkal 2014; Andersen and Markham 2006; Kuzuyama et al. 2005). The side chain can later be converted into different moieties by several reactions. It is unclear, whether the described modifications of the prenyl side-chain are natural—sunlight, the presence of oxygen and an elevated temperature can all affect the terpenoid metabolism—or are artefacts of isolation. Some of the changes in the prenyl moiety have been observed after treatment of an extract, or during the separation of a mixture in the acidic environment of silica gel (Navrátilová et al. 2013; Šmejkal 2014) (Fig. 2).

Most of the prenylated flavonoids isolated from *P. tomentosa* belong to *C*-geranylated group of flavonoids (**21**–**52**). Some of them have their side-chain further modified by hydroxylation (**35**–**44**, **50**, **51**, **53**–**59**), methoxylation (**45**–**47**, **49**, **50**), oxidation (**47**, **48**, **52**), cyclization (**51**, **53**–**59**), or reduction (**19**, **20**, **47**–**52**). Interestingly, these compounds have been isolated from the leaves, flowers and fruit, but they are most commonly isolated from the roots, root bark, or bark of different plants (Botta et al. 2005). Compounds **23**, **24**, and **28** have been found in the yellow dendritic trichomes on the adaxial side of the *P. tomentosa* leaves. On the other hand, no significant detected concentration of secondary metabolites has been detected in the white dendritic trichomes on the adaxial side of the leaves or the brown dendritic trichomes on the flower buds (Kobayashi et al. 2008). Glandular hairs found on the young reproductive organs of *P. tomentosa* are rich in flavonoids, with concentrations over 1,000 times greater than those on the surfaces of the young leaves (Kobayashi et al. 2008). Some seasonal variations in the appropriate time for harvesting the fruit have been discovered. Autumn is the best time to obtain high concentrations of flavonoids whereas early summer is better for phenylpropanoid glycosides (Holubová and Šmejkal 2011).

The antioxidant (Asai et al. 2008; Šmejkal et al. 2007a, b; Zima et al. 2010), antibacterial (Navrátilová et al. 2013; Šmejkal et al. 2008b), antiphlogistic (Hošek et al. 2010), cytotoxic (Kollár et al. 2011; Šmejkal et al. 2007a, 2008a, 2010), and severe acute respiratory syndrome coronavirus papain-like protease (SARS-CoV PLpro) activities (Cho et al. 2013) of isolated geranylated flavonoids have been described recently, together with their inhibitory effect on both human acetylcholinesterase and butyrylcholinesterase (Cho et al. 2012). The great ability of several geranylated flavanones to interact with bacterial sialidase isolated from *Clostridum perfringens* (*Cp*-NanI), a bacterium causing various gastrointestinal diseases, has recently been reported (Lee et al. 2014).

Possible relationships between structure and activity have been proposed for each of these biological activities. Nevertheless, it is difficult to evaluate real structure–activity relationships only by comparing the published studies, because the study conditions and the assays employed are often different. Generally, the

addition of an isoprenoid chain renders the derivate molecule more pharmacologically effective than the parent compound, probably because the prenyl group increases the lipophilicity and confers a strong affinity for biological membranes (Botta et al. 2005; Epifano et al. 2007; Chen et al. 2014).

Interestingly, neither the geranyl side-chain nor its substitution affects the antioxidant activity of flavonoids. The spatial arrangement of the substitution of the flavanone skeleton is more important. For example, the antiradical activity is increased by 2′-hydroxyl substitution of the ring B, whereas 4′-methoxyl substitution diminishes it. The general rules postulated for the antioxidant activity of flavonoids in vitro are applicable (Havsteen 2002; Chen et al. 2002), there are many review publications that touch on this topic, and it is not aim of this paper to delve deeply into this (Plaza et al. 2014). The type of antioxidant assays used for the experiment could also be a factor that significantly affects this activity (Zima et al. 2010).

Numerous reports about structure related antimicrobial activity have been published, but comparison shows the results to be widely conflicting (Cushnie and Lamb 2005). Based on several studies, it has been postulated that hydroxylation at position C-5 or C-7 of ring A and positions C-2′ or C-4′ of ring B increases the antibacterial activity (Šmejkal et al. 2008b; Navrátilová et al. 2013). However, contrary to this assumption, **45** and **50** had no significant antibacterial activity (Navrátilová et al. 2013). Interestingly, some C-geranylated flavonoids do not able inhibit the growth of Gram-negative bacteria (**21**, **22**, **25**–**27**, **35**, **38**, **45**, **47**–**48**, **50**, **53**, and **54**). Resistance to these compounds is probably due to the more complex structure and hydrophilic nature of G-cell walls (Navrátilová et al. 2013; Šmejkal et al. 2008b). Furthermore, substitution of the geranyl side-chain with carbonyl, hydroxyl or methoxyl groups diminishes the antibacterial activity in a manner similar to what is seen when the geranyl substituent at C-6 forms a ring by reacting with the hydroxyl group at C-7. Compounds **45**, **47**, **48**, **50**, **53**, and **54** exhibit some degree of activity in the range of the concentrations tested on the Gram-positive bacteria *Staphyloccocus aureus* and various methicillin resistant strains of *S. aureus*. The level of activity varied in depending on both the structure and the bacterial strain used in the assay. Flavonoid structures like **24** are more effective in protecting plants from water loss because of their reduced polarity (Kobayashi et al. 2008; Navrátilová et al. 2013). Compounds **45**, **47**, **48**, **50**, and **53** were also tested for their ability to affect the initiation of the eukaryotic translation via dual-luciferase reported assay (firefly and renilla), but only **45** showed a modest activity in comparison with anisomycin (Navrátilová et al. 2013).

The cytotoxicity of the prenylated flavonoids obtained from *P. tomentosa* has been tested in more than 20 different cell lines. The type of prenylation strongly affects the cytotoxicity of a flavonoid in the traditional P-388 murine leukemia model. The unmodified 3-prenyl group and the presence of corresponding *ortho*-dihydroxy or trihydroxy substitution of the flavonoid ring B are crucial to its activity against P-388 as compared with other prenyl substituents (Hakim et al. 1999, 2002, 2006). Similar findings have been observed for modified C-6 geranyl groups and the substitution of the ring B for other cell lines tested (Šmejkal et al. 2010). However, replacing the *para*-hydroxy group of the ring B of a C-8 prenylated flavanone with several different acyl substituents resulted in greater cytotoxicity (Aniol et al. 2012; Šmejkal 2014). It has also been found that cytotoxic activity is diminished by the presence of a C-3 hydroxyl substituent on the ring C, 4′-methoxy substitution of the ring B or a *para*-hydroxy substituted ring B (Šmejkal et al. 2008a). For this reason, it is important to emphasize that the relative importance of the substitution of ring B can differ according to the cell line used. Modification of a prenyl or geranyl side-chain can not only change the direct cytotoxicity, but it may also affect the proliferation cells or trigger apoptosis (Kollár et al. 2011; Šmejkal et al. 2007a, 2008a, 2010; Šmejkal 2014).

Prenylated flavonoids **55**–**59**, modified with an unusual 3,4-dihydro-2*H*-pyran moiety, have been found to inhibit the severe acute respiratory syndrome corona virus PLpro enzyme more effectively than their parent compounds, the precursors from which were they derived (Cho et al. 2013).

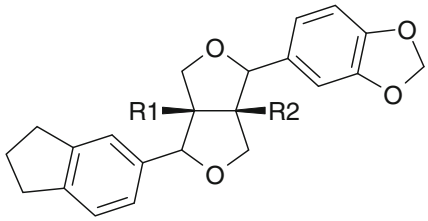
The presence of a geranyl group at the C-6 position (**21**, **22**, **24**–**26**, **30**, **31**, **33**, and **34**) seems to be crucial for the hAChE and BChE inhibitory effects. The most effective inhibitor was **22**. All of the geranylated flavonoids, apart from **26**, inhibited hAChE dose-dependently. It appears that greater inhibition is observed when ring B of the flavanone bears free hydroxyl groups (Cho et al. 2012).

The crystal structure of the bacterial sialidase *Cp*-NanI catalytic domain in a complex with the geranylated flavonoid diplacone (**22**) provides structural insights into the binding mode of natural flavonoid-based inhibitors at atomic resolution. It shows how the geranyl and C-3′ hydroxyl groups of **22** contribute to the stability of the enzyme-inhibitor complex. Time-dependent competitive inhibition patterns have been observed. Structural comparison of the human sialidases Neu1–Neu4 with the *Cp*-NanI–diplacone (**22**) complex suggests that the interaction between human sialidases and **22** is likely to be unfavourable because of polar or ionic repulsion (Lee et al. 2014).

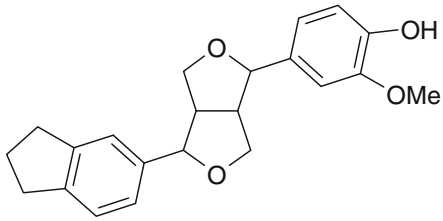
Six flavonoid glycosides have been extracted from the stem bark **60–62** (Si et al. 2009) and flowers **63–66** (Scogin 1980) of *P. tomentosa*. Apigenin-7-*O*-*β*-D-glucopyranoside (synonym: cosmosiin) (Kurkina et al. 2011) (**60**) shows anti-HIV activity in vitro on H9 cells (Tang et al. 1994) and enhances the secretion of adiponectin, the phosphorylation of the tyrosine residue of insulin receptor-β, and the translocation of GLUT5 (Rao et al. 2011). Compound **60** shows no significant hepatic Glc-6-phosphatase inhibitory activity in vitro (Kumar et al. 2010). Apigenin-7-*O*-*β*-D-glucuronopyranoside (**61**) was more potent than apigenin (**2**) and omeprazole in an assay analysing the inhibition of reflux esophagitis and gastritis promoted surgically and by application of indomethacine in rats (Min et al. 2005). No information about the biological activity of apigenin-7-*O*-[*β*-D-glucuronopyranosyl (1 → 2)-*O*-*β*-D-glucuronopyranoside] (**62**) has been found in the literature. Delphinidin-3-*O*-glucoside (synonym: myrtillin) (**63**) protects microglia from inflammation-induced stress signaling (Carey et al. 2013), is cytotoxic against the MCF-7 (breast) cancer cell line (Vareed et al. 2006), and has an the affinity for the estrogenic ERβ receptor (Hidalgo et al. 2012). Delphinidin-3,5-di-*O*-glucoside (**64**) and cyanidin-3,5-di-*O*-glucoside (**65**) are potent antioxidants (Lee et al. 2011; Tanaka et al. 2013). Compounds **63** and **65** are potent ACE inhibitors in vitro (Hidalgo et al. 2012; Persson et al. 2009).

P. tomentosa lignans and their biological activity

Only three lignans: (+)-paulownin (**66**), (+)-sesamin (**67**), (+)-piperitol (**68**) have been isolated from the wood of *P. tomentosa* (Ina et al. 1987; Takahashi and Nakagawa 1966; Zhu et al. 1986) (Fig. 3). Several reports have described their pharmacological effects (Zhang et al. 2014; Pan et al. 2009). Compound **66** is a promising antifungal agent that acts against the basidiomycetes *Fomitopsis palustris* and *Trametes versicolor* (Kawamura et al. 2004). Sesamin (**67**) has been previously isolated from the wood of *P. tomentosa*, and *P. kawakamii* and the hybrid of *P. elongata* × *P. fortunei* (Takahashi and Nakagawa 1966; Zhu et al. 1986). Compound **67** is the major lignan in sesame, and has various biological activities, such as antioxidant, angiogenic (Chung et al. 2010), antiphlogistic (Chatrattanakunchai et al. 2000), antihypertensive (Nakano et al. 2006), insecticidal (Nascimento et al. 2004), neuroprotective (Khan et al. 2010), and anticarcinogenic (Yasuda and Sakaki



66-67



68

66 R1= H, R2= OH

67 R1= R2= H

Fig. 3 Lignans

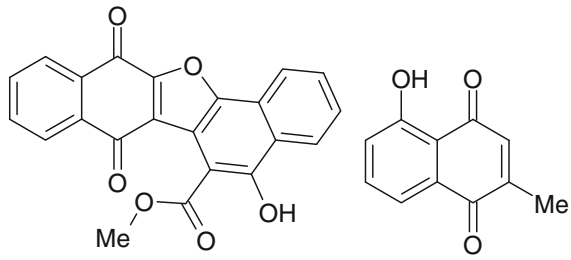
2012). However, this compound showed no significant ability to reduce the formation of atherosclerotic lesions in the ApoE (−/−) gene-knockout mouse, whereas specific dietary polyphenols, especially quercetin and theaflavin were more active (Loke et al. 2010). It has been suggested that some of the biological effects attributed to sezamine (**67**) may, in fact, be caused by its metabolites and that **67** may be acting as a proactive substance in the body (Yasuda and Sakaki 2012). The metabolism of sesamim (**67**) by cytochrome P450 and UDP-glucuronosyltransferase has been found remarkably different in humans as compared to other animals. Further investigation into the safety of taking sesamin (**67**) with therapeutic drugs that are metabolised by CYP2C9 is also needed (Yasuda and Sakaki 2012).

P. tomentosa phenolic glycosides and their biological activity

A total of thirteen phenylpropanoid glycosides (**69**–**81**) with multifarious bioactivities, natural compounds derived biosynthetically from the amino acid phenylalanine, have been isolated from different parts of the *P. tomentosa* plant (Table 4) (Damtoft and Jensen 1993; Kang et al. 1994; Ota et al. 1993; Schilling et al. 1982; Si et al. 2008b, d, Si et al. 2011b; Sticher and Lahloub 1982; Šmejkal et al. 2007b; Zhu et al. 1986). Phenylpropanoids are of great interest for fabricating effective tonic, anticancer, hepatoprotective, immunostimulating, antimicrobial, and anti-inflammatory phytopreparations (Kurkin 2003; Galvez et al. 2006; Panossian and Wagner 2005; Fu et al. 2008; Pan et al. 2003).

P. tomentosa quinones and their biological activity

A new furanoquinone, methyl-5-hydroxy-dinaphthol [1,2–2′,3′]furan-7,12-dione-6-carboxylate (MHDDC) (**82**) (Fig. 4) identified in *P. tomentosa* stem bark (MeOH extract) has been shown to possess antiviral activity against poliovirus types 1 and 3, using HeLa cells in vitro (Kang et al. 1999). Its cathepsin K and L inhibitory activities in vitro have recently been discovered. The 5-OH functional group may have a favourable effect on this reduction potential which prevents the degradation of bone the matrix carried out by osteoclasts (Park et al. 2009).



82 **83**

Fig. 4 Quinones

The naphtoquinone plumbagin (**83**) has been detected in the leaves and fruit of *P. tomentosa* (Babula et al. 2006). It has been used in traditional systems of medicine since ancient times (Pile et al. 2013). It has exhibited promising antimalarial activity in vitro with IC_{50} of 580 (270–640) nM and 370 (270–490) nM, respectively, against 3D7 chloroquine-sensitive *P. falciparum* and K1 chloroquine-resistant *P. falciparum* clones, using an assay based on SYBR Green I. Toxicity testing indicated relatively low toxicity at dose levels up to 100 mg/kg body weight (for a single oral dose) and 25 mg/kg (for daily dose given for consecutive 14 days) for acute and subacute toxicity, respectively. Based on the results of in vivo antimalarial testing, plumbagin administered at a the dose of 25 mg/kg of body weight for 4 consecutive days exhibited moderate to weak antimalarial activity with regard to its ability to reduce parasitaemia and prolong survival time (Sumsakul et al. 2014). Other published studies of plumbagin (**83**) described effects such as antifungal, antibacterial, cytotoxic (Krishnaswamy and Purushothaman 1980), anticoagulant (Santhakumari et al. 1978), anthelmintic (antischistosomal) (Zhang and Coultas 2013) and an anti-inflammatory effect on the amelioration of experimental ulcerative colitis in mice at a dose of 8–10 mg/kg (Pile et al. 2013).

P. tomentosa terpenoids and their biological activity

Six iridoids: 7-β-hydroxyharpagide (**84**), paulownioside (**85**), catalpol (**86**), aucubin (**87**), tomentoside (**88**) and 7-hydroxytomentoside (**89**) have been isolated from the leaves of *P. tomentosa* (**84**–**87**) (Adriani et al. 1981; Franzyk et al. 1999), the bark of the trunk and

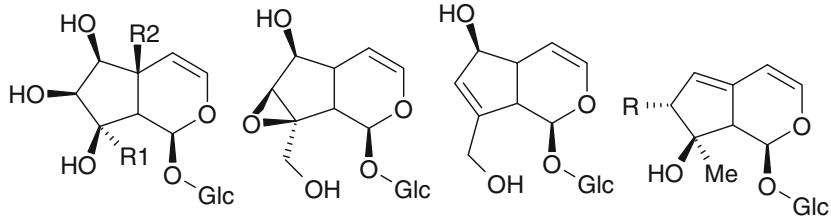
roots (**86**) (Plouvier 1971) and parts of the young plant (**85**, **86**, **88**, and **89**) (Damtoft and Jensen 1993) (Fig. 5). Compound **86** shows neuroprotective activity (Li et al. 2004), a cardioprotective effect against myocardial infarction—specifically reperfusion damage (Huang et al. 2013a, b), and radioprotective effects (Chen et al. 2013). It also increases glucose utilization by increasing the secretion of β-endorphin from the adrenal gland (Shieh et al. 2011). Compounds **86** and **87** possess antispasmodic activity (Deurbina et al. 1994). Aucubin (**87**) had antioxidant and pancreas-protective effects on streptozotocin-induced diabetes in rats (Jin et al. 2008) and it may improve obesity-induced atherosclerosis by attenuating the TNF-α-induced inflammatory response (Park 2013). A weak antibacterial effect (against *Streptococcus pneumoniae* and MG-hemolytic streptococcus, MIC 28.946 mg/ml) (Zheng et al. 2012) and neuroprotective effects of **87** on diabetes and diabetic encephalopathy (Xue et al. 2012) have also been observed.

The sesquiterpenic lacton isoatriplicolide tiglate (**90**) has been isolated from *P. tomentosa* flowers. It has neuroprotective effects against glutamate-induced neurotoxicity (Kim et al. 2010a, 2010b) and cytotoxic activity against several cancer cell lines: A549 lung carcinoma; SK-OV-3 adenocarcinoma; SK-Mel-2 malignant melanoma; XF498 central nervous system tumors; HCT15 colon adenocarcinoma, against which its effect is comparable to that of reference substance adriamycin (Moon and Zee 2001); human breast cancers MDA-MB-231, MCF7, HS578T, and T47D; and the HeLa, SiHa and C33A cervical cancer cell lines (Jung et al. 2012).

Seven phytosterols have been isolated from *P. tomentosa* leaves: ursolic acid (**91**) (Zhu et al. 1986; Zhang and Li 2011), 3-epiursolic acid (**92**), pomolic acid (**93**), corosolic acid (**94**), maslinic acid (**95**), *β*-sitosterol (**96**), and daucosterol (**97**) (Zhang and Li 2011). Most of these show various biological activities, e.g., **91** is a potentially useful for treating Alzheimer's disease (because of its ability to block the interactions of the amyloid β-CD36) (Wilkinson et al. 2011). It can prevent the recruitment of the monocytes that accelerate atherosclerosis, a major complication of diabetes, in mice (Ullevig et al. 2011), and it also possesses antibacterial (Wong et al. 2012), anti-trypanosomal, and anti-leishmanial properties (Bero et al. 2011). Compound **91** has also shown cytotoxic effects against K562 and K562/ADR human chronic myelogenous leukaemia, HL60 and HL60/ADR human acute myelocytic leukemia cancer cells, and the human colon cancer cell lines SW480 and SW620 (Shan et al. 2011). Compounds **93–96** also show promising cytotoxic potential, e.g., **93** is effective against the human chronic myelogenous leukaemia cell line 562 and also against cells derived from chronic myeloid leukaemia patients (Vasconcelos et al. 2007). Compound **94** shows cytotoxic effects against osteosarcoma MG-63 cells (Cai et al. 2011) and immunosuppressive activity on myeloid-derived suppressor cells in the murine sarcoma model (Horland et al. 2013). Compound **95** is effective against HT29 human colon cancer cells (Reyes-Zurita et al. 2011) and **96** promotes apoptosis in various cancer cells (Hac-Wydro 2013). Anti-inflammatory activities have been revealed for compounds **91**, **92**, and **96** (Deepak and Handa 2000), and **93** (Schinella et al. 2008). An immunomodulatory effect of **97** in protecting mice against candidiasis disseminated by the CD4+ Th1 immune response has been seen (Lee et al. 2007). Other recently discovered pharmacological effects include antimalarial (**95**) (Moneriz et al. 2011), hypotensive and endothelium-dependent vasorelaxant effects (**93**) (Estrada et al. 2011). Compound **95** is potentially useful for treating cerebral ischemic injuries (Guan et al. 2011), and **94** has promising antidiabetic effects (Sivakumar et al. 2009).

P. tomentosa glycerides and their biological activity

Thirty acylglycerols (**98–127**) belonging to 1,3-di-*O*-acetyl-2-*O*-(acyl)-glycerols, 1-*O*-acetyl-2-*O*-(acyl)-*sn*-glycerols and 2-*O*-(acyl)-glycerols, including only five known compounds (**99**, **106**, **108**, **114**, and **119**), have been identified in the exudates secreted from the glandular trichomes on the leaves: 1,3-di-*O*-acetyl-2-*O*-[(3*R*,6*S*)-3-(acetyloxy)-6-hydroxyeicosanoyl]-glycerol (**98**), 1-*O*-acetyl-2-*O*-[(3*R*)-3-(acetyloxy)octadecanoyl]-*sn*-glycerol (**99**), 1-*O*-acetyl-2-*O*-[(3*R*,7*R*)-3,7-*bis*(acetyloxy)octadecanoyl]-*sn*-glycerol (**100**), 1-*O*-acetyl-2-*O*-[(3*R*,6*S*)-3-(acetyloxy)-6-hydroxyoctadecanoyl]-*sn*-glycerol (**101**), 2-*O*-[(3*R*,7*R*)-3,7-dihydroxy-eicosanoyl]-glycerol (**102**), 2-*O*-[(3*R*,6*S*)-3,6-dihydroxy-eicosanoyl]-glycerol (**103**), 2-*O*-[(3*R*,8*R*)-3,8-dihydroxy-eicosanoyl]-glycerol (**104**), 2-*O*-[(3*R*,



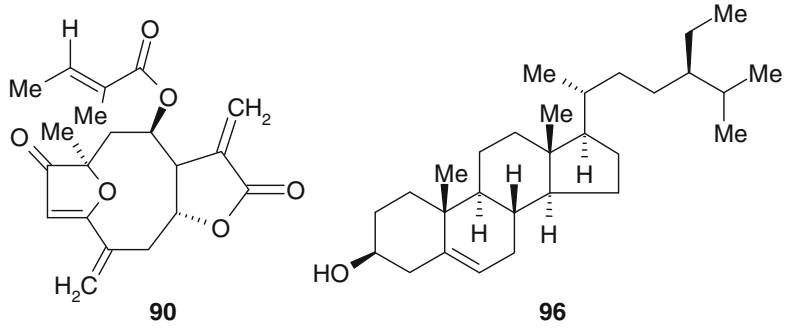
84, 85 **86** **87** **88, 89**

84 R1= Me, R2= OH

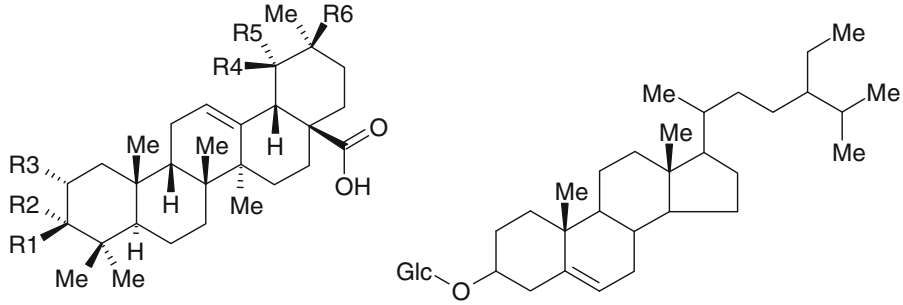
85 R1= CH_2OH, R2= OH

88 R= H

89 R= OH



90 **96**



91-95 **97**

91 R1= OH, R2= R3= R5= R6= H, R4= Me

92 R1= R3= R5= R6= H, R2= OH, R4= Me

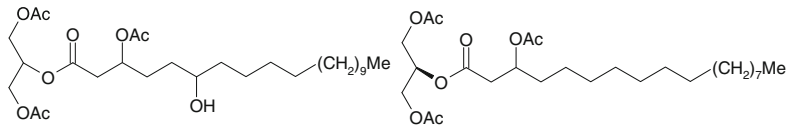
93 R1=R5= OH, R2= R3= R6= H, R4= Me

94 R1=R3= OH, R2= R5= R6= H, R4= Me

95 R1=R3= OH, R2= R4= R5= H, R6= Me

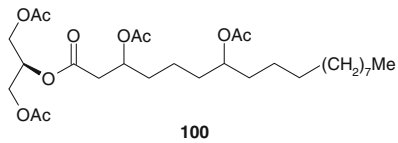
Fig. 5 Terpenoids

9*R*)-3,9-dihydroxy-eicosanoyl]-glycerol (**105**), 1-*O*-acetyl-2-*O*-[(3*R*)-3-(acetyloxy) eicosanoyl]-*sn*-glycerol (**106**), 1-*O*-acetyl-2-*O*-[(3*R*,6*S*)-3,6-*bis*(acetyloxy)eicosanoyl]-*sn*-glycerol (**107**), 1-*O*-acetyl-2-*O*-[(3*R*,7*R*)-3,7-*bis*(acetyloxy)eicosanoyl]-*sn*-glycerol (**108**), 1-*O*-acetyl-2-*O*-[(3*R*,8*R*)-3,8-*bis*(acetyloxy)eicosanoyl]-*sn*-glycerol (**109**), 1-*O*-acetyl-2-*O*-[(3*R*,9*R*)-3,9-*bis*(acetyloxy)eicosanoyl]-*sn*-glycerol (**110**), 1-*O*-

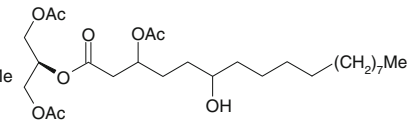


98

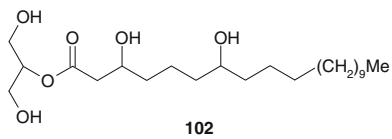
99



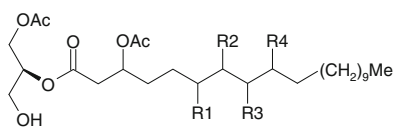
100



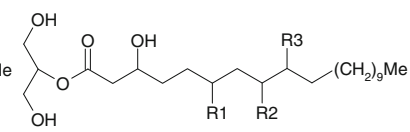
101



102



106-113



103-105

106 R1= R2= R3= R4= H

107 R1= OAc (*6S*), R2= R3= R4= H

108 R1= R3= R4= H, R2= OAc (*7R*)

109 R1= R2= R4= H, R3= OAc (*8R*)

110 R1= R2= R3= H, R4= OAc (*9R*)

111 R1= OH (*6S*), R2= R3= R4= H

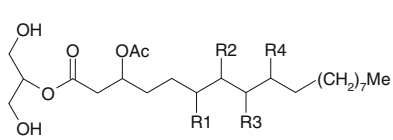
112 R1= R2= R4= H, R3= OH (*8R*)

113 R1= R2= R3= H, R4= OH (*9R*)

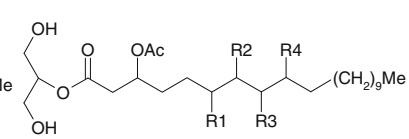
103 R1= OH (*6S*), R2= R3= H

104 R1= R3= H, R2= OH (*8R*)

105 R1= R2= H, R3= OH (*9R*)



114-120



121-127

114 R1= R2= R3=R4= H

115 R1= OH (*6S*), R2= R3=R4= H

116 R1= R3=R4= H, R2= OH (*7R*)

117 R1= R2=R4= H, R3= OH (*8R*)

118 R1= R2=R3= H, R4= OH (*9R*)

119 R1= R3=R4= H, R2= OAc (*7R*)

120 R1= R2=R4= H, R3= OAc (*8R*)

121 R1= R2=R3=R4 = H

122 R1= OH (*6S*), R2=R3= R4= H

123 R1= R3=R4= H, R2= OH (*7R*)

124 R1= R2=R4= H, R3= OH (*8R*)

125 R1= R2=R3= H, R4= OH (*9R*)

126 R1= R2=R4= H, R3= OAc (*8R*)

127 R1= R2=R3= H, R4= OAc (*9R*)

Fig. 6 Glycerides

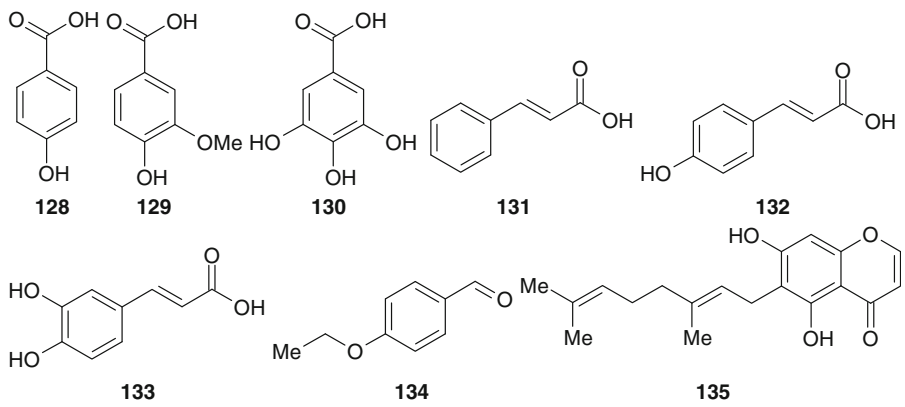


Fig. 7 Miscellaneous compounds

acetyl-2-*O*-[(3*R*,6*S*)-3-(acetyloxy)-6-hydroxyeicosanoyl]-*sn*-glycerol (**111**), 1-*O*-acetyl-2-*O*-[(3*R*,8*R*)-3-(acetyloxy)-8-hydroxyeicosanoyl]-*sn*-glycerol (**112**), 1-*O*-acetyl-2-*O*-[(3*R*,9*R*)-3-(acetyloxy)-9-hydroxyeicosanoyl]-*sn*-glycerol (**113**), 2-*O*-[(3*R*)-3-(acetyloxy) octadecanoyl]-glycerol (**114**), 2-*O*-[(3*R*,6*S*)-3-(acetyloxy)-6-hydroxy-octadecanoyl]-glycerol) (**115**), 2-*O*-[(3*R*,7*R*)-3-(acetyloxy)-7-hydroxy-octadecanoyl]-glycerol (**116**), 2-*O*-[(3*R*,8*R*)-3-(acetyloxy)-8-hydroxy-octadecanoyl]-glycerol (**117**), 2-*O*-[(3*R*,9*R*)-3-(acetyloxy)-9-hydroxy-octadecanoyl]-glycerol (**118**), 2-*O*-[(3*R*,7*R*)-3,7-*bis*(acetyloxy) octadecanoyl]-glycerol (**119**), 2-*O*-[(3*R*,8*R*)-3,8-*bis*(acetyloxy)octadecanoyl]-glycerol (**120**), 2-*O*-[(3*R*)-3-(acetyloxy)eicosanoyl]-glycerol (**121**), 2-*O*-[(3*R*,6*S*)-3-(acetyloxy)-6-hydroxy-eicosanoyl]-glycerol (**122**), 2-*O*-[(3*R*,7*R*)-3-(acetyloxy)-7-hydroxy-eicosanoyl]-glycerol (**123**), 2-*O*-[(3*R*,8*R*)-3-(acetyloxy)-8-hydroxy-eicosanoyl]-glycerol (**124**), 2-*O*-[(3*R*,9*R*)-3-(acetyloxy)-9-hydroxy-eicosanoyl]-glycerol (**125**), 2-*O*-[(3*R*,8*R*)-3,8-*bis*(acetyloxy) eicosanoyl]-glycerol (**126**), 2-*O*-[(3*R*,9*R*)-3,9-*bis*(acetyloxy)eicosanoyl]-glycerol (**127**). The relatively most abundant constituents were **111** (20 % of the total glycerides), **126** (14 %), and **120** and **127** (12 %) (Asai et al. 2009). Another analysis of the secretions of the glandular hairs on the leaves of both bud flushes and adult trees as well as the flowers of adult trees showed that these secretions contain ten glycerides (**106**, **108**–**110**, **118**, **122**, **124**–**127**). These compounds showed sticky character, but they were not toxic to several insects. Therefore, the glandular hairs on the leaves and flowers may serve only to physically deter herbivores (Kobayashi et al. 2008) (Fig. 6).

Miscellaneous *P. tomentosa* compounds and their biological activity

Six known phenolic acids, namely *p*-hydroxybenzoic acid (**128**), vanillic acid (**129**), gallic acid (**130**), cinnamic acid (**131**), *p*-coumaric acid (**132**), and caffeic acid (**133**) have been identified in the leaves of *P. tomentosa* (**128**–**133**), bark (**130** and **131**) and wood (**133**) (Ota et al. 1993; Si et al. 2008c, 2011b), and *p*-ethoxybenzaldehyde (**134**) is present in flowers (Yuan et al. 2009). The 5,7-dihydroxy-6-geranylchromone (**135**) isolated from fruits shows only moderate cytotoxic activity against a suspension culture of *Nicotiana tabacum* cv. Bright Yellow (BY-2), which confirms that ring B of the flavonoid skeleton is important for this activity (Šmejkal et al. 2008a). A large group of essential oil substances found in the flowers of *P. tomentosa* have also been identified (Oprea et al. 2004; Ibrahim et al. 2013) (Fig. 7).

Conclusions

Plants are still highly esteemed all over the world as rich sources of therapeutic agents. In this context, traditional Chinese herbal medicines, such as *Paulownia* continue to influence a modern healthcare. It has been estimated that approximately 420,000 plant species exist on Earth, but little is known about the phytochemical or therapeutic qualities of most of them. Thanks to the development of the spectral and other analytical methods used in modern phytochemistry, many of the principal physiologically active

secondary metabolites have been identified and researched in detail. The accumulated knowledge of traditional medicine is therefore, playing an important role in enhancing the success of drug discovery in herbal medicine. Approximately 80 % of the currently known antimicrobial, cardiovascular, immunosuppressive, and anticancer drugs are of plant origin (Pan et al. 2013).

As mentioned in this review, *P. tomentosa* is a rich source of multifarious secondary metabolites, mainly prenylated flavonoids. As of today 135 compounds, including flavonoids, lignans, phenolic glycosides, quinones, terpenoids, glycerides, phenolic acids, and other miscellaneous compounds have been isolated from various extracts of this plant.

Of increasing interest are the isolation and identification of *P. tomentosa* prenylated flavonoids, as they have shown promising pharmacological effects. In the first experiments, their antioxidant, antibacterial, antiphlogistic, cytotoxic, and SARS-CoV PL activities have been discovered along with inhibitory effects on human acetylcholinesterase, butyrylcholinesterase, and bacterial neuraminidases. More than 40 compounds with modified prenyl or geranyl side-chains attached at C-6 of the flavonoid skeleton have been isolated from the flowers, fruit, and leaves of *P. tomentosa*. Only two of these compounds have shown the presence of a five-carbon side-chain; for the others a ten-carbon side-chain is typical. Further, only a few compounds have shown a geranyl moiety modified by hydroxylation at C-6″ or C-7″. Some compounds have a geranyl group modified by formating a heterocyclic moiety, which is also unusual. Most of them have never been isolated from any other plant species. However, further in vivo pharmacology studies are needed to precisely elucidate biological mechanism of action, efficacy, and toxicity of these promising therapeutic agents. Elucidation of the structure–activity relationships is also crucial for their further total syntheses and introduction into medical practice. For these reasons, the study of *P. tomentosa* as a source of biologically active metabolites is significant and future interest in this plant is ensured.

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