NPC Natural Product Communications

2018
Vol. 13
No. 3
279 - 288

Natural Phenyldihydroisocoumarins: Sources, Chemistry and Bioactivity

Serhat S. Çiçek[a], Sara Vitalini[b] and Christian Zidorn[a,*]

[a]*Department of Pharmaceutical Biology, Kiel University, Gutenbergstraße 76, 24118 Kiel, Germany*
[b]*Department of Agricultural and Environmental Sciences, Milan State University, via Celoria 2, 20133 Milano, Italy*

czidorn@pharmazie.uni-kiel.de

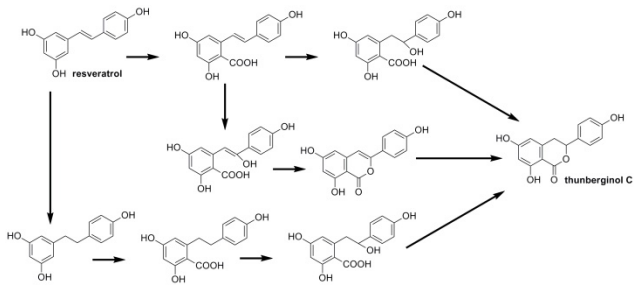
Received: October 20th, 2017; Accepted: November 2nd, 2017

The present review gives an overview about naturally occurring phenyldihydroisocoumarins, their sources, and bioactivities. In total, 54 compounds are covered, including eight substances which are in fact alkaloids or protoalkaloids. These nitrogen containing compounds were exclusively found in the Papaveraceae family. The remaining 46 compounds have been reported from twelve different source families, ranging from mosses to angiosperms. Six of the nitrogen free compounds feature additional rings, while 40 are simple phenyldihydroisocoumarins with substituents in all possible positions, except 3, 2', and 6'. Common substituents of these simple phenyldihydroisocoumarins are hydroxy groups, methoxy groups, and glucosyloxy groups; on the other hand, acuminosyloxy and rutinosyloxy groups have so far been found only in one and two naturally occurring phenyldihydroisocoumarins, respectively. Though a number of bioactivities have been proven for phenyldihydroisocoumarins, ranging from anticancer and antidiabetic to antimicrobial and anti-inflammatory activities, so far only one taxon, *Hydrangea macrophylla* var. *thunbergii*, is widely used. Moreover, the usage of this taxon is mainly due to the sweet taste properties of the contained phenyldihydroisocoumarin phyllodulcin and less based on the alleged health-promoting effects of its constituents.

Keywords: Asteraceae, Bioactivity, Biosynthesis, Chemosystematics, Hydrangeaceae, Papaveraceae, Phenyldihydroisocoumarins, Stilbenoids.

Introduction

In our continuing attempts to get an overview about the diversity of compounds biosynthetically derived from stilbenoids, we here give the first in detail review of the relatively small but fascinating natural product class of phenyldihydroisocoumarins. Based on an assumed biosynthesis starting from resveratrol, thunberginol C **11** should be the biosynthetically first dihydroisocoumarin in higher plants. Three alternative biosynthetic routes potentially leading from resveratrol to thunberginol C are depicted in scheme 1. As no further data on the exact biosynthesis are available, it is feasible that depending on the source, one or the other or even more than one of the depicted routes are realized in different species.



Scheme 1: Three alternative biosynthetic routes leading from resveratrol to thunberginol C.

Sources of phenyldihydroisocoumarins:

To get an overview about the naturally occurring diversity of phenyldihydroisocoumarins, a literature database search was carried out on January 29, 2017 using the Reaxys and Scifinder databases with 3-phenyldihydroisocoumarin (figure 1) as the starting substance. Substitutions on all atoms were admitted. In order to maintain the dihydroisocoumarin scaffold, only heterocyclic ring closures with the 3-phenyl moiety were considered; however, compound **46** and compounds with dioxomethylene moieties (**47**, **48**, **50**, **52**, and **53**) were also included. Stereochemistry, mixtures, isotopes, charges and radicals were ignored. This approach yielded 71 natural products, of which four compounds were duplicates and 13 compounds showed different configurations in at least one position, mostly in position 3. The structures were named uniformly using isochroman-1-one as basic molecular skeleton and trivial names were listed, except for compounds **37** and **41**. Due to the complexity of the resulting (semi-) systematic names, only trivial names were indicated for compounds **46-54**. The structures of these compounds are shown in figures 1-5. A concise overview about the systematic origin of the compounds is given in table 1 and full compound names, their molecular weights and exact sources are listed in table 2. In the following sections, natural sources of phenyldihydroisocoumarins are listed alphabetically by family name and within each family by taxon according to the currently accepted taxonomic classifications, which were checked using "The Plant List" [1]. Author citations for species names are not presented, because they are not meaningful in our context and because for every taxon and isolated compound we have followed the nomenclature of the original cited phytochemical publication. Obviously, we could neither judge nor ascertain whether applied nomenclature and more importantly species identifications in all cited papers had been correct.

Amaranthaceae

Haloxylon scoparium (Beni, Morocco/roots/dichloromethane) yielded compound **41** [2].

Asparagaceae

Liriope muscari, as *Liriope platyphylla,* (Taichung, Taiwan/roots/95% ethanol) yielded (+)-platyphyllarin A **43** and B **44** [3].

Asteraceae

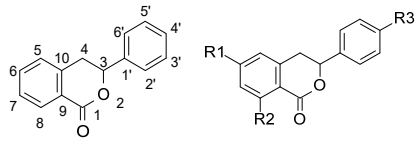
Investigations of five species (including four different *Scorzonera* species) resulted in the isolation of twelve dihydroisocoumarins, including ten novel structures.

Scorzonera cretica (Crete, Greece/whole plant/dichloromethane and methanol) yielded scorzocreticin **12** as well as scorzocreticoside I **14** and II **15** [4].

Scorzonera psychrophila, as *Scorzonera judaica,* (Dab'a desert, Jordan/roots/chloroform and methanol) yielded hydrangenol **1** along with two glucosides, **3** and **8**, and two diglycosides, **4** and **5** [5].
Scorzonera papposa (Dab'a desert, Jordan/whole plant/chloroform and methanol) yielded thunberginol G **18** [6].

Scorzonera tomentosa (East Anatolia, Turkey/subaerial parts/methanol) yielded hydrangenol **1** and scorzotomentosin **6**, along with their 4'-*O*-β-glucosides **3** and **7** [7].

Tragopogon porrifolius subsp. *porrifolius* (Andalusia, Spain/subaerial parts/methanol) yielded thunberginol C **11**, scorzocreticoside I **14** and 6-*O*-methylscorzocreticoside I **17** [8].



Compds	R1	R2	R3
1	H	OH	OH
2	H	OH	OCH_3
3	H	OH	OGlc
4	H	OH	OAcu
5	H	OH	ORut
6	H	OCH_3	OH
7	H	OCH_3	OGlc
8	H	OGlc	OH
9	H	OGlc	OGlc
10	OH	OH	H
11	OH	OH	OH
12	OH	OH	OCH_3
13	OH	OGlc	OH
14	OH	OGlc	OCH_3
15	OH	ORut	OCH_3
16	OCH_3	OH	OH
17	OCH_3	OGlc	OCH_3

Figure 1: Chemical structures of phenyldihydroisocoumarins only substituted at C-6, C-8, and/or C-4' (**1**-**17**) [Acu = β-D-acuminose, Glc = β-D-glucopyranose, Rut = α-L-rutinose].

Cannabaceae
Trema orientalis (Niamoko, Cameroon/root bark/ethyl acetate) yielded orientoside A **46**, a polyphenolic dihydroisocoumarin derivative [9].

Clusiaceae
Montrouziera sphaeroidea (New Caledonia, France/stem bark/acetone) yielded montroumarin **10** [10].

Dioscoreaceae
Dioscorea collettii var. *hypoglauca* (Zhejiang, China/rhizomes/70% ethanol) yielded montroumarin **10** [11].

Dioscorea futschauensis (Fujian, China/rhizomes/75% ethanol) also yielded montroumarin **10** [12].

Dioscorea spongiosa (Hebei, China/rhizomes/70% ethanol) yielded annulatomarin **35** and dioscoroside G **42** [13]. In this reference there is a mismatch between the title, stating that the manuscript is about natural products from *Dioscorea septemloba*, and the actual text, which describes natural products from *Dioscorea spongiosa* [13] (both combinations are accepted species names according to "The Plant List" [1]).

Hydrangeaceae
Hydrangea chinensis (Pintong, Taiwan/roots/methanol) yielded hydrangenol **1** [14].

Hydrangea macrophylla yielded more than 20 different phenyldihydroisocoumarins, with first reports in 1929, when Asahina and Asano isolated hydrangenol **1** and its methyl ether phyllodulcin **19** out of an alcoholic extract of what the authors called *H. opuloides* [15]. In the following section also several subspecies and varieties of *H. macrophylla* will be listed with var. *thunbergii* as the most prominent one. The variety *thungbergii* is also known as Hydrangeae dulcis folium (HDF) or "Amacha", *sweet tea* which is obtained by percolation of the fermented and dried leaves [16]. This fermentation process is carried out in order to increase the amount of the aglycon phyllodulcin by cleavage of sugar moieties which in turn increase the leaves' sweetness [16]. Because none of the mentioned taxa has been accepted so far, they are summarized under the name *Hydrangea macrophylla*. Nonetheless, different highlighted letters are used in Table 1 in order to maintain the taxonomic information from the original publications as well as information about an eventual fermentation of the plant material. Furthermore, all cited publications place the genus *Hydrangea* within the Saxifragaceae family, which has meanwhile been revised and changed to Hydrangeaceae.

Hydrangenol **1** was repeatedly isolated from the dried leaves of *Hydrangea macrophylla* (e.g. Nagano, Japan/leaves/methanol) [16-21]. In 1978 Suzuki *et al*. isolated hydrangenol-8-*O*-glucoside **8** and phyllodulcin 8-*O*-glucoside **25** from cultured cells (Yokohama, Japan/cultured cells/methanol) of *H. macrophylla* var. *thunbergii* along with the respective aglyca **1** and **19** [16]. Hashimoto *et al*. (Tokushima, Japan/leaves/methanol) isolated hydrangenol 8-*O*-glucoside **8** and macrophyllosides A-C (**26R**, **26S**, **34**) from *H. macrophylla* subsp. *serrata* [22] and again hydrangenol 8-*O*-glucoside **8** from *H. macrophylla* var. *otaksa* [23]. Hydrangenol 8-*O*-glucoside **8** was also isolated from an ethyl acetate partition of a hot water extract of *H. macrophylla* var. *macrophylla* by Uesato *et al*. [24].

In the 1990s Yoshikawa *et al*. extensively studied *H. macrophylla* var. *thunbergii* obtaining a number of new phenyldihydroisocoumarins such as thunberginols C **11**, D **28**, E **29**, G **18**, and H **20** as well as glycosides **3**, **4**, **8**, **21**-**23**, **25**, **27** [19-20, 25-27]. In the first three studies methanolic extracts of fermented leaves (collected in Nagano, Japan) were investigated, whereas later studies used dried plant material. In these two studies, the authors also found out that while hydrangenol and its 8-*O*-glucoside can only be obtained in a racemic 1:1 mixture (due to an isomerization reaction of the 4'-hydroxy group), phyllodulcin and its glycosides as well as hydrangenol-4'-*O*-glucoside form stable enantiomers. Thus, most of the mentioned glycosides were isolated in both – *R* and *S* – configurations.

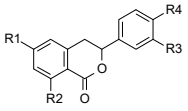
Since the year 2000 four more studies on *H. macrophylla* have been conducted [17-18,21,28]. Umehara *et al*. (Shizuoka, Japan/commercially available dried leaves/methanol) [21] isolated compounds **1**, **3**, **18**-**19**, **23**, **25**, and **28** using an anticancer activity-guided approach. Zhang *et al*. (Nagano, Japan/air dried leaves/methanol) [17] focused on anti-diabetic activity of compounds **1**, **8**, **11**, and **28**-**29**. Kikuchi *et al*. [28] obtained compound **9**, a hydrangenol 8,4'-di-*O*-glucoside, from a methanol extract of the dried leaves of *H. macrophylla* subsp. *serrata* (collected in Fukushima Prefecture, Japan). The so far most extensive study by Liu *et al*. [18] was performed on flowers of *H. macrophylla* var. *thunbergii* (Nagano Province, Japan/32.2%

methanol). This study yielded the compounds **1-3**, **8**, **13**, **18-19**, **21-22**, **24-25**, **31-33**, and **38** and constitutes the first report of compounds **24-25**, **31-33**, and **38**.

Hypericaceae

Cratoxylum sumatranum (Mae Hong Son, Thailand/roots/dichloromethane and acetone) yielded annulatomarin **36** [29].

Hypericum annulatum (Rhodope Mountains, Bulgaria/aerial parts/*n*-hexane) also yielded annulatomarin **36** [30].



Compds	R1	R2	R3	R4
18	H	OH	OH	OH
19	H	OH	OH	OCH_3
20	H	OH	OCH_3	OCH_3
21	H	OH	OCH_3	OGlc
22	H	OH	OGlc	OH
23	H	OH	OGlc	OCH_3
24	H	OGlc	OH	OH
25	H	OGlc	OH	OCH_3
26	H	OGlc	OCH_3	OH
27	H	OGlc	OCH_3	OCH_3
28	OH	OH	OH	OH
29	OH	OH	OH	OCH_3
30	OH	OH	OCH_3	OH
31	OH	OH	OGlc	OH
32	OH	OGlc	OH	OCH_3
33	OGlc	OH	OH	OCH_3

Figure 2: Chemical structures of phenyldihydroisocoumarins substituted at C-3', and/or C-6, C-8, and C-4' (**18-33**) [Glc = β-D-glucopyranosyl].

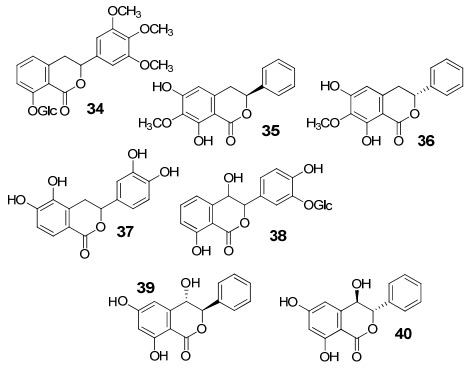


Figure 3: Chemical structures of simple phenyldihydroisocoumarins with unusual substitution patterns (**34-40**) [Glc = β-D-glucopyranosyl.].

Onocleaceae

Onoclea orientalis, as Matteuccia orientalis, (Jiangxi, China/rhizomes/ 60% ethanol) yielded (+)- and (-)-matteucen A (**40** and **39**), as well as (+/-)-matteucen B (**30**) [31].

Papaveraceae

Dactylicapnos torulosa (Sichuan, China/whole plant/95% ethanol) yielded torulosine **49** and torulosinine **51**, two dihydroisocoumarylisoquinoline alkaloids [32].

Hypecoum leptocarpum (Sichuan, China/whole plant/95% ethanol) yielded leptopidinine**48** [33]. Other studies led to the isolation of further alkaloids **50** and **53-54** [34-35].

Hypecoum pendulum, as *Hypecoum parviflorum,* yielded the protoalkaloid **47** [36].

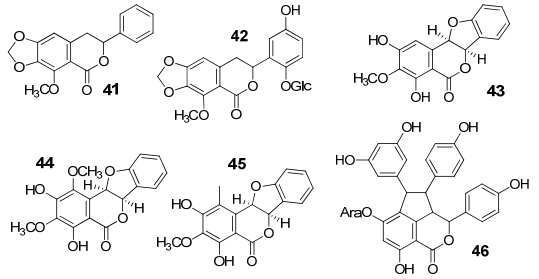


Figure 4: Chemical structures of phenyldihydroisocoumarins with additional rings (**41-46**) [Ara = α-arabinopyranosyl; Glc = β-D-glucopyranosyl.].

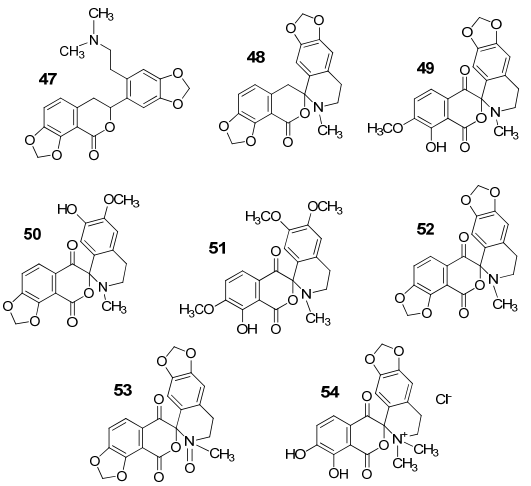


Figure 5: Protoalkaloids (**47**) and alkaloids (**48-54**) containing or formally containing phenyldihydroisocoumarin moieties.

Hypecoum procumbens var. *glaucescens* (Sinai, Egypt/whole plant/95% ethanol) yielded 8-oxohypecorinine **52** [37]. In another study (Brno, Czechoslowakia/whole plants/methanol) procumbine **50** was isolated from this taxon [34].

Plagiochilaceae

Plagiochila cristata (Cundinamarca, Colombia/whole plant/diethyl ether) yielded hydrangenol monomethyl ether **2** [38].

Polygalaceae

Polygala honkongensis (whole plant/P.R. China/methanol) yielded honkongenin **16** [39].

Pteridaceae

Pteris multifida yielded multifidarin A **45** [40]. *Onychium japonicum* (ethyl acetate) yielded compound **37** [41]. Unfortunately, the origin of the plant material of these two species was not indicated in the original publications.

Biological activities

Antiallergic activity: Hydrangenol **1**, (-)-hydrangenol 4'-*O*-glucoside **3**, phyllodulcin **19**, thunberginols C **11**, D **28**, E **29**, and G **18** showed inhibitory activity comparable to AA-861 in antigen-induced contraction of tracheal chain isolated from sensitized guinea pig [Schults-Dale model (S.D.)]. No or slight activity was detected at 10^{-5} M, 20-60% of inhibition at $3x10^{-5}$ M, and total inhibition at 10^{-4} M [19,42]. The same compounds along with hydrangenol monomethyl ether **2**, hydrangenol 8-*O*-glucoside **8**, and phyllodulcin 8-*O*-glucoside **25** confirmed these data with IC_{50} values ranging from 2.5×10^{-5} to $> 10^{-4}$, similar to those of two commercial antiallergic agents, transilat disodium and cromoglycate (DSCG) (4.7×10^{-5} and $> 10^{-4}$, respectively) [20,25,43-44].

Additionally, thunberginols D **28** and E **29** proved to be most effective against histamine release from rat mast cells when compound 48/80 was used as an inducer (84.8% and 97.9% of inhibition, respectively), while thunberginol C **11** acted significantly against calcium ionophore A-23187-induced histamine release (inhibition 72.8 %) [20,25,44-45]. Only compounds **11** and **28**-**29** also showed some inhibitory activity on histamine-induced contraction of tracheal chain (5.9%, 10.5%, and 13.2%), but their activities were weaker than that of diphenhydramine (76.9 %) at the same concentration (10^{-5} M) [19-20,25,42,44].

Hydrangenol **1** and phyllodulcin **19**, administered orally (100-250 mg/kg) to rats two hours prior to a challenge with DNP-As, had negligible inhibitory effect on their 48 h homologous passive cutaneous anaphylaxis (PCA) reaction (4.8% to 25.8%) compared to that of DSCG (91.1%) [44].

Matsuda and co-authors [46] corroborated the slight effectiveness on PCA reaction of phyllodulcin **19** – only ~10% more inhibition than control – by using anti-DPN IgE to sensitize rats. Moreover, the same authors demonstrated that hydrangenol **1** at the highest tested doses of 300 to 500 mg/kg significantly inhibited PCA reaction by more than 50%, followed by 40-50% inhibition recorded for hydrangenol 8-*O*-glucoside **8** and phyllodulcin 8-*O*-glucoside **25** [46]. Therefore, hydrangenol **1** was identified as the principal anti-type I allergic constituent in Hydrangeae dulcis folium (HDF) [46]. Hydrangenol **1** and phyllodulcin **19**, at 0-100 μM, revealed no or weak inhibitory effects on antigen-induced releases of TNF-α and IL-4 in RBL-2H3 cells (IC_{50}> 100 μM) [45]. Similar data (IC_{50} = 90 to > 100 μM) were reported for the antigen-induced release of β-hexosaminidase, a marker of the degranulation of the same cells, for hydrangenol **1**, thunberginol C **11**, phyllodulcin **19**, and thunberginol G **18** [45]. In contrast, the IC_{50} obtained for thunberginol E **29** was 48 μM [45].

Anticancer, antiproliferative and cytotoxic activity: Hydrangenol **1**, phyllodulcin **19**, thunberginols C **11**, D **28**, and G **18** showed differentiation inducing activity at a concentration greater than 200 μM against mouse myeloid M1 cells**,** while (-)-hydrangenol 4'-*O*-β-glucoside **3**, *3R*-phyllodulcin 3'-*O*-glucoside **23**, and phyllodulcin 8-*O*-glucoside **25** were inactive (data not shown) [21]. Phagocytic activity (30-50%) of compounds **1**, **11**, **18**, **19**, and **28** was observed only at concentrations of 300 μM [21].

Phyllodulcin **19** studied in relation to the effects of 50 μM dietary phytochemicals on the functions of P-glycoprotein (P-gp) and MRP1 significantly inhibited, in a concentration-dependent manner, the P-gp mediated efflux by increasing (up to 10 nmol/mg protein) the cellular accumulation of daunorubicin, a substrate of P-gp, in KB-C2 multidrug-resistant human epidermal carcinoma cells [47]. Nevertheless, the compound was excluded from further evaluation of inhibition of MRP1 [47].

Hydrangenol **1** (200 ppm) administered in the initiation phase to the experimental diet of male F344 rats treated with subcutaneous injections of azoxymethane (AOM) (15 mg/kg, once weekly for 3 weeks), tended to decrease the incidence (45% vs 68% of the group with AOM alone) and the multiplicity (0.62 vs 1.04 average number) of tumors in the entire intestine. However, the observed effect was not statistically significant [48]. The results did not confirm a clear inhibitory effect of hydrangenol **1** on AOM-induced intestinal carcinogenesis by suppressing the total number of aberrant crypt foci (ACF)/colon to 115.6 compared with 152.5 for rats treated with AOM alone. In addition, indicator values of cell proliferation such as mean colonic ODC activities (4.3 vs 22.1 pmol $^{14}CO_2$/h/mg protein) and AgNOR enumerations (1.05 vs 1.44 of AgNORs/nucleus), which reflect the number of AgNORs in rat colonic mucosal epithelium, were lowered [49]. Hydrangenol **1**, hydrangenol 4'-*O*-β-D-glucopyranoside **3**, hydrangenol 4'-*O*-β- D-apiofuranosyl-(1→6)-β- D-glucopyranoside **4**, *3S*-hydrangenol 4'-*O*-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranoside **5**, scorzotomentosin **6**, and hydrangenol 8-*O*-glucoside **8** showed no significant cytotoxicity against three human cell lines, cervical adenocarcinoma (HeLa), lymphocytes T (Jurkat), and breast adenocarcinoma (MCF7), with IC_{50} values higher than 100 μM [5].

Annulatomarin **36** was found to be a modest growth-inhibitor of human chronic myeloid leukaemia LAMA-84 cells with an IC_{50} value of 111 μM [30].

Antidiabetic activity: In the search for new natural antidiabetic compounds from *Hydrangea macrophylla* var. *thunbergii*, thunberginols C **11**, D **28**, E **29**, and phyllodulcin 8-*O*-glucoside **25** were found to reduce triglyceride (TG) levels, up to -17.6% [17]. On the contrary, hydrangenol **1**, hydrangenol 8-*O*-glucoside **8,** and phyllodulcin **19** promoted the accumulation of TGs with percentages ranging from 1.2 to 41.3% in murine 3T3-L1 adipocytes at concentrations ranging from 1 to 100 mM. Hydrangenol **1** exhibited the strongest activity, though still lower than that of troglitazone (33.8 to 40.5%) used as reference compound [17]. Furthermore, hydrangenol **1** (at 30 and 100 mM) was shown to enhance concentration-dependently the gene expression (target gene/b-actin mRNA) of peroxisome proliferator-activated receptor g2 (PPARg2) (1.92 and 2.65 vs 1.00 of the control) involved in adipogenesis as well as the gene expression of glucose transporter 4 (GLUT-4) (1.12 and 1.38 vs 1.00) and adiponectin (1.98 and 2.46 vs 1.00). These values were similar to those of troglitazone (1.09, 2.92, and 3.01, respectively) [17, 50]. Hydrangenol **1** also increased the amount of adiponectin released into the medium (from 65.7 to 94.0 and 99.0 ng/mL) as well as the uptake of 2-deoxyglucose (2-DG) into the cells (245 and 302 μM). In contrast, hydrangenol **1** decreased the expression of interleukin 6 (IL-6) associated with insulin resistance (from 1.00 to 0.78 and 0.51) [17]. Tested in type 2 diabetic KK-A^y mice, hydrangenol **1**, compared to the control, lowered blood glucose (411.2 mg/dL vs 491.3 mg/dL), TG (428.8 vs 538.8 mg/dL) and free fatty acid (0.89 mEq/L vs 1.16 mEq/L) levels two weeks after its administration at 200 mg/kg/d [17].

Anti-inflammatory activity: Hydrangenol **1** was found to be a promising therapeutic agent for the treatment of lipopolysaccharide (LPS)-mediated inflammatory diseases without influence on the cell viability in concentrations of up to 40 μM in 24 h. In particular, the compound was able to decrease nitric oxide (NO) production in pretreated LPS-stimulated BV2 microglial cells in a dose-dependent manner (from 18.9 μM to 13.1, 10,9, and 8.8 μM at 10, 20 and 40 μM, respectively), though at levels higher than those of untreated control (4.2 μM). A pretreatment with hydrangenol **1** also significantly inhibited iNOS mRNA expression in the same cells, especially at concentration of 40 μM (relative intensity from 1.0 to ~ 0.3 iNOS/β-actin) [51]. Hydrangenol **1**, in fact, completely suppressed LPS-induced NF-*k*B activation with values of relative intensity ranging from 1.0 to 0.2. Moreover, it lowered LPS-induced nuclear translocation of NF-*k*B subunits p50 and p65 and sustained their levels in the cytosol [51]. Its preventive effect on NO release was also due to its ability to activate the Nrf-2-mediated HO-1 pathway. The presence of hydrangenol **1** remarkably increased Nrf-2 activity (from 0.2 to 1.0 at 40 μM) by regulating, accordingly, the expression of antioxidant stress-related protein

OH-1 and subsequent production of NO [51]. On the other hand, hydrangenol **1**, at concentrations of 10, 20, and 40 μM, possessed only a weak inhibiting effect in LPS-mediated NO production (from 25 μM to 20 μM vs 4 μM of the control) [51]. Hydrangenol 8-*O*-glucoside **8** is one of the main compounds of the ethyl acetate fraction of a *Scorzonera latifolia* methanol extract [52]. Evaluated in TNF-α and IL-1β production inhibition assays this ethyl acetate fraction showed high anti-inflammatory activity. However, at concentration of 10 μM, compound **8** showed no statistically significant activity (~ 6000 pg/mL and ~ 200 pg/mL, respectively) compared to the reference compound prednisone (< 3000 pg/mL and ~ 100 pg/mL) [52].

Antimicrobial activity: Hydrangenol **1** tested on a set of 24 microorganisms was found effective with MIC values ranging from 5 to 25 ppm against six bacteria causing periodontal disease and halitosis: *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, *Porphyromonas gingivalis*, *Prerotella intermedia*, *Capnocytophaga sputigena*, and *Haemophilus actinomycetemcomitans* [19-20,25]. In contrast, hydrangenol **1** did not show any activity (MICs ≥ 100 ppm) towards the other 14 tested bacteria: *Acinetobacter calcoaceticus*, *Bacillus subtilis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Proteus vulgaris*, *P. mirabilis*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus mutans*, *S. pyrogenes*, and *S. faecalis*; nor towards four tested fungi: *Aspergillus fumigatus*, *Candida albicans*, *Cryptococcus neoformans*, and *Trichophyton mentagrophytes* [25]. Phyllodulcin **19** had only weak or no activity on the same set of microbes (MICs, 50 to 150 ppm) [19-20,25]. These results confirmed the previous ones of Ueno and co-worker [53] on *E. coli* and *S. aureus* at concentrations over 5000 μg/mL. Both compounds showed antifungal activity against *Alternaria maritima*, *Cochliobolus miyabeanus*, *Fusarium splendens*, *Giberella zeae*, *Helminthosporium maydis*, and *Penicillium expansum* by completely inhibiting their growth with MICs ranging from 25 to 200 μg/mL [54]. Glucosides of hydrangenol **1** and phyllodulcin **19**, i.e. hydrangenol 4'-*O*-glucoside **3**, hydrangenol 8-*O*-glucoside **8**, and phyllodulcin 8-*O*-glucoside **25**, were not able to exhibit antibacterial activity (≥ 100 ppm MICs) [19,25].

Thunberginols C **11**, D **28**, E **29**, and G **18** counteracted two out of six periodontopathic bacteria: *B. melaninogenicus* and *F. nucleatum* - with MIC values from 10 to 50 ppm [19,25].

Antioxidant activity: The results obtained by 2,2-diphenyl-1-picrylhydrazil (DPPH) test proved thunberginol C **11** and scorzocreticoside I **14** as weak radical scavengers with IC_{50} values of 115.6 ± 12.6 and 59.15 ± 7.38 μg/mL, respectively, much higher than those of ascorbic acid (2.49 ± 0.32), caffeic acid (1.78 ± 0.03), and chlorogenic acid (1.28 ± 0.38) used as reference compounds. In the same assay, no significant activity was detected for 6-*O*-methylscorzocreticoside I **17** (IC_{50}>200 μg/mL) [8]. On the contrary, thunberginol G **18** was found to be active both in the β-carotene bleaching assay (BCB) (46.1% of antioxidant activity) and FRAP (82.6 ± 5.1 mg Trolox equivalents/g) test, with a relative antioxidant capacity index (RACI) of 0.17 [6]. Hydrangenol 4'-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside **4** showed a higher BCB activity (55.3%), but a lower FRAP value (7.4 ± 0.5 mg Trolox equivalents/g). A similar change was detected for hydrangenol **1** (40.5% and 9.2 ± 0.7 mg Trolox equivalents/g, respectively), while the opposite capacity was recorded for hydrangenol 8-*O*-glucoside **8** (28.3% and 80.9 ± 5.1 mg Trolox equivalents/g, respectively). 3*S*-Hydrangenol 4'-*O*-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranoside **5** showed weak activities in both assays (11.6% and 0.3 ± 0.0 mg Trolox equivalents/g) [6].

Antiplatelet activity: Effects of (+)-platyphyllarins A **43** and B **44** against washed human platelet aggregation induced by collagen (10 μg/mL) were studied. The obtained results showed IC_{50} values of 14.0 μM and 65.8 μM, respectively, suggesting a moderate activity for the first compound only [3].

Antiulcer activity: Hydrangenol **1** and phyllodulcin **19** administered orally to rats (75 mg/kg) 1 h before HCl/EtOH treatment inducing gastric erosions were found to possess no or weak antiulcer activity with an inhibition percentage of 0.0 and 23.2%, respectively, unlike the standard cetraxate (79.2%) [44].

Choleretic activity: Hydrangenol **1** and phyllodulcin **19** showed no significant effect on 'cholagogic' action in rats. At a dose of 200 mg/kg, the compounds were able to increase the bile secretion by only a few percentage points (plus 9 % and plus 19 %, respectively) relative to control, over the monitored five-hour period [44].

Enzyme inhibition activities ─

Aldose reductase inhibitory activity: Sixteen dihydro-isocoumarins were investigated in relation to their inhibitory action against aldose reductase, an enzyme involved in intracellular sorbitol accumulation, which is implicated in chronic diabetic cataracts. Only hydrangenol **1** and thunberginol G **18** were moderately effective with IC_{50} values of 47.8 μM and 58.3 μM, respectively, much higher than that of positive control chlorogenic acid (IC_{50} = 0.41 μM) [18]. All other compounds, i.e. hydrangenol monomethyl ether **2**, (+)-hydrangenol 4'-*O*-β-D-glucopyranoside **3**, hydrangenol 8-*O*-glucoside **8**, thunberginol C 8-*O*-β-D-glucopyranoside **13**, phyllodulcin **19**, (3*R*)-thunberginol I 4'-*O*-glucoside **21**, thunberginol G 3'-*O*-glucoside **22**, thunberginol G 8-*O*-β-D-glucopyranoside **24**, (3*R*)-phyllodulcin 8-*O*-β-D-glucopyranoside **25**, (3*S*)-phyllodulcin 8-*O*-β-D-glucopyranoside **25**, thunberginol D 3'-*O*-β-D-glucopyranoside **31**, florahydroside I **32**, florahydroside II **33**, and 4-hydroxythunberginol G 3'-*O*-β-D-glucopyranoside **38**, showed no inhibitory activity on aldose reductase with IC_{50} values of more than 100 μM [18].

Phosphodiesterase inhibitory activity: Phyllodulcin **19** was found to enhance cyclic AMP-induced steroidogenesis in bovine adrenocortical cells (~300 to ~600 pmol/10^5 cells/h), at low concentrations (5-40 μM) [55]. These data suggested the compound as an upstream regulator of intracellular phosphodiesterase activity. Phyllodulcin **19**, in fact, acted as a non-selective phosphodiesterase inhibitor in a dose-dependent manner (50-800 μM) with a potency similar to theophylline (IC_{50} = 100 μM for both compounds), succeeding in reducing the bioconversion of cyclic AMP to inactive compound 5'-AMP [55].

Immunomodulatory activity: Some phenyldihydroisocoumarins were investigated for their effects on spleen lymphocyte proliferation induced by various mitogens [56]. Hydrangenol **1** was found able to act ($p < 0.01$) against T lymphocyte proliferation induced by concanavalin A (Con A) at 10^{-5} M [56], while the same compound as well as phyllodulcin **19**, thunberginols C **11**, D **28**, E **29**, and G **18** showed no suppressive effect when the proliferation was activated by phytohemagglutinin (PHA) both at 10^{-5} and 10^{-6} M [56]. In particular, thunberginol D **28** significantly increased PHA induced-T lymphocyte proliferation (up to 33.3%) [57]. On the other hand, all molecules significantly potentiated (up to 35%) B lymphocyte activation by LPS at 10^{-5} M [56-57]. Thunberginol E **29**

and hydrangenol **1** tested on splenocyte viability showed no influence both on LDH release and antigen-specific T lymphocyte proliferation (KLH) in mice lymph node cells [57].

Neuroprotective activity: (3*S*)-8-methoxy-6,7-methylendioxy-3-phenylisochroman-1-one **41** enhanced I_{GABA} at a GABA EC_{5-10} in a dose dependent manner [2]. The compound was also found able to act as a positive allosteric modulator of the $GABA_A$ receptor (data not shown) [2].

Estrogenic activity: (+)-Platyphyllarins A **43** and B **44** were tested using the pER8:GUS reporter assay system in transgenic *Arabidopsis*. At 0.33 μM, both compounds exhibited considerable activity with MAC values of 166.7 μM and 9.45 μM, respectively. These values were, however, lower than those of the isoflavandiol equol and of 17β-estradiol, which were used as controls (0.198 μM and 1.00 nM, respectively) [3]. Their estrogenic activity was only partially confirmed using a SEAP reporter gene assay system in MFC-7 cell-line. At six concentrations ranging from 1.00 nM to 100 μM, the relative luminescence and MTT cell survival levels of the two platyphyllarins were always slightly higher than those of the basal control (100%) [3].

Summary of potential health promoting bioactivities: More than half of the known phenyldihydroisocoumarins were investigated to assay potential beneficial effects on human health. Hydrangenol **1** and phyllodulcin **19** are the most widely tested compounds, followed by thunberginols **11**, **18**, and **28**-**29**. Researchers focused their attention primarily on antiallergic and antitumor activities. They obtained results needing to be confirmed and advanced. A limited number of studies were carried out on bioactivities for which some phenyldihydroisocoumarins showed promising data such as anti-inflammatory, antimicrobial, and antioxidant agents as well as phosphodiesterase inhibitors. The interesting outcomes found *in vitro* for immunomodulatory and estrogenic activities were noticeably resized in cell lines.

Accordingly, for using phenyldihydroisocoumarins to prevent and treat some diseases, additional studies on pharmacological properties and possible therapeutic applications are required.

Published data suggest that phenyldihydroisocoumarin bioactivities are depending on the number and location of hydroxyl groups. When the structural requirements were examined, the hydroxyl group at position 6 did not have any negative effect, for example, on the inhibitory action of histamine release and triglyceride accumulation. The presence of a 6-OH group also had no effect on T lymphocyte suppression; neither had the 3'-OH group. On the other hand, the latter seems to be essential for antiallergic activity together with OH groups in positions 8- and 4'. Moreover, glycosidation and methylation of the hydroxy group seemed to lead to reduction of antibacterial activity and antiproliferative activity.

Taste properties of phyllodulcin 19 and related compounds

The sweet taste of fermented leaves of *Hydrangea macrophylla* var. *thungbergii* has been appreciated in Japan since immemorial times. Preparations of such leaves as a tea, "amacha" or *sweet tea*, are a regional specialty also used in religious ceremonies [16]. Due to this longstanding use of "amacha", Japanese research groups, beginning in the 1920s [15], extensively studied the chemical composition of *Hydrangea macrophylla* (see sections above) and the taste properties of its compounds [58-64]. From these extensive synthetic studies, the natural compound phyllodulcin **19** emerged as the highest potency sweetener and a β-(3-hydroxy,4-methoxyphenyl) ethylbenzene moiety as a requirement for sweet taste. In successive studies, 2-(3-hydroxy-4-methoxypheny1)-1,3-benzodioxan was identified as an intensely sweet fully synthetic analogue of phyllodulcin [65]. While phyllodulcin and *Hydrangea* derived preparations (tea, confectionary, and medicinal products) are still widely used in Japan, usage of phyllodulcin outside Japan seems to be hampered by its low solubility in water and some sensory peculiarities of the compound such as a delay in sweetness onset and a licorice-like aftertaste [66].

Tragoponol 55, aphenyldihydroisocoumarin dimer

Though formally not included in the search parameters of our review, tragoponol **55**, a dimer derived from crosswise esterification of two open-chained simple phenyldihydrosiocoumarin moieties, scorzocreticin **12** and honkongenin **16**, which was found in *Tragopogon porrifolius* subsp. *porrifolius*, is displayed here (Figure 6) [67]. The compound features a unique twelve-membered ring system; interestingly first attempts of the total synthesis of this natural compound were not successful [68].

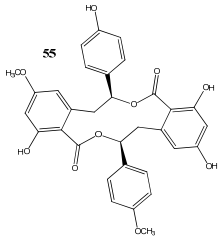


Figure 6: Structure of the dimeric phenyldihydroisocoumarin tragoponol (**55**).

Table 1: Overview about the source families of phenyldihydroisocoumarins, the number of compounds per family and the number of known source species per family.

Family	n cpds	n spec.	Compounds
Amaranthaceae	1	1	**41**
Asparagaceae	2	1	**43**-**44**
Asteraceae	12	5	**1**, **3**-**8**, **11**-**12**, **14**, **15**,**17**
Cannabaceae	1	1	**46**
Clusiaceae	1	1	**10**
Dioscoreaceae	3	3	**10**, **35**, **42**
Hydrangeaceae	23	2	**1**, **3**-**4**, **8**-**9**, **11**, **13**, **18**-**29**, **31**- **34**, **37**
Hypericaceae	1	2	**36**
Onocleaceae	3	2	**30**, **39**-**40**
Papaveraceae	8	4	**47**-**54**
Plagiochilaceae	1	1	**2**
Polygalaceae	1	1	**16**
Pteridaceae	2	2	**37**, **45**

Discussion

Though some of the information provided here was already included in earlier reviews on stilbenoids in general [69], we here provide the first modern and up to date review focused on phenyldihydroisocoumarins. The present review complements a slightly earlier review focusing on dihydroresveratrol type dihydrostilbenoids [70]. Phenyldihydroisocoumarins are a relatively small group of natural products with so far 54 known members, reported from only 13 plant families. Interestingly, these 13 families belong to very diverse groups of the plant kingdom, including mosses and ferns as well as mono- and dicotyledonous higher plants. Because of the biosynthetic origin of phenyldihydro-isocoumarins from simple and widespread precursors, more sources and source families and also of course more new members of this compound class are likely to be found in the future. We are convinced that the present review will be an excellent starting point for a rational search of these secondary metabolites.

Though the array of bioactivities studied and reported so far for phenyldihydroisocoumarins is very diverse, none of these bioactivities justifies a use of any of the known source species of phenyldihydroisocoumarins as a medical drug primarily because of

the presence of this compound class. In contrast, the strong sweet taste (> 400 times the sweetness of sucrose) of phyllodulcin **19** is the reason for using fermented leaves of *Hydrangea macrophylla* var. *thunbergii* as an ingredient of traditional beverages and confectionaries in Japan.

Acknowledgments - Our sincere thanks go to two anonymous reviewers whose comments helped to improve this review. Special thanks go to Professor Sebastian Granica/Warsaw, for providing access to difficult to access literature.

Table 2: Phenyldihydroisocoumarins ordered by chemical structure, their names, masses, and sources.

Compds	Config	Trivial name	Compd name	Molecular mass	Name according to Plant List	Family	References
1	*	hydrangenol	3-(4-hydroxyphenyl)-8-hydroxy-isochroman-1-one	256.3	*Scorzonera psychrophila*[h]	Asteraceae	[5]
1	*	hydrangenol	3-(4-hydroxyphenyl)- 8-hydroxy-isochroman-1-one	256.3	*Scorzonera tomentosa*	Asteraceae	[7]
1	*	hydrangenol	3-(4-hydroxyphenyl)-8-hydroxy-isochroman-1-one	256.3	*Hydrangea chinensis*	Hydrangeaceae	[14]
1	*	hydrangenol	3-(4-hydroxyphenyl)-8-hydroxy-isochroman-1-one	256.3	*Hydrangea macrophylla*[a,b,c]	Hydrangeaceae	[15-21]
2	*R*	hydrangenol monomethyl ether	(3*R*)-8-3-(4-methoxyphenyl)-hydroxyisochroman-1-one	270.3	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
2	*R*	hydrangenol monomethyl ether	(3*R*)-8-3-(4-methoxyphenyl)-hydroxyisochroman-1-one	270.3	*Plagiochila cristata*	Plagiochilaceae	[38]
3	*	hydrangenol 4'-*O*-β-D-glucopyranoside	3-(4-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	418.4	*Scorzonera psychrophila*[h]	Asteraceae	[5]
3	*R*	(+)-hydrangenol 4'-*O*-β-D-glucoside	(3*R*)-3-(4-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	418.4	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[18,25,27]
3	*S*	(-)-hydrangenol 4'-*O*-β-D-glucoside	(3*S*)-3-(4-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	418.4	*Scorzonera tomentosa*	Asteraceae	[7]
3	*S*	(-)-hydrangenol 4'-*O*-β-D-glucoside	(3*S*)-3-(4-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	418.4	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[19,21,25,27]
4	*	hydrangenol 4'-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside	3-(4-β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	550.5	*Scorzonera psychrophila*[h]	Asteraceae	[5]
4	*R*	3*R*-hydrangenol 4'-*O*-apiosylglucoside	(3*R*)-3-(4-β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	550.5	*Hydrangea macrophylla*[a]	Hydrangeaceae	[26]
4	*S*	3*S*-hydrangenol 4'-*O*-apiosylglucoside	(3*S*)-3-(4-β-D-apiofuranosyl-(1→6)-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	550.5	*Hydrangea macrophylla*[a]	Hydrangeaceae	[26]
5	*S*	3*S*-hydrangenol 4'-*O*-α-L-rhamnopyranosyl-(1→3)- *O*-β-D-glucopyranoside	3-(4-α-L-rhamnopyranosyl-(1→3)-β-D-glucopyranosyloxyphenyl)-8-hydroxyisochroman-1-one	564.5	*Scorzonera psychrophila*[h]	Asteraceae	[5]
6	*RS*	(+/-)-scorzotomentosin	(3*RS*)-3-(4-hydroxyphenyl)-8-methoxy-isochroman-1-one	270.3	*Scorzonera tomentosa*	Asteraceae	[7]
7	*S*	(-)-scorzotomentosin 4'-*O*-β-glucoside	(3*S*)-3-(4-β-D-glucopyranosyloxyphenyl)-8-methoxy-isochroman-1-one	432.4	*Scorzonera tomentosa*	Asteraceae	[7]
8	*	Hydrangenol 8-*O*-glucoside	8-β-D-glucopyranosyloxy-3-(4-hydroxyphenyl)-isochroman-1-one	418.4	*Scorzonera psychrophila*[h]	Asteraceae	[5]
8	*	Hydrangenol 8-*O*-glucoside	8-β-D-glucopyranosyloxy-3-(4-hydroxyphenyl)-isochroman-1-one	418.4	*Hydrangea macrophylla*[a,d,e,f,g]	Hydrangeaceae	[16-18, 22-24,27]
9	*R*	(3*R*)-hydrangenol 8,4'-di-*O*-β-D-glucopyranoside	(3*R*)-8-β-D-glucopyranosyloxy-3-(4-β-D-glucopyranosyloxyphenyl)-isochroman-1-one	580.5	*Hydrangea macrophylla*[d]	Hydrangeaceae	[28]
10	*S*	montroumarin	(3*S*)-6,8-dihydroxy-3-phenylisochroman-1-one	256.3	*Montrouziera sphaeroidea*[i]	Clusiaceae	[10]
10	*S*	montroumarin	(3*S*)-6,8-dihydroxy-3-phenylisochroman-1-one	256.3	*Dioscorea collettii* var. *hypoglauca*	Dioscoreaceae	[11]
10	*	montroumarin	6,8-dihydroxy-3-phenylisochroman-1-one	256.3	*Dioscorea futschauensis*	Dioscoreaceae	[12]
11	*	thunberginol C	3-(4-hydroxyphenyl)-6,8-dihydroxyisochroman-1-one	272.3	*Tragopogon porrifolius* subsp. *porrifolius*	Asteraceae	[8]
11	*	thunberginol C	3-(4-hydroxyphenyl)-6,8-dihydroxyisochroman-1-one	272.3	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[17,19,21,25]
12	*S*	scorzocreticin	(3*S*)-6,8-dihydroxy-3-(4-methoxyphenyl)-isochroman-1-one	286.3	*Scorzonera cretica*	Asteraceae	[4]
13	*	thunberginol C 8-*O*-β-D-glucopyranoside	3-(4-hydroxyphenyl)-8-β-D-glucopyranosyloxyisochroman-1-one	434.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
14	*S*	scorzocreticoside I	(3*S*)-8-β-D-glucopyranosyloxy-6-hydroxy-3-(4-methoxyphenyl)-isochroman-1-one	448.4	*Scorzonera cretica*	Asteraceae	[4]
14	*S*	scorzocreticoside I	(3*S*)-8-β-D-glucopyranosyloxy-6-hydroxy-3-(4-methoxyphenyl)-isochroman-1-one	448.4	*Tragopogon porrifolius* subsp. *porrifolius*	Asteraceae	[8]
15	*S*	scorzocreticoside II	(3*S*)-6-hydroxy-3-(4-methoxyphenyl)-8-(α-L-rhamnopyranosyloxy-(1→6)-β-D-glucopyranosyloxy)-isochroman-1-one	594.6	*Scorzonera cretica*	Asteraceae	[4]
16	*S*	honkongenin	3-(4-hydroxyphenyl)-6-methoxy-8-hydroxyisochroman-1-one	462.5	*Polygala honkongensis*	Polygalaceae	[39]
17	*S*	6-*O*-methyl-scorzocreticoside I	3-(4-methoxyphenyl)-6-methoxy-8-β-D-glucopyranosyloxyisochroman-1-one	462.5	*Tragopogon porrifolius* subsp. *porrifolius*	Asteraceae	[8]
18	*	thunberginol G	3-(3,4-dihydroxyphenyl)-8-hydroxyisochroman-1-one	272.3	*Scorzonera papposa*	Asteraceae	[6]
18	*	thunberginol G	3-(3,4-dihydroxyphenyl)-8-hydroxyisochroman-1-one	272.3	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[18,21 25]
19	*	phyllodulcin	3-(3'-hydroxy-4'-methoxyphenyl)-8-hydroxy-3,4-dihydrobenzopyran-1-one	286.3	*Hydrangea macrophylla*[b,c,g]	Hydrangeaceae	[15-16,20]
19	*R*	(+)-phyllodulcin	(3*R*)-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman-1-one	286.3	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[17-19,21,27]
19	*S*	(-)-phyllodulcin	(3*S*)-8-hydroxy-3-(3-hydroxy-4-methoxy-phenyl)-isochroman-1-one	286.3	*Hydrangea macrophylla*[a]	Hydrangeaceae	[26-27]
20	*	thunberginol H	3-(3,4-dimethoxyphenyl)-8-hydroxyisochroman-1-one	300.3	*Hydrangea macrophylla*[b]	Hydrangeaceae	[20]
21	*R*	3*R*-thunberginol I 4'-*O*-glucoside	(3*R*)-3-(4-β-D-glucopyranosyloxy-3-methoxyphenyl)-8-hydroxyisochroman-1-one	448.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18, 26]
21	*S*	3*S*-thunberginol I 4'-*O*-glucoside	(3*S*)-3-(4-β-D-glucopyranosyloxy-3-methoxyphenyl)-8-hydroxyisochroman-1-one	448.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[26]
22	*	thunberginol G 3'-*O*-glucoside	(3*R*)-3-(3-β-D-glucopyranosyloxy-4-hydroxyphenyl)-8-hydroxyisochroman-1-one	434.4	*Hydrangea macrophylla* var. *thunbergii*	Hydrangeaceae	[18-19,25,27]
23	*R*	3*R*-phyllodulcin 3'-*O*-glucoside	(3*R*)-3-(3-β-D-glucopyranosyloxy-4-methoxyphenyl)-8-hydroxyisochroman-1-one	448.4	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[21,26]

Compds	Config	Trivial name	Compd name	Molecular mass	Name according to Plant List	Family	References
23	*S*	3*S*-phyllodulcin 3'-*O*-glucoside	(3*S*)-3-(3-β-D-glucopyranosyloxy-4-methoxyphenyl)-8-hydroxyisochroman-1-one	448.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[26]
23	*	phyllodulcin 8-*O*-glucoside; phyllodulcin 8-β-D-glucoside	3-(3-hydroxy-4-methoxyphenyl)-8-β-D-glucopyranosyloxyisochroman-1-one	448.4	*Hydrangea macrophylla*[g]	Hydrangeaceae	[16]
24	*	thunberginol G 8-*O*-β-D-glucopyranoside	8-β-D-glucopyranosyloxy-3-(3,4-dihydroxyphenyl)-isochroman-1-one	450.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
25	*R*	3*R*-phyllodulcin 8-*O*-β-D-glucopyranoside	(3*R*)-3-(3-hydroxy-4-methoxyphenyl)-8-β-D-glucopyranosyloxyisochroman-1-one	448.4	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[17-18,21,27]
25	*S*	*3S*-phyllodulcin 8-*O*-β-D-glucopyranoside	(3*S*)-3-(3-hydroxy-4-methoxyphenyl)-8-β-D-glucopyranosyloxyisochroman-1-one;	448.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18,26-27]
26	*R*	macrophyllosides B	(3*R*)-8-β-D-glucopyranosyloxy-3-(4-hydroxy-3,5-dimethoxyphenyl)-isochroman-1-one	478.5	*Hydrangea macrophylla*[d]	Hydrangeaceae	[22]
26	*S*	macrophyllosides C	(3*S*)-8-β-D-glucopyranosyloxy-3-(4-hydroxy-3,5-dimethoxyphenyl)-isochroman-1-one	478.5	*Hydrangea macrophylla*[d]	Hydrangeaceae	[22]
27	*R*	3*R*-thunberginol H 8-*O*-glucoside	(3*R*)-8-β-D-glucopyranosyloxy-3-(3,4-dimethoxyphenyl)-isochroman-1-one	462.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[27]
27	*S*	3*S*-thunberginol H 8-*O*-glucoside	(3*S*)-8-β-D-glucopyranosyloxy-3-(3,4-dimethoxyphenyl)-isochroman-1-one	462.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[27]
28	*	thunberginol D	3-(3,4-dihydroxyphenyl)-6,8-dihydroxyisochroman-1-one	288.3	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[17,19,21,25]
29	*	thunberginol E	(3*R*)-3-(3-hydroxy-4-methoxyphenyl)-6,8-dihydroxyisochroman-1-one	302.3	*Hydrangea macrophylla*[b]	Hydrangeaceae	[19]
29	*R*	thunberginol E	(3*R*)-3-(3-hydroxy-4-methoxyphenyl)-6,8-dihydroxyisochroman-1-one	302.3	*Hydrangea macrophylla*[a,b]	Hydrangeaceae	[17,25]
30	*RS*	(+/-)-matteucen B	3-(4-hydroxy-3-methoxyphenyl)-6,8-dihydroxyisochroman-1-one	302.3	*Onoclea orientalis*[j]	Onocleaceae	[31]
31	*	thunberginol D 3'-*O*-β-D-glucopyranoside	3-(3-β-D-glucopyranosyloxy-4-hydroxyphenyl)-6,8-dihydroxyisochroman-1-one	450.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
32	*S*	florahydroside I	(3*S*)-8-β-D-glucopyranosyloxy-3-(3-hydroxy-4-methoxyphenyl)-6-hydroxyisochroman-1-one	464.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
33	*S*	florahydroside II	(3*S*)-6-β-D-glucopyranosyloxy-3-(3-hydroxy-4-methoxyphenyl)-8-hydroxyisochroman-1-one	464.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
34	*S*	macrophylloside A	(3*S*)-8-β-D-glucopyranosyloxy-3-(3,4,5-trimethoxyphenyl)-isochroman-1-one	492.5	*Hydrangea macrophylla*[d]	Hydrangeaceae	[22]
35	*S*	annulatomarin	(3*S*)-6,8-dihydroxy-7-methoxy-3-phenylisochroman-1-one	286.3	*Dioscorea spongiosa*	Dioscoreaceae	[13]
36	*	annulatomarin	6,8-dihydroxy-7-methoxy-3-phenylisochroman-1-one	286.3	*Hypericum annulatum*[k]	Hypericaceae	[30]
36	*R*	annulatomarin	(3*R*)-6,8-dihydroxy-7-methoxy-3-phenylisochroman-1-one	286.3	*Cratoxylum sumatranum*	Hypericaceae	[29]
37	*		3-(3,4-dihydroxyphenyl)-5,6-dihydroxyisochroman-1-one	288.3	*Onychium japonicum*	Pteridaceae	[41]
38		4-hydroxythunberginol G 3'-*O*-β-D-glucopyranoside	3-(3-β-D-glucopyranosyloxy-4-hydroxyphenyl)-4,8-dihydroxyisochroman-1-one	450.4	*Hydrangea macrophylla*[a]	Hydrangeaceae	[18]
39	3*R, 4S*	(-)-matteucen A	(3*R*,4*S*)- 4,6,8-trihydroxy-3-phenyl-isochroman-1-one	272.3	*Onoclea orientalis*[j]	Onocleaceae	[31]
40	3*S, 4R*	(+)-matteucen A	(3*S*,4*R*)- 4,6,8-trihydroxy-3-phenyl-isochroman-1-one	272.3	*Onoclea orientalis*[j]	Onocleaceae	[31]
41	*S*		(3*S*)-8-methoxy-6,7-methylendioxy-3-phenylisochroman-1-one	298.3	*Haloxylon scoparium*	Amaranthaceae	[2]
42	*R*	dioscoroside G	(3*R*)-3-(2-β-D-glucopyranosyloxy-5-hydroxyphenyl)-8-hydroxy-6,7-methylendioxoisochroman-1-one	478.4	*Dioscorea spongiosa*	Dioscoreaceae	[13]
43	3*R,4R*	(+)-platyphyllarin A	(3*R*,4*R*)-6,8-dihydroxy-7-methoxybenzofuroisochroman-1-one	300.3	*Liriope muscari*[l]	Asparagaceae	[3]
44	3*R,4R*	(+)-platyphyllarin B	(3*R*,4*R*)-6,8-dihydroxy-5,7-dimethoxybenzofuroisochroman-1-one	330.3	*Liriope muscari*[l]	Asparagaceae	[3]
45	3*R,4R*	multifidarin A	(3*R*,4*R*)-6,8-dihydroxy-7-methoxy-5-methylbenzofuroisochroman-1-one	314.3	*Pteris multifida*	Pteridaceae	[40]
46	*3R,3aR,4R,5S*	orientoside A		630.6	*Trema orientalis*	Cannabaceae	[9]
47	*RS*	(+/-)-peshawarine		383.4	*Hypecoum pendulum*[m]	Papaveraceae	[36]
48	*	leptopidinine		367.4	*Hypecoum leptocarpum*	Papaveraceae	[33]
49		torulosine		383.4	*Dactylicapnos torulosa*	Papaveraceae	[32]
50		procumbine		383.4	*Hypecoum leptocarpum*	Papaveraceae	[34]
50		procumbine		383.4	*Hypecoum procumbens*	Papaveraceae	[34]
51		torulosinine		399.4	*Dactylicapnos torulosa*	Papaveraceae	[32]
52		(+/-)-8-oxohypecorinine		381.3	*Hypecoum procumbens*	Papaveraceae	[37]
53		(+/-)-8-oxohyperorinine N-oxide		397.3	*Hypecoum leptocarpum*	Papaveraceae	[35]
54		demethyltorulosine N-methochloride		384.1	*Hypecoum leptocarpum*	Papaveraceae	[35]

Codes for subspecies, varieties and treatment of *Hydrangea macrophylla* and other species names in the original publications and comments on status of taxa according to The Plant List: [a]*H. macrophylla* var. *thunbergii* dried leaves or flowers (only in [18]), [b]*H. macrophylla* var. *thunbergii* fermented leaves, (Hydrangeae dulcis folium), [c]*H. opuloides* (only in [15]), [d]*H. macrophylla* subsp. *serrata*, [e]*H. macrophylla* var. *macrophylla*, [f] *H. macrophylla* var. *otaksa*, [g] cultured cells of *H. macrophylla*, [h] as *Scorzonera judaica*, [i] unassessed, [j] as *Matteucia orientalis*, [k] unresolved, [l] as *Liriope platiphylla*, [m] as *Hypecoum parviflorum*.

References

[1] The Plant List. http://www.theplantlist.org/ (June 6, 2017).

[2] Li Y, Plitzko I, Zaugg J, Hering S, Hamburger M. **(2010)** HPLC-based activity profiling for GABA(A) receptor modulators: a new dihydroisocoumarin from *Haloxylon scoparium*. *Journal of Natural Products*, ***73***, 768-770.

[3] Tsai Y-C, Chiang S-Y, El-Shazly M, Wu C-C, Beerhues L, Lai W-C. (**2013**) The oestrogenic and anti-platelet activities of dihydrobenzofuroisocoumarins and homoisoflavonoids from *Liriope platyphylla* roots. *Food Chemistry*, ***140***, 305–314.

[4] Paraschos S, Magiatis P, Kalpoutzakis E, Harvala C, Skaltsounis AL. (**2001**) Three New dihydroisocoumarins from the Greek endemic species *Scorzonera cretica*. *Journal of Natural Products*, ***64***, 1585-1587.

[5] Bader A, Tommasi N, Cotugno R, Braca A. (**2011**) Phenolic compounds from the roots of Jordanian viper's grass, *Scorzonera judaica*. *Journal of Natural Products*, ***74***, 1421-1426.

[6] Milella L, Bader A, Tommasi N, Russo D, Braca A. (**2014**) Antioxidant and free radical-scavenging activity of constituents from two *Scorzonera* species. *Food Chemistry,* ***160***, 298-304.

[7] Sarı A, Zidorn C, Ellmerer EP, Özgökçe F, Ongania KH, Stuppner H. (**2007**) Phenolic compounds from *Scorzonera tomentosa* L. *Helvetica Chimica Acta*, ***90***, 311-317.

[8] Zidorn C, Lohwasser U, Pschorr S, Salvenmoser D, Ongania KH, Ellmerer EP. (**2005**) Bibenzyls and dihydroisocoumarins from white salsify (*Tragopogon porrifolius* subsp. *porrifolius*). *Phytochemistry*, ***66***, 1691-1697.

[9] Dijoux-Franca MG, Tchamo DN, Cherel B, Cussac M, Tsamo E, Mariotte AM. (**2001**) New dihydrophenanthrene and phenyldihydroisocoumarin constituents of *Trema orientalis*. *Journal of Natural Products*, ***64***, 832-835.

[10] Ito C, Mishina Y, Litaudon M, Cosson JP, Furukawa H. (**2000**) Xanthone and dihydroisocoumarin from *Montrouziera sphaeroidea*. *Phytochemistry*, ***53***, 1043-1046.

[11] She GM, Xiao X, Ba YY, Shi RB, Zhang LZ. (**2013**) Chemical constituents of *Dioscorea collettii* var. *hypoglauca*. *Chemistry of Natural Compounds*, ***49***, 983-984.

[12] Liu HW, Wang SL, Cai B, Yao XS. (**2003**) Two new non-steroidal constituents from *Dioscorea futschauensis* R. Kunth. *Die Pharmazie*, ***58***, 214-215.

[13] Zhang Y, Chao L, Ruan J, Zheng C, Yu H, Qu L. (**2016**) Bioactive constituents from the rhizomes of *Dioscorea septemloba* Thunb. *Fitoterapia*, ***115***, 165-172.

[14] Patnam R, Chang FR, Chen CY, Kuo RY, Lee YH, Wu YC. (**2001**) Hydrachine A, a novel alkaloid from the roots of *Hydrangea chinensis*. *Journal of Natural Products*, ***64***, 948-949.

[15] Asahina Y, Asano J. (**1929**) Über die Konstitution von Hydrangenol und Phyllodulcin. *Berichte der deutschen Chemischen Gesellschaft A/B*, ***62***, 171-177.

[16] Suzuki H, Ikeda T, Matsumoto T, Noguchi M. (**1978**) Polyphenol components in cultured cells of amacha (*Hydrangea macrophylla* Seringe var. *thunbergii* Makino). *Agricultural and Biological Chemistry*, ***42***, 1133-1137.

[17] Zhang H, Matsuda H, Kumahara A, Ito Y, Nakamura S, Yoshikawa M. (**2007**) New type of anti-diabetic compounds from the processed leaves of *Hydrangea macrophylla* var. *thunbergii* (Hydrangeae Dulcis Folium). *Bioorganic and Medicinal Chemistry Letters*, ***17***, 4972–4976.

[18] Liu J, Nakamura S, Zhuang Y, Yoshikawa M, Hussein GME, Matsuo K, Matsuda H. (**2013**) Medicinal Flowers. XXXX. 1) Structures of dihydroisocoumarin glycosides and inhibitory effects on aldose reductase from the flowers of *Hydrangea macrophylla* var. *thunbergii*. *Chemical and Pharmaceutical Bulletin*, ***61***, 655-661.

[19] Yoshikawa M, Uchida E, Chatani N, Kobayashi H, Naitoh Y, OkunoY. (**1992b**) Thunberginols C, D, and E, new antiallergic and antimicrobial dihydroisocoumarins, and thunberginol G 3'-*O*-glucoside and (-)-hydrangenol 4'-*O*-glucoside, new dihydroisocoumarin glycosides, from Hydrangeae Dulcis Folium. *Chemical and Pharmaceutical Bulletin*, ***40***, 3352–3354.

[20] Yoshikawa M, Harada E, Naitoh Y, Inoue K, Matsuda H, Shimoda H. (**1994**) Development of bioactive functions in Hydrangeae Dulcis Folium. III. On the antiallergic and antimicrobial principles of Hydrangeae Dulcis Folium. (1). Thunberginols A, B, and F. *Chemical and Pharmaceutical Bulletin*, ***42***, 2225-2230.

[21] Umehara K, Matsumoto M, Nakamura M, Miyase T, Kuroyanagi M, Noguchi H. (**2000**) Differentiation inducing activities of isocoumarins from Hydrangea Dulcis Folium. *Chemical and Pharmaceutical Bulletin*, ***48***, 566–567.

[22] Hashimoto T, Tori M, Asakawa Y. (**1987**) Three dihydroisocoumarin glucosides from *Hydrangea macrophylla* subsp. *serrata*. *Phytochemistry*, ***26***, 3323-3330.

[23] Hashimoto T, Tori M, Asakawa Y. (**1988**) A Highly efficient preparation of lunularic acid and some biological activities of stilbene and dihydrostilbene derivatives. *Phytochemistry*, ***27***, 109-113.

[24] Uesato S, Takeda Y, Hashimoto T, Uobe K, Inouye H, Taguchi H, Endo T. (**1984**) Studies on monoterpene glucosides and related natural products part 51. Absolutes structures of hydrangenosides A, B, C, D, E, F, and G. Novel type secoiridoid glucosides from two *Hydrangea* plants. *Helvetica Chimica Acta*, ***67***, 2111-2127.

[25] Yoshikawa M, Matsuda H, Shimoda H, Shimada H, Harada E, Naitoh Y. (**1996**) Development of bioactive functions in Hydrangeae Dulcis Folium. V. On the antiallergic and antimicrobial principles of Hydrangeae Dulcis Folium. (2). Thunberginols C, D, and E, thunberginol G 3'-*O*-glucoside, (-)-hydrangenol 4'-*O*-glucoside, and (+)-hydrangenol 4'-*O*-glucoside. *Chemical and Pharmaceutical* Bulletin, ***44***, 1440–1447.

[26] Yoshikawa M, Ueda T, Shimoda H, Murakami T, Yamahara J, Matsuda H. (**1999**) Dihydroisocoumarin constituents from the leaves of *Hydrangea macrophylla* var. *thunbergii*. (2). Absolute stereostructures of hydrangenol, thunberginol I, and phyllodulcin glycosides and isomerization reaction at the 3-positions of phyllodulcin and its glycosides. *Chemical and Pharmaceutical Bulletin*, ***47***, 383-387.

[27] Yoshikawa M, Murakami T, Ueda T, Shimoda H, Yamahara J, Matsuda H. (**1999b**) Absolute stereostructures of *3S*-phyllodulcin, *3R*- and *3S*-phyllodulcin glycosides, and *3R*- and *3S*-thunberginol H glycosides from the leaves of *Hydrangea macrophylla* Seringe var. *thunbergii* Makino. *Heterocycles*, ***50***, 411-418.

[28] Kikuchi M, Kakuda R, Kikuchi M, Yaoita Y. (**2008**) Three new glycosides from the leaves of *Hydrangea macrophylla* subsp. *serrata* (Thunb.) Makino. *Chemical and Pharmaceutical Bulletin*, ***56***, 610-611.

[29] Tantapakul C, Maneerat W, Sripisut T, Ritthiwigrom T, Andersen RJ, Cheng P. (**2016**) New benzophenones and xanthones from *Cratoxylum sumatranum* ssp. *neriifolium* and their antibacterial and antioxidant activities. *Journal of Agricultural and Food Chemistry*, ***64***, 8755-8762.

[30] Nedialkov PT, Zheleva-Dimitrova D, Girreser U, Kitanov GM. (**2007**) A new isocoumarin from *Hypericum annulatum*. *Natural Product Research*, ***21***, 1056-1060.

[31] Shao P, Zhang X, Li B, Jiao WH; Wu LJ, Yao XS. (**2010**) New isocourmarin and phthalide derivatives from the rhizomes of *Matteuccia orientalis*. *Chemical and Pharmaceutical Bulletin*, ***58***, 1650-1654.

[32] Rücker G, Breitmaier E, Zhang GL, Mayer R. (**1994**) Alkaloids from *Dactylicapnos torulosa*. *Phytochemistry*, ***36***, 519-523.

[33] Zhou Y, Zhang G, Li B. (**1999**) Five alkaloids from *Hypecoum leptocarpum*. *Phytochemistry*, ***50***, 339-343.

[34] Táborská E, Mikešová M, Věžník F, Slavík J. (**1987**) Alkaloids of the two *Hypecoum* L. species. *Collection of Czechoslovak Chemical Communications*, ***52***, 508-513.

[35] Li BG, Zhou M, Zhang GL. (**2001**) Four new alkaloids from *Hypecoum leptocarpum* Hook. f. et Thoms. *Indian Journal of Chemistry*, ***40B***, 1215-1218.

[36] Shamma M, Rothenberg A, Jayatilake G, Fazal Hussain S. (**1976**) Peshawarine, an unusual isoquinoline alkaloid. *Heterocycles*, ***5***, 41-45.

[37] Saad, HEA. (**1995**) (±)-8-Oxohypecorinine from *Hypecoum procumbens* var. *glaucescens*. *Phytochemistry*, ***38***, 1049-1051.

[38] Valcic S, Zapp J, Becker H. (**1997**) Plagiochilines and other sesquiterpenoids from *Plagiochila* (Hepaticae). *Phytochemistry*, ***44***, 89-99.
[39] WuJ-F, Chen S-B, Gao J-C, Song H-L, Wu L-J, Chen S-I, Tu P-F. (**2007**) Antioxidants and a new dihydroisocoumarins from *Polygala honkongensis* Hemsl. *Journal of Asian Natural Products Research*, ***17***, 423-429.
[40] Ni G, Fu NJ, Di Z, Yang HZ, Chen XG, Yu DQ. (**2015**) An unusual dihydrobenzofuroisocoumarin and ent-kaurane diterpenoids from *Pteris multifida*. *Natural Product Research*, ***21***, 580-584.
[41] Li MC, Yao Z, Takaishi Y, Tang SA, Duan HQ. (**2011**) Isolation of novel phenolic compounds with multidrug resistance (MDR) reversal properties from *Onychium japonicum*. *Chemistry and Biodiversity*, ***8***, 1112-1120.
[42] Yoshikawa M, Uchida E, Chatani N, Murakami N, Yamahara J. (**1992a**) Thunberginols A, B, and F, new antiallergic and antimicrobial principles from Hydrangeae Dulcis Folium. *Chemical and Pharmaceutical Bulletin*, ***40***, 3121-3123.
[43] Matsuda H, Shimoda H, Yoshikawa M, (**1999a**) Structure-requirements of isocoumarins, phthalides, and stilbenes from Hydrangeae Dulcis Folium for inhibitory activity on histamine release from rat peritoneal mast cells. *Bioorganic and Medicinal Chemistry*, ***7***, 1445-1450.
[44] Yamahara J, Matsuda I, Shimoda H, Ishikawa H, Kawamori S, Wariishi N, Harada E, Murakami N, Yoshikawa M. (**1994**): Development of bioactive functions in Hydrangeae Dulcis Folium. II. Antiulcer, antiallergy, and cholagoic effects of the extract from Hydrangeae Dulcis Folium. *Yakugaku Zasshi*, ***114***, 401-413.
[45] Wang Q, Matsuda H, Matsuhira K, Yuan D, Yoshikawa M. (**2007**). Inhibitory effects of thunberginols A, B, and F on degranulations and releases of TNF-α and IL-4 in RBL-2H3 cells. *Biological and Pharmaceutical Bulletin*, ***30***, 388-392.
[46] Matsuda H, Shimoda H, Yamahara J, Yoshikawa M. (**1999b**) Effects of phyllodulcin, hydrangenol, and their 8-*O*-glucosides, and thunberginols A and F from *Hydrangea macrophylla* Seringe var. *thunbergii* Makino on passive cutaneous anaphylaxis reaction in rats. *Biological and Pharmaceutical Bulletin*, ***22***, 870-872.
[47] Nabekura T, Yamaki T, Ueno K, Kitagawa S. (**2008**) Inhibition of P-glycoprotein and multidrug resistance protein 1 by dietary phytochemicals. *Cancer Chemotherapy and Pharmacology*, ***62***, 867-873.
[48] Sugie S, Okamoto K, Rahman WKM, Tanaka T, Kawai K, Yamahara J, Mori H. (**1998**). Inhibitory effects of plumbagin and juglone on azoxymethane-induced intestinal carcinogenesis in rats. *Cancer Letters*, ***127***, 177-183.
[49] Kawamori T, Tanaka T, Hara A, Yamahara J, Mori H. (**1995**). Modifying effects of naturally occurring products on the development of colonic aberrant crypt foci induced by azoxymethane in F344 rats. *Cancer Research,* ***55***, 1277-1282.
[50] Matsuda H, Nakamura S, Yoshikawa M. (**2014**) Search for new type of PPARγ agonist like anti-diabetic compounds from medicinal plants. *Biological and Pharmaceutical Bulletin*, ***37***, 884-891.
[51] Kim H-J, Kang C-H, Jayasooriya RGP, Dilshara MG, Lee S, Choi YH, Seo YT, Kim G-Y. (**2016**) Hydrangenol inhibits lipopolysaccharide-induced nitric oxide production n BV2 microglial cells by suppressing the NF-*k*B pathway and activing the Nrf2-mediated HO-1 pathway. *International Immunopharmacology*, ***35***, 61-69.
[52] Acikara OB, Hošek J, Babula P, Cvačka J, Budešínský M. (**2016**) Turkish *Scorzonera* species extracts attenuate cytokine secretion via inhibition of NF-κB activation, showing anti-inflammatory effect *in vitro*. *Molecules,* ***21***, 43.
[53] Ueno M, Mori R (**1931**) On the activity of sweet compounds of amacha, phyllodulcin, against bacteria. *Yakugaku Zasshi*, ***51***, 227-230.
[54] Nozawa K, Yamada M, Tsuda Y, Kawai K-I, Nakajima S. (**1981)** Antifungal activity of oospnol, oospolactone, phyllodulcin, hydrangenol, and some related compounds. *Chemical and Pharmaceutical Bulletin*, ***29***, 2689-2691.
[55] Kawamura M, Kagata M, Masaki E, Nishi H. (**2002**) Phyllodulcin, a constituent of ''Amacha'', inhibits phosphodiesterase in bovine adrenocortical cells. *Pharmacology and Toxicology*, ***90***, 106-108.
[56] Matsuda H, Shimoda H, Yamahara J, Yoshikawa M. (**1998**) Immunomodulatory activity of thunberginol A and related compounds isolated from Hydrangeae Dulcis Folium on splenocyte proliferation activated by mitogens. *Bioorganic and Medicinal Chemistry Letters*, ***8***, 215-220.
[57] Shimoda H, Matsuda H, Yamahara J, Yoshikawa M. (**1998**) Development of bioactive functions in Hydrangeae Dulcis Folium. VII. Immunomodulatory activities of thunberginol A and related compounds on lymphocyte proliferation. *Chemical and Pharmaceutical Bulletin*, ***21***, 809-813.
[58] Yamato, M, Hashigaki K, Honda E, Sato K, Koyama T. (**1977**) Chemical structure and sweet taste of isocoumarin and related compounds. VII. *Chemical and Pharmaceutical Bulletin*, ***25***, 695-699.
[59] Yamato, M, Hashigaki K, Uenishi J, Yamakawa I, Sato N, Koyama T. (**1975**) Chemical structure and sweet taste of isocoumarin and related compounds. VI. *Chemical and Pharmaceutical Bulletin*, ***23***, 3101-3105.
[60] Yamato, M, Sato K, Hashigaki T, Ishikawa M, Òki M, Koyama T. (**1974**) Chemical structure and sweet taste of isocoumarins and related compounds. V. *Yakugaku Zasshi*, ***94***, 359-361.
[61] Yamato, M, Sato K, Hashigaki T, Ishikawa M, Koyama T. (**1973**) Chemical structure and sweet taste of isocoumarins and its derivatives. IV. *Yakugaku Zasshi*, ***93***, 1639-1642.
[62] Yamato, M, Kitamura T, Hashigaki K, Kuwano Y, Murakami S, Koyama T. (**1972**) Syntheses of biologically active isocoumarins III. Chemical structure and sweet taste of 3,4-dihydroisocoumarins. *Yakugaku Zasshi*, ***92***, 850-853.
[63] Yamato, M, Hashigaki T, Kuwano Y, Koyama T. (**1972**) Syntheses of biologically active isocoumarins II. Chemical structure and sweet taste of 3,4-dihydroisocoumarins. *Yakugaku Zasshi*, ***92***, 535-538.
[64] Yamato, M, Kitamura T, Hashigaki T, Kuwano Y, Yoshido N, Koyama T. (**1972**) Syntheses of biologically active isocoumarins I. Chemical structure and sweet taste of 3,4-dihydroisocoumarins. *Yakugaku Zasshi*, ***92***, 367-370.
[65] Dick WE, Hodge JE (**1978**) An intensely sweet analogue of phyllodulcin: 2-(3-Hydroxy-4-mehtoxypheny1)-1,3-benzodioxan. *Journal of Agricultural and Food Chemistry*, ***26***, 723-725.
[66] Kinghorn AD, Compadre CM (**1978)** Less common high potency sweeteners. In: O'Brien Nabors L (Ed.) *Alternative Sweeteners, 3rd Ed.* Decker, New York, pp. 209-233.
[67] Zidorn C, Petersen BO, Sareedenchai V, Ellmerer EP, Duus JØ (**2010**) Tragoponol, a dimeric dihydroisocoumarin from *Tragopogon porrifolius* L. *Tetrahedron Letters*, ***51***, 1390-1393.
[68] Miyatake-Ondozabal H, Barrett AGM (**2013**) Synthetic studies towards tragoponol: preparation of a highly functionalized resorcylate. *Tetrahedron Letters*, ***54***, 4817-4820.
[69] Gorham, J. (**1980**) The stilbenoids. *Progress in Phytochemistry*, ***6***, 203-257.
[70] Vitalini S., Çiçek SS, Granica S, Zidorn C (**2018**) Dihydroresveratrol type dihydrostilbenoids: chemical diversity, chemosystematics, and bioactivity. *Current Medicinal Chemistry*, ***25***, 1194-1240.