Progress in the Chemistry of Organic Natural Products

A. Douglas Kinghorn · Heinz Falk · Simon Gibbons · Jun'ichi Kobayashi · Yoshinori Asakawa · Ji-Kai Liu *Editors*

112

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Editors

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Volume 112

With contributions by

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Allelopathy: The Chemical Language of Plants

Francisco A. Macías, Alexandra G. Durán, and José M. G. Molinillo

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1 Introduction

In Nature, the oldest method of communication between living systems is the chemical language. Plants in particular, due to their lack of mobility, have developed the most sophisticated way of chemical communication, which is mainly based on specialized metabolites belonging to secondary metabolism [1, 2]. The most relevant aspects regarding the chemical language of plants will be described in this chapter. Only those examples with a growing body of evidence of allelopathic phenomena will be discussed and these will be categorized by plant families and listed in alphabetical order.

The term allelopathy (Greek: ἀλλήλων, allelon = each other, πάθος, pathos = suffering, mutual interaction) was introduced for the first time by Hans Molisch (1937) to refer to biochemical interactions (both inhibitory and stimulatory) between plants, including microorganisms [3, 4]. This definition was slightly modified by Rice (1974) to any direct or indirect, beneficial or destructive effect by one plant (including microorganisms) on another through the production of chemical compounds (allelochemicals) released into the environment [5]. The most commonly accepted definition is described by the International Allelopathy Society (IAS) (1996), which recommended the term allelopathy to mean the science that concerns any process involving mainly secondary metabolites, produced by plants, algae, bacteria, and fungi, that influence the growth and development of agricultural and biological systems (Fig. 1) [6–8].

Allelochemicals can be released into the environment by four main pathways: (i) exudation from roots, (ii) leaching from aerial parts by rain, fog, or dew, (iii) volatilization, and (iv) decomposition of plant remains [9, 10] (Fig. 2). These compounds can affect the development of neighboring plants, mainly on germination and root or shoot growth.

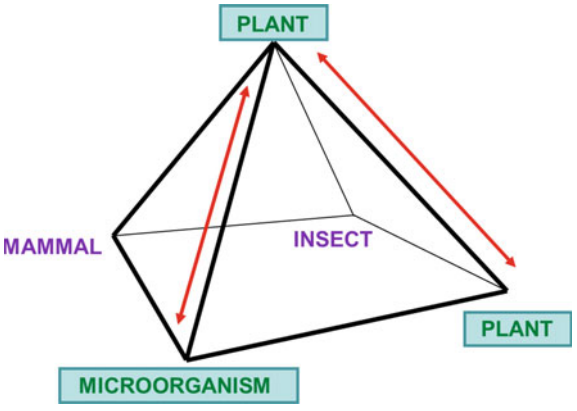


Fig. 1 Different interactions encompassed by allelopathy

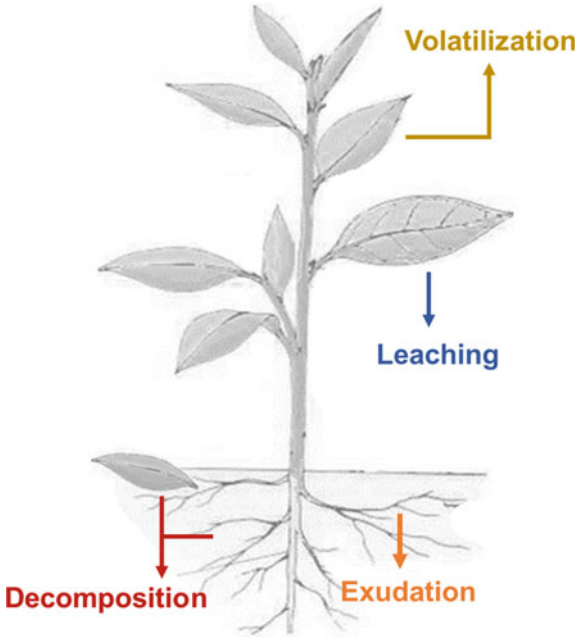


Fig. 2 The main pathways for the release of allelochemicals

2 Exudation

The most widely known allelochemicals have been identified in root exudates. The synthesis and exudation of allelochemicals in root exudates is typically enhanced by abiotic and biotic stress conditions encountered by the plant, which include plant competitors, extreme temperature, drought, and UV exposure [11]. These exudates play a key role in the rhizosphere and some of the most relevant aspects are described below.

2.1 Plant–Plant Interaction

2.1.1 Asteraceae

Centaurea diffusa Lam.

Centaurea diffusa (Asteraceae), also known as diffuse knapweed, is native to the eastern Mediterranean Eurasian range and it is an exotic invasive species and a prominent threat in North American grasslands [12]. This plant has invaded more than 1.4 million ha since its introduction as a seed contaminant prior to 1907 [13]. This species is one of the main examples in the field of allelopathy, and it has been

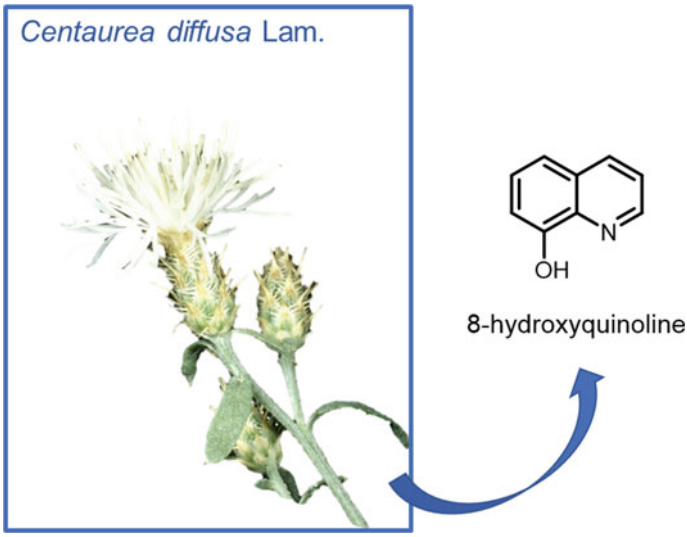


Fig. 3 Structure of 8-hydroxyquinoline (**1**), a putative allelochemical from *C. diffusa* roots. Image adapted from USDA APHIS PPQ, Bugwood.org

suggested that the allelochemicals exuded or leached from this weed might explain its invasion success [14]. It has been reported that 8-hydroxyquinoline (**1**) (Fig. 3) is exuded from its roots, and this compound has shown phytotoxic activity on neighboring species [15]. The concentration of this compound was three times higher in *C. diffusa*-invaded North American soils than in its native Eurasian soils. Furthermore, it has a strong affinity for divalent and trivalent cations such as aluminum, magnesium, and iron. Since this species mostly invades alkaline calcareous soils, the relationship between this compound and nutrition uptake was investigated. Studies carried out by Tharayil and co-workers [16] demonstrated that 8-hydroxyquinoline is used by the plant to facilitate iron uptake (a nutrient deficient in most of its invaded soils) in its complexed form. This represents a possible adaptive mechanism that confers a competitive advantage over native species in alkaline soils. This compound can be released from the roots of *C. diffusa* following a diurnal rhythm. The authors indicated that this temporal pattern is similar to the exudation of phytosiderophores by the roots of graminaceous species to enhance their uptake of metals. The phytotoxicity of 8-hydroxyquinoline was influenced by the presence of metals and it was significantly reduced when complexed with metal ions, including copper and iron [17].

However, in subsequent studies clear evidence was not found that this species produces this compound at ecologically meaningful concentrations. For instance, Norton et al. were unable to detect 8-hydroxyquinoline (**1**) in experimental or field collected soils infected by *C. diffusa*, and Quintana et al. did not detect it in root exudates or root extracts of in vitro growth [13, 14]. Additional studies are required to establish the role of this putative phytotoxin, to corroborate its presence in a soil

environment and to ascertain how soil factors and microorganisms mediate its allelopathic activity [18].

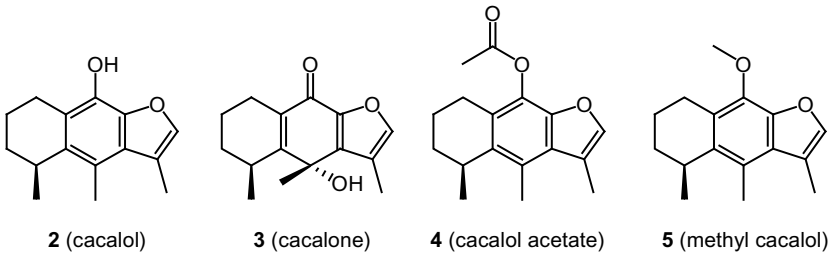
Flaveria bidentis (L.) Kuntze

Flaveria bidentis (Asteraceae) is an annual herb that is native to South America and was discovered as an exotic plant in China. It is also known as "eco-killer" due to its high adaptation to new environments, high rate of germination, and well-developed root system, as well as the production of large amounts of allelochemicals that inhibit the growth of surrounding plants. Despite this potential allelopathic activity, there are very few studies on its root exudates [19]. Recently, Xing and co-workers [20] identified by GC/MS a large variety of compounds suggested as allelochemicals.

Psacalium decompositum (Gray) Rob. ex Brett.

Psacalium decompositum (Gray) (Asteraceae) is a shrub that is native to northern Mexico and southern North America and it is called locally "matarique" or "maturin" [21]. The infusion of both the roots and rhizomes of this plant has been used for the treatment of rheumatism, pains, diabetes, snakebites, and renal, hepatic, and gastrointestinal ailments [22]. Phytochemical studies have revealed that the most abundant constituents in the hexane extract of its roots are two sesquiterpene compounds (furanoeremophilanes), namely, cacalol (**2**) and cacalone (**3**) [23] (Fig. 4). These particular compounds possess an unusual tetrahydronaphthofuran structure and their isolation led to the first report of this kind of backbone in Nature [21]. Cacalol is an unstable compound that forms a homodimer upon exposure to UV radiation and it is also oxidized by oxygen and light [24]. Additionally, these sesquiterpenes and related structures have been found in aqueous decoctions of the roots and rhizomes, thus explaining the pungent odor and bitter taste of the traditional infusions used for medicinal purposes. These compounds were detected by thin-layer chromatography using standards, after extraction of the aqueous infusion with chloroform and then ethyl acetate. Moreover, it has been reported that cacalol (**2**) inhibits ATP synthesis, proton uptake, and electron transport at the oxygen evolution level. A concentration of 60 μM of cacalol completely inhibited the electron transport from water to 2,6-dichlorophenolindophenol (DCIP). This suggested that cacalol could act as an allelochemical agent to interfere with the growth of photosynthetic organisms [24].

The effect of the aqueous extract (obtained from 1 g of roots soaked with 100 cm^3 of distilled water for 4 h), *n*-hexane extract, and cacalol (**2**) on the germination and radicle growth of *Amaranthus hypochondriacus* L. and *Echinochloa crus-galli* L. was studied. Significant inhibition of the germination of *A. hypochondriacus* and on the radicle growth of both species was noted, especially by the aqueous extract and **2**. In previous studies it was suggested that the hydroxy group of **2** plays an important



2 (cacalol) **3** (cacalone) **4** (cacalol acetate) **5** (methyl cacalol)

Fig. 4 Structures of the main constituents of *Psacalium decompositum* (cacalol and cacalone) and synthetic derivatives (cacalol acetate and methyl cacalol)

role in the inhibition of oxygen evolution in photosynthesis. Therefore, two synthetic derivatives with higher lipophilicity (cacalol acetate (**4**) and methyl cacalol (**5**)) (Fig. 4) were prepared in order to evaluate their influence on the activity. The results showed that the methyl ether **5** was less active than the other compounds and a potent radicle growth inhibition of *E. crus-galli* was observed for the acetate **4**. However, significant effects were not observed in *A. hypochondriacus* for the latter compound. These results indicated that substitution of the free hydroxy group in the cacalol structure did not enhance the activity on radicle growth inhibition for either species, although greater selectivity was achieved. An enzymatic biotransformation of cacalol acetate (**4**) to cacalol (**2**) inside the seeds of *E. crus-galli* was proposed. Regarding *A. hypochondriacus*, this biotransformation would not occur and cacalol acetate would remain in its seeds without any effect [21, 25]. The typical pappus of the Asteraceae is shown in Plate 1.

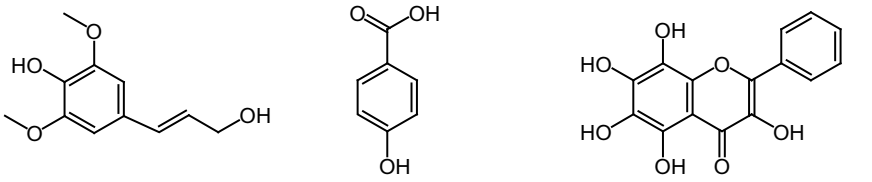
Plate 1 Asteraceae. Pappus (flower structure) of Asteraceae. Cabrera de Mar (Barcelona). Image from Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Papus_(Asteraceae).jpg)

2.1.2 Brassicaceae

Brassica napus L.

Brassica napus (Brassicaceae) (Plate 2), commonly known as canola, is one of the main crops for the production of vegetable oil for human consumption and animal nutrition worldwide. Recently, this plant has also been used for the production of biodiesel [26]. Asaduzzaman et al. [27] evaluated the allelopathic potential of this crop against annual ryegrass by comparing different canola genotypes (strongly and weakly competitive). Metabolomic analysis by LC-QTOF-MS of shoots, roots, and root exudates was performed. A greater number of secondary metabolites were found in the roots than in the shoot extracts, and a few of these compounds were identified in the root exudates. Previous research findings have also led to the same conclusion in the study of other species. It is suggested, therefore, that shoots and roots contain many metabolites, but only some of these are released into the soil environment in a process that depends on particular plant-soil conditions. Significant differences were observed between growth inhibition of annual ryegrass and the tested canola genotypes, including in chemical composition. Sinapyl alcohol (**6**), 4-hydroxybenzoic acid (**7**), and 3,5,6,7,8-pentahydroxyflavone (**8**) (Fig. 5) were found in the root exudates of the most suppressive genotypes, and it was suggested that these compounds were probably responsible for the allelopathic activity that was observed [27]. Furthermore, Uremis and co-workers [28] evaluated the allelopathic potential of different canola cultivars on the seed germination and shoot and root growth of several weed species. Root exudates showed inhibition of seed germination although root and shoot extracts had higher

Plate 2 Brassicaceae. *Brassica napus* L. Image from Tilo Hauke (http://commons.wikimedia.org/wiki/File:Brassica_napus_2.jpg)



6 (sinapyl alcohol) **7** (4-hydroxybenzoic acid) **8** (3,5,6,7,8-pentahydroxyflavone)

Fig. 5 Metabolites isolated from the root exudates of *Brassica napus* that are probably responsible for the allelopathic activity observed

inhibition potential. It was demonstrated that those cultivars with higher levels of benzyl and allyl isothiocyanate had stronger allelopathic effects.

2.1.3 Boraginaceae

Echium spp.

Isohexenylnaphthazarins (alkannin and shikonin derivatives) are found in the root periderm of several Boraginaceous plants, including *Echium* species (Fig. 6) [29].

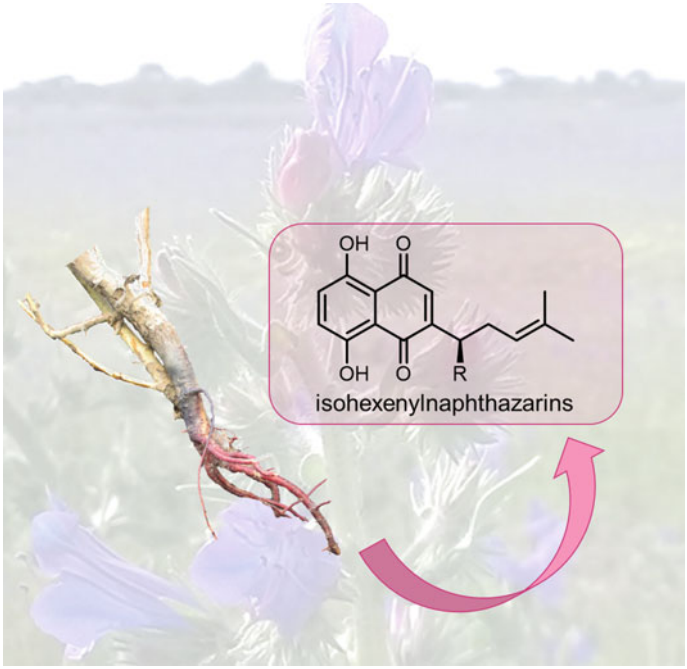
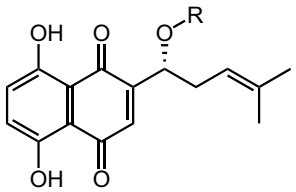


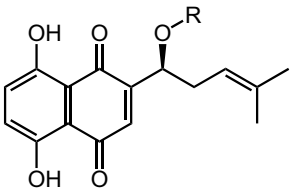
Fig. 6 Isohexenylnaphthazarins released from the roots of *Echium* spp.

Plate 3 Boraginaceae. Viper's bugloss (*Echium vulgare*) flower. Copyright Evelyn Simak and licensed for reuse under creativecommons.org/licenses/by-sa/2.0. (https://www.geograph.org.uk/reuse.php?id=5801578)

These compounds are characteristically red and are often light- and oxygen-labile, which makes their isolation difficult and methods for their separation rather few in number [30]. It has been suggested that in the soil the naphthoquinones released by *Echium vulgare* (Plate 3) roots may act as defense compounds and they are produced potentially as a result of plant stress [31, 32].

Durán and co-workers [33] quantified the content of these allelochemicals by LC-MS-MS from the periderm roots of two *Echium* spp., namely, *E. plantagineum* and *E. gaditanum*, to assess their impact on their native and invaded ranges. *E. plantagineum*, also known as Paterson's curse or Salvation Jane, is a successful invader in Australia that was introduced in the 1800s [34]. In contrast to the above, *E. gaditanum* is perennial and its toxicity does not have a major impact on agriculture in its native range. Phytochemical studies of this plant are uncommon and previously only the fatty acid composition of the seed oil has been reported [35]. The results highlighted that the abundance of certain pigments is closely related to climatic conditions. Thus, root extracts from both species collected in late spring were more inhibitory in the wheat coleoptile bioassay. Acetylshikonin (**9**) and acetylalkannin (**10**) versus dimethylacrylshikonin (**11**) and dimethylacrylalkannin (**12**) were present in the highest concentrations in extracts from both species.





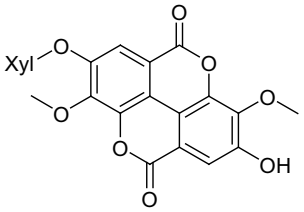
9 R = $COCH_3$ (acetylshikonin) **11** R = $COCH{=}C(CH_3)_2$ (dimethylacrylshikonin)

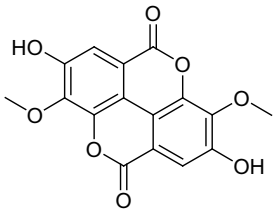
10 R = $COCH_3$ (acetylalkannin) **12** R = $COCH{=}C(CH_3)_2$ (dimethylacrylalkannin)

2.1.4 Euphorbiaceae

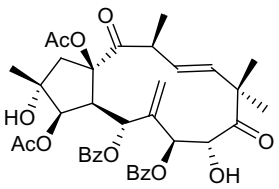
Euphorbia himalayensis (Klotzsch) Boiss.

Euphorbia himalayensis is a noxious weed to livestock and humans, in addition to affecting the performance of crops in the Tibetan Plateau. Liu and co-workers [36] isolated three compounds from the root extracts, including 4-*O*-[*β*-D-xylopyranosyl]-3,3′-di-*O*-methylellagic acid (**13**), 3,3′-di-*O*-methylellagic acid (**14**), and esulone A (**15**) (Fig. 7). Furthermore, these compounds were also identified in the rhizosphere soil. Root exudates showed inhibitory growth activity on wheat seedlings at lower concentrations while an increase in plant growth was produced when the concentration





13 (4-*O*-[ß-D-xylopyranosyl]-3,3'-di-*O*-methylellagic acid) **14** (3,3'-di-*O*-methylellagic acid)



15 (esulone A)

Fig. 7 Possible allelochemicals from root exudates of *E. himalayensis*

Plate 4 Euphorbiaceae. *Euphorbia milii* Des Moul. flowers. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Euphorbia_Milii_flowers.jpg)

was higher. This finding suggests that the combination of these allelochemicals could provide a selective plant growth regulator. It was also proposed that these allelochemicals enable this species to become a successful competitor. To illustrate a typical Euphorbiaceae species, the flowers of *Euphorbia milii* are shown in Plate 4.

2.1.5 Fabaceae

Mucuna pruriens (L.) DC.

Mucuna pruriens (Fabaceae), also named velvet bean, is a popular Indian medicinal plant widely distributed throughout India and in other parts of the tropics, including Central and South America [37]. This plant has also been cultivated for intercropping with maize, sorghum, and millet in tropical regions to provide soil and crop benefits and for the management of various pests. In this way, the quantity of synthetic agrochemicals needed for the crops is reduced. The main allelochemical, which is exuded from the roots of this species, is the non-protein amino acid 3,4-dihydroxyphenyl-L-alanine [38] **16** (L-DOPA) (Fig. 8) and this reaches 1 ppm in water culture solution and 50 ppm in the vicinity of the roots. These concentrations are sufficient to affect the growth of surrounding plants by inhibition of seed and root growth. For instance, the growth of maize roots and the activities of phenylalanine ammonia-lyase (PAL), tyrosine ammonia-lyase (TAL), and peroxidase (POD) were reduced, while the contents of phenylalanine, tyrosine, and lignin were increased after exposure to L-DOPA (**16**) (39). These findings suggest that the inhibition of these activities could lead to a major incorporation of phenylalanine

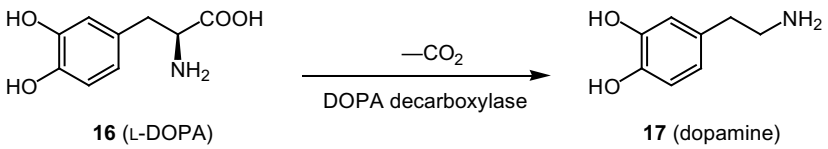


Fig. 8 Detoxification of L-DOPA to form dopamine through the action of L-DOPA decarboxylase

and tyrosine levels into the cell wall and this would be followed by lignin deposition. Therefore, cell expansion is restricted and the root growth reduced.

Moreover, this allelochemical has also been found in large amounts in leaves and seeds from this species [40]. These phytotoxic effects are generally less damaging in Gramineae and Leguminosae species. It has been reported that some plants are able to detoxify L-DOPA (**16**) to form dopamine (**17**) or 3-*O*-methyldopa through the action of L-DOPA-decarboxylase and catechol-*O*-methyltransferase, respectively [41].

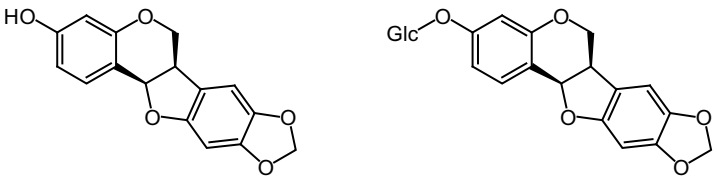
Dopamine (**17**) (Fig. 8) is an allelochemical that is widespread in animals and has also been detected in many plant families. For example, Wichers et al. [42] used HPLC coupled with mass spectrometry to identify **17** in 2–3-week-old leaves of *Mucuna pruriens.* The dopamine content of the leaves even exceeded the content of L-DOPA (**16**), the most abundant allelochemical in *Mucuna*. However, **17** could not be detected in the roots, stems, or seeds at any stage of development. Matsumoto [43] reported that *Mucuna* metabolizes **16** to **17** in leaves as a protective mechanism against the toxicity of **16**. Dopamine (**17**) has also been detected in numerous other plant families; for example, **17** is one of the major bioactive components of *Portulaca oleracea* L. [44], potato (*Solanum tuberosum*), the pulp of yellow banana (*Musa acuminata*), and fuerte avocado (*Persea americana*) [45, 46].

However, the role of dopamine (**17**) in plants has not been widely studied. In some studies, **17** has been proposed as a precursor for alkaloids and others revealed its allelopathic activity as it is involved in processes such as flowering, nitrogen fixation, and photophosphorylation of chloroplasts. For example, **17** has been shown to inhibit soybean root elongation [47].

Trifolium pratense L.

Trifolium pratense (Fabaceae) (Plate 5), also known as red clover, is a forage plant that is widely distributed worldwide and has a wide range of biological activities [48, 49]. Although its phytotoxicity on other plants has been reported, the identity of the responsible active metabolites has not been further explored. It was found in recent studies that isoflavonoids, namely, (6a*R*,11a*R*)-maackiain (**18**) and (6a*R*,11a*R*)-trifolirhizin (**19**), are the major components in root extracts of this species (Fig. 9). Furthermore, some of the compounds from the soil were identified as allelochemicals, showing remarkable phytotoxic activity on one of the most widely distributed weed species, *Poa annua* [50].

Plate 5 Fabaceae. *Trifolium pratense*. Photograph courtesy Ivar Leidus (https://reativecommons.org/licenses/by-sa/4.0)



18 ((6a*R*,11a*R*)-maackiain) **19** ((6a*R*,11a*R*)-trifolirhizin)

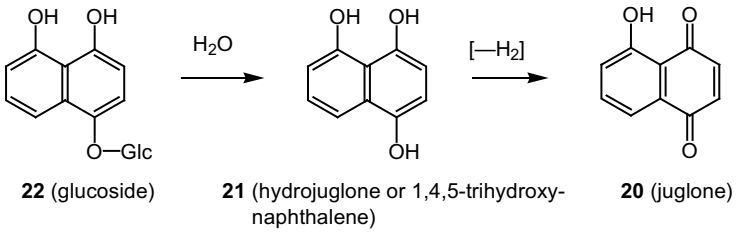
Fig. 9 Allelochemicals identified in *Trifolium pratense*

2.1.6 Juglandaceae

Juglans nigra L.

Juglans nigra (Juglandaceae) (Plate 6), also named black walnut, is one of the most notable and oldest examples in allelopathy since juglone (**20**) (5-hydroxy-1,4-naphthoquinone) was the first allelopathic agent to be described. Juglone (**20**) is mainly obtained from the leaves, roots, and husks of species belonging to this family and it has shown growth inhibitory effects for the whole plant on herbaceous and woody species, such as tomato, alfalfa, soy, and cucumber [51–54]. Pliny the Elder (23–79 AD) was the first to observe that "the shadow of walnut trees is poison to all plants within its compass" [55]. In living plant tissues, a colorless non-toxic reduced

Plate 6 Juglandaceae. *Juglans nigra*, Walnut tree. Photograph Georg Slickers, licensed under the Creative Commons Attribution-Share Alike 2.5 license. (https://es.m.wikipedia.org/wiki/Archivo:Walnut-tree_20041012_2599.JPG)



22 (glucoside) **21** (hydrojuglone or 1,4,5-trihydroxy-naphthalene) **20** (juglone)

Fig. 10 The presence of hydrojuglone in living tissues of walnut tree and subsequent formation of the allelopathic compound, juglone

form of this compound, hydrojuglone (**21**), is abundant—especially in the leaves, fruit hulls, and roots of walnut. When this compound is exposed to air or to an oxidizing compound, hydrojuglone is oxidized to its toxic form, juglone (**20**) (Fig. 10). Therefore, plants in the vicinity of the walnut tree are affected by absorbing **20** through their roots [53]. With respect to biosynthesis, juglone is presumed to be produced by hydrolysis of its glucoside **22**.

2.1.7 Poaceae

Avena fatua L.

Avena fatua (Poaceae) (Plate 7), or wild oat, is one of the worst annual grass weeds in the world (especially on wheat and other cereals). It has been reported that phenolic acids (such as *p*-coumaric (**93**), vanillic (**46**), and ferulic (**44**) acids) and

Plate 7 Poaceae. *Avena fatua* L. This file is licensed under Creative Commons Attribution—Partage dans les Mêmes Conditions 4.0 International. (https://fr.wikipedia.org/wiki/Fichier:Avena_fatua-Folle_avoine-20150527.jpg)

scopoletin are the major compounds released from its roots [56]. Additionally, it has been demonstrated that the concentration of these phenolic acids depends on the plant growth stage. The highest concentration of these allelochemicals in the rhizospheric soil was recorded at the stem extension and heading stages [57].

Oryza sativa L.

Rice, *Oryza sativa* (Poaceae or Gramineae), is one of the main food crops worldwide [58]. Previous studies have shown that the allelopathic activity of this species is varied and dependent on the origin. Large amounts of allelochemicals are released from rice plants under biotic and abiotic conditions for defense and protection [59]. Among these compounds, phenolic acids (vanillic (**46**) or benzoic (**47**) acids), diterpenoids, and momilactones have been described [60–63]. A study performed by Khanh et al. relied on the allelopathic responses of two rice varieties (Koshihikari and Jasmine) under abiotic stresses: temperature and complete submergence (one of the most harmful abiotic stresses). The results revealed that the total phenolic content was higher in extracts and root exudates from rice seedlings under the abiotic stresses evaluated, especially for the Koshihikari variety. Five phenolic acids were found to be involved in the allelopathic response, with syringic and benzoic acids being the most prominent. Moreover, root exudates of Koshihikari rice seedlings reduced the number of total weeds by up to 60% at 32°C [64]. Likewise, the secretion of the allelochemical momilactone B was increased by the presence of barnyardgrass seedlings or barnyardgrass root exudates [65].

Li and co-workers [66] investigated whether the phenomenon of rice allelopathy could be related to root fineness (roots ≤ 0.2 mm diameter). The results showed that allelopathic rice cultivars had higher length, a greater number of root tips of fine roots, and a direct correlation between the phenolic acids content in root exudates, and allelopathic activity was noted. These findings were not evident in roots with a diameter greater than 0.2 mm. It is believed that fine-root traits could accumulate more allelochemicals and release them into the environment. Moreover, the release of greater quantities of allelochemicals could be related to phytohormone regulation. It has been proposed that the phytohormones jasmonic acid and salicylic acid play a crucial role in the signaling pathway in rice-barnyard recognition [67, 68].

Phragmites australis (Cav.) Trin. ex Steud.

Phragmites australis (Poaceae) is one of the most invasive species in the world [69]. Several studies have shown that aqueous extracts of different parts of this plant (leaves, stems, rhizomes, and roots), as well as root exudates, have strong phytotoxic effects on the germination and growth of other plant species [70]. This activity has been related to the presence of phenolic compounds. Moreover, gallic acid was identified as the major compound in leaf extracts, which showed the highest activity, followed by the inflorescence, rhizomes, roots, and finally stems. Aqueous extracts caused oxidative stress through the production of reactive oxygen species, which resulted in cell death and inhibition of plant growth. A decrease in water uptake and a delay in total carbohydrate degradation were also noted, thus providing evidence of a negative effect on the overall germination process [71].

Secale cereale L. (rye)

Secale cereale became a crop about 2000 years ago. It is used as a grain, forage, green manure crop, or for hay, as well as a cover crop or mulch for allelopathic weed control. The major allelochemicals reported and identified for the first time in this species are benzoxazinoids [72]. Macías and co-workers described for the first time the allelochemical pathway of benzoxazinoids released by rye (donor plant) on *Avena fatua* L. (target plant) [73]. This kind of compound has been found in *S. cereale* as well as in other Gramineae crops. Glucosylated benzoxazinoids are found inside the plants and they are released into the environment without the sugar moiety [74]. These compounds can be classified into three categories: benzoxazolinones (**23, 24**), lactams (**25**), and hydroxamic acids (**26, 27**) [75] (Fig. 11). These metabolites have attracted great interest due to the wide spectrum of biological bioactivities and remarkable allelopathic effects reported [76]. Additionally, these compounds are transformed by soil microbiota into benzoxazolin-2-one (BOA) and 2-aminophenol derivatives, which are subsequently oxidized to 2-amino-3*H*-phenoxazin-3-one (**28**) (APO) and other related products (Fig. 12). These findings showed that, besides the allelochemicals released into the environment, the degradation products after biotic and abiotic stresses are also decisive.

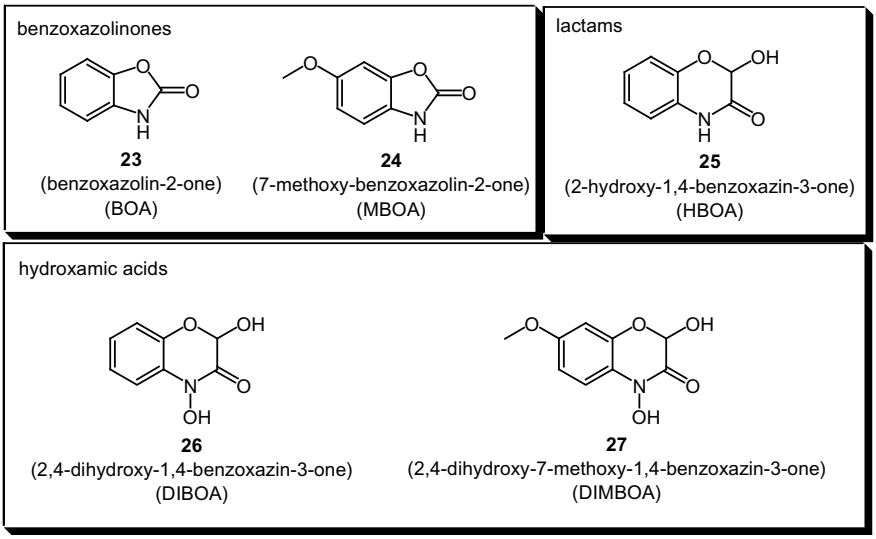


Fig. 11 Benzoxazinoids found in rye and other cereal plants

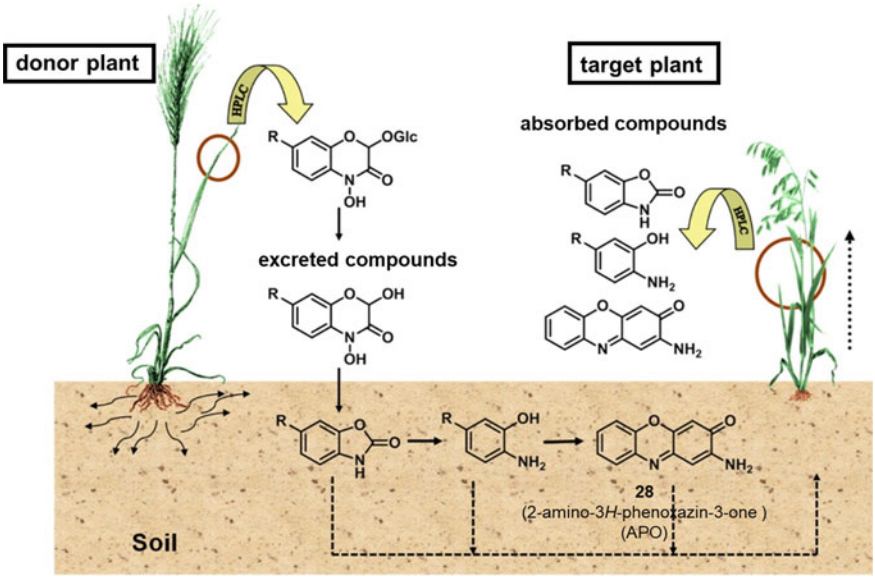
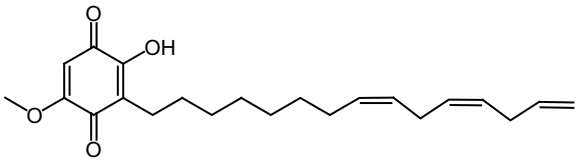


Fig. 12 Allelochemical pathway of benzoxazinoids released by *S. cereale* on *A. fatua*. Reprinted with permission from J. Agric. Food Chem. (2014), 62:9450. Copyright (2014) American Chemical Society



29 (sorgoleone)

Fig. 13 Main allelochemical exuded from the roots of sorghum

Sorghum bicolor (L.) Moench

Sorgoleone (**29**) (Fig. 13) is one of the main allelochemicals exuded from the roots of sorghum (*Sorghum bicolor* (L.) Moench) [77]. It has shown phytotoxic activity against a wide variety of plant species, but is most active on small-seeded plants. This allelochemical is released continually from the roots during its growing season, thereby some persistence in soil has been estimated and its half-life is around ten days. This property is due to its hydrophobic character, which leads to a strong sorption in the soil with organic matter and other hydrophobic components [78]. The molecular target sites affected by this allelochemical include photosynthetic and mitochondrial electron transport. It has been demonstrated that sorgoleone does not have an effect on the photosynthesis of older plants but it can cause inhibition of photosynthesis in young seedlings [79]. Moreover, through the use of different microscopic techniques, it has been demonstrated that this allelochemical, its resorcinol analog, and other related hydroquinones are exuded from the tips of root hairs [31, 80].

It is worth noting that the phytotoxic activity of sorgoleone (**29**) can be compared with those of commercial herbicides, including atrazine and metribuzin [81]. Recently, Uddin and co-workers [82] evaluated the crop selectivity of this compound using its formulated wettable powder (WP) form. The results revealed that sorgoleone as a 4.6WP (4.6% **29**) product inhibited most of the weed species tested and most crop species showed tolerance to it. This opens up the possibility of developing more effective environmentally friendly herbicides.

Triticum aestivum L. (wheat)

Wheat constitutes one of the major crops and it is a staple food for more than 35% of the world population [83]. A study performed by Kong and co-workers demonstrated that (–)-loliolide (see later on: **50**) and jasmonic acid are found in the root exudates of a diverse range of plant species and these compounds could act as signaling chemicals to trigger an allelochemical response in wheat [84, 85]. The allelochemicals discussed above (benzoxazinoids) are also present in wheat and they affect the growth of plant competitors [86, 87]. A higher concentration of 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one (DIMBOA, **27**) was observed when wheat was co-cultivated with other weed species. Additionally, this concentration was higher in roots than in shoots and the responses were density-dependent. It is worth noting that below-ground plant–plant interactions potentially affect the performance of plants and alter interspecific and intraspecific interactions [88].

2.1.8 Solanaceae

Solanum lycopersicum L.

Solanum lycopersicum (Plate 8), commonly known as tomato, is an important edible crop in Southern Europe, the Americas, the Middle East, and India. Numerous metabolites have been described with a wide range of biological activities, although phytotoxicity studies on tomato are scarce. Recently, Rial and co-workers [89] isolated α-tomatine (**30**) from the roots of tomato and this compound was also identified in root exudates by LC-MS/MS (Fig. 14). The

Plate 8 Solanaceae. *Solanum lycopersicum* L. This file is licensed under the Creative Commons Attribution 3.0 United States license. (https://commons.wikimedia.org/wiki/File:Starr-090814-4325-Solanum_lycopersicum-fruit-Industrial_area_Mokulele_Hwy-Maui_(24854266132).jpg)

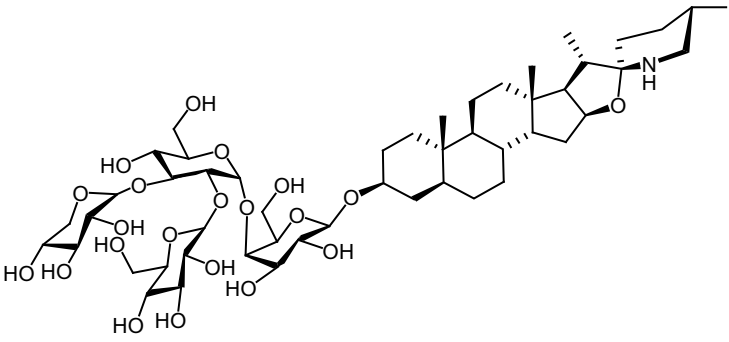


Fig. 14 Allelochemical released from the roots of *S. lycopersicum*

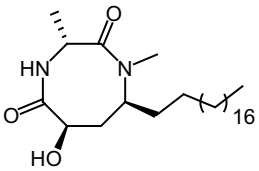
phytotoxicity of **30** was tested on *L. sativa*, *E. crus-galli*, and *L. perenne* and the most affected parameter was root length. Moreover, **30** showed stimulation of the germination of the tomato parasite (*P. ramosa*), thus acting as a chemical signal. These results highlight the multipurpose behavior of this allelochemical.

2.1.9 Cupressaceae

Cunninghamia lanceolata (Lamb.) Hook.

Chinese fir (*Cunninghamia lanceolata*) (Plate 9) is a subtropical coniferous tree species that has a considerable litterfall and fine roots. This species is grown widely in the subtropical areas in China and covers around a quarter of the plantation area, thus making it an important economic commodity for industrial wood production. However, there is a regeneration failure and productivity decline in successive plantations [90, 91]. It has been reported that the roots of Chinese fir release into the soil environment the allelochemical cyclic dipeptide **31**, (6-hydroxy-1,3-dimethyl-8-nonadecyl-[1,4]-diazocane-2,5-diketone) (Fig. 15), which causes self-growth inhibition and thereby regeneration failure and productivity decline. This cyclic dipeptide has also been found in leaf litter and soils, in which its concentration was higher in replanted Chinese fir plantations [91]. In order to mitigate this problem, several experimental studies have demonstrated that there is a positive interaction when this species is grown with broadleaf species, specifically

Plate 9 Cupressaceae. *Cunninghamia lanceolata* branch. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Cunninghamia_lanceolata_branch.jpg)



31 (6-hydroxy-1,3-dimethyl-8-nonadecyl-[1,4]-diazocane-2,5-diketone)

Fig. 15 Allelochemical described from the root exudates of Chinese fir

with *Mitrephora macclurei* Weeras. & R. M. K. Saunders and *Eucalyptus decipiens* Endl. Significant differences were observed and these included an increase in the total and available amount of phosphorus, reducing release and increasing degradation of the allelochemical cyclic dipeptide, improvement of the soil microbial community by increasing arbuscular mycorrhizal fungi community development, and production and distribution of Chinese fir roots. This novel mechanism has led to a reduction in problems related to self-growth inhibition or autotoxicity [88]. Nevertheless, when Chinese fir and *C. camphora* (*Cinnamomum camphora* (L.) J. Presl) were grown together, an unfavorable response was produced, and this resulted in growth inhibition of Chinese fir and changes in the composition of the soil microbial community. These results highlighted the key role of root–root interactions and the various complex processes that take place. Further research is required to specify which compounds are responsible for these interspecific interactions between Chinese fir and broadleaf tree species [92].

Other significant examples of autotoxicity are produced by phenolic acids exuded from the roots of *Camellia sinensis*. These cases are described below.

2.1.10 Theaceae

Camellia sinensis L.

Camellia sinensis (Theaceae) (Plate 10), tea tree, is cultivated extensively in many countries in Asia and Africa and it produces one of the most popular beverages. However, tea yield and quality decrease rapidly after the initial establishment of these trees. It has been reported that autotoxicity is the main factor in regeneration failure and productivity decline [93–95]. A study performed by Cao and co-workers [96] identified seven phenolic acids in root exudates and soil extracts, including ferulic (**44**), cinnamic (**45**), vanillic (**46**), *p*-coumaric (**93**), caffeic, chlorogenic, and gallic acids. Furthermore, it was also noted that the content of total phenolic acids in soil extracts increased with the age of tea trees and therefore these compounds could be responsible for the autotoxicity, which results in a decline in productivity in successive plantations.

Plate 10 Theaceae. *Camellia sinensis* L. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Camellia_sinensis_Bois_Cheri.jpg?uselang=fr)

2.1.11 Root Parasitic Plants: Chemical Signaling Hunters

Broomrapes are obligate plant-parasitic plants from the genera *Orobanche* and *Phelipanche* (family Orobanchaceae). They cause significant damage and yield loss in a variety of main crops, including sunflower, fava bean, tomato, and carrot, among others [97]. The damage depends on the specific broomrape-host association but, in general, parasitized crops suffer from reduction of total biomass and negative effects on the crop photosynthetic machinery and hormonal balance [98]. Seeds from parasitic plants can remain dormant in the soil for many years as they wait for a chemical signal exuded from the root of the host to start their germination and development of the haustorium [99]. All such features make the control of these plants difficult and not fully effective, with only a few herbicides able to control broomrapes selectively [100]. One of the main ways to control parasitic weeds is the inhibition or stimulation of parasitic seed germination and haustorium growth. The latter strategy (stimulation of parasitic seed germination) is also known as "suicidal germination" and more recently as the "honey-pot strategy" [101, 102].

Strigolactones (apocarotenoids that regulate shoot branching) (Fig. 16) are among the most potent germination-inducing factors for broomrapes [103]. These allelochemicals are released from the host plant, into the soil environment, to promote arbuscular mycorrhizal fungi symbiosis and facilitate nutrition uptake by the plant. Nevertheless, this chemical signal is used by the plant for its own adaptation and it benefits the parasitic plants as a perception of their hosts and thus as a trigger to germinate [104]. The strigolactones isolated from host and non-host plants, and also identified in the root exudates [105], include didehydro-orobanchol (identified from roots of Poaceae and Solanaceae species), orobanchol (**32**) (the first

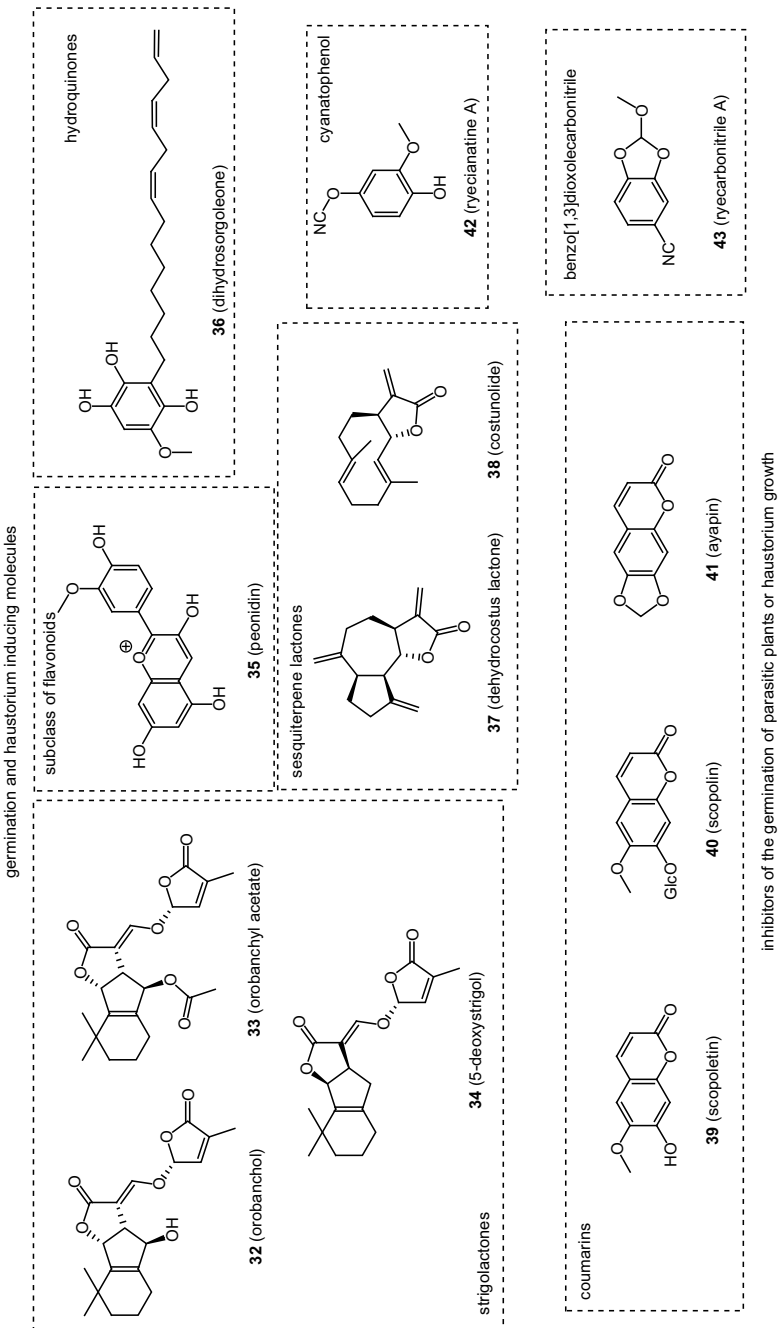


Fig. 16 Allelochemicals reported to inhibit or stimulate the germination of parasitic plants or haustorium growth

described *Orobanche* germination stimulant, isolated from red clover), orobanchyl acetate (**33**) (previously named alectrol and isolated from cowpea root exudates), and 5-deoxystrigol (**34**) (isolated from the root exudates of *Lotus japonicus*) (Fig. 16) [106–108].

Moreover, other haustorium-inducing molecules have been reported, such as several flavonoids (e.g. **35**), phenolic acids, hydroquinones (**36**), and sesquiterpene lactones (e.g. **37** (dehydrocostus lactone) and **38** (costunolide)) (Fig. 16) [109–112]. For instance, it has been demonstrated that the anthocyanidin peonidin (**35**) (found in maize-seed rinses) induces haustorium in vitro in the facultative parasite *Triphysaria versicolor* (Orobanchaceae), even at a concentration of 10 μ*M*. However, although this effect was observed in vitro, the role of **35** as a chemical signal for parasitic plants in the soil is not clear because this kind of compound is not usually found in root exudates [109]. The reduced form of one of the main allelochemicals exuded from the roots of sorghum (*Sorghum bicolor* (L.) Moench), dihydrosorgoleone (**36**) (or sorghum xenognosin), has been reported as the first germination stimulant of *Striga*. Nevertheless, the low solubility of this compound in aqueous media, and its rapid oxidation to its quinone form (sorgoleone), would seem to indicate that only those *Striga* seeds close to the host root would germinate. It has been highlighted that sorgoleone is inactive as a stimulant of *Striga* seed germination [113, 114]. Also worth mentioning is a group of compounds with structural features related to strigolactones, namely, sesquiterpene lactones (**37, 38**). These compounds have shown stimulation of the germination of the sunflower parasite *Orobanche cumana* and this activity was not produced on *O. crenata* (Plate 11) or *O. ramosa* [110].

Plate 11 Root parasitic plants. *Orobanche crenata* Forssk. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Orobanche_crenata_3.jpg)

On the whole, it is thought that the induction of the germination of parasitic plants is not caused by a single chemical compound, but is rather due to the interaction of several such compounds [110].

There are also allelochemicals that inhibit the germination of parasitic plants or haustorium growth (Fig. 16). One of the significant examples concerns 7-hydroxylated and 7-oxygenated simple coumarins **39–41** (also described as phytoalexins), which are found in the aerial parts and roots of sunflower varieties resistant to broomrape. These play an important defensive role in preventing parasitic plant infection. Such compounds prevent germination and intrusion of the parasite *Orobanche cernua* to the host vascular system, and ultimately cause parasite plant death. It has been suggested that these phytoalexins are synthesized in the aerial parts and then translocated to the roots through the phloem. Accumulation of these metabolites is tissue- and plant age-dependent [115–117].

A recent study performed by Cimmino and co-workers [100] concerned the allelopathic effect on broomrapes of novel metabolites (substituted cyanatophenol (e.g. ryecianatine A (**42**)) and cyanatobenzo[1,3]dixole, as well as substituted benzo [1,3]dioxole-carbonitriles (e.g. ryecarbonitrile A (**43**)), isolated from rye root exudates (*Secale cereale* L.). Different opposite effects on early stages (seed germination and radicle growth) of *Orobanche* development were noted.

Ryecarbonitrile A (**43**) induced *O. cumana* seed germination significantly, while ryecyanatine A (**42**) inhibited both seed germination and seedling growth. All of these effects were dependent on the broomrape species tested and the metabolite applied. Likewise, it has been demonstrated that the di-*C*-glycosylflavone isoschaftoside (released from the roots of *Desmodium* spp.) affects *Striga* development and results in the death of the parasite and the reduction of its seed bank [118].

Other examples that are worth highlighting are the plants belonging to the genus *Desmodium*. These plants are used as intercrops owing to their ability to fix atmospheric nitrogen and provide organic carbon [119, 120]. Furthermore, it has also been reported that the use of these forage legumes as intercrops is an effective strategy for the control of the *Striga* parasite. *Desmodium* is able to stimulate the germination of *Striga* and interfere with the subsequent development of the germinated parasitic seed. Therefore, a reduction in the *Striga* seed bank is produced [121]. It has been reported that the allelochemical compounds responsible for this activity and released by *Desmodium* root exudates are di-*C*-glycosylflavones that possess *C*-linked glucose, galactose, and arabinose [121, 122].

2.2 Plant–Microbe Interaction

2.2.1 Araceae

Pistia stratiotes L.

Increases of eutrophication and cyanobacteria blooms in lakes seriously affect water environmental safety. Such blooms, commonly, have been controlled by physical

Plate 12 Araceae. *Pistia stratiotes* L. This file is licensed under the Creative Commons Attribution 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:%E5%A4%A7%E8%90%8D_Water_cabbage_(Pistia_stratiotes_Linn.)panoramio.jpg)

methods (e.g. filtering, changing water, and aeration), chemical methods (e.g. coagulating sedimentation and the use of cupric sulfate and ozone), and biological methods (e.g. breeding fish, aquatic plants, and microorganisms). Studies with aquatic plant allelochemicals have shown their anticyanobacteria activity, thus providing a new method and new ideas for eutrophication management. *Pistia stratiotes* L. (Plate 12), often called water cabbage or water lettuce, Nile cabbage or shellflower, is an aquatic plant from the Araceae family. This plant was first discovered in the Nile near Lake Victoria in Africa but it is now present, either naturally or through human introduction, in nearly all tropical and subtropical fresh waterways and it is considered an invasive species as well as a mosquito breeding habitat. Allelochemicals of this plant displayed clear inhibitory effects on the growth of the cyanobacteria *Microcystis aeruginosa* [123]. Root exudation was the main release route for anti-cyanobacteria allelochemicals.

2.2.2 Cucurbitaceae

Cucumis sativus L.

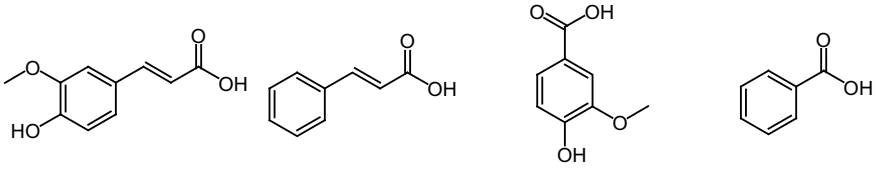
Cucumis sativus (Plate 13) is a vegetable cultivated throughout the world. It has been reported that phenolic acids are the main allelochemicals released from root exudates of this species and, in addition to affecting neighboring plants, it has shown autotoxicity [124]. Chen and co-workers [125] reported that the fungus *Trichoderma harzianum* (strain SQR-T037) is able to degrade six phenolic acids identified in cucumber root exudates in continuous cropping soils: 4-hydroxybenzoic acid (**7**), vanillic acid (**46**), ferulic acid (**44**), benzoic acid (**47**),

Plate 13 Cucurbitaceae. *Cucumis sativus* L. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Cucumis_sativus_0003.JPG)

3-phenylpropanoic acid, and cinnamic acid (**45**). The use of microorganisms that could biodegrade phenolic acids could be a promising strategy to reduce the autotoxicity produced by these metabolites exuded by crop roots as well as by plant residues.

Citrullus lanatus (Thunb.) Matsum. et Nakai (watermelon)

Studies on the evaluation of plant–microbe interactions and the kinds of allelochemicals involved are scarce. Pathogenic invasion has been associated with host activity, including root exudates and decaying residues. Many of the allelochemicals found in these residues and exudates are phytotoxic and it has been demonstrated that phenolic acids, such as ferulic (**44**), cinnamic (**45**), or vanillic acid (**46**), play a key role in root–microbe communication (Fig. 17). For instance, it has been



44 (ferulic acid) **45** (cinnamic acid) **46** (vanillic acid) **47** (benzoic acid)

Fig. 17 Allelochemicals found in root exudates and decaying residues from the watermelon plant

suggested that benzoic acid (**47**) is involved in the cell wall extensibility that plays a significant role in cell defense [126]. These secondary metabolites are distributed widely in plants and are released during the catabolic metabolism of lignin [127].

Some of the most harmful fungi that cause vascular disease in plants are those belonging to *Fusarium* species. *Fusarium oxysporum* f.sp. *niveum* is the most important soil-borne pathogen that limits watermelon production [128]. The allelopathic potential of artificially added benzoic acid (**47**) to this fungus has been evaluated by Wu and co-workers in an effort to identify the possible relationships between this phenolic acid and virulence factors of *Fusarium oxysporum* f. sp. *niveum*. The results showed suppression of hyphal growth, sporulation, conidial germination, and a negative effect on proteinase activity. Nevertheless, mycotoxin production by *Fusarium oxysporum* was greatly increased in a concentration-dependent manner after treatment with benzoic acid (**47**). It was suggested that this strange effect might result in an evolution of this fungus to produce greater quantities of mycotoxin to enhance its virulence and offset the growth impedance when confronted with biotic stress such as benzoic acid (**47**) released from the host plant. This research indicated that **47** could be a signal molecule in the process of ecological watermelon-*Fusarium oxysporum* interactions [129]. This allelochemical and other related phenolic acids, such as ferulic (**44**), cinnamic (**45**), and vanillic (**46**) acids, have been detected in root exudates and extracts of decayed plant residues of watermelon plants [128].

2.2.3 Poaceae

Digitaria sanguinalis (L.) Scop.

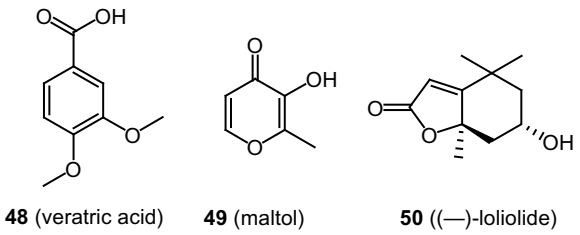
Digitaria sanguinalis (L.) Scop. (Poaceae) (Plate 14), also known as crabgrass, is a widespread annual weed species that affects the growth and performance of crop plants, particularly wheat, maize, and soybean [130]. A study performed by Zhou and co-workers demonstrated the presence of three isolated compounds from air-dried crabgrass plants in root exudates and rhizosphere soils. Veratric acid (**48**), maltol (**49**), and (−)-loliolide (**50**) (Fig. 18) were identified as possible allelochemicals and they showed phytotoxicity on wheat, maize, and soybean. In addition, these compounds produced an inhibition in soil microbial biomass and changes in the microbial community [131].

2.2.4 Solanaceae

Nicotiana tabacum L.

Among the most problematic soil-borne diseases in tobacco (*Nicotiana tabacum* L., Plate 15) cultivation are those bacterial wilt illnesses caused by *Ralstonia solanacearum*. It has been reported that organic acids are the major compounds in tobacco

Plate 14 Poaceae. *Digitaria sanguinalis* (L.) Scop. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://commons.wikimedia.org/wiki/File:Digitaria_sanguinalis_(3874835780).jpg)



48 (veratric acid) **49** (maltol) **50** ((—)-loliolide)

Fig. 18 Putative allelochemicals from *Digitaria sanguinalis*

root exudates and they play key roles in rhizosphere ecology, nutrient acquisition, and plant–microbe interactions. The function and relationship between the production of these allelochemicals and colonization of *R. solanacearum* have been investigated by Li and co-workers [132]. The results showed that myristic, cinnamic, and fumaric acids are the main chemoattractants that recruit *R. solanacearum* to the tobacco rhizosphere and induce biofilm formation, thereby accelerating disease progression in tobacco.

Plate 15 Solanaceae. *Nicotiana tabacum* L. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Nicotiana_tabacum_002.JPG)

2.2.5 Cupressaceae

Cunninghamia lanceolata (Lamb.) Hook.

As mentioned in Section 2.1.9, *C. lanceolata* (Plate 16), commonly known as Chinese fir, is one of the most important timber tree species in China. Nevertheless, a productivity decline is produced in monoculture plantations [90]. Studies carried out by Xia and co-workers [88, 92] demonstrated that broadleaf species affect chemically the growth of Chinese fir through below-ground interactions. An important role in plant growth and soil microbiota was noted. Chinese fir mixed planting with *M. macclurei* and *E. decipiens* produced a similar composition of main soil microbial groups, resulting in a positive feedback effect on plant performance. However, the root exudates of *C. camphora* strongly inhibited the growth of Chinese fir and changes in the soil microbiota were observed. Continuous Chinese fir monoculture plantations or Chinese fir mixed planting with *C. camphora* resulted in the deterioration and reduction of the soil microbial community. Further investigations are being conducted to determine the allelochemicals or signaling molecules responsible for these findings.

Plate 16 Taxodiaceae. *Cunninghamia lanceolata* (Lamb.) Hook. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license

2.2.6 Root Parasitic Plants

Parasitic plants like *Cuscuta campestris* (Plate 17) constitute one of the most damaging and difficult weed-control problems, as previously mentioned. These plants parasitize a wide range of crops and their noxious effects arise because they

Plate 17 Root parasitic plants. *Cuscuta campestris* Yunck. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Cuscuta_campestris.jpeg)

are able to synchronize their life cycles with the chemical signals from the hosts [103]. It has been suggested that the production of strigolactones is stimulated under phosphate-limited conditions in communication with arbuscular mycorrhizal fungi, and parasitic plants would benefit from this chemical clue to begin their life cycle. Studies concerning molecular mechanisms that govern signaling and recognition between arbuscular mycorrhizal fungi and their host plants are scarce. It is well known that roots from host plants release signaling molecules that promote hyphal branching. This is a critical step in the life cycle of arbuscular mycorrhizal fungi to ensure their symbiosis with the host root. Akiyama and co-workers isolated a branching factor from the root exudates of *L. japonicus* (Fabaceae), namely, strigolactone 5-deoxystrigol [107].

3 Leaching

Water-soluble allelochemicals such as phenolics, alkaloids, and terpenoids are released from different plant organs by rain, fog, or dew, in the form of leachates that affect the germination and development of accepter plants [133]. Despite evidence revealing that phytotoxicity depends on the types and quantities of allelochemicals released by the donor plants, most studies focus on allelopathic studies of extracts and there is still a lack of information about the presence of specific allelochemicals in many species [134]. There is also a need to perform more studies under field conditions. These findings are critical to gain a better understanding of the role of these compounds in the plant and possible synergistic interactions.

3.1 Plant–Plant Interaction

3.1.1 Apiaceae

Heracleum sosnowskyi Manden

Heracleum sosnowskyi Manden (Plate 18), also named Sosnowskyi's hogweed, is an invasive species in parts of the Baltic region of Northern Europe as well as in Eastern Europe, such as Latvia, Estonia, Ukraine, and Russia. This plant is native to the Caucasus Mountains and it damages native plant species and reduces their biodiversity. This plant can also produce a large number of seeds (around 15,000 seeds/plant), of which up to 90% germinate successfully. All of these features make this weed noxious. Mishyna and co-workers [135] evaluated the allelopathic potential and accumulation of furocoumarins (**51**–**54**) in fruit coats and seeds from this species before and after stratification treatments (Fig. 19). The results revealed that the concentration of detected furocoumarins was higher in the fruit coats than in the seeds before stratification. After this stratification period, their content

Plate 18 Apiaceae. *Heracleum sosnowskyi* Manden. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Heracleum_sosnowskyi20090702_100.jpg)

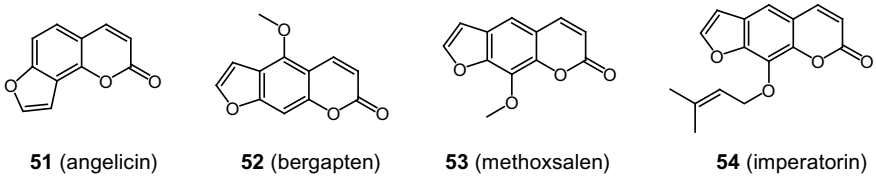


Fig. 19 Furocoumarins found in Sosnowskyi's hogweed

decreased significantly. These metabolites are considered to be seed auto-inhibitors and, as a consequence, this decrease in their concentration could lead to seed dormancy breaking, and leaching of these allelochemicals into the environment. Moreover, extracts from the fruit coats and seeds from this species were tested on *Lactuca sativa* and an inhibitory activity on seedling growth was observed. The authors proposed that these compounds could play a significant role in plant–plant interactions.

3.1.2 Asteraceae

Chrysanthemoides monilifera (L.) Nordlinh

Chrysanthemoides monilifera subsp. *monilifera*, also named boneseed, is an invasive noxious species in Australia. This South African plant was introduced into

Australia as an ornamental garden plant in the mid-nineteenth century. In order to investigate the mechanisms involved in boneseed invasion, the allelopathic potential of boneseed aqueous extract and leachate was studied by Al Harun and co-workers [134, 136]. It was found that leaves had the highest total phenolic content, followed by roots, stems, infested soils and, finally, outside soils. Allelochemicals that were identified in the different organs from this species are ferulic acid (**44**), phloridzin, catechin (**91**), and *p*-coumaric acid (**93**) [134].

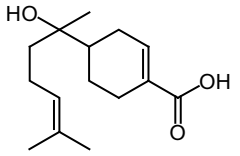
Flourensia campestris Grieseb.

Flourensia campestris (Asteraceae), commonly known as chilca, is an endemic species of the arid central region of Argentina. Aqueous extracts from leaves of *F. campestris* showed strong inhibitory effects on the germination and root and shoot growth of *L. sativa*. Bio-guided isolation of an aqueous extract from dry and fresh leaves led to the structural elucidation of (–)-hamanasic acid A (**55**). Based on the concentration and generalized distribution of this compound throughout the plant, the authors suggested that it is an allelochemical in this species (Fig. 20) [137].

Helianthus annuus L.

Helianthus annuus (Asteraceae) (Plate 19), which is commonly known as sunflower, is one of the most valuable crops and it is used in the food industry for the production of edible oil [138, 139]. Several parts of this plant have been identified as a rich source of a wide family of natural products that include sesquiterpenes, diterpenes, flavonoids, and coumarins [140, 141]. A large number of allelochemicals are located in the leaves [142]. The research group of Macías and co-workers studied the allelopathic potential of this species and examined the allelochemicals present in leaf aqueous extracts, both fresh and dried [143–145]. It is worth noting that these results led to the discovery of two novel families of bioactive sesquiterpenes: heliannuoles (**56–60**) and heliespirones (**61–63**) [146, 147]. Subsequent studies led to the isolation of a wide range of bioactive metabolites through a more efficient and environmentally friendly technique, supercritical fluid extraction [148, 149]. Some of the most significant allelochemicals (**64–69**) are shown in Fig. 21.

Fig. 20 Putative allelochemical from *F. campestris*



55 ((—)-hamanasic acid A)

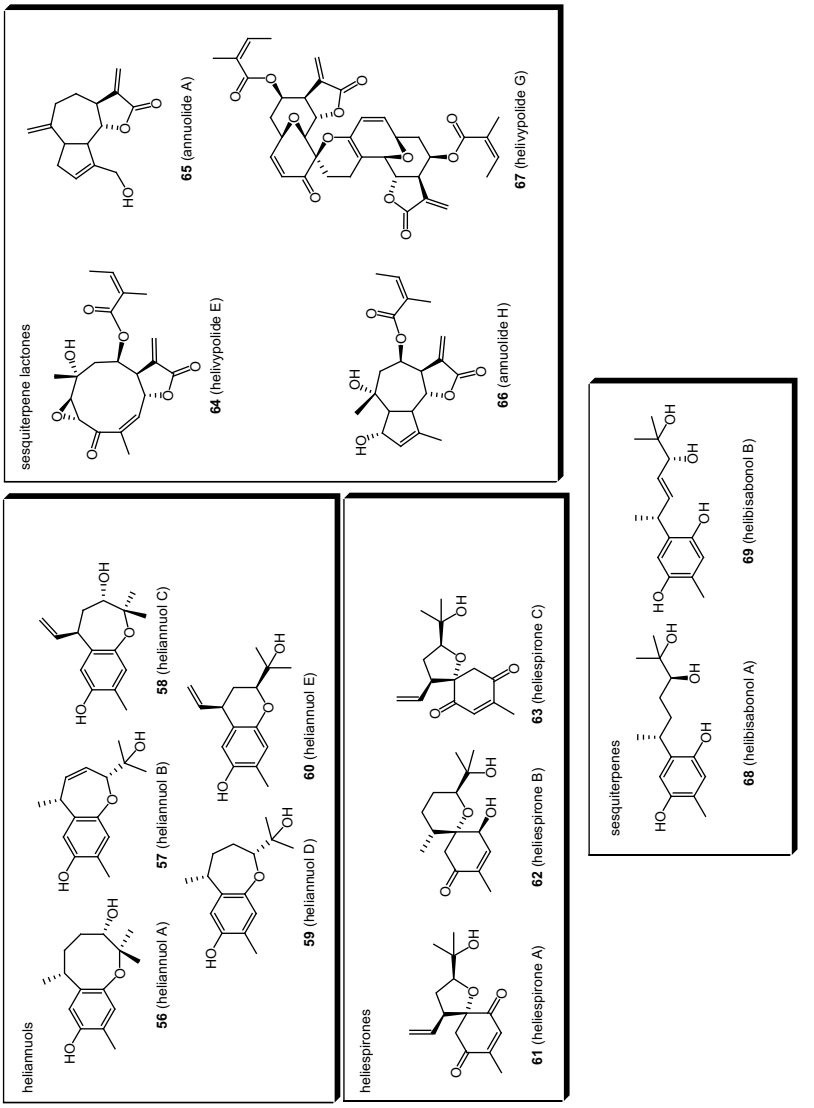


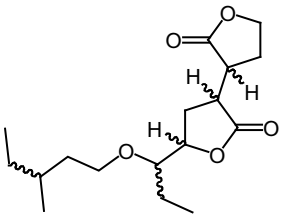
Fig. 21 Chemical structures of some allelochemicals isolated from sunflower

Plate 19 Asteraceae. *Helianthus annuus* L. Public domain image from Creative Commons. (https://commons.wikimedia.org/wiki/File:Sunflowers_helianthus_annuus.jpg?uselang=ca)

It has also been demonstrated that sunflower residues improve soil health and weed management in mung bean. Sunflower residues showed the highest allelopathic potential when compared to treatments with aqueous extracts. This allelopathic activity has been attributed to the presence of phenolic compounds (chlorogenic, caffeic, syringic, vanillic (**46**), and ferulic (**44**) acids) and terpenoids (sesquiterpene lactones) [150].

Synedrella nodiflora (L.) Gaertn.

Synedrella nodiflora (Asteraceae) is native to tropical America and it has become a widely distributed invasive weed species, including in Australia, China, India, and the Philippines, which affects many tropical crops [151, 152]. It has been reported that aqueous leaf leachates from *S. nodiflora* have shown phytotoxic effects on the growth of crop plants [153]. Some major stem volatile compounds have been identified by GC/MS and these include 2-pentadecanone, hexadecanoic acid, and phytol. Ghayal and co-workers [154] described a complex mixture of different compounds in leaf leachates and from an ethanol extract of *S. nodiflora* leaves, they isolated and characterized the ketone **70** (5-{1-[(3-methyl-pentyl)oxy]propyl}tetrahydro-[3,3′-bifuran]-2,2′(3*H*,3′*H*)-dione) (Fig. 22).



70 (5-{1-[(3-methylpentyl)oxy]propyl}tetrahydro-[3,3'-bifuran]-2,2'(*3H*,*3'H*)-dione)

Fig. 22 Allelochemical found in *S. nodiflora* leaves

3.1.3 Brassicaceae

Bunias orientalis L.

Bunias orientalis (Brassicaceae) (Plate 20) is a perennial plant native to Armenia and widely naturalized in Europe. The aqueous extraction of *B. orientalis* leaves was performed by simulating leaf leaching with the aim of studying the allelopathic potential. Significant germination inhibition was observed when the crude aqueous extract was applied on three species (*L. sativa*, *H. vulgare*, and *M. inodora*) in petri-dish bioassays. *p*-Coumaric acid (**93**), ferulic acid (**44**), sinapic acid, and 3-hydroxy-5,6-epoxy-β-ionol were identified as the major allelochemicals in the leaf leachate solutions [155].

Plate 20 Brassicaceae. *Bunias orientalis* L. This file is licenced under Creative Commons Zero—CC0 license. (https://www.pxfuel.com/es/free-photo-xijbg)

3.1.4 Cistaceae

Cistus ladanifer L.

Cistus ladanifer (Cistaceae) (Plate 21), commonly known as the rock-rose or "jara" [156], is a shrub that produces large amounts of leachates from its leaves and stems. These leachates constitute around 15% of the dry weight of the leaf in some populations. This plant possesses allelopathic activity by inhibiting the germination and growth of competing herb seedlings, especially due to the presence of aglycone flavonoids (**71**–**75**) (Fig. 23) [157]. Moreover, it has also been reported that these allelochemicals have persistence in the soil [158]. They degrade very slowly and thus inhibit the germination and growth of other species. Sosa and co-workers [159] demonstrated that 3-*O*-methyl-kaempferol (**71**), 3,7-di-*O*-methyl-kaempferol (**72**), apigenin (**73**), 4′-*O*-methyl-apigenin (**74**), and 7-*O*-methyl-apigenin (**75**) are present in the soil for a long period of time. However, a marked seasonal variation in the production of these flavonoids has been found. The highest concentration was observed in summer, when the flavonol content was more prevalent than flavones [157].

Plate 21 Cistaceae. *Cistus ladanifer* L. Public domain image from Creative Commons. (https://commons.wikimedia.org/wiki/File:Cistus_ladanifer_-_University_of_California_Botanical_Garden_-_DSC08907.jpg)

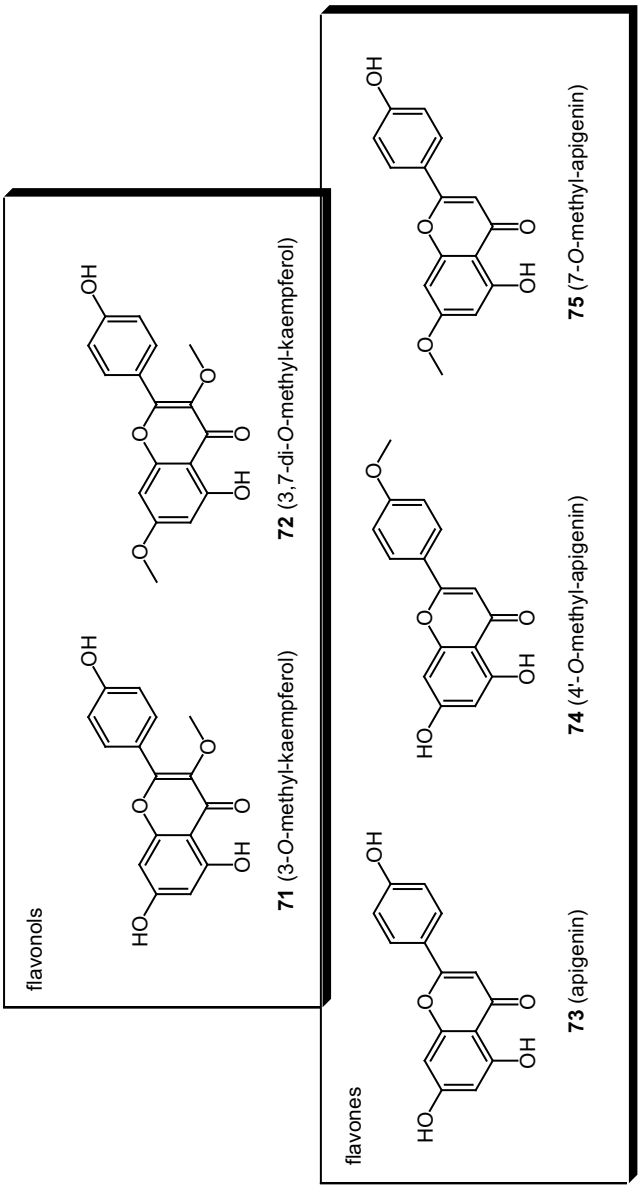


Fig. 23 Flavonoids found in leachates from *C. ladanifer*

Plate 22 Fabaceae. *Acacia auriculaeformis* A. Cunn. ex Benth. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license (https://commons.wikimedia.org/wiki/File:Flowers_%26_leaves_I_IMG_8639.jpg)

3.1.5 Fabaceae

Acacia auriculaeformis A. Cunn. ex Benth.

Acacia auriculaeformis (Plate 22) is a tree that is native to Papua New Guinea, Northern Australia, and Indonesia [160]. A study performed by Dash and co-workers showed that aqueous leachates of phyllodes from this species have a marked effect on the synthesis of chlorophyll pigments of test rice seedlings. This effect is probably due to the phenolic compounds present in the leachates, which are able to form reactive oxygen species and degrade different biomacromolecules [161].

3.1.6 Lamiaceae

Mentha pulegium L.

Mentha pulegium (Plate 23), also known as pennyroyal, is a perennial aromatic herb of the mint family [162]. It is characterized by the production of a high content of essential oils, with the major compound being the monoterpene ketone pulegone

Plate 23 Lamiaceae. *Mentha pulegium* L. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://en.wikipedia.org/wiki/Mentha_pulegium#/media/File:Gardenology.org-IMG_2751_rbgs11jan.jpg)

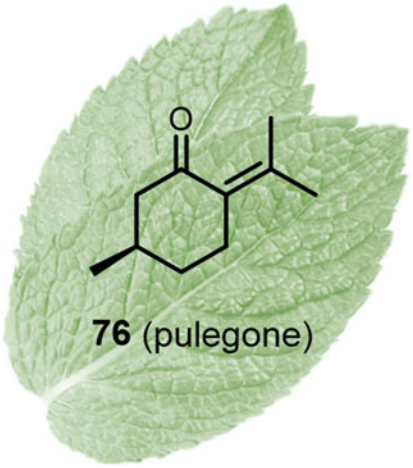


Fig. 24 Allelochemical released from the glandular tricomes of *M. pulegium*. Leaf image adapted from Creative Commons 4.0 BY-NC, http://www.pngall.com/?p=28962

(**76**) (Fig. 24). Pulegone and other essential oil constituents are present in glandular trichomes and leaf hairs. It was asserted that **76** is the main defense compound released into the environment from pennyroyal [163].

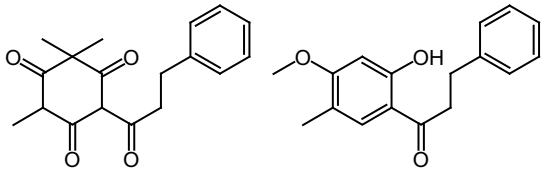
3.1.7 Myricaceae

Myrica gale L.

Myrica gale L. (Plate 24), also known as "sweet gale" or "bog myrtle", is a deciduous shrub that is widely distributed in Northern and Western Europe and on the American continent. Leaf and fruit leachates from *M. gale* have shown phytotoxic activity on seedling growth of several species. It is worth highlighting that the leaves and fruits are covered with droplets of secreted resin that contains a variety of different secondary metabolites [164]. A number of uncommon flavonoid compounds, which are quite rare in the plant kingdom, were from the leaves and fruit exudates (contained in droplets of resin) and these are *C*-methylated dihydrochalcones. Myrigalone A (2,2,4-trimethyl-6-(3-phenylpropanoyl)-cyclohexane-1,3,5-trione) (**77**) and myrigalone B (2′,6′-dihydroxy-4′-methoxy-3′,5′-dimethyldihydrochalcone) (**78**) are the two main phloroglucinols present [165, 166] (Fig. 25).

Besides these particular compounds, a variety of terpenes, sesquiterpenes, and other flavonoids were also identified in this resin. A photodegradation study of myrigalone A (**77**), as well as the influence of other terpenes detected in *M. gale*

Plate 24 Myricaceae. *Myrica gale* L. Copyright Phil Champion and licensed for reuse under creativecommons.org/licenses/by-sa/2.0. (https://www.geograph.org.uk/reuse.php?id=5639228)



77 (myrigalone A) **78** (myrigalone B)

Fig. 25 Two main flavonoids found in *M. gale*

leaf glands, such as germacrone and eucalyptol, was carried out by Khaled and co-workers. The results showed that the irradiation of **77** led to a variety of volatile and non-volatile products and two types of reactions had taken place: oxidation as for the natural β-triketones and a Norrish cleavage. Photoproducts found under laboratory conditions were also detected in natural samples, thus showing that this process can take place in the field. Furthermore, in the presence of germacrone and eucalyptol, the photodegradation of myrigalone A (**77**) ($t_{1/2}$ = 38 and 60 min, respectively] was slower than for **77** itself ($t_{1/2}$ = 25 min). This finding suggests that these terpenes play a significant role in the lifetime of **77** [167].

Oracz and co-workers described a novel mode of action on seed germination after treatment with myrigalone A (**77**). This compound caused a delay in endosperm rupture of *L. sativum* seeds that was two-fold higher than the control in greening of seedlings, inhibition of ROS-mediated cell extension and atypical endosperm rupture. The authors proposed that **77** could interfere with processes regulated by gibberellin and ethylene metabolism, and also decrease apoplastic superoxide radical content. The production of these radicals mediates embryo cell extension required to complete seed germination and seedling establishment. None of the terpenes tested caused these effects and this suggests that the targets should be different [168, 169].

3.1.8 Pinaceae

Pinus ponderosa Dougl.

Many gymnospermous trees are reported to exhibit allelopathy, among them *Pinus ponderosa* [170] (Plate 25). The first reports on allelopathy of *Pinus* spp. date back to around 300 years ago, where in ancient Japanese documents, Banzan Kumazawa mentioned that the rain water or dew that washes off the leaves of red-pine (*Pinus densiflora* Sieb. et Zucc.) are harmful to crops that grow beneath [171]. It has been demonstrated that decaying needles, needle leachate, and field soils significantly reduced germination and radicle growth of pine-associated herbaceous species. Some of the allelochemicals described are stilbenes, tannins, caffeic acid, chlorogenic acid, and quercetin, which were extracted from the bark and bark extracts [172] and also identified in various plant parts and associated soils [173]. It has also been reported that the most drastic radicle growth inhibition was found with extracts that contained tannins. Lodhi and Killingbeck found that *P. ponderosa* needles and associated soils contained large amounts of these allelochemicals [174].

Plate 25 Pinaceae. *Pinus ponderosa* Dougl. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://commons.wikimedia.org/wiki/File:Pinus_ponderosa_17040.JPG?uselang=fr)

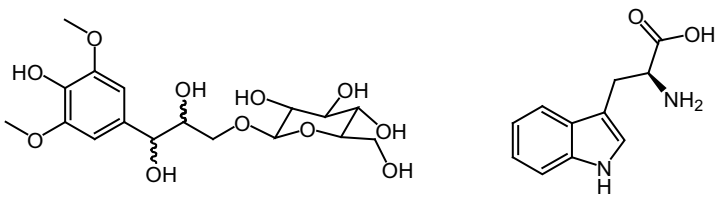
3.1.9 Poaceae

Triticum aestivum L.

As mentioned in Section 2.1.7, wheat is one of the major staple food crops (Plate 26). Previous studies have demonstrated the allelopathic potential of the aqueous leachate of wheat straw on weed species [175]. Nevertheless, knowledge about the phytochemicals leached from wheat straw is limited. Recently, two major allelochemicals were isolated from the leachate of wheat straw, namely, syringoylglycerol 9-*O*-*β*-D-glucopyranoside (**79**) and L-tryptophan (**80**) (Fig. 26) [176].

Moreover, the latter allelochemical has also been found in large amounts in leaves and seeds from this species [40]. These phytotoxic effects are generally less damaging in Gramineae and Leguminosae species. It has been reported that some plants are able to detoxify L-DOPA (**16**) to form dopamine (**17**) or 3-*O*-methyldopa through the action of L-DOPA-decarboxylase and catechol-*O*-methyltransferase, respectively [41].

Plate 26 Poaceae. *Triticum aestivum* L. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://www.flickr.com/photos/dag_endresen/4190570128)



79 (syringoylglycerol 9-*O*-ß-D-glucopyranoside) **80** (L-tryptophan)

Fig. 26 Allelochemicals isolated from the leachate of wheat

3.1.10 Verbenaceae

Gmelina arborea Roxb.

Gmelina arborea (Plate 27), also called white beech, is a deciduous tree that is native to India and Southeast Asia and it is considered as a potentially invasive woody species in West Africa [177, 178]. This tree has shown deleterious allelopathic effects on germination and seedling growth of several species growing in its vicinity [179, 180]. Phytochemical analysis of leaf leachates from white beech indicated the presence of phenols and alkaloids. The compounds 3,4,5-trihydroxybenzoic acid, 3-(4-hydroxyphenyl)-prop-2-enoic acid, and 4-hydroxy-3-methoxybenzoic acid have been identified. Moreover, phytotoxic

Plate 27 Verbenaceae. *Gmelina arborea* Roxb. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://www.flickr.com/photos/dinesh_valke/2366330381)

studies of leaf leachate showed a significant inhibition of the germination of chickpea. Total chlorophyll and relative water contents were reduced in all treated seeds [181].

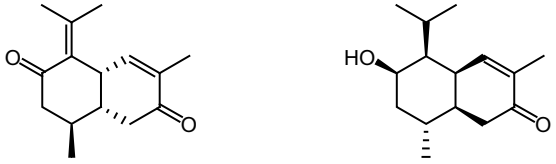
3.2 Plant–Microbe Interaction

3.2.1 Asteraceae

Eupatorium adenophorum Spreng.

Eupatorium adenophorum (Croftonweed) (Plate 28) is an invasive weed in China and provides one of the most dramatic examples of the replacement of native vegetation by exotic plant species. This species has long been suspected of having allelopathic effects on resident native plants in its invaded range. For instance, aqueous leachates, particularly from *E. adenophorum* leaves, significantly inhibit the germination and seedling growth of other plant species, including *Brassica rapa* and *Mariscus cyperinus.* Several organic compounds have been identified in *E. adenophorum*, but 9-oxo-10,11-dehydroageraphorone (= 4,7-dimethyl-1-(propan-2-ylidene)-1,4,4a,8a-tetrahydronaphthalene-2,6(1*H*,7*H*)-dione) (**81**) and 9β-hydroxyageraphorone (= 6-hydroxy-5-isopropyl-3,8-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1*H*)-one) (**82**) have been identified as the primary

Plate 28 Asteraceae. *Eupatorium adenophorum* Spreng. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://commons.wikimedia.org/wiki/File:Ageratina_adenophora_1.jpg?uselang=es)



81 (9-oxo-10,11-dehydroageraphorone) **82** (9ß-hydroxyageraphorone)

Fig. 27 Primary phytotoxins identified in *E. adenophorum*

phytotoxins (Fig. 27). In an experiment on the influence of *E. adenophorum* on native *Brassica rapa* growth in both sand and native soil, Zhu and co-workers demonstrated that natural soils from different invaded habitats alleviated or eliminated the efficacy of potential allelochemicals relative to sand cultures. When the soil was sterilized however, the allelopathic effects returned, thus suggesting that soil biota were responsible for the reduced phytotoxicity in natural soils. The allelopathic compounds **81** and **82** could not be found in natural soils infested by the invader, and they showed substantial degradation after 24 h in natural soils but not in sand. These results confirm the key role played by soil biota in reducing the allelopathic effects of invaders on other plants [182].

3.2.2 Myricaceae

Myrica gale L.

As described in Section "*Myrica gale* L.", *M. gale* is a shrub that is very common on moist ground with a wide distribution over Northern and Western Europe, as well as on the American continent. Several unusual flavonoids (Fig. 25) from the stems, leaves, and fruits have been identified (*C*-methylated dihydrochalcones) in this species [183]. This plant grows in symbiotic association with an endophytic nitrogen-fixing fungus of the genus *Frankia* [183] and it has been reported that these characteristic compounds could act as chemical signals during biotic interactions. These molecules have induced modifications of bacterial growth and nitrogen fixation according to specific symbioses, therefore enhancing compatible *Frankia* strains and inhibiting incompatible ones. However, a significant difference in dose concentration was found on using either the single compounds (dihydrochalcones, not active below 1000 μg/dm^3) or the total methanol fruit extract (remains active at 1 μg/dm^3). This fact could indicate a synergistic effect of the different compounds in their involvement in the *Frankia-M. gale* symbiosis [184].

4 Volatilization

Volatilization releases allelochemicals into the atmosphere and this process is only significant under arid or semi-arid conditions. Compounds may be absorbed in a vapor by surrounding plants, or be absorbed from condensate in dew, or may reach the soil and be taken up by the roots [4]. The major components in essential oils include monoterpenoids and sesquiterpenoids. The most significant examples of the allelochemicals released by this mechanism are described below.

4.1 Plant–Plant Interaction

4.1.1 Asteraceae

Artemisia vulgaris L.

Mugwort (*Artemisia vulgaris* L.) (Plate 29) is a rhizomatous perennial weed that commonly infests roadsides, waste areas, and landscapes. Barney and Weston [185] determined that mugwort leaf tissues produce biologically active volatiles. When suspended above small quantities of soil in an enclosed environment, released volatiles quickly adsorbed onto the soil surface and caused subsequent growth inhibition of seedlings [186]. In addition, the volatiles produced by their leaves

Plate 29 Asteraceae. *Artemisia vulgaris* L. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://es.m.wikipedia.org/wiki/Archivo:ArtemisiaVulgaris.jpg)

inhibited the radicle elongation of curly cress. This inhibitory effect was higher with younger plants. Eight monoterpenes were identified as constituents of the volatile atmosphere of mugwort, including santolina triene (**83**), α-pinene (**84**), camphene (**85**), β-pinene (**86**), β-myrcene (**87**), limonene (**88**), eucalyptol (**89**) (1,8-cineole), and camphor (**90**) (Fig. 28). Camphor was the only monoterpene that slightly reduced the root and shoot growth of various indicator species [185].

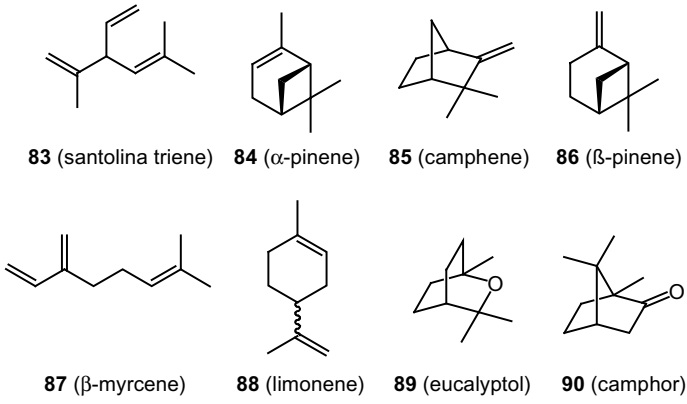


Fig. 28 Terpene structures identified as volatiles of plants

Plate 30 Cupressaceae. *Juniperus ashei* L. Photograph Ddal (https://upload.wikimedia/commons/0/o4/Juniperushasei1224.jpg)

4.1.2 Cupressaceae

Juniperus ashei Buchh.

Juniperus ashei (Ashe juniper) (Plate 30) is native to the limestone slopes of central Texas, USA. Co-occurring over much of *J. ashei*'s range is the native grass *Bouteloua curtipendula.* Grass and forb production and species diversity are greatly reduced under the canopy of *J. ashei* [187]. A study has identified camphor (**90**) at 68.5%, bornyl acetate at 12.2%, and limonene (**88**) at 5.8% in the essential oil of *J. ashei* acquired by steam distillation [188].

4.1.3 Lamiaceae

Salvia leucophylla Greene

The presence of volatile allelochemicals was first established in the early 1960s in aromatic shrubs in the semi-arid chaparral regions of California [189, 190]. The major inhibitory components of the California chaparral shrubs are terpenes. Several monoterpenes inhibit seedling root and shoot growth [191], with specific cytotoxic effects that include the reduction of intracellular mitochondrial and Golgi body populations, inhibition of respiration and photosynthesis, a decrease in cell

Plate 31 Lamiaceae. *Salvia leucophylla* Greene. This file is licensed under the Creative Commons Attribution-Share Alike 2.5 Generic license. (https://commons.wikimedia.org/wiki/File:Salvia_leucophylla.jpg)

wall permeability, as well as acceleration of the oxidative destruction of chloroplast pigments [192].

One of the most highly studied examples of allelopathy is the "*Salvia* phenomenon" [189]. *Salvia leucophylla* (Plate 31), a shrub from the coastal area of south California, forms soft chaparral vegetation adjacent to areas of annual grassland. This species shows a characteristic vegetation patterning: annual grasses and forbs are excluded from the interior of the shrub thickets, and the thickets are frequently surrounded by areas of bare soil without grasses that extend 1–2 m beyond the crowns of the shrubs. Around the shrub is dense, but stunted, herbage and this inhibited vegetation gradually merges with normal grassland 6–10 m beyond the shrubs. After several studies it was found that this shrub produces several volatile monoterpenoids (camphor (**90**), 1,8-cineole (**89**) β-pinene (**86**), α-pinene (**84**) and camphene (**85**)) (Fig. 28) and two of them (camphor and 1,8-cineole) were detected in the air around *Salvia* thickets and act potentially as allelochemicals [190]. The effects of these monoterpenoids were examined by Nishida et al. [193] using *Brassica campestris* as the test plant. Camphor, 1,8-cineole, and β-pinene inhibited germination of *B. campestris* seeds at high concentrations, whereas α-pinene and camphene did not. Root growth was inhibited by all five monoterpenoids in a dose-dependent manner, but hypocotyl growth was largely unaffected. The monoterpenoids inhibited both cell-nuclear and organelle DNA synthesis in the root apical meristem. These results suggest that the monoterpenoids produced by *S. leucophylla* could interfere with the growth of other plants in its vicinity through inhibition of cell proliferation in the root apical meristem [193].

These volatile compounds have also been detected in the soil around *Salvia* shrubs, with this soil becoming toxic. Such results indicate that *S. leucophylla* produces and releases monoterpenoids, which are adsorbed in the soil in its vicinity and inhibit the growth of other plants, thus resulting in the characteristic vegetation patterning.

Salvia syriaca L.

Syrian sage (*Salvia syriaca*) is a perennial rhizomatous and root creeping weed belonging to the Lamiaceae family. This plant is widespread in cultivated fields in Jordan and invades field crops as well as orchards, inhibiting growth patterns of crop species in the vicinity of this weed in nature. Together with its deep, penetrating, and extensive roots, its allelopathic activity against crops makes it difficult to eradicate. Qasem demonstrated that volatiles from Syrian sage inhibited the growth of cabbage, cucumber, squash, onion, tomato, and carrot [194]. This phytotoxic activity of volatiles was also observed in other common weed species in Jordan, for instance, *Amaranthus gracilis* inhibited seed germination of carrot, shoot growth of cabbage and tomato, and root growth of carrot and pepper. *Convolvulus arvensis* inhibited germination of pepper and tomato, shoot dry weights of carrot and cucumber, and root dry weights of cabbage, carrot, onion, pepper, and squash. Furthermore, *Lactuca serriola* inhibited the germination of carrot, shoot dry weights of cabbage, carrot, and pepper, and root dry weights of carrot, pepper, and squash [133, 195].

5 Decomposition

Allelochemicals can accumulate in the soil by decomposition of plant residues (leaves, fruits, twigs, or sloughed roots) and these could have some persistence in the soil. They can also be formed by the action of microbes, which can cause soil sickness or problems related to autotoxicity. The accumulation of allelochemicals in soil can lead to a reduction in seed and plant performance, along with chlorosis, poor nutrient uptake, and productivity decline.

5.1 Plant–Plant Interaction

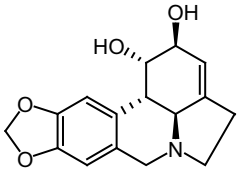
5.1.1 Amaryllidaceae

Lycoris radiata Herb.

Lycoris radiata (Japanese name: Higan-bana) (Plate 32) is an herbaceous perennial and sterile triploid that grows in moist places in Japan, Korea, China, and Nepal. Japanese ancestors used its bulbs, which contain 30% starch, as a food before rice became their main staple. It is a traditional ground cover plant in the levee of paddy fields and it protects the levee from soil erosion and suppresses weeds. This phytotoxic activity has been explained by the presence of lycorine (**91**) (Fig. 29), which is a very active phytotoxic compound even at 10^{-6} mol/dm^3, inhibiting cell division in plants. This high activity of **91** explains the success of *Lycoris radiata* as a cover

Plate 32 Amaryllidaceae. *Lycoris radiata* Herb. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://en.wikipedia.org/wiki/Lycoris_radiata#/media/File:Lycoris_radiata_Higanbana_in_a_woods.jpg)

Fig. 29 Chemical structure of lycorine



91 (lycorine)

crop plant and, in addition, the fact that dead leaves can be used as cover mulch to control weeds [196].

5.1.2 Araliaceae

Panax notoginseng (Burk.) F.H. Chen

Sanqi ginseng (*Panax notoginseng*) is a valuable perennial herb of the Araliaceae family that has been used in China for hundreds of years for its medicinal properties. Its bioactive constituents have multiple pharmacological effects, such as anticancer, antiatherosclerotic, and antihypertensive properties [197, 198]. The bioactive compounds are produced by the plant in larger amounts when the plant is grown under specific conditions. These conditions are particularly good in a limited area in the Wenshan County of Yunnan Province, which is the best region for the production of Sanqi ginseng [199]. Therefore, driven by limited land resources and increasing demand, the large-scale artificial cultivation of Sanqi ginseng, coupled with the use of consecutive monoculture systems, has led to serious replant problems that have threatened the Sanqi ginseng industry severely. Several studies have demonstrated that autotoxicity is the key factor that causes replant failure [200, 201]. For instance, ginsenosides (steroid glycosides and triterpene saponins, mostly of the dammarane family), the primary allelochemicals of Sanqi ginseng, not only exhibit allelopathic inhibitory effects on seedling germination and growth, but also act as allelopathic stimulators for the growth of soil-borne pathogens, such as *Phytophthora cactorum*, *Pythium irregulare*, and *Cylindrocarpon destructans* [201]. Moreover, other studies have shown that ginsenoside levels could be enhanced by some root-rot pathogens [202]. All of these factors explain the difficulties observed in the replanted Sanqi ginseng crops. To alleviate this autotoxicity, the use of maize as an alternating crop planting has been studied and this was found to improve the soil microbial activity, decrease the proportion of *F. oxysporum* in the fungal communities in Sanqi ginseng cultivated soils and stimulate the ginsenoside-degrading microbes [203, 204]. The use of reductive soil disinfestation has also proven to alleviate the replant failure of Sanqi ginseng seedlings by rebalancing the soil microbiome and ginsenoside degradation. These two techniques were studied together by Li and co-workers, who demonstrated that they reinforced the degradation capacity of allelochemicals, thereby ultimately resulting in the highest survival rate of replanted Sanqi ginseng seedlings. Therefore, reductive soil disinfestation treatment coupled with short-term maize planting is conducive to eliminating many of the factors that hinder Sanqi ginseng cultivation, and this could act as a potential agricultural regimen to overcome the replant failure of Sanqi ginseng [204].

5.1.3 Asteraceae

Centaurea maculosa Loscos & J. Pardo

Centaurea maculosa (Plate 33), spotted knapweed, is a noxious and economically destructive invasive weed for which its invasiveness has been attributed to the root exudation of racemic (±)-catechin (**91**) (Fig. 30). However, Tharayil and co-workers identified, after seven days into litter decomposition, three benzoic acid derivatives (protocatechuic acid (**92**), 4-hydroxybenzoic acid (**7**), and vanillic acid (**46**)) and two cinnamic acid derivatives (*p*-coumaric (**93**) and ferulic acid (**44**)) (Fig. 30) in the decomposition of plant litter, while **91** was undetectable. Although litter decomposition progressed with incubation time, the phenolic acid recovery showed an inverse trend, with a decrease in the number of phenolic compounds from 7 to 14 days, after which only protocatechuic acid and *p*-hydroxybenzoic acid were detectable. After 24 days, 4-hydroxybenzoic acid (**7**) was the only phenolic acid present in soil. Regarding catechin (**91**), it was also demonstrated that polymerization to procyanidins reduces the persistence and toxicity of **91** and hence catechin bioactivity may occur under conditions that delay these condensation reactions. On the basis of their study, Tharayil and co-workers suggested that the phytotoxicity of *C. maculosa*, if any, could be brought about by a complex interaction of its different allelochemicals [205].

Plate 33 Asteraceae. *Centaurea maculosa* Loscos & J. Pardo. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://commons.wikimedia.org/wiki/File:Centaurea_maculosa_Bozeman.jpg?uselang=es)

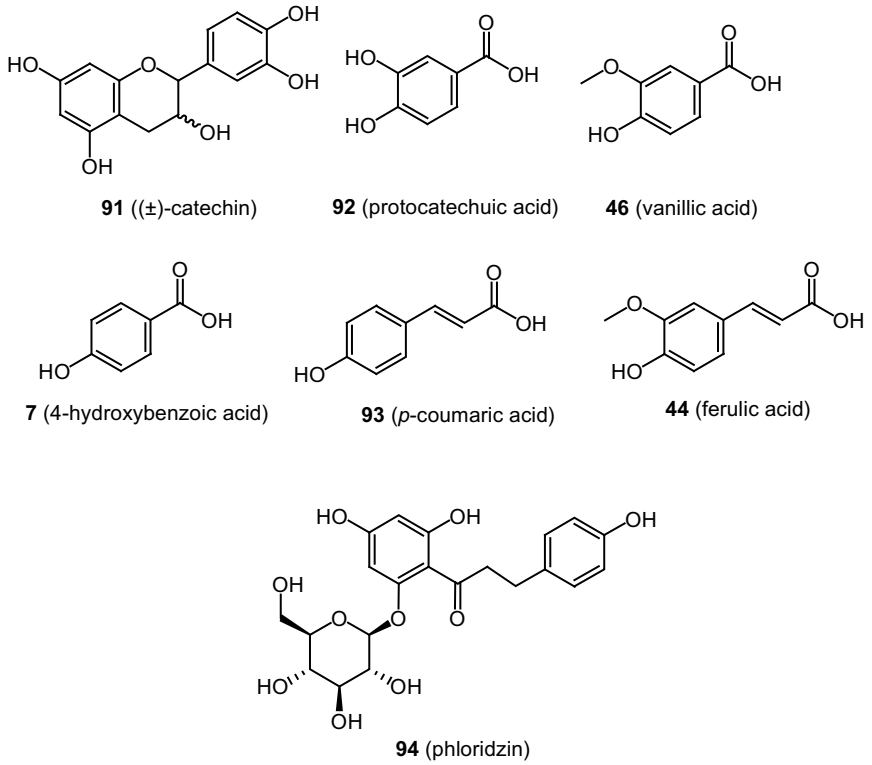


Fig. 30 Chemical structures of compounds identified in *Centaurea maculosa* and *Chrysanthemoides monilifera*

Chrysanthemoides monilifera (L.) Norlindh

Boneseed (*Chrysanthemoides monilifera* subsp. *monilifera*) was introduced to Australia in the mid-nineteenth century and was proclaimed a noxious weed in Victoria in 1969. This weed threatens around 200 indigenous species in Australia, including significant rare species such as *Pterostylis truncata*. It is now a Weed of National Significance (WoNS) in Australia and listed on the National Pest Plant Accord in New Zealand. In bioassays *Isotoma axillaris* and *Xerochrysum bracteatum*, which grow in the same environment, have been inhibited by boneseed [206]. As previously mentioned, phenolic compounds have been identified as the allelochemicals responsible for its phytotoxicity, with boneseed litter having the highest content of phenolic compounds. The relative phenolic concentration in boneseed was ranked as ferulic acid (**44**) > phloridzin (**94**) > catechin (**91**) > *p*-coumaric acid (**93**) (Fig. 30). However, mixtures of these compounds in the soil were more active than the isolated compounds and their presence was significantly reduced to non-toxic levels in the decomposed leachate. Therefore, the phytotoxic effect of decomposed litter-mediated soil leachate was probably due to other

chemical compounds with allelopathic potential and further studies are needed to identify the phytotoxic allelochemicals in boneseed, particularly under field conditions [134].

5.1.4 Cupressaceae

Cunninghamia lanceolata (Lamb.) Hook.

Chinese fir, *Cunninghamia lanceolata* (Plate 34), is a native species that has been widely grown in the subtropical areas in China. This tree covers around a quarter of the plantation area and has become an important economic commodity for industrial wood production. However, productivity decline in replanted Chinese fir plantations due to autotoxicity has remained a serious problem, as mentioned previously. The biomass of Chinese fir stump-roots left in the cutting area makes up 10–25% of tree biomass, and the content of allelopathic compounds in roots was thought to be the highest among all parts of the tree. Stump-roots are the most important residue left in the replant area, because in traditional forestry operations in the south of China, most of the other residues are burned before replanting. A previous survey in one Chinese fir continuous planting area showed that the survival of replanted Chinese fir saplings close to stump-roots was less than that further away [207]. In this case, the concentration of the cyclic dipeptide 6-hydroxy-1,3-dimethyl-8-nonadecyl-[1,4]-diazocane-2,5-dione (**31**) (Fig. 15) in the soil increased with successive rotations. Although the release of this cyclic dipeptide through root exudation was the predominant liberation mechanism of this

Plate 34 Cupressaceae. *Cunninghamia lanceolata* (Lamb.) Hook. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://www.flickr.com/photos/harumkoh/17331495235)

compound, decomposing litter also released this phytotoxic compound into the soil [91]. The presence of phenolic compounds has also been identified in Chinese fir stump-roots and some researchers have attributed the observed phytotoxic activity to these compounds [207].

5.1.5 Euphorbiaceae

Macaranga tanarius (L.) Muell.-Arg.

Macaranga tanarius (Plate 35) is an endemic species commonly distributed in abandoned areas throughout Taiwan. It is an evergreen species but leaf-fall may take place at any time of year and results in large quantities of fallen leaves underneath tree stands. *M. tanarius* is an early succession tree and often spreads into adjacent grasslands, thus resulting in a secondary forest with few other species growing in the understory. Tseng and co-workers carried out a bioassay on lettuce, *Bidens pilosa* and *Leucaena leucocephala*, grown in a soil mixed with powdered leaves of *M. tanarius*. It was found that the phytotoxins produced during the decomposition of the leaves inhibited the growth of the seedlings. The compounds nymphaeol-A (**95**), nymphaeol-B (**96**), nymphaeol-C (**97**), quercetin (**98**), abscisic acid (**99**), blumenol A (**100**), blumenol B (**101**), roseoside II (**102**), and tanariflavanones A (**103**) and B (**104**) (Fig. 31) were identified from leaves, with abscisic acid (**99**) being the most phytotoxic. These results explain how fallen leaves

Plate 35 Euphorbiaceae. *Macaranga tanarius*. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license. (https://www.flickr.com/photos/tgerus/4559853159)

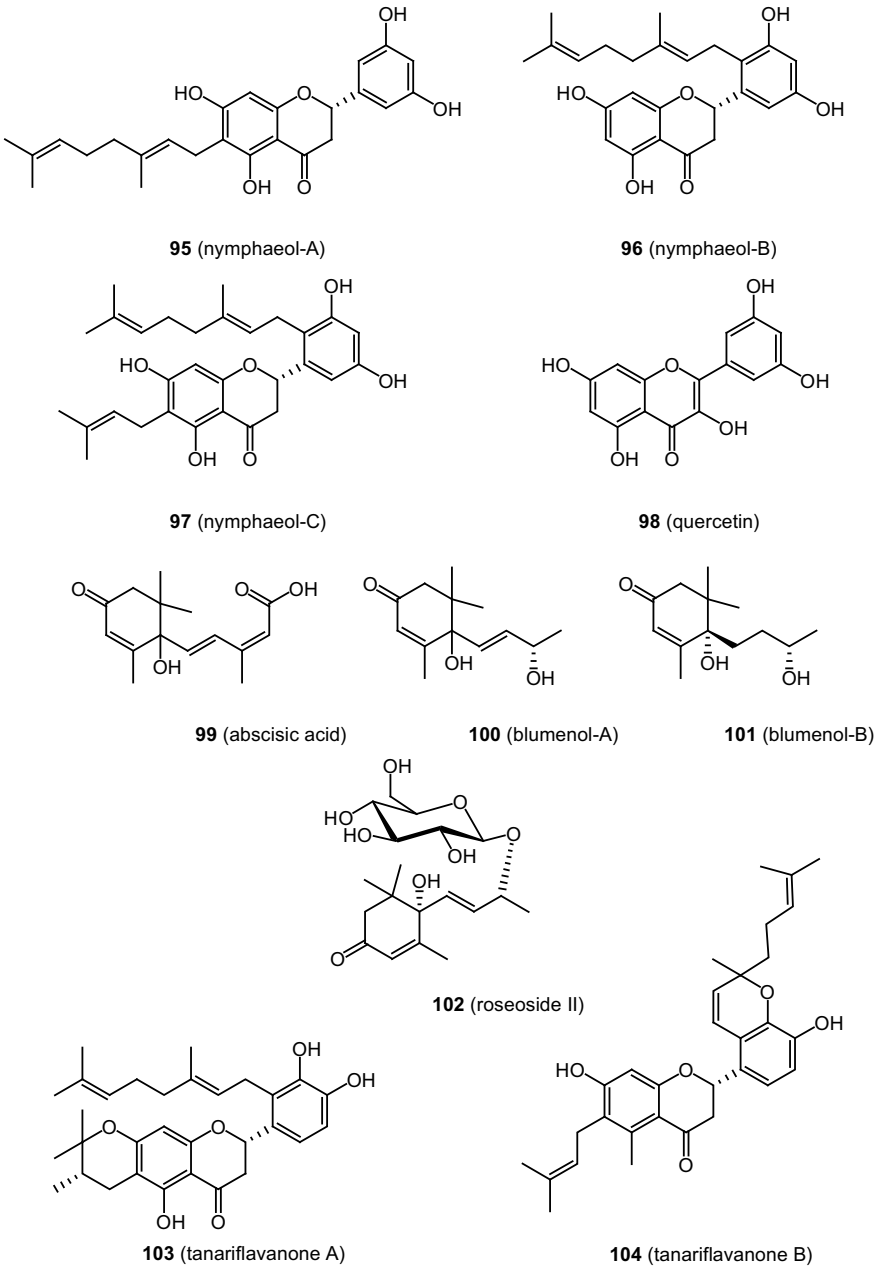


Fig. 31 Chemical structures of the compounds identified in *Macaranga tanarius* leaves

accumulate on the ground over time and can inhibit the growth of the nearby weeds, thus allowing the plant to compete for more resources [208].

5.1.6 Fabaceae

Arachis hypogaea L.

Peanuts (*Arachis hypogaea*) (Plate 36) are an important source of oil and an economic crop worldwide and they are often continuously grown as a monocrop in the same field for many years, which leads to a significant decline in crop yield and quality as well as increased disease [209]. In order to provide carbon and nitrogen sources to the soil, peanut residues are always buried after harvest and this causes autotoxicity. This autotoxicity has been generally attributed to the presence of phenolic acids, but many other synthesized phytoalexins may contribute to allelopathy in the peanut mono-cropping system [210]. For example, peanut plants are well known to produce stilbene phytoalexins, such as resveratrol ((*E*)-3,5,4′-trihydroxystilbene), as a defensive response to fungal invasion [211]. In an effort to confirm the contribution of resveratrol to the autotoxicity of peanut crops, Wang and co-workers quantified the resveratrol released from peanut residues and observed a maximum concentration of 0.18 μg/g in soil. They also confirmed that resveratrol inhibited peanut growth, nodule formation, and soil dehydrogenase activity, as well as reducing the soil microbial biomass carbon content and bacterial abundance, thus indicating an allelopathic role in peanut growth [212].

Plate 36 Fabaceae. *Arachis hypogaea* L. This file is licensed under the Creative Commons Attribution-Share Alike 2.0 Generic license (https://www.flickr.com/photos/dinesh_valke/3870805747)

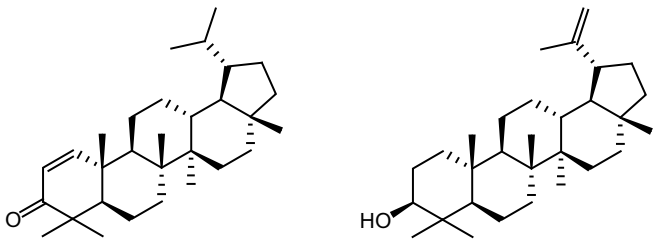
Medicago sativa L.

Bladygrass (*Imperata cylindrica* L. Beauv.) is an upright rhizomatous grass widespread throughout the tropics and subtropics and is considered one of the world's worst weeds. Alfalfa (*Medicago sativa*) has shown that it is able to halt bladygrass seedling emergence for periods ranging between two and four years. This activity could be due mainly to physical competition (light and nutrients). However, alfalfa has been reported to contain water-soluble compounds that are toxic to plants and they reduce shoot and root growth of several plants. Abdul-Rahman and Habib corroborated that alfalfa soil residues and alfalfa roots reduced germination and seedling growth of bladygrass, with this inhibition being higher when the period of decomposition was longer. Several phenolic acids have been identified in alfalfa root residues and could be responsible for the bioactivity observed [213].

5.1.7 Juglandaceae

Juglans nigra L.

Black walnut (*Juglans nigra* L.) (Plate 6) is very suitable for use in intercropping systems and has attracted significant attention for that purpose, although its toxicity and allelopathic effects are also known. The majority of the research on walnut allelopathy has focused on juglone, but the contribution of this compound to the phytotoxicity of walnut leaf litter is negligible. In an experiment on lettuce plants, walnut leaf litter induced allelopathic stress on this crop. The triterpenoids lupenone (**105**) and lupeol (**106**) (Fig. 32) and phenolic acids have been identified in walnut leaf litter and may be responsible for these effects. These results confirm that excessive leaf litter should be removed from walnut agroforestry systems to reduce economic losses [214].



105 (lupenone) **106** (lupeol)

Fig. 32 Chemical structures of the compounds identified in walnut leaf litter

5.1.8 Lauraceae

Cinnamomum septentrionale Hand.-Mazz.

Cinnamomum septentrionale (Plate 37) is a member of the Lauraceae family, an evergreen broadleaf tree species that primarily grows in areas such as the Sichuan basin, south Shanxi province, south Gansu province, and Hunan province, among other areas in China. Given its exuberant branches and leaves, beautiful tree appearance, and sweet fragrance, *C. septentrionale* has been used widely as a rural four-sided gardening tree and landscape tree in China [215]. Numerous studies have shown that plants of this genus possess large amounts of volatile allelopathic chemicals in essential oils. Most of the chemical components of the essential oils are terpenoids, including monoterpenes, sesquiterpenes, and their oxygenated derivatives [216]. The essential oils have shown notable toxicity on wheat seed germination [217] and they induce electrolyte leakage, which results in the death of *Taraxacum officinale* [218].

In a pot experiment, Huang and co-workers evaluated the phytotoxic activity of *C. septentrionale* leaf litter on the growth of *Eucalyptus grandis*, which is the most widely cultivated species for industrial purposes due to its fast growth, high yield, quality, and good adaptability. The results showed that *C. septentrionale* leaf litter significantly inhibited the growth of *E. grandis* saplings (height, basal diameter,

Plate 37 Laureaceae. *Cinnamomum septentrionale* Hand.-Mazz. This file is made available under the Creative Commons CC0 1.0 Universal Public Domain Dedication (https://upload.wikimedia.org/wikipedia/commons/2/22/Cinnamomum_septentrionale_Chengdu_Botanical_Garden_Chengdu%2C_China_DSC03499.jpg)

biomass). After five months, the height growth rate of *E. grandis* saplings increased, thereby improving the ability of these trees to resist an adverse environment. However, due to the severe harm produced during the initial litter decomposition, the stem, leaf, branch, and root biomass remained poor. Altogether, 31 volatile compounds were identified in *C. septentrionale* leaf litter as being responsible for this effect during the initial growth stages. This number was reduced to 14 after eleven months of decomposition in the soil. Therefore, most allelochemicals of *C. septentrionale* might be released during the initial decomposition process and these inhibit plant growth, but some nutrients might be released later and promote the height growth of plants [215].

5.1.9 Poaceae

Phragmites australis (Car.) Trin. ex Streud.

Phragmites australis is an invasive plant that dominates a wide variety of wetland ecosystems in temperate regions throughout the world. It grows in aquatic, semi-aquatic, and even moist terrestrial environments, as described previously [219]. *Phragmites australis* is a noxious weed in North America, European countries, and most parts of Canada. The ecological impacts of *P. australis* invasions are many, the most notable being habitat and subsequent biodiversity loss and native species extinction. For example, in some long-term invaded wetlands in Australia, there are no other plant species recorded within the stands of *Phragmites* when compared with newly invaded sites, which are floristically more diverse [220]. This plant uses different invasion mechanisms, including resource competition, allelochemical phytotoxicity, and alteration of ecosystem processes [221]. The large volumes of biomass produced by *P. australis* (it is one of the largest biomass producers in aquatic ecosystems), its worldwide distribution and the large areas covered, lead to the accumulation of large amounts of phytotoxins released by decomposition [222].

Uddin and co-workers demonstrated that an aqueous extract of *P. australis* inhibited germination, growth, and some biochemical parameters of various test and associated plant species [70]. Different studies pointed to phenolic compounds as being responsible for the phytotoxic activity. Uddin and co-workers also demonstrated that the decomposition of *P. australis* residue did not diminish phytotoxicity completely in the short term and this also aligned with other studies, in which it was demonstrated that phenolics obtained by decomposition may persist for months or longer in the soil environment [220].

Sorghum bicolor L.

Sorghum (*Sorghum bicolor*, Plate 38) possesses phytotoxic properties and suppresses many weed species due to the action of cyanogenic glycosides and

Plate 38 Poaceae. *Sorghum bicolor* L. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://upload.wikimedia.org/wikipedia/commons/8/84/Sorghum_bicolor03.jpg)

numerous phenolic compounds. By-products of these glycosides contribute to short-term plant growth suppression in field and greenhouse experiments. The residues of sorghum-sudangrass hybrid cover crops also provide short-term weed suppression due to the action of phenolic compounds released from the decomposing sorghum shoot residues [223].

Triticum aestivum L.

Wheat straw has been used for many years to manage pests, weeds, and diseases. Phytotoxic compounds are released from the straw during decomposition, or are produced by the microorganisms that utilize the straw as a carbon and nutrient source to help to control the weeds. For example, Khaliq and co-workers found that wheat straw-amended and infested-rhizosphere soil had allelopathic effects on *T. portulacastrum* and significantly reduced its germination, seedling growth, and biochemical attributes [224]. Wang and Cui described how weeds such as *Leptochloa chinensis* L., *Echinochloa crus-galli,* or *Commelina diffusa* were significantly decreased upon increasing the levels of wheat straw mulch [225]. Moreover, it has been reported that wheat straw inflicted a 16.8% reduction of broad-leaved weeds but was less effective against grassy weeds. Both above- and below-ground wheat residues were allelopathic against broad-leaved weeds, such as redroot pigweed, prickly sida, and ivy-leaf morning glory. This activity has been attributed to the presence of phytotoxins, such as phenolic acids and triterpenoids, in wheat straw residues [3].

Zea mays L.

Winter wheat-summer maize rotation is the main cropping system used in northern China to maintain the cultivated soil and water, regulate the soil temperature and moisture, and improve the organic matter content and productivity. This technique also helps to reduce the environmental pollution caused by burning maize (*Zea mais* L.) straw [226, 227]. However, the soil-borne diseases of wheat have increased in prevalence in recent years due to the use of this technique [228].

In culture dish and pot experiments, Qi and co-workers observed that the occurrence of soil-borne diseases were reduced by decomposed maize straw products after irrigation and were increased by decomposed products. The incidence rates and disease indices recorded were significantly promoted after irrigation with the decomposed products, while the occurrences of common rot did not change significantly. The compounds in the decomposed products mainly consisted of organic acids, esters, hydrocarbons, amides, and aldehydes [228].

5.1.10 Rosaceae

Malus domestica Borkh.

Replant disease has been reported in apple orchards (Plate 39) upon replanting. In this orchard type, phenolic compounds have been detected at high levels. These

Plate 39 Rosaceae. *Malus domestica* Borkh. This file is licensed under the Creative Commons Attribution-Share Alike 4.0 International license. (https://upload.wikimedia.org/wikipedia/commons/f/ff/Malus_domestica_Fuji_Apple_Hirosaki_Aomori_Japan_20161016a.jpg)

phenolic compounds showed an inhibitory effect on young apple (*Malus domestica* Borkh.) trees. This hypothesis was supported by the fact that at negative temperatures, the unfavorable allelochemical effect may last for a longer period of time because the degradation processes are slower [229].

5.1.11 Rutaceae

Stauranthus perforates Liebm.

Stauranthus perforatus, along with other species of the Rutaceae family, are known as "tankasche" in Mexico. This tree grows up to 30 m high and is restricted to the coast of the Gulf of Mexico and the Yucatan Peninsula from sea level to 700 m altitude. It is found in the medium or high canopy of semi-evergreen tropical forests. The leaves and roots of this species are used by local people to treat gastrointestinal diseases, headaches, epilepsy, and common colds, and it is also a diuretic agent. With the aim of identifying some natural techniques to control weeds using allelopathic plants as green manures, the effect of the decomposition of the leaves and roots of *S. perforatus* was tested on the emergence of weeds in soil in pots in a greenhouse experiment. Leaves of *S. perforatus* showed the highest phytotoxic activity six weeks after the treatment [230]. A total of ten known compounds (Fig. 33), which included two pyranocoumarins (xanthyletin (**107**) and 3-(1′,1′-dimethylallyl)-xanthyletin (**108**)), four furanocoumarins (chalepensin (**109**), ammirin (**110**), chalepin (**111**), and 2′-isopropyl-psoralen (**112**)), two lignans (asarinin (**113**) and fargesin (**114**)), one sesquiterpene (4,5-epoxy-β-caryophyllene (**115**)), and one amide (pellitorine (**116**)) have been isolated from aqueous leachates, with xanthyletin (**107**) being the most active compound against *A. hypochondriacus* (IC_{50} 69.5 and 59.8 μg/dm^3 for root growth and germination inhibition, respectively) [230]. For typical Rutaceae flowers, fruits, and seeds, see Plate 40.

5.1.12 Lignin and Polyphenols from Vegetal Wastes as Bio-Herbicides

Microbiological action transforms lignin from vegetal wastes at soil level into organic prebiotic products with physiological activity on plant development. However, some micromolecular compounds resulting from plant waste decomposition, along with polyphenols arising from the extraction of plant residues, could play a role as allelochemicals that could be used as natural herbicides, pesticides, and growth stimulants [231].

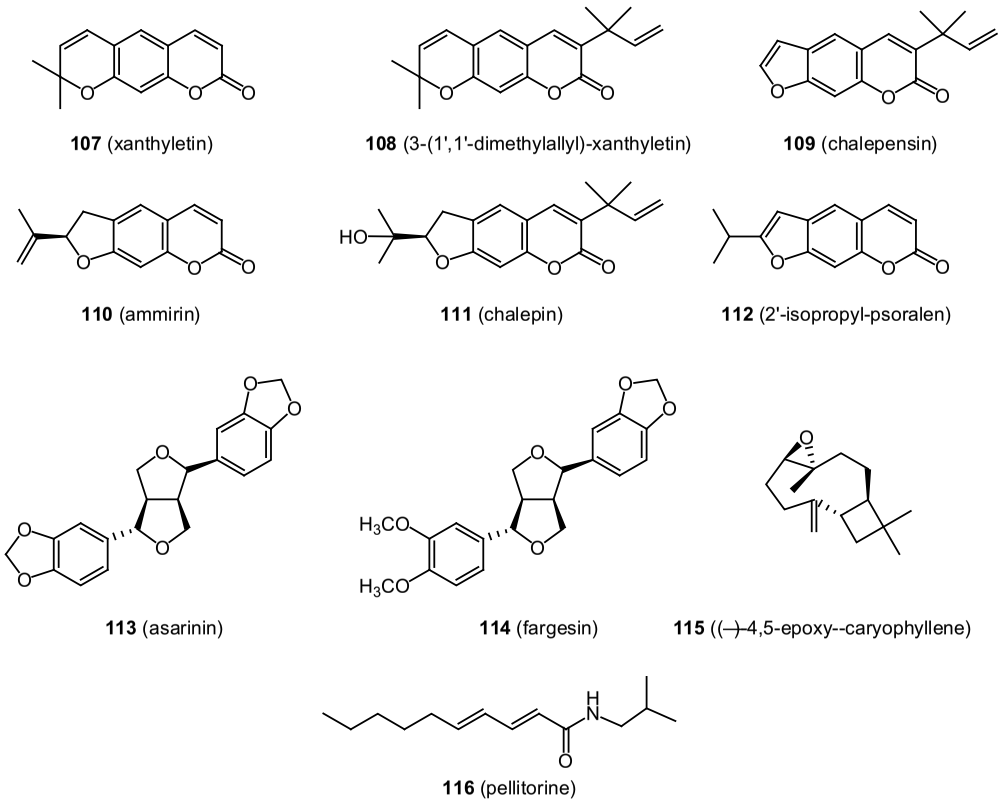


Fig. 33 Structures of compounds isolated from aqueous leachate of *S. perforatus*

Plate 40 Rutaceae flowers, fruits and seeds. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Serbia license. (https://commons.wikimedia.org/wiki/File:Rutaceae_f,_f_and_s.jpg)

5.2 *Plant–Microbe Interaction*

5.2.1 Fabaceae

Arachis hypogaea L.

As mentioned above, peanut (*Arachis hypogaea*, Plate 36) is an important crop that is affected by autotoxicity because it is grown as a monocrop. This autotoxicity is attributed to the presence of phenolic acids and also to other phytoalexins such as resveratrol. Environmental microorganisms are the major contributors to the

bioremediation of toxic substances and plant residues and they are considered to be a permanent solution to the problem of contaminated environments. With the aim of alleviating autotoxicity produced by resveratrol in peanut crops, Wang and co-workers studied the degradation of this compound by the fungal endophyte *P. liquidambari*. They confirmed that *P. liquidambari* has the capacity to degrade resveratrol as the sole carbon source and this could help to alleviate the autotoxicity of peanut crops [212].

5.2.2 Rosaceae

Fragaria ananassa Duch.

Strawberry (*Fragaria ananassa*, Plate 41) is a crop of economic importance and strawberry anthracnose is one of the most serious diseases that affects its survival. *Colletotrichum gloeosporioides* causes strawberry anthracnose crown rot, a destructive disease typically found in strawberry nurseries [232]. Phenolic compounds have also been implicated as autotoxins of strawberry under mono-cropping management systems. However, diverse phenolic acids in plow soil had a different influence on strawberry anthracnose crown rot. The effects of phenolic acids were concentration-dependent and *C. gloeosporioides* was sensitive to phenolic acid concentration. Therefore, phenolic acids can be regulated to control for the occurrence of strawberry anthracnose crown rot [233].

Plate 41 Rosaceae. *Fragaria ananassa* Duch. This file is licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license. (https://upload.wikimedia.org/wikipedia/commons/4/45/Strawberry_plant%2C_Tongging%2C_Karo.jpg)

5.2.3 Ferulic Acid Degradation by Microorganisms

Ferulic acid (**44**) is a precursor in lignin formation and some researchers have shown that it is involved in cell wall extensibility. Ferulic and other phenolic acids are released by living roots and by decomposing plant residues [234]. Low concentrations of phenolic acids in the root environment may stimulate plant growth, but phytotoxic effects often occur at higher concentrations [235]. Caspersen and co-workers [236] demonstrated how microorganisms isolated from a commercial hydroponic lettuce culture supplemented with ferulic acid (**44**) degraded this compound, which was undetectable after two weeks, and ameliorated the phytotoxic effects of this allelochemical. These results also highlight the symbiosis between plants and microorganisms in the rhizosphere, where plants may be protected against potentially toxic compounds in the soil by the metabolic detoxification capabilities of the rhizosphere microbial community [237].

6 Applications

Examples that involve allelopathy have been well known since ancient times. Detrimental effects of crop plants on other plants, as well as the interaction with microorganisms, have been reported in early manuscripts. The present contribution provides a better understanding of the types of allelochemicals produced by plants, their purpose, and how they are used, and this knowledge may be acquired from Nature to open up a wide range of possibilities and applications.

Allelopathy could be used for two main purposes: agriculture and phytomedicine. Within the area of agriculture, plant extracts or enriched fractions, plant residues, or even pure bioactive compounds or newly developed formulations with encapsulation methods can be applied to: (i) the control of noxious weeds and broomrapes in a more environmentally friendly way, (ii) increase the development and performance of other crops, (iii) insect pest management, (iv) control diseases caused by microorganisms, and (v) enhance pesticide soil penetration and solubility [238–242]. Moreover, within the field of phytomedicine [243], these approaches could also be used for the development of new drugs through the synthetic modification of lead compounds, the improvement of bioavailability, as well as the application of an enriched extract in the search for more efficient and effective illnesses treatments.

7 Future Studies

Allelopathy studies are emerging as a challenge for the development of new structural determination techniques, bio-guided extraction and isolation, and advanced techniques for the characterization of these allelochemicals in the

different organs of the plant and in the soil. All of these tools could provide (i) the discovery of novel multipurpose compounds, (ii) a better understanding of the chemistry underground, (iii) the identification of possible synergistic effects, (iv) a knowledge of possible changes in the physicochemical properties based on natural encapsulation by forming micromicelles with fatty acids, terpenoids, or polysaccharides, and (v) a way to solve problems like autotoxicity or detrimental effects on living plants by weeds or microorganisms.

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Francisco A. Macías was born in La Línea de la Concepción, Cádiz, Spain (1956). He has been Professor of Organic Chemistry at the University of Cadiz, (Spain) since 2000 and Head of the Institute of Biomolecules (INBIO) since 2014. He has been honored with the 1999 Rhône-Poulenc Rorer Award, Amsterdam, The Netherlands, from the Phytochemical Society of Europe (PSE), the 2011 Molish Award, Guangzhou, China, from the International Allelopathy Society (IAS) and a Gold Medal, in Recognition of Research Excellence, Dedication, and Humanity, The European 2001 Forum, February 2015. His general philosophy is to learn from Nature. His research interests are related to different aspects of allelopathy dealing with higher plants and microorganisms, involving studies on natural and modified ecosystems, and developing new methodologies for allelopathic studies including mode of action. He heads the "Cadiz Allelopathy Group" a pioneering team in Europe in allelopathic studies from the organic chemistry perspective that has a multidisciplinary structure. Over the years, his group has isolated, identified, characterized, synthesized, and tested the bioactivity of more than 2600 potential allelochemicals and derivatives belonging to a wide range of chemical families including aglycones and/or glycosides (simple phenolics, coumarins, flavonoids, lignans, mono-, sesqui-, di-, spirodi-, mero-, and triterpenoids, steroids, and benzoxacinoids, among others) to permit their corresponding SAR studies. He has been named as a co-inventor of 12 international patents. His publications exceed 300, inclusive of book chapters. He has co-edited two books on "Recent Advances in Allelopathy" and has supervised 31 doctoral theses, and delivered more than 370 lectures around the world.

Alexandra García Durán after earning her Bachelor's degree in Chemistry, she received her Ph.D. degree in Sciences from the University of Cadiz. During this period, she has specialized in isolation and synthesis to modify the physico-chemical properties of natural products in order to obtain enhanced biological activities. Furthermore, she was an international visiting scientist at Charles Sturt University in Wagga Wagga (Australia) and a postdoctoral fellow at Università degli Studi della Campania "Luigi Vanvitelli" (Caserta, Italy), which introduced her to the isolation and purification of natural products in NMR-based metabolomics studies. Currently, her main research interests are related to bioactivity, modes of action, mass spectrometry, and NMR spectroscopy.

José M. G. Molinillo obtained a Ph.D. degree from the University of Cadiz. He visited the University of Tübingen, to learn new techniques for incorporation into his new research field, allelopathy. One of the main aspects he studied has been the search for new herbicides based on natural product lead compounds. He has investigated different plant species, with sunflower being noteworthy, from which he isolated numerous sesquiterpene lactones and two new families of natural products, heliannuoles and helispiranes. Another highlight of his work is the study of benzohydroxamic acids and their degradation compounds, which occur in plants of the family Poaceae, such as wheat, corn, and barley. He has published 124 articles and 14 book chapters, and edited two books. His publications cover the organic chemistry of natural products and the search for new herbicides.

The Phytochemistry and Pharmacology of *Hypericum*

Chuan-Yun Xiao, Qing Mu, and Simon Gibbons

Contents

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1 Introduction

The genus *Hypericum* L. (Hypericaceae) includes, at the most recent count, 469 species that are distributed on every continent, except Antarctica [1]. Plants of this genus have been used as traditional remedies in several parts of the world [2]. A large number of studies on the chemical constituents of its species have been performed worldwide because of their diverse activities. Extracts from various *Hypericum* species possess antibacterial, antidepressant, antiviral, anti-inflammatory, and antioxidant activities [3].

Several reviews on *Hypericum* have been published in recent years, including the chemistry and pharmacology of phloroglucinol derivatives [4], the distribution of prenylated acylphloroglucinols and meroterpenoids [5], and an overview on dimeric acylphloroglucinols in *Hypericum* species [6]. Additionally, some reviews have focused on essential oils and applications of *Hypericum* species [7–9].

Nonetheless, the science related to *Hypericum* species is growing rapidly, with most of the primary literature concentrating on the specific chemical components of *Hypericum*, but there is less information available on pharmacological effects. The present contribution gives an up-to-date and comprehensive overview of the chemical constituents of *Hypericum* species and their biological activities, in order to provide scientific support for this genus for potential drug development. For a photograph of three species including *Hypericum perforatum* (St. John's wort), see Plate 1. This member of the genus *Hypericum* is worthy of special mention, since it has long been used as a phytomedicine in Europe and remains a major dietary supplement used in the United States today [10–12].

Plate 1 *Hypericum perforatum, Hypericum chinensis,* and *Hypericum sampsonii*

2 Phytochemical Investigations

To date, 768 phytochemicals are known from various *Hypericum* species and a summary of the distribution of secondary metabolites represented within this genus is shown in Fig. 1.

Research on hyperforin derivatives has occurred principally on the species *H. ascyron*, *H. attenuatum*, *H. cohaerens*, *H. monogynum*, *H. perforatum*, *H. scabrum*, and *H. sampsonii*. Rottlerin-type metabolites are well represented among *H. attenuatum*, *H. henryi*, *H. hookerianum*, *H. perforatum*, *H. sampsonii*, and *H. uralum,* with the two last-mentioned species being the phytochemical "hotspots" for these fascinating metabolites. Research on spirocyclic phloroglucinols has focused mainly on *H. drummondii* and *H. japonicum*, and many compounds isolated from *H. andinum, H. austrobrasiliense*, *H. brasiliense*, *H. drummondii*, *H. laricifolium*, and *H. thesiifolium* are of this type.

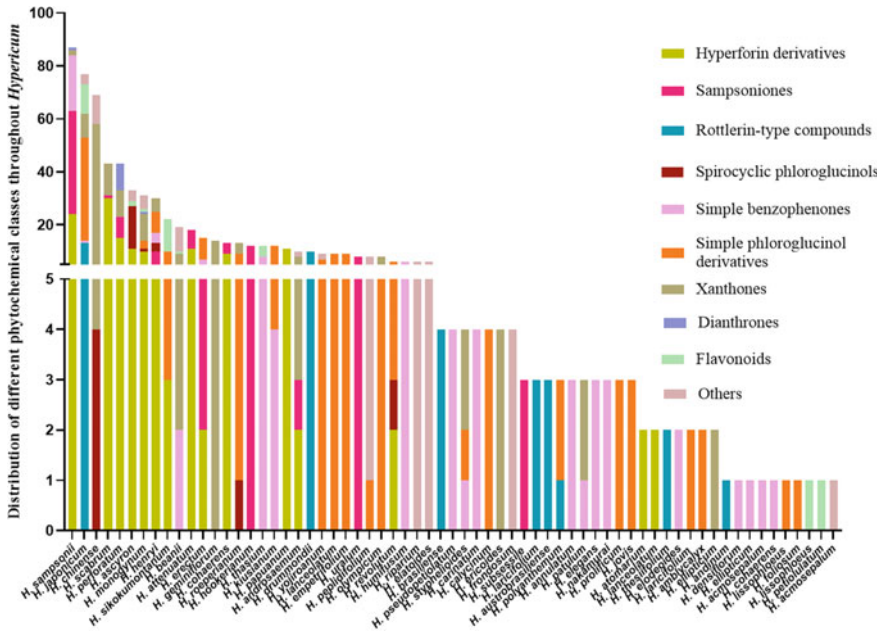


Fig. 1 Distribution of phytochemical classes throughout the genus *Hypericum*

Dianthrones are commonly found in *H. monogynum*, *H. perforatum*, and *H. sampsonii*, while simple benzophenones occur in *H. acmosepalum*, *H. annulatum*, *H. carinatum*, *H. densiflorum*, *H. elegans*, *H. ellipticum*, *H. elodeoides*, *H. humifusum*, *H. nakamurai*, and *H. pseudopetiolatum*. Simple phloroglucinol derivatives have been reported from *H. japonicum* and compounds of this group have been extracted from *H. amblycalyx*, *H. calycinum*, *H. empetrifolium*, *H. foliosum*, *H. jovis*, *H. lanceolatum*, *H. laricifolium*, *H. lissophloeus*, and *H. prolificum*.

Progress in research made on xanthones has occurred mainly from studies of *H. chinense*, with further compounds of this class purified and characterized from *H. ellipticum*, *H. ericoides*, and *H. geminiflorum*. It should be noted that xanthones may be regarded as ring-closed benzoyl phloroglucinols. Flavonoid research has focused mainly on *H. japonicum* and *H. sikokumontanum*, and several compounds of this structural class have also been obtained from extracts of *H. lissophloeus, H. thasium* and *H. petiolulatum*.

2.1 Phloroglucinol Derivatives

The chemical structures of natural phloroglucinol derivatives are highly diverse. Usually, the phloroglucinol derivatives bear side chains, and most contain various

groups, such as acyl, OH, OMe, prenyl, geranyl, and cyclized (poly)-prenyl. Iterative cellular reactions lead to rearranged prenyl and geranyl groups producing some novel and highly unusual complex ring systems. According to their structural characteristics, phloroglucinol derivatives can be divided into five types: (1) hyperforin derivatives, (2) sampsoniones, (3) rottlerin-type compounds, (4) spirocyclic phloroglucinols, (5) simple benzophenones, and (6) simple phloroglucinol derivatives. Currently, 516 phloroglucinol derivatives have been isolated from *Hypericum* species. Due to their high structural diversity, chirality, iteration chemistry, and abundant pharmacological effects, phloroglucinol derivatives in general have become a research topic of high interest.

2.1.1 Hyperforin Derivatives

Generally, the majority of the reported hyperforin derivatives isolated from *Hypericum* species form a unique family of structurally related cage-like metabolites that are most likely to be formed *ortho* to the carbonyl groups in the keto form of the phloroglucinol nucleus, thereby allowing pendant prenyl and geranyl groups to form five- or six-membered rings by rearrangement.

The first hyperforin derivative characterized in 1975 [13] and designated hyperforin (**5**) was isolated from *Hypericum perforatum* L. (St. John's wort) [14]. Thereafter, due to their structural diversity and abundant biological activity, the hyperforin derivatives have attracted considerable attention [15].

From *H. scabrum*, hyperibrins A (**1**) and B (**2**) [16], and hyperscabrones H (**3**) and I (**4**) [17] were identified. Hyperibrin A (**1**) and hyperscabrone I (**4**) exhibit neuroprotective and hepatoprotective effects, respectively.

Adhyperforin (**6**), a hyperforin analogue from *H. perforatum*, was isolated along with four oxygenated hyperforin derivatives: furohyperforin (**7**), 33-deoxy-33-hydroperoxyfurohyperforin (**8**), oxepahyperforin (**9**), and 8-hydroxy-hyperforin-8,1-hemiacetal (**10**) [18, 19].

The same species afforded other hyperforin analogues, such as pyrano[7,28-*b*] hyperforin (**11**), (2*R*,3*R*,4*S*,6*R*)-6-methoxycarbonyl-3-methyl-4,6-di(3-methyl-2-butenyl)-2-(2-methyl-1-oxopropyl)-3-(4-methyl-3-pentenyl)cyclohexanone (**12**), (2*R*,3*R*,4*S*,6*S*)-3-methyl-4,6-di(3-methyl-2-butenyl)-2-(2-methyl-1-oxopropyl)-3-(4-methyl-3-pentenyl)cyclo-hexanone (**13**) [20], furoadhyperforin (**14**), furohyperforin isomer 1 (**15**) and furohyperforin isomer 2 (**16**) [21]. From *H. perforatum*, three hyperforin derivatives, the furoadhyperforin isomers A (**17**) and B (**18**) and the 27-epifurohyperforin isomer 1 (**19**) [22, 23], were reported. Hyperforin (**5**), as present in St. John's wort (*H. perforatum*), has been found to target cytochrome P450 enzymes, in particular CYP3A4, which has led to drug interactions leading to altered plasma concentrations of certain prescription drugs such as amitriptyline, digoxin, indinavir, irinotecan, and warfarin, when co-administered with this plant [24].

The aerial parts of *H. erectum* afforded otogirinins D (**20**) and E (**21**) [25]. Moreover, from *H. attenuatum* six hyperforin derivatives, attenuatumiones B (**22**) and C (**23**) and attenuatumiones E–H (**24**–**27**), were obtained [26].

Recently, studies carried out with the same species resulted in the isolation of five compounds, namely, hyperattenins A–E (**28**–**32**) and propolone A (**33**) [27]. From *H. sikokumontanum*, three hyperforin analogues, takaneones A–C (**34**–**36**), were isolated [28]. The flowers of *H. monogynum* have afforded hypermongones A–J (**37**–**46**) [29], while studies on *H. cohaerens* led to the elucidation of hypercohins B–J (**47**–**55**) [30].

Hyphenrone C (**56**), G (**57**), and uralodins A–C (**58**–**60**) were characterized from *H. henryi* [31]. Even St John's wort has the ability to produce further iterations of the beautiful hyperforin core [32]. *Hypericum scabrum* L. is a plentiful source of hyperforin derivatives and prenylated benzophenones [33], producing hyperibones A–I (**61**–**69**) [34] and the related phytochemicals, hyperibones J (**70**) and L (**71a/b**) (with the latter isolated as a keto-enol tautomeric mixture) have also been reported [22].

This above-mentioned species produces a range of related hyperforins, such as (17*R*),18-dihydroxy-furohyperforin (**72**), hyperscabrin L (**73**) [34], furoadhyperforin isomer 2A (**74**), and furoadhyperforin isomer 2B (**75**), and the hyperibrins C (**76**) and D (**77**) [16]. The hyperscabrones A–G (**78**–**84**) and the known compound scrobiculatone B (**85**) were also identified [17].

Investigation of *H. sampsonii* led to the identification of sampsoniones K–P (**86**–**91**), together with two known compounds, clusianone (**92**) and 7-*epi*-clusianone (**93**) [35, 36]. Hypersampsone F (**94**), hypersampsone H (**95**), hypersampsone K (**96**), and hypersampsones L (**97**) and S (**98**) were also found from the same plant [37–40]. Additionally, hypersampsones S–W (**98**–**102**) were identified as further constituents from this species and demonstrate the extensive ability of *Hypericum* prenyltransferases and cyclases to elaborate structural variants of the phloroglucinol core [41].

An unusual *nor*-polycyclic polyprenylated acylphloroglucinol, hypersampsone R (**103**), with the loss of C-31—C-33 of the isopentenyl side chain, was isolated from the aerial parts of *H. sampsonii* [42]. Hyperisampsins H–M (**104**–**109**) were also identified from this species and some differ from "normal" hyperforin in possessing an unprecedented 1,2-dioxane ring [43].

From *H. androsaemum*, the more "biosynthetically classical" androforin A (**110**) was isolated [42] and, in 2003, Benkiki and coworkers identified hyperfoliatin (**111**) in *H. perfoliatum* L. [44]. Hyperatomarin (**112a/b**), occurring as a mixture of two tautomeric forms, was isolated from *H. atomarium* by bioactivity-guided preparative TLC and was identified on the basis of spectroscopic data interpretation [45, 46]. *Hypericum papuanum* Ridl. afforded five hyperforin derivatives, papuaforins A–E (**113**–**117**) [47].

From the same species, by bioactivity-guided fractionation of the petroleum ether extract of its aerial parts, six new tricyclic phloroglucinol derivatives, 1′-hydroxyialibinone A (**118**) and B (**119**) and 1′-hydroxyialibinone D (**120**), together with three bicyclic compounds, named enaimeones A–C (**121**–**123**), were isolated [48]. From the roots of *H. revolutum*, hyperevolutins A (**124**) and B (**125**)

were characterized, and were obtained as a crystalline mixture [49]. Moreover, two novel hyperforin derivatives, hyperselancins A (**126**) and B (**127**), were discovered from *H. lanceolatum* [50].

In 2018, hyperascyrins A–K (**128**–**138**) were reported from the air-dried aerial parts of *H. ascyron* [51]. Additionally, (1*S*,32*R*,5*S*,6*R*,7*R*)-6-((*R*)-3,4-dihydroxy-4-methylpentyl)-2-(2-hydroxypropan-2-yl)-7-isobutyryl-6-methyl-5,9-bis(3-methyl-but-2-en-1-yl)-4,5,6,7-tetrahydro-2*H*-32,7-methano-cyclooct[*b*]furan-8,10(3*H*)-dione (**139**) and (4*R*,5*R*,7*R*)-4-((*R*)-3,4-dihydroxy-4-methylpentyl)-2,2,4-trimethyl-5,7-bis(3-methyl-but-2-en-1-yl)-7-(5-methylhex-4-enoyl)-4,5,6,7-tetrahydrobenzofuran-3(2*H*)-one (**140**) were identified from *H. scabrum* [52].

The biological properties of hyperforin derivatives **1**–**140** isolated from *Hypericum* species are summarized in Table 1, and their chemistry has been reviewed [13]. These compounds show a wide array of effects, ranging from well-known antidepressant activity that is classical for some members of this structural class, to cancer cell line cytotoxicity.

Table 1 Hyperforin derivatives

Compound name	Species	Biological activity	Ref.
Hyperibrin A (**1**)	*H. scabrum*	Exhibited neuroprotective and hepatoprotective effects	[16]
Hyperibrin B (**2**)	*H. scabrum*		[16]
Hyperscabrone H (**3**)	*H. scabrum*		[17]
Hyperscabrone I (**4**)	*H. scabrum*	Exhibited moderate hepatoprotective activity at 10 μ*M*	[17]
Hyperforin (**5**)	*H. perforatum*	1. Demonstrated effectiveness against Gram-positive bacteria 2. Antidepressant-like effect in rats (20 mg/kg/day for 3 days)	[14, 15]
Adhyperforin (**6**)	*H. perforatum*	Antidepressant-like activity in mice (16 mg/kg, p.o.)	[18, 19]
Furohyperforin (**7**)	*H. perforatum*		[18, 19]
33-Deoxy-33-hydroperoxyfurohyperforin (**8**)	*H. perforatum*		[18, 19]
Oxepahyperforin (**9**)	*H. perforatum*		[18, 19]
8-Hydroxy-hyperforin-8,1-hemiacetal (**10**)	*H. perforatum*		[18, 19]
Pyrano[7,28-*b*]hyperforin (**11**)	*H. perforatum*		[20]
(2*R*,3*R*,4*S*,6*R*)-6-Methoxycarbonyl-3-methyl-4,6-di(3-methyl-2-butenyl)-2-(2-methyl-1-oxopropyl)-3-(4-methyl-3-pentenyl)cyclohexanone (**12**)	*H. perforatum*		[20]
(2*R*,3*R*,4*S*,6*S*)-3-Methyl-4,6-di(3-methyl-2-butenyl)-2-(2-methyl-1-oxopropyl)-3-(4-methyl-3-pentenyl)cyclohexanone (**13**)	*H. perforatum*		[20]
Furoadhyperforin (**14**)	*H. perforatum*	Inhibitor of cytochrome P450 (CYP3A4) enzyme activity (IC_{50} 0.072 μ*M*)	[21]
Furohyperforin isomer 1 (**15**)	*H. perforatum*	Inhibitor of cytochrome P450 (CYP3A4) enzyme activity (IC_{50} 0.079 μ*M*)	[21]

(continued)

Table 1 (continued)

Compound name	Species	Biological activity	Ref.
Furohyperforin isomer 2 (**16**)	*H. perforatum*	Inhibitor of cytochrome P450 (CYP3A4) enzyme activity (IC_{50} 0.23 μ*M*)	[21]
Furoadhyperforin isomer A (**17**)	*H. perforatum*		[22]
Furoadhyperforin isomer B (**18**)	*H. perforatum*		[22]
27-Epifurohyperforin isomer 1 (**19**)	*H. perforatum*		[22]
Otogirinin D (**20**)	*H. erectum*		[25]
Otogirinin E (**21**)	*H. erectum*		[25]
Attenuatumione B (**22**)	*H. attenuatum*		[26, 53]
Attenuatumione C (**23**)	*H. attenuatum*		[25, 26]
Attenuatumione E (**24**)	*H. attenuatum*		[25, 26]
Attenuatumione F (**25**)	*H. attenuatum*		[25, 26]
Attenuatumione G (**26**)	*H. attenuatum*		[25, 26]
Attenuatumione H (**27**)	*H. attenuatum*		[26, 54]
Hyperattenin A (**28**)	*H. attenuatum*		[27]
Hyperattenin B (**29**)	*H. attenuatum*		[27]
Hyperattenin C (**30**)	*H. attenuatum*		[27]
Hyperattenin D (**31**)	*H. attenuatum*		[27]
Hyperattenin E (**32**)	*H. attenuatum*		[27]
Propolone A (**33**)	*H. attenuatum*		[27]
Takaneone A (**34**)	*H. sikokumontanum*	Exhibited cytotoxicity against five cancer cell lines (IC_{50} 9.6 – 24.1 μ*M*)	[28]
Takaneone B (**35**)	*H. sikokumontanum*	Exhibited cytotoxicity against five cancer cell lines (IC_{50} 9.6 – 24.1 μ*M*)	[28]
Takaneone C (**36**)	*H. sikokumontanum*	Exhibited cytotoxicity against five cancer cell lines (IC_{50} 9.6 – 24.1 μ*M*)	[28]
Hypermongone A (**37**)	*H. monogynum*		[29]
Hypermongone B (**38**)	*H. monogynum*		[29]
Hypermongone C (**39**)	*H. monogynum*		[29]
Hypermongone D (**40**)	*H. monogynum*		[29]
Hypermongone E (**41**)	*H. monogynum*		[29]
Hypermongone F (**42**)	*H. monogynum*		[29]
Hypermongone G (**43**)	*H. monogynum*	Displayed inhibitory effect on nitric oxide production (IC_{50} 9.5 μ*M*), which can be associated with anti-inflammatory activity	[29]
Hypermongone H (**44**)	*H. monogynum*		[29]
Hypermongone I (**45**)	*H. monogynum*		[29]
Hypermongone J (**46**)	*H. monogynum*		[29]
Hypercohin B (**47**)	*H. cohaerens*	Exhibited cytotoxic activity (IC_{50} 5.8 – 17.9 μ*M*) against five cancer cell lines	[30]
Hypercohin C (**48**)	*H. cohaerens*	Exhibited cytotoxic activity (IC_{50} 5.8 – 17.9 μ*M*) against five cancer cell lines	[30]
Hypercohin D (**49**)	*H. cohaerens*	Exhibited cytotoxic activity (IC_{50} 5.8 – 17.9 μ*M*) against five cancer cell lines	[30]
Hypercohin E (**50**)	*H. cohaerens*		[30]
Hypercohin F (**51**)	*H. cohaerens*		[30]
Hypercohin G (**52**)	*H. cohaerens*		[30]

(continued)

Table 1 (continued)

Compound name	Species	Biological activity	Ref.
Hypercohin H (**53**)	*H. cohaerens*		[30]
Hypercohin I (**54**)	*H. cohaerens*		[30]
Hypercohin J (**55**)	*H. cohaerens*		[30]
Hyphenrone C (**56**)	*H. henryi*		[55]
Hyphenrone G (**57**)	*H. henryi*		[55]
Uralodin A (**58**)	*H. henryi*		[31]
Uralodin B (**59**)	*H. henryi*		[31]
Uralodin C (**60**)	*H. henryi*		[31]
Hyperibone A (**61**)	*H. scabrum*		[34]
Hyperibone B (**62**)	*H. scabrum*		[34]
Hyperibone C (**63**)	*H. scabrum*		[34]
Hyperibone D (**64**)	*H. scabrum*		[34]
Hyperibone E (**65**)	*H. scabrum*		[34]
Hyperibone F (**66**)	*H. scabrum*		[34]
Hyperibone G (**67**)	*H. scabrum*		[34]
Hyperibone H (**68**)	*H. scabrum*		[34]
Hyperibone I (**69**)	*H. scabrum*		[34]
Hyperibone J (**70**)	*H. scabrum*		[34]
Hyperibone L (**71a**)	*H. scabrum*		[34]
Hyperibone L (**71b**)	*H. scabrum*		[34]
(17*R*),18-Dihydroxy-furohyperforin (**72**)	*H. scabrum*		[52]
Hyperscabrin L (**73**)	*H. scabrum*		[52]
Furoadhyperforin isomer 2A (**74**)	*H. scabrum*		[16]
Furoadhyperforin isomer 2B (**75**)	*H. scabrum*		[16]
Hyperibrin C (**76**)	*H. scabrum*		[16]
Hyperibrin D (**77**)	*H. scabrum*		[16]
Hyperscabrone A (**78**)	*H. scabrum*		[17]
Hyperscabrone B (**79**)	*H. scabrum*		[17]
Hyperscabrone C (**80**)	*H. scabrum*	Exhibited hepatoprotective activity (10 μ*M*)	[17]
Hyperscabrone D (**81**)	*H. scabrum*	1. Displayed neuroprotective activity (10 μ*M*) 2. Exhibited hepatoprotective activity (10 μ*M*)	[17]
Hyperscabrone E (**82**)	*H. scabrum*	1. Displayed neuroprotective activity (10 μ*M*) 2. Exhibited hepatoprotective activity (10 μ*M*)	[17]
Hyperscabrone F (**83**)	*H. scabrum*	Displayed neuroprotective activity (10 μ*M*)	[17]
Hyperscabrone G (**84**)	*H. scabrum*	1. Displayed neuroprotective activity (10 μ*M*) 2. Exhibited hepatoprotective activity (10 μ*M*)	[17]
Scrobiculatone B (**85**)	*H. scabrum*	Exhibited hepatoprotective activity (10 μ*M*)	[17]
Sampsonione K (**86**)	*H. sampsonii*		[35, 36]
Sampsonione L (**87**)	*H. sampsonii*		[35, 36]
Sampsonione M (**88**)	*H. sampsonii*		[35, 36]

(continued)

Table 1 (continued)

Compound name	Species	Biological activity	Ref.
Sampsonione N (**89**)	*H. sampsonii*		[35, 36]
Sampsonione O (**90**)	*H. sampsonii*		[35, 36]
Sampsonione P (**91**)	*H. sampsonii*		[35, 36]
Clusianone (**92**)	*H. sampsonii*		[35, 36]
7-*epi*-Clusianone (**93**)	*H. sampsonii*	Exhibited antibacterial activity against norfloxacin-resistant *S. aureus* (*MIC* 7.3 μ*M*)	[35, 36]
Hypersampsone F (**94**)	*H. sampsonii*		[37]
Hypersampsone H (**95**)	*H. sampsonii*	Showed cytotoxic activity against human lung adenocarcinoma A549 cells (IC_{50} 120 μ*M*)	[38]
Hypersampsone K (**96**)	*H. sampsonii*		[38]
Hypersampsone L (**97**)	*H. sampsonii*		[39, 40]
Hypersampsone S (**98**)	*H. sampsonii*		[41]
Hypersampsone T (**99**)	*H. sampsonii*		[41]
Hypersampsone U (**100**)	*H. sampsonii*		[41]
Hypersampsone V (**101**)	*H. sampsonii*		[41]
Hypersampsone W (**102**)	*H. sampsonii*		[41]
Hypersampsone R (**103**)	*H. sampsonii*	Inhibited cellular proliferation at 20 μ*M* in HeLa cells (60% of cell death)	[42]
Hyperisampsin H (**104**)	*H. sampsonii*		[43]
Hyperisampsin I (**105**)	*H. sampsonii*	Showed cytotoxic activity against HL-60 (IC_{50} 0.56 μ*M*), A594 (IC_{50} 0.53 μ*M*), SMMC-7721 (IC_{50} 0.58 μ*M*), MCF-7 (IC_{50} 0.88 μ*M*), SW480 (IC_{50} 2.49 μ*M*), and BEAS-2B (IC_{50} 1.50 μ*M*) cancer cells	[41]
Hyperisampsin J (**106**)	*H. sampsonii*	Showed cytotoxic activity against HL-60 (IC_{50} 1.67 μ*M*), A594 (IC_{50} 2.13 μ*M*), SMMC-7721 (IC_{50} 2.15 μ*M*), MCF-7 (IC_{50} 2.73 μ*M*), SW480 (IC_{50} 3.00 μ*M*), and BEAS-2B (IC_{50} 2.71 μ*M*) cancer cells	[43]
Hyperisampsin K (**107**)	*H. sampsonii*	Showed cytotoxic activity against HL-60 (IC_{50} 3.03 μ*M*), A594 (IC_{50} 11.13 μ*M*), SMMC-7721 (IC_{50} 11.30 μ*M*), MCF-7 (IC_{50} 11.54 μ*M*), SW480 (IC_{50} 13.59 μ*M*), and BEAS-2B (IC_{50} 15.77 μ*M*) cancer cells	[43]
Hyperisampsin L (**108**)	*H. sampsonii*	Showed cytotoxic activity against HL-60 (IC_{50} 1.42 μ*M*), A594 (IC_{50} 1.89 μ*M*), SMMC-7721 (IC_{50} 2.28 μ*M*), MCF-7 (IC_{50} 1.66 μ*M*), SW480 (IC_{50} 2.90 μ*M*), and BEAS-2B (IC_{50} 3.04 μ*M*) cancer cells	[43]

(continued)

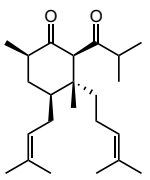
Table 1 (continued)

Compound name	Species	Biological activity	Ref.
Hyperisampsin M (**109**)	*H. sampsonii*	Showed cytotoxic activity against HL-60 (IC_{50} 15.52 μ*M*), A594 (IC_{50} 15.19 μ*M*), SMMC-7721 (IC_{50} 18.36 μ*M*), MCF-7 (IC_{50} 5.72 μ*M*), SW480 (IC_{50} 20.10 μ*M*), and BEAS-2B (IC_{50} 17.08 μ*M*) cancer cells	[43]
Androforin A (**110**)	*H. androsaemum*		[56]
Hyperfoliatin (**111**)	*H. perfoliatum*	Exhibited antidepressant-like activity in mice (10 mg/kg; i.p.), associated with an inhibition of neuronal monoamine uptake	[44, 57]
Hyperatomarin (**112a**)	*H.atomarium*, *H. annulatum*	1. Exhibited antibacterial activity against *S. aureus*, *M. luteus*, and *B. subtilis* (MIC 1.56–3.12 μg/cm^3). 2. Showed cytotoxic effects for seven tumor cell lines (SKW-3, U-266, DOHH-2, HD-MY-Z, EJ, MCF-7, and SAOS-2 with IC_{50} values of 3.04, 0.49, 0.14, 4.97, 8.75, 0.79, and 1.18 μ*M*)	[45, 46]
Hyperatomarin (**112b**)	*H. atomarium* *H. annulatum*	Exhibited antibacterial activity against *S. aureus*, *M. luteus*, and *B. subtilis* (*MIC* 1.56–3.12 μg/cm^3)	[45, 46]
Papuaforin A (**113**)	*H. papuanum*		[47]
Papuaforin B (**114**)	*H. papuanum*		[47]
Papuaforin C (**115**)	*H. papuanum*		[47]
Papuaforin D (**116**)	*H. papuanum*		[47]
Papuaforin E (**117**)	*H. papuanum*		[47]
1′-Hydroxyialibinone A (**118**)	*H. papuanum*		[48]
1′-Hydroxyialibinone B (**119**)	*H. papuanum*		[48]
1′-Hydroxyialibinone D (**120**)	*H. papuanum*		[48]
Enaimeone A (**121**)	*H. papuanum*		[58]
Enaimeone B (**122**)	*H. papuanum*		[48]
Enaimeone C (**123**)	*H. papuanum*		[48]
Hyperevolutin A (**124**)	*H. revolutum*	Exhibited growth inhibitory activity of a colon carcinoma cell line (ED_{50} 0.35 μg/cm^3)	[47]
Hyperevolutin B (**125**)	*H. revolutum*		[49]
Hyperselancin A (**126**)	*H. lanceolatum*		[50]
Hyperselancin B (**127**)	*H. lanceolatum*		[50]
Hyperascyrin A (**128**)	*H. ascyron*	Exhibited neuroprotective activity against glutamate-induced toxicity in SK-N-SH cells (10 μ*M*)	[51]
Hyperascyrin B (**129**)	*H. ascyron*		[51]
Hyperascyrin C (**130**)	*H. ascyron*		[51]
Hyperascyrin D (**131**)	*H. ascyron*		[51]
Hyperascyrin E (**132**)	*H. ascyron*		[51]
Hyperascyrin F (**133**)	*H. ascyron*		[51]
Hyperascyrin G (**134**)	*H. ascyron*		[51]

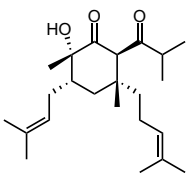
(continued)

Table 1 (continued)

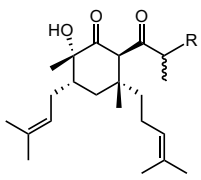
Compound name	Species	Biological activity	Ref.
Hyperascyrin H (**135**)	*H. ascyron*	1. Exhibited neuroprotective activity against glutamate-induced toxicity in SK-N-SH cells (10 μ*M*) 2. Showed protection against paracetamol-induced HepG2 cell damage (10 μ*M*)	[51]
Hyperascyrin I (**136**)	*H. ascyron*	Showed protection against paracetamol-induced HepG2 cell damage (10 μ*M*)	[51]
Hyperascyrin J (**137**)	*H. ascyron*		[51]
Hyperascyrin K (**138**)	*H. ascyron*		[51]
(1*S*,32*R*,5*S*,6*R*,7*R*)-6-((*R*)-3,4-dihydroxy-4-methylpentyl)-2-(2-hydroxypropan-2-yl)-7-isobutyryl-6-methyl-5,9-bis(3-methylbut-2-en-1-yl)-4,5,6,7-tetrahydro-2*H*-32,7-methano-cycloocta[*b*]furan-8,10-(3*H*)-dione (**139**)	*H. scabrum*		[52]
(4*R*,5*R*,7*R*)-4-((*R*)-3,4-dihydroxy-4-methylpentyl)-2,2,4-trimethyl-5,7-bis(3-methyl-but-2-en-1-yl)-7-(5-methylhex-4-enoyl)-4,5,6,7-tetrahydrobenzofuran-3(2*H*)-one (**140**)	*H. scabrum*		[52]



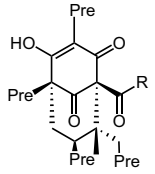
1 (hyperibrin A)



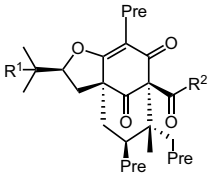
2 (hyperibrin B)



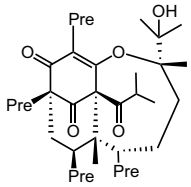
3 R = CH_3 (hyperscabrone H)
4 R = (*S*)-CH_2CH_3 (hyperscabrone I)



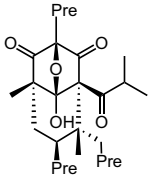
5 R = $CH(CH_3)_2$ (hyperforin)
6 R = $CH(CH_3)CH_2CH_3$ (adhyperforin)



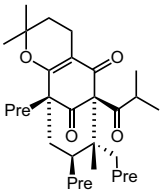
7 R^1 = OH, R^2 = $CH(CH_3)_2$ (furohyperforin)
8 R^1 = OOH, R^2 = $CH(CH_3)_2$ (33-deoxy-33-hydroperoxyfurohyperforin)
14 R^1 = OH, R^2 = $CH(CH_3)CH_2CH_3$ (furoadhyperforin)



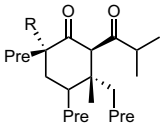
9 (oxepahyperforin)



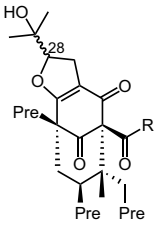
10 (8-hydroxy-hyperforin-8,1-hemiacetal)



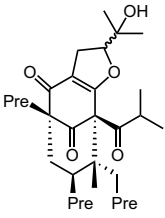
11 (pyrano[7,28-*b*]hyperforin)



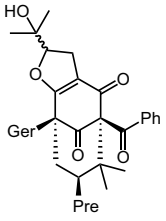
12 R = $COOCH_3$ ((2*R*,3*R*,4*S*,6*R*)-6-methoxycarbonyl-3-methyl-4,6-di(3-methyl-2-butenyl)-2-(2-methyl-1-oxopropyl)-3-(4-methyl-3-pentenyl)cyclohexanone)
13 R = H ((2*R*,3*R*,4*S*,6*S*)-3-methyl-4,6-di(3-methyl-2-butenyl)-2-(2-methyl-1-oxopropyl)-3-(4-methyl-3-pentenyl)cyclohexanone)



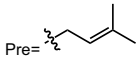
15 R = $CH(CH_3)_2$ (furohyperforin isomer 1)
17 R = $CH(CH_3)CH_2CH_3$, 28α-H (furoadhyperforin isomer A)
18 R = $CH(CH_3)CH_2CH_3$, 28β-H (furoadhyperforin isomer B)
19 R = $CH(CH_3)_2$, 28β-H (27-epifurohyperforin isomer 1)



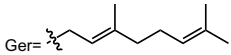
16 (furohyperforin isomer 2)



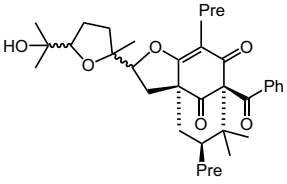
20 (otogirinin D)



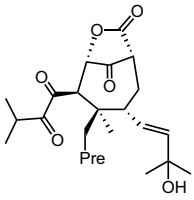
Pre=



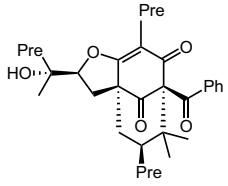
Ger=



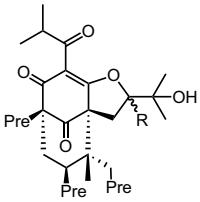
21 (otogirinin E)



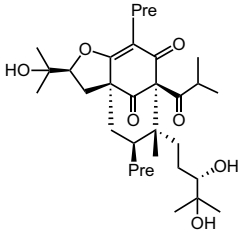
22 (attenuatumione B)



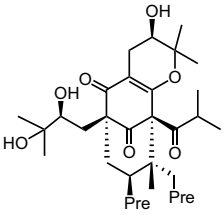
23 (attenuatumione C)



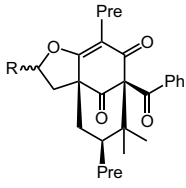
24 R = α-H (attenuatumione E)
25 R = β-H (attenuatumione F)



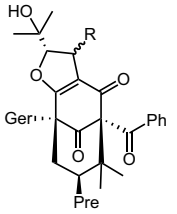
26 (attenuatumione G)



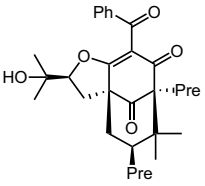
27 (attenuatumione H)



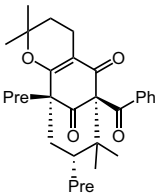
28 R = β-OH (hyperattenin A)
29 R = H (hyperattenin B)



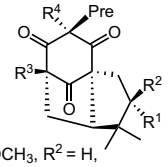
30 R = H (hyperattenin C)
31 R = OCH_2CH_3 (hyperattenin D)



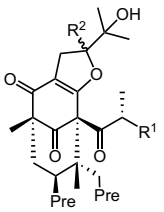
32 (hyperattenin E)



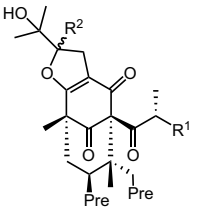
33 (propolone A)



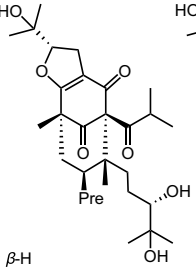
34 R^1 = $COCH_3$, R^2 = H,
R^3 = CH_3, R^4 = $COCH(CH_3)_2$ (takaneone A)
35 R^1 = H, R^2 = $COCH_3$,
R^3 = CH_3, R^4 = $COCH(CH_3)_2$ (takaneone B)
36 R^1 = H, R^2 = $COCH_3$,
R^3 = $COCH(CH_3)_2$, R^4 = CH_3 (takaneone C)



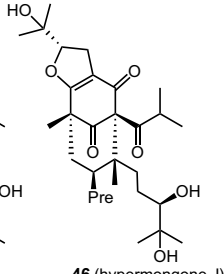
37 R^1 = CH_2CH_3, R^2 = β-H
(hypermongone A)
38 R^1 = CH_2CH_3, R^2 = α-H
(hypermongone B)
39 R^1 = CH_3, R^2 = β-H
(hypermongone C)
40 R^1 = CH_3, R^2 = α-H
(hypermongone D)



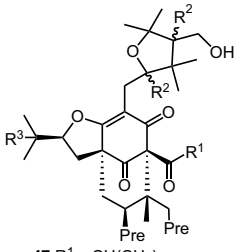
41 R^1 = CH_2CH_3, R^2 = β-H
(hypermongone E)
42 R^1 = CH_2CH_3, R^2 = α-H
(hypermongone F)
43 R^1 = CH_3, R^2 = β-H
(hypermongone G)
44 R^1 = CH_3, R^2 = α-H
(hypermongone H)



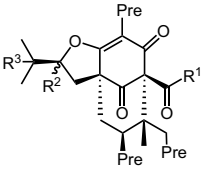
45 (hypermongone I)



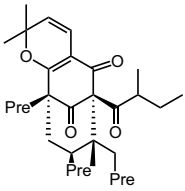
46 (hypermongone J)



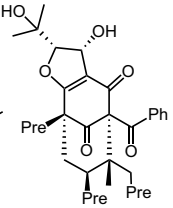
47 R^1 = $CH(CH_3)_2$,
R^2 = β-H, R^3 = α-H
(hypercohin B)
48 R^1 = Phenyl,
R^2 = β-H, R^3 = α-H
(hypercohin C)
49 R^1 = $CH(CH_3)_2$,
R^2 = α-H, R^3 = β-H
(hypercohin D)



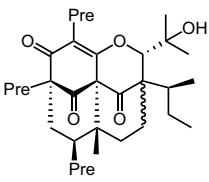
50 R^1 = $CH(CH_3)_2$,
R^2 = β-H, R^3 = OH
(hypercohin E)
51 R^1 = $CH_2CH(CH_3)_2$,
R^2 = β-H, R^3 = OH
(hypercohin F)
52 R^1 = $CH(CH_3)_2$,
R^2 = α-H, R^3 = H
(hypercohin G)
53 R^1 = Phenyl,
R^2 = α-H, R^3 = H
(hypercohin H)



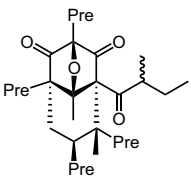
54 (hypercohin I)



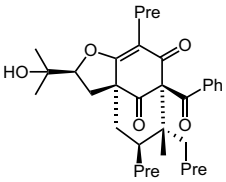
55 (hypercohin J)



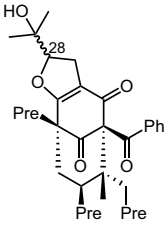
56 (hyphenrone C)



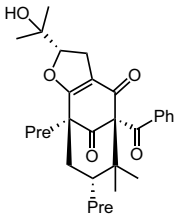
57 (hyphenrone G)



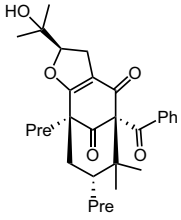
58 (uralodin A)



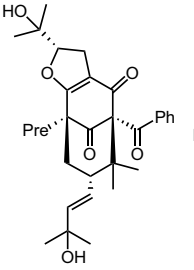
59 28α-H (uralodin B)
60 28β-H (uralodin C)



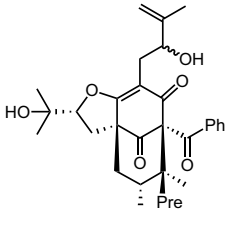
61 (hyperibone A)



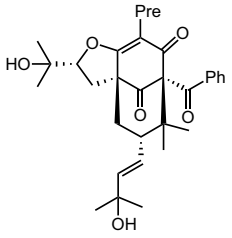
62 (hyperibone B)



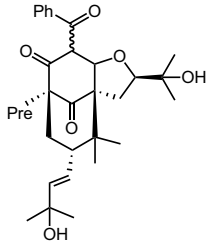
63 (hyperibone C)



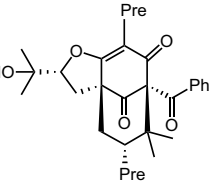
64 (hyperibone D)



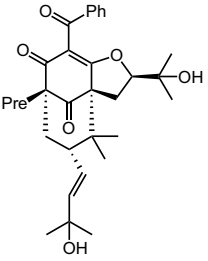
65 (hyperibone E)



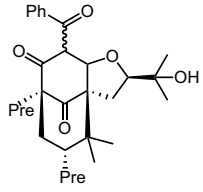
66 (hyperibone F)



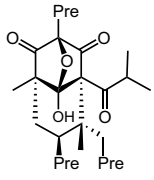
67 (hyperibone G)



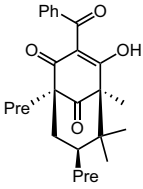
68 (hyperibone H)



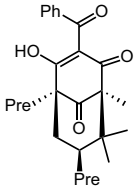
69 (hyperibone I)



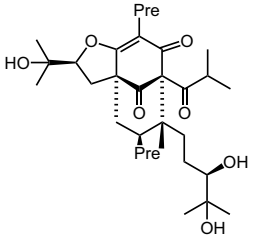
70 (hyperibone J)



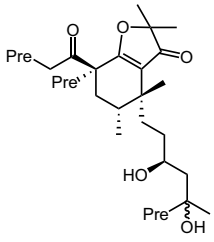
71a (hyperibone L 1)



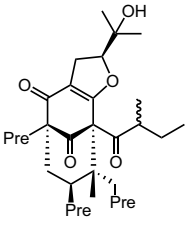
71b (hyperibone L 2)



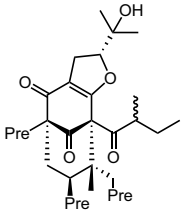
72 ((17*R*),18-dihydroxy-furohyperforin)



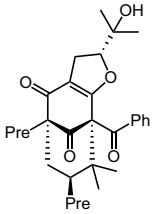
73 (hyperscabrin L)



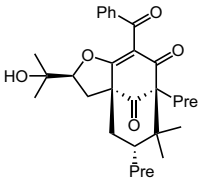
74 (furoadhyperforin isomer 2A)



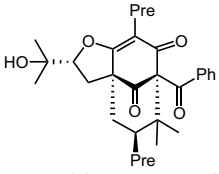
75 (furoadhyperforin isomer 2B)



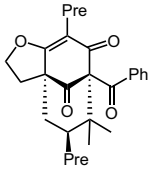
76 (hyperibrin C)



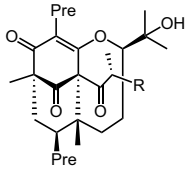
77 (hyperibrin D)



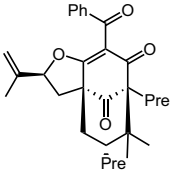
78 (hyperscabrone A)



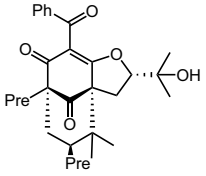
79 (hyperscabrone B)



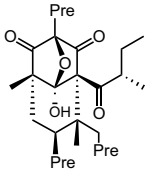
80 R = CH_3 (hyperscabrone C)
81 R = CH_2CH_3 (hyperscabrone D)



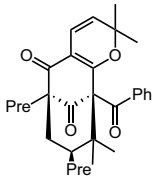
82 (hyperscabrone E)



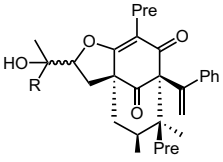
83 (hyperscabrone F)



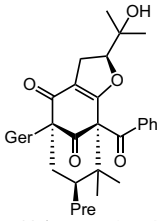
84 (hyperscabrone G)



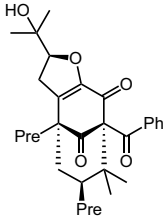
85 (scrobiculatone B)



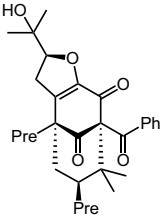
86 R = Prenyl (sampsonione K)
87 R = CH_3 (sampsonione L)



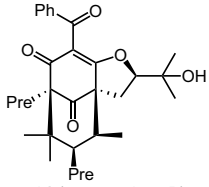
88 (sampsonione M)



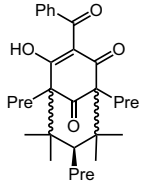
89 (sampsonione N)



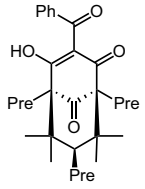
90 (sampsonione O)



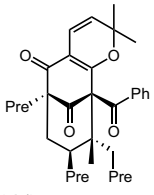
91 (sampsonione P)



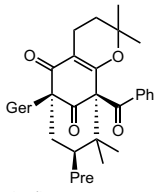
92 (clusianone)



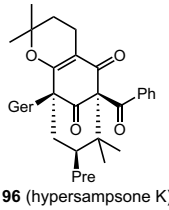
93 (7-*epi*-clusianone)



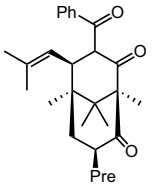
94 (hypersampsone F)



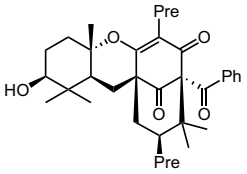
95 (hypersampsone H)



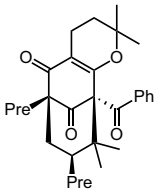
96 (hypersampsone K)



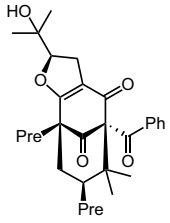
97 (hypersampsone L)



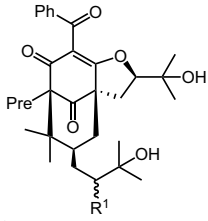
98 (hypersampsone S)



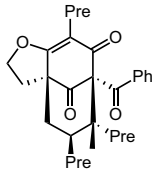
99 (hypersampsone T)



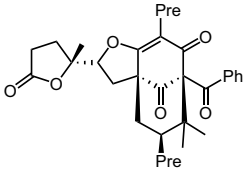
100 (hypersampsone U)



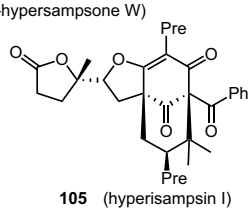
101 R^1 = OH, ((*R*)-hypersampsone V)
102 R^1 = OH, ((*S*)-hypersampsone W)



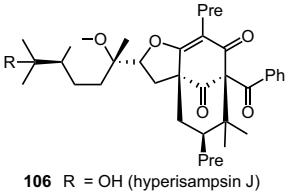
103 (hypersampsone R)



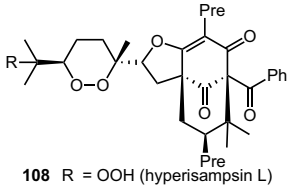
104 (hyperisampsin H)



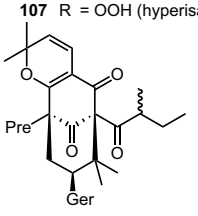
105 (hyperisampsin I)



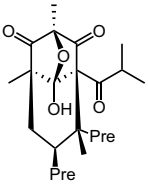
106 R = OH (hyperisampsin J)
107 R = OOH (hyperisampsin K)



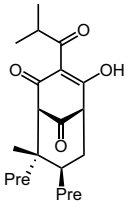
108 R = OOH (hyperisampsin L)
109 R = OH (hyperisampsin M)



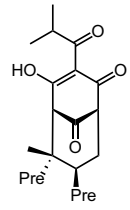
110 (androforin A)



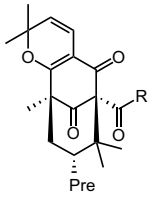
111 (hyperfoliatin)



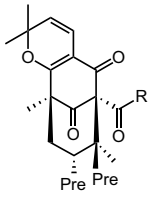
112a (hyperatomarin)



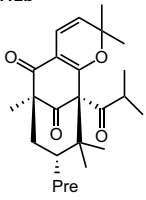
112b



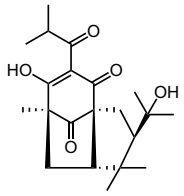
113 R = $CH(CH_3)_2$ (papuaforin A)
114 R = $CH(CH_3)CH_2CH_3$ (papuaforin B)



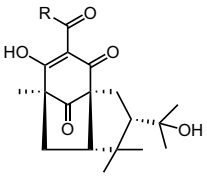
115 R = $CH(CH_3)_2$ (papuaforin C)
116 R = $CH(CH_3)CH_2CH_3$ (papuaforin D)



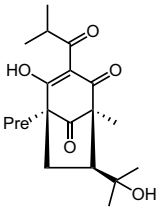
117 (papuaforin E)



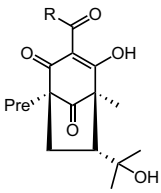
118 (1′-hydroxyialibinone A)



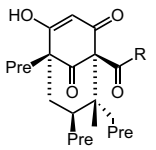
119 R = $CH(CH_3)_2$ (1′-hydroxyialibinone B)
120 R = $CH(CH_3)CH_2CH_3$ (1′-hydroxyialibinone D)



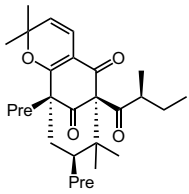
121 (enaimeone A)



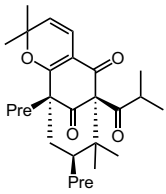
122 R = $CH(CH_3)_2$ (enaimeone B)
123 R = $CH(CH_3)CH_2CH_3$ (enaimeone C)



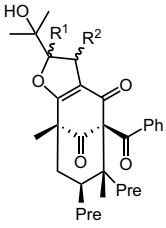
124 R = $CH(CH_3)_2$ (hyperevolutin A)
125 R = $CH(CH_3)CH_2CH_3$ (hyperevolutin B)



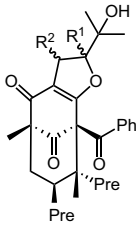
126 (hyperselancin A)



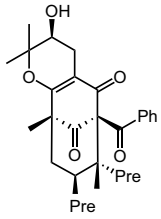
127 (hyperselancin B)



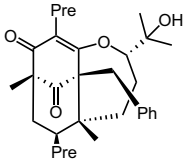
128 R^1 = α-H R^2 = H (hyperascyrin A)
129 R^1 = β-H R^2 = H (hyperascyrin B)
130 R^1 = α-H R^2 = β-OH (hyperascyrin C)
131 R^1 = β-H R^2 = α-OH (hyperascyrin D)



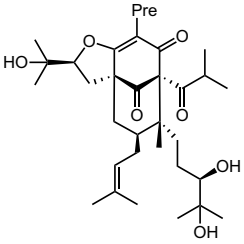
132 R^1 = α-H R^2 = H (hyperascyrin E)
133 R^1 = β-H R^2 = H (hyperascyrin F)
134 R^1 = α-H R^2 = β-OH (hyperascyrin G)
135 R^1 = α-H R^2 = α-OH (hyperascyrin H)
136 R^1 = β-H R^2 = α-OH (hyperascyrin I)



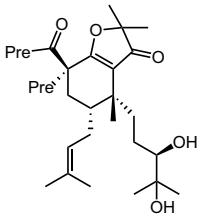
137 (hyperascyrin J)



138 (hyperascyrin K)



139 ((1*S*,32*R*,5*S*,6*R*,7*R*)-6-((*R*)-3,4-dihydroxy-4-methylpentyl)-2-(2-hydroxypropan-2-yl)-7-isobutyryl-6-methyl-5,9-bis(3-methylbut-2-en-1-yl)-4,5,6,7-tetrahydro-2*H*-32,7-methano-cycloocta[*b*]furan-8,10-(3*H*)-dione)



140 ((4*R*,5*R*,7*R*)-4-((*R*)-3,4-dihydroxy-4-methylpentyl)-2,2,4-trimethyl-5,7-bis(3-methyl-but-2-en-1-yl)-7-(5-methylhex-4-enoyl)-4,5,6,7-tetrahydrobenzofuran-3(2*H*)-one)

2.2 Sampsoniones

The sampsoniones have been isolated mainly from *H. sampsonii* and these compounds are unique in possessing a four-ring caged skeleton. The structural diversity of sampsoniones is due to differential substitution of prenyl and geranyl groups as well as the hydroxy group of ring B, allowing many possibilities for rearrangement to form new skeletons [59].

From the aerial parts of *H. erectum*, three sampsoniones, otogirinins A–C (**141**–**143**), were identified [25]. In addition, from *H. attenuatum*, attenuatumione A (**144**) and attenuatumione D (**145**) were obtained, together with the known compound plukenetione B (**146**) [26, 53]. From *H. attenuatum*, hyperattenins F–I (**147**–**150**) were isolated, along with the known compound peroxysampsone B (**151**) [27].

In 2005, Liao et al. isolated three sampsoniones, the hypersubones A–C (**152**–**154**), from *H. subsessile* [60]. In studies on *H. cohaerens*, hypercohin A (**155**) was isolated, the first of a series of compounds that possess the unusual bicyclic [5.3.1] hendecane core [61]. About the same time, three *homo*-adamantyl-type compounds, hypercohones A–C (**156**–**158**) also were identified from this species [62].

As a result of investigating *H. henryi*, hyphenrones A–F (**159**–**163**) were documented, and they were found to display three unprecedented cores [63]. From the same species, hyphenrones H (**164**) and I (**165**) and hyphenrones L–Q (**166**–**171**) were reported [55].

From *H. uralum*, Zhang et al. isolated hyperuralones A–H (**172**–**179**) [64]. More recently, from *H. hookerianum*, hookeriones A–H (**180**–**187**) were described, along with three known compounds, namely, 28,29-epoxyplukenetione A (**188**), plukenetione A (**189**), and sampsonione Q (**190**) [65].

In 2004, Tanaka et al. isolated three new compounds from *H. scabrum*; one of them was the sampsonione, hyperibone K (**191**), with two prenyl residues linked to phloroglucin [33]. From *H. sampsonii* sampsoniones A–J (**192**–**201**) were isolated [35, 36].

Study of an anti-HBV active fraction of this same species resulted in the isolation of hypersampsones A–E (**204**–**208**) [37]. In turn, hyperisampsin G (**203**), hypersampsone G (**209**), hypersampsones I–Q (**210**–**217**), and hypersampsone S (**218**), and the oxidized compounds **219**–**223**, together with the known analogue, sampsonione R (**202**), were also isolated from this species [38–40]. More recently, hyperisampsins A–D (**224**–**227**), with a tetracyclo-[6.3.1.$1^{3,10}$.$0^{3,7}$]tridecane skeleton, and two biogenetically related congeners, hyperisampsins E (**228**) and F (**229**), were isolated from *H. sampsonii* [53].

Zhu et al. reported hyperisampsins N (**230**) and O (**231**) from this same species [66]. From the aerial parts of *H. androsaemum*, hyperandrone A (**232**) [56] was isolated and, in addition, two new sampsoniones, hyperattenins L (**233**) and M (**234**), possessing unusual adamantyl and homo-adamantyl core structures, were purified from the aerial parts of *H. attenuatum* [67].

The biological properties of sampsoniones **141**–**234** as isolated from *Hypericum* species are summarized in Table 2.

Table 2 Sampsonione compounds

Compound name	Species	Biological activity	Ref.
Otogirinin A (**141**)	*H. erectum*		[25]
Otogirinin B (**142**)	*H. erectum*		[25]
Otogirinin C (**143**)	*H. erectum*		[25]
Attenuatumione A (**144**)	*H. attenuatum*		[26]
Attenuatumione D (**145**)	*H. attenuatum*		[26]
Plukenetione B (**146**)	*H. sampsonii*		[53]
Hyperattenin F (**147**)	*H. attenuatum*		[27]
Hyperattenin G (**148**)	*H. attenuatum*		[27]
Hyperattenin H (**149**)	*H. attenuatum*		[27]
Hyperattenin I (**150**)	*H. attenuatum*	Exhibited cytotoxic activity for myeloid leukemia (HL-60) and lung cancer (A549) cell lines, (IC_{50} 2.04 and 3.26 μ*M*)	[27]
Peroxysampsone B (**151**)	*H. attenuatum*		[27]
Hypersubone A (**152**)	*H. subsessile*	Showed cytotoxic activity for three human cancer cell lines (HepG2, Eca109, and HeLa; IC_{50} 17.74, 13.54, and 42.46 μ*M*)	[60]
Hypersubone B (**153**)	*H. subsessile*	Showed cytotoxic activity for four human cancer cell lines (HepG2, Eca109, HeLa, and A549; IC_{50} 1.58, 0.07, 3.54, and 7.52 μ*M*)	[60]
Hypersubone C (**154**)	*H. subsessile*	Showed cytotoxic activity for four human cancer cell lines (HepG2, Eca109, HeLa, and A549; IC_{50} 9.74, 6.71, 9.33, and 17.23 μ*M*)	[60]
Hypercohin A (**155**)	*H. cohaerens*		[68]
Hypercohone A (**156**)	*H. cohaerens*		[62]
Hypercohone B (**157**)	*H. cohaerens*		[62]
Hypercohone C (**158**)	*H. cohaerens*		[62]
Hyphenrone A (**159**)	*H. henryi*		[63]
Hyphenrone B (**160**)	*H. henryi*		[63]
Hyphenrone C (**161**)	*H. henryi*		[63]
Hyphenrone D (**162**)	*H. henryi*	Showed cytotoxic activity for four human cancer cell lines (HL-60, SMMC-7721, A549, and MCF-7; IC_{50} 12.2, 25.5, 16.0, and 24.1 μ*M*)	[63]
Hyphenrone F (**163**)	*H. henryi*		[63]
Hyphenrone H (**164**)	*H. perforatum* *H. henryi*		[55]
Hyphenrone I (**165**)	*H. perforatum* *H. henryi*		[55]
Hyphenrone L (**166**)	*H. perforatum* *H. henryi*	Showed cytotoxic activity for four human cancer cell lines (HL-60, SMMC-772, A549, and MCF-7; IC_{50} 12.2, 25.5, 16.0, and 24.1 μ*M*)	[55]
Hyphenrone M (**167**)	*H. perforatum* *H. henryi*		[55]
Hyphenrone N (**168**)	*H. perforatum* *H. henryi*	Showed cytotoxic activity for five human cancer cell lines (HL-60, SMMC-7721, A549, MCF-7, and SW480; IC_{50} 14.5, 11.8, 13.9, 14.4, and 16.0 μ*M*)	[55]

(continued)

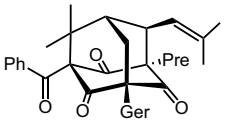
Table 2 (continued)

Compound name	Species	Biological activity	Ref.
Hyphenrone O (**169**)	*H. perforatum* *H. henryi*		[55]
Hyphenrone P (**170**)	*H. perforatum* *H. henryi*		[55]
Hyphenrone Q (**171**)	*H. perforatum* *H. henryi*		[55]
Hyperuralone A (**172**)	*H. uralum*		[64]
Hyperuralone B (**173**)	*H. uralum*		[62, 63]
Hyperuralone C (**174**)	*H. uralum*	Exhibited acetylcholinesterase inhibitory activity (IC_{50} 9.6 μ*M*)	[64]
Hyperuralone D (**175**)	*H. uralum*	1. Exhibited acetylcholinesterase inhibitory activity (IC_{50} 7.1 μ*M*) 2. Showed cytotoxic activity for three human cancer cell lines (H460, HCT-15, and MCF-7; IC_{50} 26.1, 29.8, and 32.1 μ*M*)	[64]
Hyperuralone E (**176**)	*H. uralum*	Showed cytotoxic activity for four human cancer cell lines (H460, HCT-15, MCF-7, and PC3; IC_{50} 7.0, 2.4, 6.6, and 23.8 μ*M*)	[64]
Hyperuralone F (**177**)	*H. uralum*		[64]
Hyperuralone G (**178**)	*H. uralum*		[64]
Hyperuralone H (**179**)	*H. uralum*		[64]
Hookerione A (**180**)	*H. hookerianum*		[65]
Hookerione B (**181**)	*H. hookerianum*		[65]
Hookerione C (**182**)	*H. hookerianum*		[65]
Hookerion D (**183**)	*H. hookerianum*		[65]
Hookerione E (**184**)	*H. hookerianum*		[65]
Hookerione F (**185**)	*H. hookerianum*		[65]
Hookerione G (**186**)	*H. hookerianum*		[65]
Hookerione H (**187**)	*H. hookerianum*		[65]
28,29-Epoxyplukenetione A (**188**)	*H. hookerianum*		[65]
Plukenetione A (**189**)	*H. hookerianum*		[65]
Sampsonione Q (**190**)	*H. hookerianum*	Exhibited antibacterial activity against MDR *S. aureus* strain SA-1199B (*MIC* 7.3 μ*M*)	[36, 65]
Hyperibone K (**191**)	*H. scabrum*		[33]
Sampsonione A (**192**)	*H. sampsonii*	Showed cytotoxic activity for P388 cancer cells (IC_{50} 22.2 μ*M*)	[35]
Sampsonione B (**193**)	*H. sampsonii*		[35]
Sampsonione C (**194**)	*H. sampsonii*		[35]
Sampsonione D (**195**)	*H. sampsonii*		[35]
Sampsonione E (**196**)	*H. sampsonii*		[35]
Sampsonione F (**197**)	*H. sampsonii*		[35]
Sampsonione G (**198**)	*H. sampsonii*		[35]
Sampsonione H (**199**)	*H. sampsonii*		[35]
Sampsonione I (**200**)	*H. sampsonii*	Showed cytotoxic activity for P388 cancer cells (IC_{50} 11.8 μ*M*)	[35]
Sampsonione J (**201**)	*H. sampsonii*		[35]
Sampsonione R (**202**)	*H. sampsonii*		[39]
Hyperisampsin G (**203**)	*H. hookerianum*		[65]

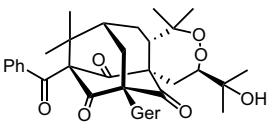
(continued)

Table 2 (continued)

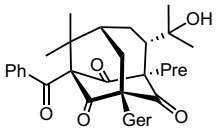
Compound name	Species	Biological activity	Ref.
Hypersampsone A (**204**)	*H. sampsonii*		[37]
Hypersampsone B (**205**)	*H. sampsonii*		[37]
Hypersampsone C (**206**)	*H. sampsonii*		[37]
Hypersampsone D (**207**)	*H. sampsonii*		[37]
Hypersampsone E (**208**)	*H. sampsonii*		[37]
Hypersampsone G (**209**)	*H. sampsonii*		[38]
Hypersampsone I (**210**)	*H. sampsonii*		[38]
Hypersampsone J (**211**)	*H. sampsonii*		[38]
Hypersampsone K (**212**)	*H. sampsonii*		[38]
Hypersampsone M (**213**)	*H. sampsonii*		[38]
Hypersampsone N (**214**)	*H. sampsonii*		[39, 40]
Hypersampsone O (**215**)	*H. sampsonii*		[39, 40]
Hypersampsone P (**216**)	*H. sampsonii*		[39, 40]
Hypersampsone Q (**217**)	*H. sampsonii*		[39, 40]
Hypersampsone S (**218**)	*H. sampsonii*		[39, 40]
Peroxysampsone A (**219**)	*H. sampsonii*	Showed antibacterial activity against a MDR strain of *S. aureus* (SA-1199B; *MIC* 79 mg/cm^3)	[69]
Peroxysampsone B (**220**)	*H. sampsonii*		[69]
Plukenetione C (**221**)	*H. sampsonii*		[69]
Dioxasampsone A (**222**)	*H. sampsonii*	Showed inhibition of cellular proliferation at 20 μ*M* (HeLa cells, 60% of cell death)	[40]
Dioxasampsone B (**223**)	*H. sampsonii*		[40]
Hyperisampsin A (**224**)	*H. sampsonii*	Showed anti-HIV activity (EC_{50} 2.97 μ*M*; selectivity index 4.80	[53]
Hyperisampsin B (**225**)	*H. sampsonii*		[53]
Hyperisampsin C (**226**)	*H. sampsonii*		[53]
Hyperisampsin D (**227**)	*H. sampsonii*	Showed anti-HIV activity (EC_{50} 0.97 μ*M*; selectivity index 7.70	[53]
Hyperisampsin E (**228**)	*H. sampsonii*		[53]
Hyperisampsin F (**229**)	*H. sampsonii*		[53]
Hyperisampsin N (**230**)	*H. sampsonii*		[66]
Hyperisampsin O (**231**)	*H. sampsonii*		[66]
Hyperandrone A (**232**)	*H. androsaemum*		[56]
Hyperattenin L (**233**)	*H. attenuatum*	Showed inhibitory activities against the HL-60, A594, and MCF-7 cancer cell lines (IC_{50} 3.86, 4.34, and 5.78 μ*M*)	[67]
Hyperattenin M (**234**)	*H. attenuatum*		[67]



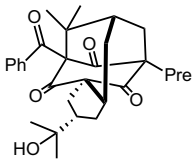
141 (otogirinin A)



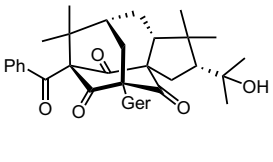
142 (otogirinin B)



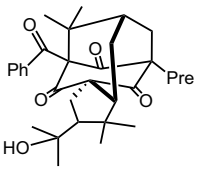
143 (otogirinin C)



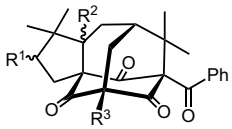
144 (attenuatumione A)



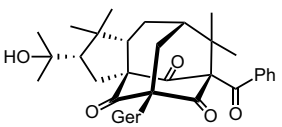
145 (attenuatumione D)



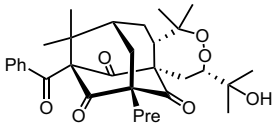
146 (plukenetione B)



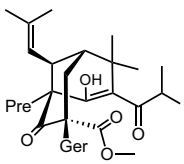
147 R^1 = OH, R^2 = β-H, R^3 = Pre (hyperattenin F)
148 R^1 = OH, R^2 = β-H, R^3 = Ger (hyperattenin G)
149 R^1 = β-OH, R^2 = β-H, R^3 = Ger (hyperattenin H)



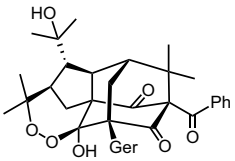
150 (hyperattenin I)



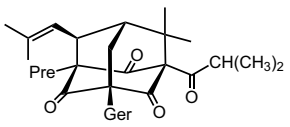
151 (peroxysampsone B)



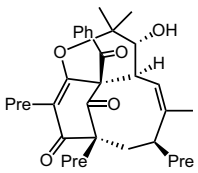
152 (hypersubone A)



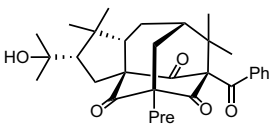
153 (hypersubone B)



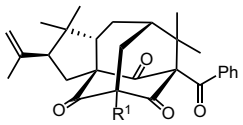
154 (hypersubone C)



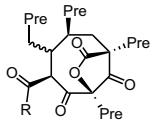
155 (hypercohin A)



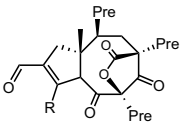
156 (hypercohone A)



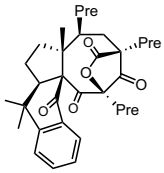
157 R = Pre (hypercohone B)
158 R = Ger (hypercohone C)



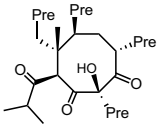
159 R = $CH(CH_3)_2$ (hyphenrone A)
160 R = Pre (hyphenrone B)
164 R = $CH(CH_3)CH_2CH_3$ (hyphenrone H)



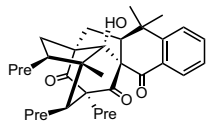
161 R = $CH(CH_3)_2$ (hyphenrone C)
165 R = $CH(CH_3)CH_2CH_3$ (hyphenrone I)



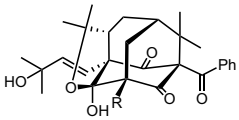
162 (hyphenrone D)



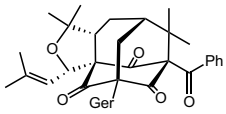
163 (hyphenrone F)



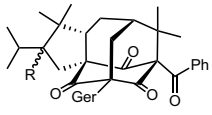
166 (hyphenrone L)



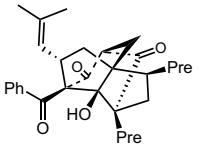
167 R = Pre (hyphenrone M)
168 R = Ger (hyphenrone N)



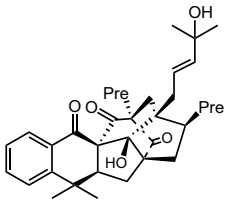
169 (hyphenrone O)



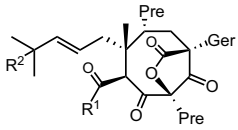
170 R = *α*-H (hyphenrone P)
171 R = *β*-H (hyphenrone Q)



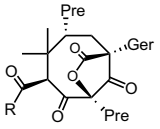
172 (hyperuralone A)



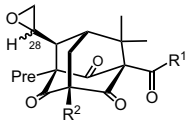
173 (hyperuralone B)



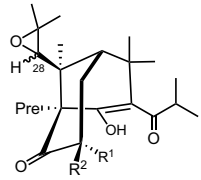
174 $R^1 = CH(CH_3)_2$, R^2 = OH (hyperuralone C)
175 $R^1 = CH(CH_3)CH_2CH_3$, R^2 = OH (hyperuralone D)
176 $R^1 = CH(CH_3)_2$, R^2 = OOH (hyperuralone E)
177 $R^1 = CH(CH_3)CH_2CH_3$, R^2 = OOH (hyperuralone F)



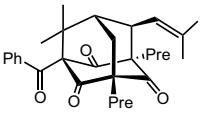
178 R = $CH(CH_3)_2$ (hyperuralone G)
179 R = $CH(CH_3)CH_2CH_3$ (hyperuralone H)



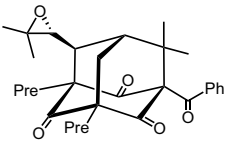
180 $R^1 = CH(CH_3)_2$, R^2 = Prenyl, ((28*S*)-hookerione A)
181 $R^1 = CH(CH_3)_2$, R^2 = Prenyl, ((28*R*)-hookerione B)
182 $R^1 = CH(CH_3)_2$, R^2 = H, ((28*R*)-hookerione C)
183 $R^1 = CH(CH_3)CH_2CH_3$, R^2 = Prenyl, ((28*R*)-hookerione D)
188 R^1 = Prenyl, R^2 = Prenyl, ((28*R*),29-epoxyplukenetione A)



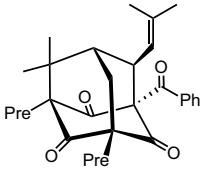
184 $R^1 = CO_2CH_3$, R^2 = geranyl, ((28*S*)-hookerione E)
185 $R^1 = CO_2CH_3$, R^2 = geranyl, ((28*R*)-hookerione F)
186 $R^1 = CO_2CH_3$, R^2 = prenyl, ((28*R*)-hookerione G)
187 R^1 = H, R^2 = geranyl, ((28*R*)-hookerione H)



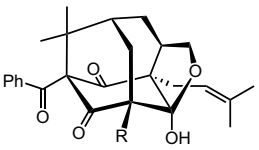
189 (plukenetione A)



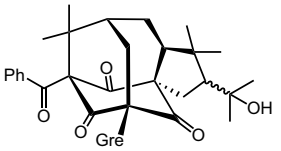
190 (sampsonione Q)



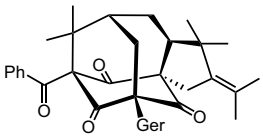
191 (hyperibone K)



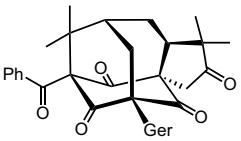
192 R = Ger (sampsonione A)
193 R = Pre (sampsonione B)



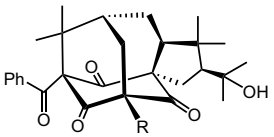
194 (sampsonione C)



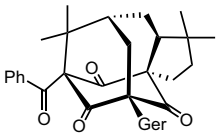
195 (sampsonione D)



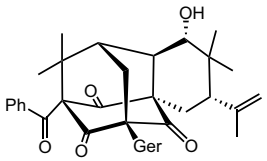
196 (sampsonione E)



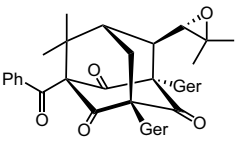
197 R = Ger (sampsonione F)
198 R = Pre (sampsonione G)



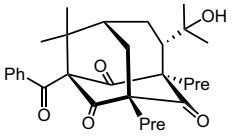
199 (sampsonione H)



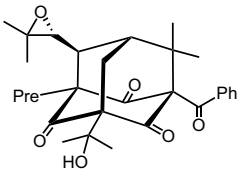
200 (sampsonione I)



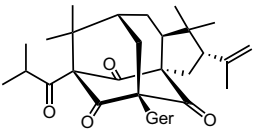
201 (sampsonione J)



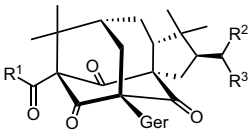
202 (sampsonione R)



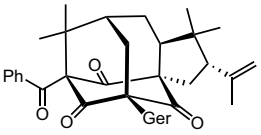
203 (hyperisampsin G)



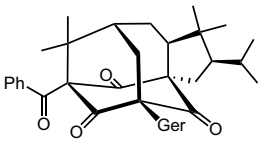
204 (hypersampsone A)



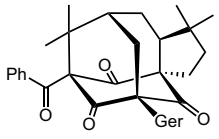
205 R^1 = $CH(CH_3)_2$, R^2 = R^3 = CH_3
(hypersampsone B)
206 R^1 = $CH(CH_3)_2$, R^2 = R^3 = H
(hypersampsone C)
208 R^1 = Prenyl, R^2 = R^3 = CH_3
(hypersampsone E)



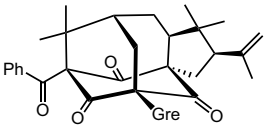
207 (hypersampsone D)



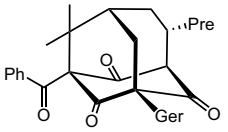
209 (hypersampsone G)



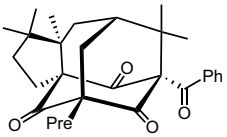
210 (hypersampsone I)



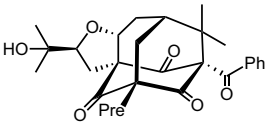
211 (hypersampsone J)



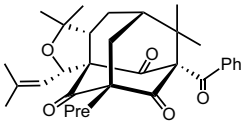
212 (hypersampsone K)



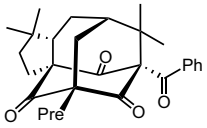
213 (hypersampsone M)



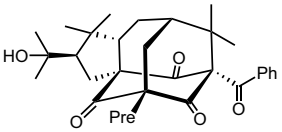
214 (hypersampsone N)



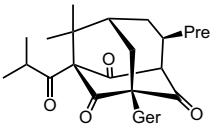
215 (hypersampsone O)



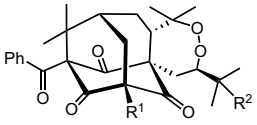
216 (hypersampsone P)



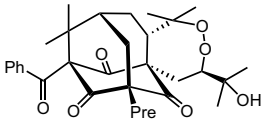
217 (hypersampsone Q)



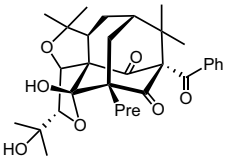
218 (hypersampsone S)



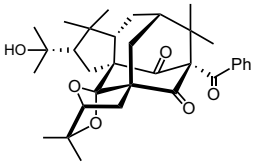
219 R^1 = Pre, R^2 = OH
(peroxysampsone A)



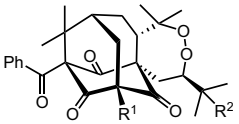
220 (peroxysampsone B)



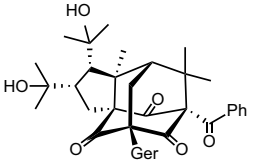
221 (plukenetione C)



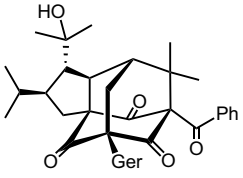
222 (dioxasampsone A)



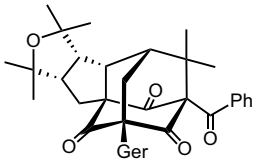
223 R^1 = Pre, R^2 = OOH
(dioxasampsone B)



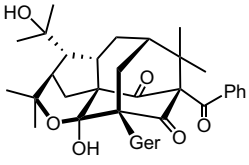
224 (hyperisampsin A)



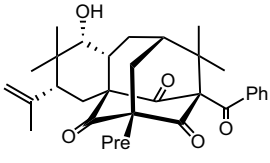
225 (hyperisampsin B)



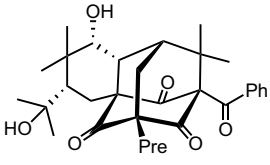
226 (hyperisampsin C)



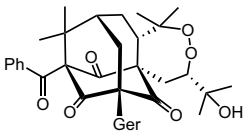
227 (hyperisampsin D)



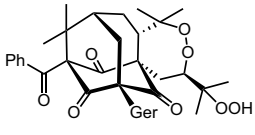
228 (hyperisampsin E)



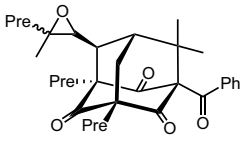
229 (hyperisampsin F)



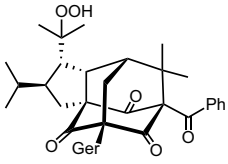
230 (hyperisampsin N)



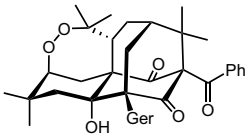
231 (hyperisampsin O)



232 (hyperandrone A)



233 (hyperattenin L)



234 (hyperattenin M)

2.2.1 Rottlerin-Type Compounds

Rottlerin-type compounds, with phloroglucinol and filicinic acid moieties linked by a methylene bridge, possess acetyl, *n*-propionyl, *iso*-butyryl, or 2-methylbutyryl residues attached to the two carbocyclic rings present [6]. Rottlerin-type compounds can be found as constituents of plants in the sections Brathys and Trigynobrathys of the genus *Hypericum* [6]. Rottlerin-type compounds are the main phloroglucinols in *Hypericum perforatum* (St. John's wort).

From *H. uligunosum*, uliginosins A (**235**) and B (**236**) were isolated in 1968 [70], and isouliginosin B (**237**) has been found in many *Hypericum* species, such as *H. andinum*, *H. brevistylum*, and *H. laricifolium* [6]. Further to an investigation of *H. japonicum*, sarothralens A–D (**238**–**241**) were identified [71, 72]. Additionally, sarothralin (**242**), sarothralin G (**243**) [71], and the saroaspidins A–C (**244**–**246**) [73] were also obtained from this species.

From phytochemical investigations of *H. drummondii*, drummondins A–F (**247**–**252**), albaspidin AA (**255**), albaspidin PP (**256**) [74, 75], and isodrummondins C (**253**) and D (**254**) [76] were purified and characterized structurally.

In 1988, Gu et al. isolated four new acylphloroglucinol derivatives, japonicines A–D (**257**–**260**), from the medicinal plant *H. japonicum* [77].

Other rottlerin-type compounds found in *H. brasiliense* have been hyperbrasilol A (**261**) and hyperbrasilol C (**263**) [78]. In studies of *H. brasiliense*, *H. caprifoliatum*, *H. connatum*, and *H. laricifolium*, hyperbrasilol B (**262**) was found [79]. Isohyperbrasilol B (**264**), an isomer of hyperbrasilol B (**262**), was isolated from *H. brasiliense,* along with hyperlaricifolin (**266**) [78].

Recently, andinin A (**265**) was obtained from *H. andinum* [80]. In a further investigation of *H. austrobrasiliense,* three rottlerin-type compounds, austrobrasilol A (**267**) and B (**268**) and isoaustrobrasilol B (**269**) were identified [81]. Furthermore, five rottlerin-type compounds, hyperjaponicols A–D (**270**–**273**) and

sarothralen C (**274**), were reported from *H. japonicum,* and most of them displayed appreciable antibacterial activity [82]. Finally, from the roots of *H. polyanthemum*, a mixture of japonicines A (**275a/b**) was isolated [83].

The biological properties of rottlerin-type compounds **235**–**275** as isolated from *Hypericum* species are summarized in Table 3.

Table 3 Rottlerin-type compounds

Compound name	Species	Biological activity	Ref.
Uliginosin A (**235**)	*H. thesiifolium*	1. Antinociceptive effects in mice (15 mg/kg) 2. Antidepressant-like activity in mice (10 mg/kg) 3. Anti-*Trichomonas vaginalis* activity (IC_{50} 125.5 μ*M*)	[84, 85, 70, 86]
Uliginosin B (**236**)	*H. uliginosum*	1. Antinociceptive activity in mice (15 mg/kg; p.o.) 2. Antidepressant-like activity in mice (10 mg/kg; p.o.) 3. Antiprotozoal activity against *Trichomonas vaginalis* (IC_{50} 122.0 μ*M*) 4. Antibacterial activity against *S. aureus* (MIC_{50} 6 μ*M*)	[70]
Isouliginosin B (**237**)	*H. andinum*	Antibacterial activities against *S. aureus* (*MIC* 3 μ*M*) and *S. epidermidis* (*MIC* 6 μ*M*)	[6]
Sarothralen A (**238**)	*H. japonicum*		[71, 72]
Sarothralen B (**239**)	*H. japonicum*		[71, 72]
Sarothralen C (**240**)	*H. japonicum*		[71, 72]
Sarothralen D (**241**)	*H. japonicum*		[71, 72]
Sarothralin (**242**)	*H. japonicum*		[71, 72]
Sarothralin G (**243**)	*H. japonicum*		[71]
Saroaspidin A (**244**)	*H. japonicum*		[73]
Saroaspidin B (**245**)	*H. japonicum*		[73]
Saroaspidin C (**246**)	*H. japonicum*		[73]
Drummondin A (**247**)	*H. drummondii*	1. Exhibited antibacterial activitity against *S. aureus*, *B. subtilis*, and *M. smegmatis* (*MIC* 1.56, 0.78, and 1.56 μg/cm^3) 2. Showed cytotoxic activity for murine and human cancer cell lines (P388, KB, breast, colon, lung, and melanoma; ED_{50} 2.1, 4.5, 3.4, 6.6, 4.5, and 8.0 μg/cm^3)	[74, 75]
Drummondin B (**248**)	*H. drummondii*	1. Exhibited antibacterial activitity against *S. aureus*, *B. subtilis*, and *M. smegmatis* (*MIC* 3.12, 0.39, and 1.56 μg/cm^3) 2. Showed cytotoxic activity for murine and human cancer cell lines (P388, KB, colon, lung, and melanoma; ED_{50} 1.9, 3.1, 6.3, 7.0, and 5.0 μg/cm^3)	[74, 75]
Drummondin C (**249**)	*H. drummondii*	1. Exhibited antibacterial activitity against *S. aureus*, *B. subtilis*, and *M. smegmatis* (*MIC* 3.12, 1.56, and 6.25 μg/cm^3) 2. Showed cytotoxic activity for murine and human cancer cell lines (P388, KB, breast, colon, lung, and melanoma; ED_{50} 2.8, 8.6, 5.1, 11, 8.7, and 12 μg/cm^3)	[74, 75]
Drummondin D (**250**)	*H. drummondii*		[74, 75]
Drummondin E (**251**)	*H. drummondii*		[74, 75]
Drummondin F (**252**)	*H. drummondii*	1. Exhibited antibacterial activity against *S. aureus*, *B. subtilis*, and *M. smegmatis* (*MIC* 0.78, 0.78, and 1.5 6 μg/cm^3) 2. Showed cytotoxic activity for five murine and human cancer cell lines (P388, KB, breast, colon, lung; IC_{50} 18 – >50 μg/cm^3)	[74, 75]

(continued)

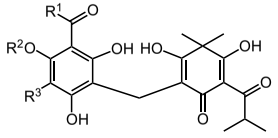
Table 3 (continued)

Compound name	Species	Biological activity	Ref.
Isodrummondin C (**253**)	*H. drummondii*		[74, 75]
Isodrummondin D (**254**)	*H. drummondii*		[74, 75]
Albaspidin AA (**255**)	*H. drummondii*		[74]
Albaspidin PP (**256**)	*H. drummondii*		[74]
Japonicine A (**257**)	*H. japonicum* *H. brasiliense* *H. myrianthum* *H. ternum*		[87, 88, 77]
Japonicine B (**258**)	*H. japonicum*		[77]
Japonicine C (**259**)	*H. japonicum*		[77]
Japonicine D (**260**)	*H. japonicum*		[77]
Hyperbrasilol A (**261**)	*H. brasiliense*		[78]
Hyperbrasilol B (**262**)	*H. laricifolium*	Antidepressant-like activity in mice (10 mg/kg, p.o.)	[79]
Hyperbrasilol C (**263**)	*H. brasiliense*		[78]
Isohyperbrasilol B (**264**)	*H. brasiliense* *H. laricifolium*		[6, 78]
Andinin A (**265**)	*H. andinum*	Antidepressant-like activity in mice (3 mg/kg)	[80]
Hyperlaricifolin (**266**)	*H. laricifolium*		[78]
Austrobrasilol A (**267**)	*H. austrobrasiliense*	Exhibited antinociceptive activity in mice (16.7 mg/kg, p.o.)	[81]
Austrobrasilol B (**268**)	*H. austrobrasiliense*	Exhibited antinociceptive activity in mice (16.6 mg/kg, p.o.)	[81]
Isoaustrobrasilol B (**269**)	*H. austrobrasiliense*	Exhibited antinociceptive activity in mice (16.5 mg/kg, p.o.)	[81]
Hyperjaponicol A (**270**)	*H. japonicum*	Exhibited antibacterial activity against *E. coli* (*MIC* 1.8 μ*M*), *S. aureus* (1.8 μ*M*), *S. typhimurium* (0.9 μ*M*), and *E. faecalis* (1.8 μ*M*)	[82]
Hyperjaponicol B (**271**)	*H. japonicum*	Exhibited antibacterial activity against *E. coli* (*MIC* 0.9 μ*M*), *S. aureus* (3.4 μ*M*), *S. typhimurium* (1.7 μ*M*), and *E. faecalis* (1.7 μ*M*)	[82]
Hyperjaponicol C (**272**)	*H. japonicum*	Showed lipase inhibitory activity (IC_{50} 8.3 μ*M*)	[82]
Hyperjaponicol D (**273**)	*H. japonicum*	Exhibited antibacterial activity against *E. coli* (*MIC* 0.9 μ*M*), *S. aureus* (1.7 μ*M*), *S. typhimurium* (0.9 μ*M*), and *E. faecalis* (0.9 μ*M*)	[82]
Sarothralen C (**274**)	*H. japonicum*		[82]
Japonicines A (**275a/b**)	*H. polyanthemum*	Exhibited antinociceptive activity in the mouse hot-plate test but did not induce motor impairment using the rotarod apparatus	[83]

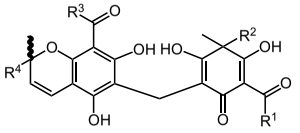
2.2.2 Spirocyclic Phloroglucinols

The naturally occurring spirocyclic phloroglucinols are a special subgroup of phloroglucinol derivatives characterized by a 6/6/5 tricyclic spiro ring system, and have attracted extensive interest in the chemical and pharmacological communities due to their complex chemical structures and notable bioactivities [89].

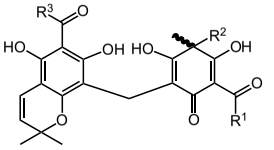
From *H. chinense*, the spirocyclic phloroglucinol presenting a cyclopenta-1,3-dione moiety, biyouanagiol (**276**) was isolated [90]. Investigation of this species led to the purification of chipericumins A–D (**277**–**280**) [91]. Recently, from *H. riparium*, chipericumin E (**281**) was reported [92].



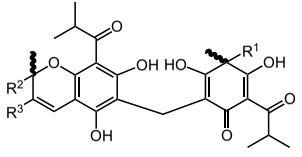
235 R^1 = $CH(CH_3)_2$, R^2 = H, R^3 = Pre (uliginosin A)
238 R^1 = $CH(CH_3)_2$, R^2 = H, R^3 = Ger (sarothralen A)
242 R^1 = Pre, R^2 = Pre, R^3 = H (sarothralin)
243 R^1 = Pre, R^2 = H, R^3 = Ger (sarothralin G)
259 R^1 = Pre, R^2 = Pre, R^3 = H (japonicine C)



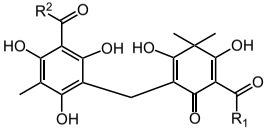
236 R^1 = R^3 = $CH(CH_3)_2$, R^2 = R^4 = CH_3 (uliginosin B)
239 R^1 = R^3 = $CH(CH_3)_2$, R^2 = CH_3, R^4 = Pre (sarothralen B)
250 R^1 = R^3 = R^4 = CH_3, R^2 = Pre (drummondin D)
258 R^1 = R^3 = $CH(CH_3)_2$, R^2 = CH_3, R^4 = Pre (japonicine B)



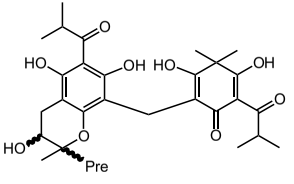
237 R^1 = R^3 = $CH(CH_3)_2$, R^2 = CH_3 (isouliginosin B)
253 R^1 = R^3 = CH_3, R^2 = Pre (isodrummondin C)
254 R_1 = R^2 = R_3= CH_3 (isodrummondin D)



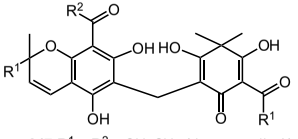
240 R^1 = CH_3, R^2 = Pre, R^3 = OH (sarothralen C)
266 R^1 = R^2 = Pre, R^3 = H (hyperlaricifolin)



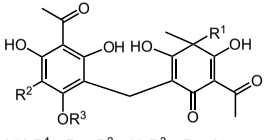
244 R^1 = R^2 = $CH(CH_3)_2$ (saroaspidin A)
245 R^1 = $CH(CH_3)_2$, R^2 = $CH(CH_3)CH_2CH_3$ (saroaspidin B)
246 R^1 = R^2 = $CH(CH_3)CH_2CH_3$ (saroaspidin C)



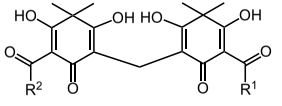
241 (sarothralen D)



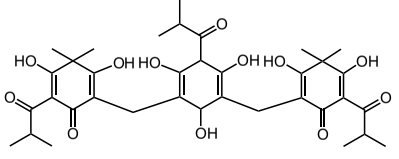
247 R^1 = R^2 = CH_2CH_3 (drummondin A)
248 R^1 = CH_3, R^2 = CH_2CH_3 (drummondin B)
249 R^1 = R^2 = CH_3 (drummondin C)



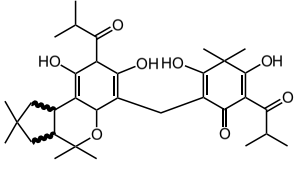
251 R^1 = Pre, R^2 = H, R^3 = Pre (drummondin E)
252 R^1 = Pre, R^2 = Pre, R^3 = H (drummondin F)



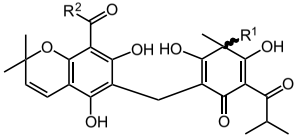
255 R^1 = R^2 = CH_2CH_3 (albaspidin AA)
256 R^1 = R^2 = CH_3 (albaspidin PP)
257 R^1 = R^2 = $CH(CH_3)_2$ (japonicine A)



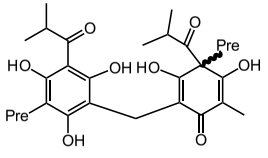
260 (japonicine D)



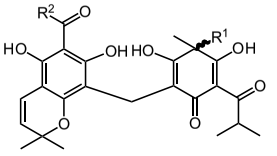
261 (hyperbrasilol A)



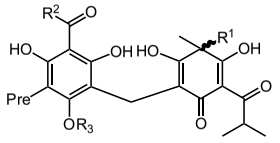
262 R^1 = Pre, R^2 = $CH(CH_3)_2$ (hyperbrasilol B)
268 R^1 = Pre, R^2 = $CH_2CH_2CH_3$ (austrobrasilol B)



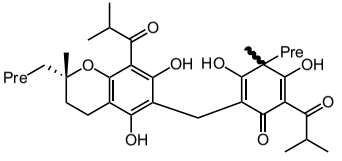
263 (hyperbrasilol C)



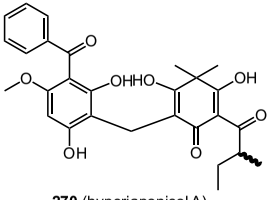
264 R^1 = Pre, R^2 = $CH(CH_3)_2$ (isohyperbrasilol B)
269 R^1 = Pre, R^2 = $CH_2CH_2CH_3$ (isoaustrobrasilol B)



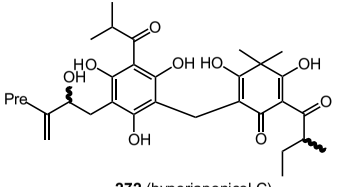
265 R^1 = CH_3, R^2 = $CH(CH_3)_2$, R^3 = Pre (andinin A)
267 R^1 = Pre, R^2 = $CH_2CH_2CH_3$, R^3 = H (austrobrasilol A)



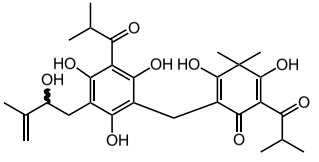
266 (hyperlaricifolin)



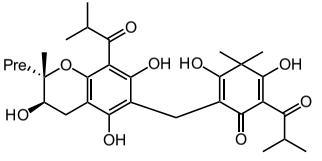
270 (hyperjaponicol A)



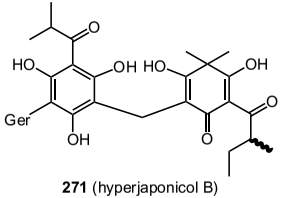
272 (hyperjaponicol C)



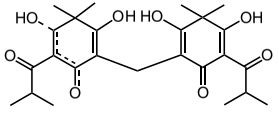
273 (hyperjaponicol D)



274 (sarothralen C)



271 (hyperjaponicol B)



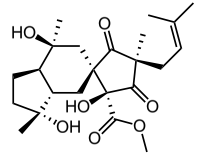
275a/b (japonicines A)

In 2008, Hashida et al. reported eight spirocyclic phloroglucinols, tomoeones A–H (**282**–**289**), from *H. ascyron* [93]. Further investigation of the same species resulted in eight analogues, namely, hyperascyrones A–H (**290**–**297**) [89]. In a study on stems and leaves of *H. perforatum*, spirohypolactone A (**298**) was found [94]. From the ethyl acetate fraction of *H. henryi*, three spirocyclic polycyclic polyprenylated acylphloroglucinols, hyperhenones G–I (**299**–**301**), were characterized [95].

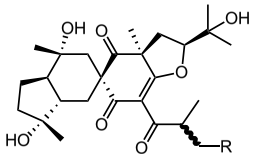
The biological properties of the spirocyclic phloroglucinols **276**–**301** as isolated from *Hypericum* species are shown in Table 4. These molecules are unusual and would present a considerable challenge in terms of chemical synthesis. However, given their complex and unusual molecular shapes, they may well attract considerable future interest from synthesis-oriented chemists.

Table 4 Spirocyclic phloroglucinols

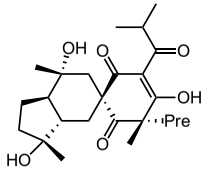
Compound name	Species	Biological activity	Ref.
Biyouanagiol (**276**)	*H. chinense*	Showed cytotoxicity for KB-C2 multidrug resistant (MDR) cancer cells (IC_{50} 47.8 μg/cm^3)	[91]
Chipericumin A (**277**)	*H. chinense*		[91]
Chipericumin B (**278**)	*H. chinense*		[91]
Chipericumin C (**279**)	*H. chinense*		[91]
Chipericumin D (**280**)	*H. chinense*		[91]
Chipericumin E (**281**)	*H. riparium*		[93]
Tomoeone A (**282**)	*H. ascyron*		[93]
Tomoeone B (**283**)	*H. ascyron*		[93]
Tomoeone C (**284**)	*H. ascyron*		[93]
Tomoeone D (**285**)	*H. ascyron*		[93]
Tomoeone E (**286**)	*H. ascyron*		[93]
Tomoeone F (**287**)	*H. ascyron*	Showed cytotoxicity for an epidermoid carcinoma cell line (KB; IC_{50} 6.2 μ*M*)	[93]
Tomoeone G (**288**)	*H. ascyron*		[93]
Tomoeone H (**289**)	*H. ascyron*		[93]
Hyperascyrone A (**290**)	*H. ascyron*		[89]
Hyperascyrone B (**291**)	*H. ascyron*		[89]
Hyperascyrone C (**292**)	*H. ascyron*	Showed cytotoxicity for a human cancer cell line (HL-60, myeloid leukemia; IC_{50} 4.22 μ*M*)	[89]
Hyperascyrone D (**293**)	*H. ascyron*		[89]
Hyperascyrone E (**294**)	*H. ascyron*		[89]
Hyperascyrone F (**295**)	*H. ascyron*		[89]
Hyperascyrone G (**296**)	*H. ascyron*	Showed cytotoxicity for a human cancer cell line (HL-60, myeloid leukemia; IC_{50} 8.36 μ*M*)	[89]
Hyperascyrone H (**297**)	*H. ascyron*		[89]
Spirohypolactone A (**298**)	*H. revolutum*		[95]
Hyperhenone G (**299**)	*H. henryi*		[95]
Hyperhenone H (**300**)	*H. henryi*		[95]
Hyperhenone I (**301**)	*H. henryi*		[95]



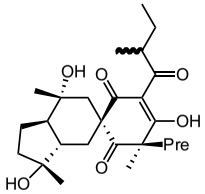
276 (biyouanagiol)



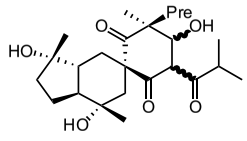
277 R = H (chipericumin A)
278 R = CH_3 (chipericumin B)



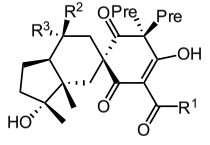
279 (chipericumin C)



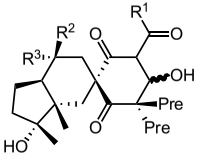
280 (chipericumin D)



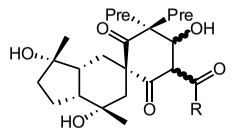
281 (chipericumin E)



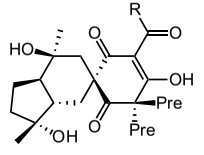
282 R^1 = $CH(CH_3)_2$, R^2 = CH_3, R^3 = OH (tomoeone A)
284 R^1 = $CH(CH_3)_2$, R^2 = OH, R^3 = CH_3 (tomoeone C)
286 R^1 = $CH_2CH(CH_3)_2$, R_2 = CH_3, R^3 = OH (tomoeone E)
288 R^1 = $CH_2CH(CH_3)_2$, R_2 = OH, R^3 = CH_3 (tomoeone G)



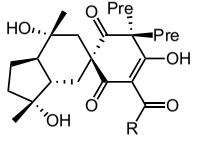
283 R^1 = $CH(CH_3)_2$, R^2 = CH_3, R^3 = OH (tomoeone B)
285 R^1 = $CH(CH_3)_2$, R^2 = OH, R^3 = CH_3 (tomoeone D)
287 R^1 = $CH_2CH(CH_3)_2$, R^2 = CH_3, R^3 = OH (tomoeone F)
289 R^1 = $CH_2CH(CH_3)_2$, R^2 = OH, R^3 = CH_3 (tomoeone H)



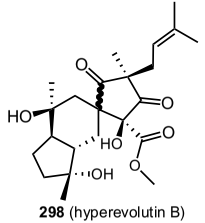
290 R = Ph (hyperascyrone A)
291 R = $CH(CH_3)_2$ (hyperascyrone B)
292 R = $CH_2CH(CH_3)_2$ (hyperascyrone C)



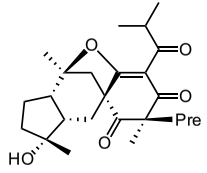
293 R = $CH(CH_3)_2$ (hyperascyrone D)
294 R = $CH_2CH(CH_3)_2$ (hyperascyrone E)



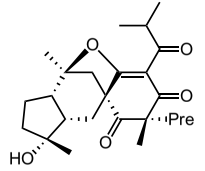
295 R = $CH(CH_3)CH_2CH_3$ (hyperascyrone F)
296 R = $CH(CH_3)_2$ (hyperascyrone G)
297 R = $CH_2CHCH_2(CH_3)_2$ (hyperascyrone H)



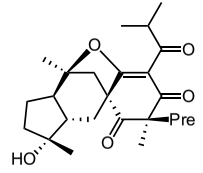
298 (hyperevolutin B)



299 (hyperhenone G)



300 (hyperhenone H)



301 (hyperhenone I)

2.2.3 Simple Benzophenones

Simple benzophenones are a class of phloroglucinol derivatives that consist of 87 members, as isolated from the species in the genus *Hypericum*. Many of the simple benzophenones contain benzoyl groups and most are substituted with sugar units, or prenyl and geranyl residues.

In 2009, after investigation of the AcOEt extract of *H. thasium*, four benzophenone derivatives, 2-(3,5-dihydroxybenzoyl)-3,5-dihydroxyphenyl-*β*-D-xylopyranoside (**302**), 2-(3,5-dihydroxybenzoyl)-3-hydroxy-5-methoxyphenyl-*β*-D-xylopyranoside (**303**), 2-(3,5-dihydroxybenzoyl)-3,5-dihydroxyphenyl 4-*O*-acetyl-*β*-D-xylopyranoside (**304**), 2-(3,5-dihydroxy-benzoyl)-3,5-dihydroxyphenyl-3-*O*-acetyl-α-L-arabinopyranoside (**305**) and the known compound garcimangosone D (**306**) [96] were reported. Annulatophenonoside (**307**) and acetylannulatophenonoside (**308**), two benzophenone *O*-arabinosides, were found in a methanol extract of *H. annulatum* [97]. From a cell suspension culture of *H. patulum*, paglucinol (**309**) was isolated [98]. As a result of a chemical study on the aerial parts of *H. pseudopetiolatum*, four benzophenone *O*-rhamnosides, petiolins F–I (**310**–**313**), were isolated and characterized [99].

Elegaphenonoside (**314**) was identified from the aerial parts of *H. elegans*, along with the two known compounds, hypericophenonoside (**315**) and neoannulatophenonoside (**316**) [100]. In 2004, as a result of the phytochemical investigation of *H. styphelioides*, 4-benzoyl-2,6-dihydroxyphenyl-*β*-D-glucopyranoside (**317**) was isolated [101]. Two new benzophenones, cariphenones A (**318**) and B (**319**), were isolated from the leaves of *H. carinatum* [102]. From *H. sampsonii*, (*E*)-(2,6-dihydroxy-4-((7-hydroxy-3,7-dimethyloct-2-en-1-yl)oxy)phenyl)(phenyl) methanone (**320**) and (*E*)-(2,6-dihydroxy-4-((5-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)oxy)phenyl)(phenyl)methanone (**321**), were obtained [103]. Based on co-treatment with copper sulfate and methyl jasmonate in comparison of the profile by TLC with methyl jasmonate alone, the authors studied the roots of *H. erectum*, and, consequently, otogirinins F (**322**) and G (**323**) were found [104].

Four simple benzophenones, hyperbeanols A–D (**324**–**327**), were reported from *H. beanii* in 2011 [105]. In turn, norsampsones A–D (**328**–**331**), with an unusual skeleton, have been found to occur in *H. sampsonii* [106]. From *H. densiflorum*, 4-geranyloxy-2,6-dihydroxybenzophenone (**332**) was isolated, and its biological activities have been studied extensively [107].

Ellipticophenone A (**333**) was identified from *H. ellipticum* [108] and cariphenones A (**334**) and B (**335**), phloroglucinol derivatives with a benzophenone skeleton, were characterized from *H. carinatum* [102]. In 2013, Cheng et al. isolated three new simple benzophenones, namely, hyperinakin (**336**), (*R*)-phenyl (2,4,6-trihydroxy-3-(2-hydroxy-7-methyl-3-methyleneoct-6-en-1-yl)phenyl)methanone (**337**), and (*E*)-(3-(3,7-dimethylocta-2,6-dien-1-yl)-2,4,6-trihydroxyphenyl) (phenyl)methanone (**338**) from *H. nakamurai* [109]. From *H. annulatum*, hypericophenoside (**339**), annulate–phenonoside (**340**), and acetylannulatophenonoside (**341**) were obtained [110]. In 2009, Tanaka et al. studied *H. kiusianum,* and, as a result, four new compounds, petiolins F–I (**342**–**345**) were documented [99].

From *H. thasium*, 4,3′,5′-trihydroxy-6-methoxy-2-*O*-α-L-arabinosyl-benzophenone (**346**), 4,6,3′,5′-tetrahydroxy-2-*O*-α-L-arabinosyl-benzophenone (**347**), 4,3′-dihydroxy-5′-methoxy-2-*O*-α-L-arabinosyl-6-*O*-β-D-xylosyl-benzophenone (**348**) were isolated [111]. Other glycosylated benzophenones have also been isolated from *Hypericum humifusum* ssp. *austral*. including 2,4,6,3′,5′-pentahydroxy-benzophenone 4-*O*-(6″-benzoyl)-β-D-glucopyranoside (**349**), 2,4,6,3′,5′-pentahydroxy-benzophenone 4-*O*-β-D-glucopyranoside (**350**), 2,4,6,3′,5′-pentahydroxy-benzophenone 2-*O*-(2″-benzoyl)-α-L-arabinopyranoside (**351**), 2,4,6,3′,5′-pentahydroxy-benzophenone-2-*O*-α-L-arabino-pyranoside (**352**), 2,4,6,3′,5′-pentahydroxy-benzophenone 2-*O*-(4″-acetyl)-β-D-xylopyranoside (**353**), and 2,4,6,3′,5′-pentahydroxy-benzophenone-3-*C*-(4″-benzoyl)-β-D-glucopyranoside (**354**) [112].

In 2012, Osman et al. reported the new benzophenone hypercalin B (**355**) in *H. acmosepalum*, in which two prenyl residues are linked to phloroglucin [113]. From a study of the chemical constituents of the aerial parts of *H. beanii,* hypercohone G (**356**) was isolated [114]. By chirospecific separation, two diastereomeric enantiomeric benzophenone pairs, (+)- and (–)-sampsonins A and B (**357**–**360**), were characterized from *H. sampsonii* [115]. Similarly, the two enantiomers (+)-(**361**) and (–)-japonicol H (**362**) were acquired from *H. japonicum* [116].

More recently, from *H. elodeoides*, two benzophenones, hypelodins A (**363**) and B (**364**), were isolated [117]. From *H. patulum*, hyperpatulone E (**365**) [118], and the hyperpatulols A (**366**) and B (**367**) were isolated [119]. Norascyrononeses A (**368**) and B (**369**), characterized as 2,3,4-*nor*-polycyclic polyprenylated acylphloroglucinols, together with norascyronone C (**370**) were obtained from *H. ascyron* [120].

Hypercohin K (**371**), with an unusual spiro-fused cyclopropane ring, was obtained from *H. cohaerens* [121]. Studies carried out with *H. sampsonii* resulted in the isolation of six compounds, norsampsones A–D (**328**–**331**), norhypersampsone A (**372**), and phenyl(2,4,6-trihydroxy-3-(2-hydroxy-7-methyl-3-methyleneoct-6-en-1-yl)-5-(3-methylbut-2-en-1-yl)phenyl)methanone (**373**) [106].

From *H. sampsonii*, sampbenzophenones A–G (**374**–**380**), seven new benzophenones were reported [122]. Finally, hyperhenones J–M (**381**–**384**) were found in *H. henryi* [95].

The biological properties of the simple benzophenones **302**–**384** isolated from *Hypericum* species are shown in Table 5.

Table 5 Simple benzophenones

Compound name	Species	Biological activity	Ref.
2-(3,5-Dihydroxybenzoyl)-3,5-dihydroxyphenyl-*β*-D-xylopyranoside (**302**)	*H. thasium*		[96]
2-(3,5-Dihydroxybenzoyl)-3-hydroxy-5-methoxyphenyl-*β*-D-xylopyranoside (**303**)	*H. thasium*		[96]
2-(3,5-Dihydroxybenzoyl)-3,5-dihydroxyphenyl-l4-*O*-acetyl-*β*-D-xylopyranoside (**304**)	*H. thasium*		[96]
2-(3,5-Dihydroxybenzoyl)-3,5-dihydroxyphenyl-3-*O*-acetyl-α-L-arabinopyranoside (**305**)	*H. thasium*		[96]
Garcimangosone D (**306**)	*H. thasium*		[96]
Annulatophenonoside (**307**)	*H. annulatum*		[98]
Acetylannulatophenonoside (**308**)	*H. annulatum*		[98]
Paglucinol (**309**)	*H. patulum*		[98]
Petiolin F (**310**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Petiolin G (**311**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Petiolin H (**312**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Petiolin I (**313**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Elegaphenonoside (**314**)	*H. elegans*		[100]
Hypericophenonoside (**315**)	*H. elegans*		[100]
Neoannulatophenonoside (**316**)	*H. elegans*		[100]
4-Benzoyl-2,6-dihydroxyphenyl-*β*-D-glucopyranoside (**317**)	*H. styphelioides*		[101]
Cariphenone A (**318**)	*H. carinatum*		[102]
Cariphenone B (**319**)	*H. carinatum*		[102]
(*E*)-(2,6-Dihydroxy-4-((7-hydroxy-3,7-dimethyloct-2-en-1-yl)oxy)phenyl)(phenyl)methanone (**320**)	*H. sampsonii*		[103]
(*E*)-(2,6-Dihydroxy-4-((5-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)oxy)phenyl)(phenyl)methanone (**321**)	*H. sampsonii*		[103]
Otogirinin F (**322**)	*H. erectum*		[104]
Otogirinin G (**323**)	*H. erectum*		[104]
Hyperbeanol A (**324**)	*H. beanii*		[105]
Hyperbeanol B (**325**)	*H. beanii*	Showed cytotoxicity for a tumor cell line (K-562, chronic myelogenous leukemia; IC_{50} 16.9 μ*M*)	[105]
Hyperbeanol C (**326**)	*H. beanii*		[105]
Hyperbeanol D (**327**)	*H. beanii*	Showed cytotoxicity for a tumor cell line (K-562, chronic myelogenous leukemia; IC_{50} 20.7 μ*M*)	[105]
Norsampsone A (**328**)	*H. sampsonii*		[106]
Norsampsone B (**329**)	*H. sampsonii*		[106]
Norsampsone C (**330**)	*H. sampsonii*		[106]

(continued)

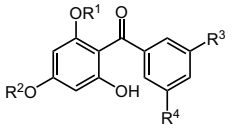
Table 5 (continued)

Compound name	Species	Biological activity	Ref.
Norsampsone D (**331**)	*H. sampsonii*		[106]
4-Geranyloxy-2,6-dihydroxybenzophenone (**332**)	*H. densiflorum*	1. Showed antibiotic effects against *MRSA* (IC_{50} 0.87 μg/cm^3) and *M. smegmatis* (ATCC 607; IC_{50} 12.5 mg/cm^3 2. Demonstrated cytotoxic activity against five cancer cell lines (MCF-7, NCI: H460, AGS, and HCT-116; IC_{50} 14.9, 4.1, 28.6, 12.4, and 8.2 μg/cm^3)	[107]
Ellipticophenone A (**333**)	*H. ellipticum*		[108]
Cariphenone A (**334**)	*H. carinatum*	Showed antioxidant activity	[102]
Cariphenone B (**335**)	*H. carinatum*		[102]
Hyperinakin (**336**)	*H. nakamurai*	Demonstrated an anti-inflammatory effect (IC_{50} 20 μ*M*)	[109]
(*R*)-Phenyl(2,4,6-trihydroxy-3-(2-hydroxy-7-methyl-3-methyleneoct-6-en-1-yl) phenyl)methanone (**337**)	*H. nakamurai*		[109]
(*E*)-(3-(3,7-Dimethylocta-2,6-dien-1-yl)-2,4,6-trihydroxyphenyl)(phenyl) methanone (**338**)	*H. nakamurai*		[109]
Hypericophenoside (**339**)	*H. annulatum*		[110]
Annulatophenonoside (**340**)	*H. annulatum*		[110]
Acetylannulatophenonoside (**341**)	*H. annulatum*		[110]
Petiolin F (**342**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Petiolin G (**343**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Petiolin H (**344**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
Petiolin I (**345**)	*H. pseudopetiolatum* var. *kiusianum*		[99]
4,3′,5′-Trihydroxy-6-methoxy-2-*O*-α-L-arabinosylbenzophenone (**346**)	*H. humifusum* ssp. *austral*		[111]
4,3′,5′,6-Tetrahydroxy-2-*O*-α-L-arabinosylbenzophenone (**347**)	*H. humifusum* ssp. *austral*		[111]
4,3′-Dihydroxy-5′-methoxy-2-*O*-α-L-arabinosyl-6-*O*-β-D-xylosylbenzophenone (**348**)	*H. humifusum* ssp. *austral*		[111]
2,4,6,3′,5′-Pentahydroxy-benzophenone-4-*O*-(6″-benzoyl)-β-D-glucopyranoside (**349**)	*H. humifusum* ssp. *austral*		[112]
2,4,6,3′,5′-Pentahydroxy-benzophenone-4-*O*-β-D-glucopyranoside (**350**)	*H. humifusum* ssp. *austral*		[112]
2,4,6,3′,5′-Pentahydroxy-benzophenone-2-*O*-(2″-benzoyl)-α-L-arabinopyranoside (**351**)	*H. humifusum* ssp. *austral*		[112]
2,4,6,3′,5′-Pentahydroxy-benzophenone-2-*O*-α-L-arabinopyranoside (**352**)	*H. humifusum* ssp. *austral*		[112]
2,4,6,3′,5′-Pentahydroxy-benzophenone-2-*O*-(4″-acetyl)-β-D-xylopyranoside (**353**)	*H. humifusum* ssp. *austral*		[112]
2,4,6,3′,5′-Pentahydroxy-benzophenone-3-*C*-(4″-benzoyl)-β-D-glucopyranoside (**354**)	*H. humifusum* ssp. *austral*		[112]

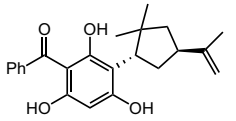
(continued)

Table 5 (continued)

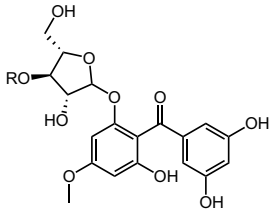
Compound name	Species	Biological activity	Ref.
Hypercalin B (**355**)	*H. acmosepalum*		[113]
Hypercohone G (**356**)	*H. beanii*		[114]
(+)-Sampsonin A (**357**)	*H. sampsonii*	Inhibited proliferation of Hela cells (20 μ*M*)	[115]
(–)-Sampsonin A (**358**)	*H. sampsonii*	Inhibited proliferation of Hela cells (20 μ*M*)	[115]
(+)-Sampsonin B (**359**)	*H. sampsonii*	Inhibited proliferation of Hela cells (20 μ*M*)	[115]
(–)-Sampsonin B (**360**)	*H. sampsonii*	Inhibited proliferation of Hela cells (20 μ*M*)	[115]
(+)-Japonicol H (**361**)	*H. japonicum*	Exhibited inhibitory activity towards the lytic replication of KSHV in Vero cells (IC_{50} 4.90 μ*M*; selectivity index 25.70)	[116]
(–)-Japonicol H (**362**)	*H. japonicum*		[116]
Hypelodin A (**363**)	*H. elodeoides*		[117]
Hypelodin B (**364**)	*H. elodeoides*		[117]
Hyperpatulone E (**365**)	*H. patulum*		[118]
Hyperpatulol A (**366**)	*H. patulum*		[119]
Hyperpatulol B (**367**)	*H. patulum*		[119]
Norascyronone A (**368**)	*H. ascyron*		[120]
Norascyronone B (**369**)	*H. ascyron*		[120]
Norascyronone C (**370**)	*H. ascyron*		[120]
Hypercohin K (**371**)	*H. cohaerens*	Demonstrated activity against acetylcholinesterase (AChE) and against four human tumor cell lines HL-60; IC_{50} 18.2 μ*M*; SMMC-7721; IC_{50} 18.1 μ*M*; A549; IC_{50} 23.3 μ*M*; MCF-7; IC_{50} 23.5 μ*M*)	[121]
Norhypersampsone A (**372**)	*H. sampsonii*	Inhibitory activity against LPS-induced NO production in RAW 264.7 macrophages (IC_{50} 30.2 μ*M*)	[106]
Phenyl(2,4,6-trihydroxy-3-(2-hydroxy-7-methyl-3-methyleneoct-6-en-1-yl)-5-(3-methylbut-2-en-1-yl)phenyl) methanone (**373**)	*H. sampsonii*		[106]
Sampbenzophenone A (**374**)	*H. sampsonii*	Exhibited cytotoxic activities against several human cancer cell lines (IC_{50} values ranging from 13.32 to 29.65 μ*M*)	[122]
Sampbenzophenone B (**375**)	*H. sampsonii*		[122]
Sampbenzophenone C (**376**)	*H. sampsonii*		[122]
Sampbenzophenone D (**377**)	*H. sampsonii*		[122]
Sampbenzophenone E (**378**)	*H. sampsonii*		[122]
Sampbenzophenone F (**379**)	*H. sampsonii*		[122]
Sampbenzophenone G (**380**)	*H. sampsonii*		[122]
Hyperhenone J (**381**)	*H. henryi*	Suppressed the metastasis of A549 cells in vitro (40 μ*M*)	[95]
Hyperhenone K (**382**)	*H. henryi*		[95]
Hyperhenone L (**383**)	*H. henryi*		[95]
Hyperhenone M (**384**)	*H. henryi*		[95]



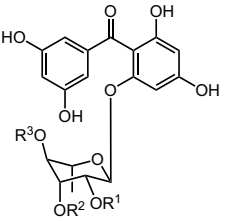
302 R^1 = β-D-Xyl, R^2 = H, R^3 = OH R^4 = OH
303 R^1 = β-D-Xyl, R^2 = Me, R^3 = OH, R^4 = OH
304 R^1 = 4-*O*-Ac-β-D-Xyl, R^2 = H, R^3 = OH, R^4 = OH
305 R^1 = 3-*O*-Ac-α-L-Ara, R^2 = H, R^3 = OH, R^4 = OH
306 R^1 = β-D-Glc, R^2 = H, R^3 = H, R^4 = H (garcimangosone D)



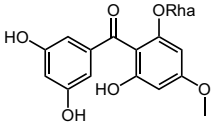
309 (paglucinol)



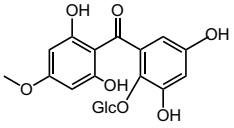
307 R = H (annulatophenonoside)
308 R = Ac (acetylannulatophenonoside)



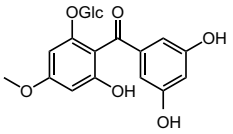
310 R^1 = H R^2 = H R^3 = H (petiolin F)
311 R^1 = H R^2 = H R^3 = Ac (petiolin G)
312 R^1 = H R^2 = Bz R^3 = Ac (petiolin H)
313 R^1 = Bz R^2 = H R^3 = Ac (petiolin I)



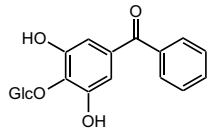
314 (elegaphenonoside)



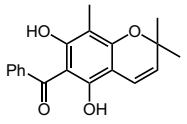
315 (hypericophenonoside)



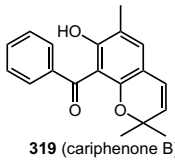
316 (neoannulatophenonoside)



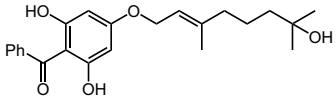
317 (4-benzoyl-2,6-dihydroxy-phenyl-β-D-glucopyranoside)



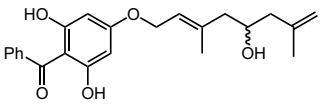
318 (cariphenone A)



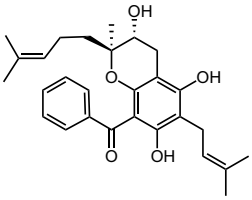
319 (cariphenone B)



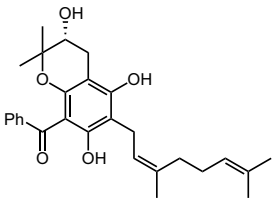
320 ((*E*)-(2,6-dihydroxy-4-((7-hydroxy-3,7-dimethyloct-2-en-1-yl)oxy)phenyl)(phenyl)methanone)



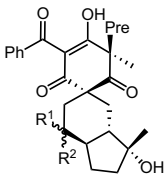
321 ((*E*)-(2,6-dihydroxy-4-((5-hydroxy-3,7-dimethylocta-2,7-dien-1-yl)oxy)phenyl)(phenyl)methanone)



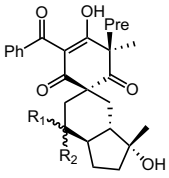
322 (otogirinin F)



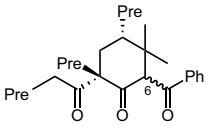
323 (otogirinin G)



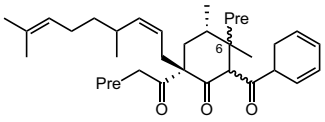
324 R^1 = β-CH_3, R^2 = α-OH (hyperbeanol A)
325 R^1 = α-OH, R^2 = β-CH_3 (hyperbeanol B)



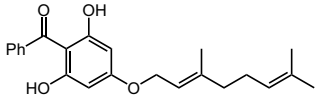
326 R^1 = β-CH_3, R^2 = α-OH (hyperbeanol C)
327 R^1 = β-CH_3, R^2 = α-OOH (hyperbeanol D)



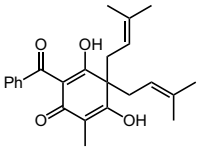
328 ((6*R*)-norsampsone A)
329 ((6*S*)-norsampsone B)



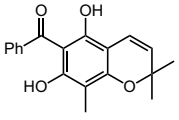
330 ((6*R*)-norsampsone C)
331 ((6*S*)-norsampsone D)



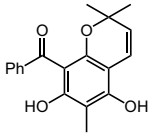
332 (4-geranyloxy-2,6-dihydroxybenzophenone)



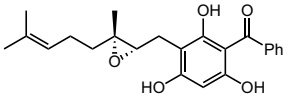
333 (ellipticophenone A)



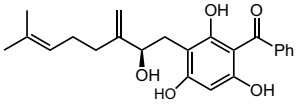
334 (cariphenone A)



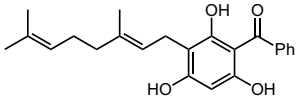
335 (cariphenone B)



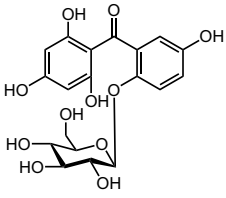
336 (hyperinakin)



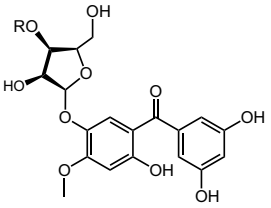
337 ((*R*)-phenyl(2,4,6-trihydroxy-3-(2-hydroxy-7-methyl-3-methylene-oct-6-en-1-yl)phenyl)methanone)



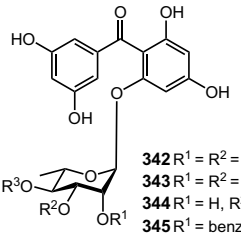
338 ((*E*)-(3-(3,7-dimethylocta-2,6-dien-1-yl)-2,4,6-trihydroxyphenyl)(phenyl)methanone)



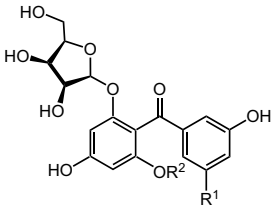
339 (hypericophenoside)



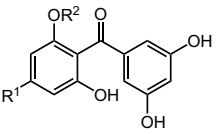
340 R = H (annulatophenonoside)
341 R = Ac (acetylannulatophenonoside)



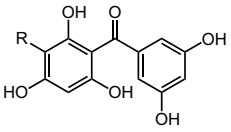
342 $R^1 = R^2 = R^3 = H$ (petiolin F)
343 $R^1 = R^2 = H$, $R^3 = Ac$ (petiolin G)
344 $R^1 = H$, R^2 = benzoyl, $R^3 = Ac$ (petiolin H)
345 R^1 = benzoyl, $R_2 = H$, $R^3 = Ac$ (petiolin I)



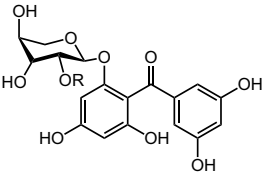
346 R^1 = OH, R^2 = H
347 R^1 = OH, R^2 = Me
348 R^1 = OMe, R^2 = Ara



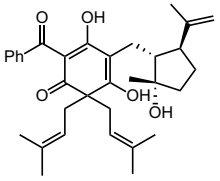
349 R^1 = 5-*O*-Bz-*β*-D-Glc, R^2 = H
350 R^1 = Glc, R^2 = H
353 R^1 = OH, R^2 = 4-*O*-Ac-*α*-L-Ara



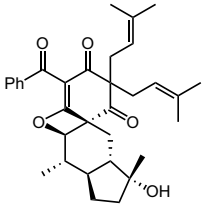
354 R = 4-*O*-Bz-*β*-D-Glc



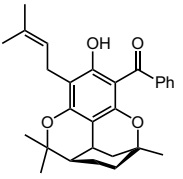
351 R = Bz
352 R = H



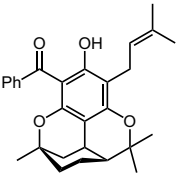
355 (hypercalin B)



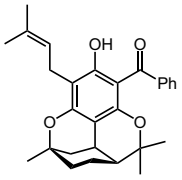
356 (hypercohone G)



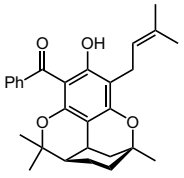
357 ((+)-sampsonin A)



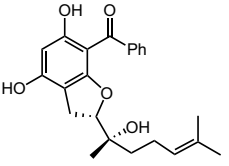
358 ((–)-sampsonin A)



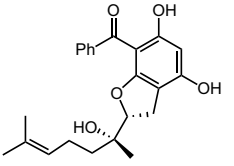
359 ((+)-sampsonin B)



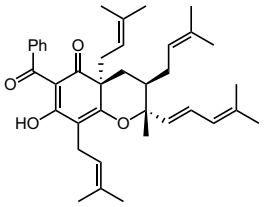
360 ((–)-sampsonin B)



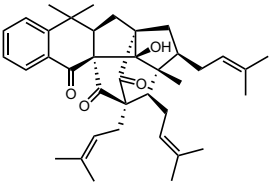
361 ((+)-japonicol H)



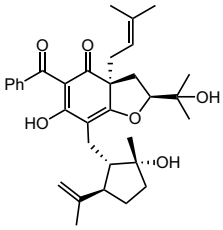
362 ((–)-japonicol H)



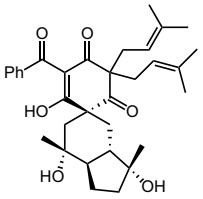
363 (hypelodin A)



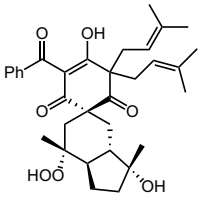
364 (hypelodin B)



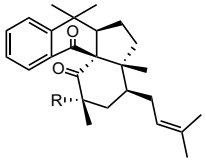
365 (hyperpatulone E)



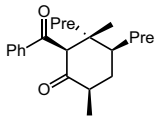
366 (hyperpatulol A)



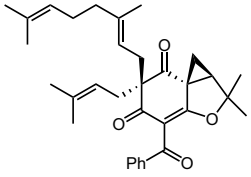
367 (hyperpatulol B)



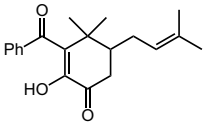
368 R = H (norascyronone A)
369 R = OH (norascyronone B)



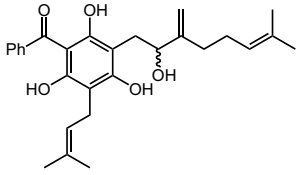
370 (norascyronone C)



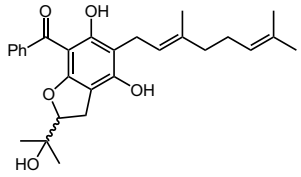
371 (hypercohin K)



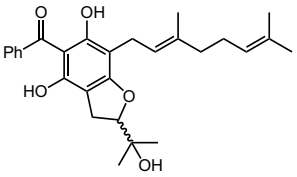
372 (norhypersampsone A)



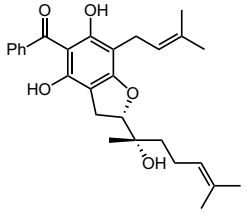
373 (phenyl(2,4,6-trihydroxy-3-(2-hydroxy-7-methyl-3-methyleneoct-6-en-1-yl)-5-(3-methylbut-2-en-1-yl)phenyl)methanone)



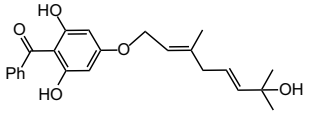
374 (sampbenzophenone A)



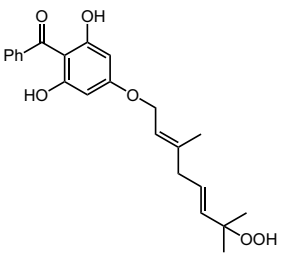
375 (sampbenzophenone B)



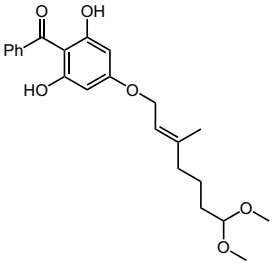
376 (sampbenzophenone C)



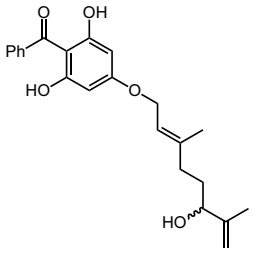
377 (sampbenzophenone D)



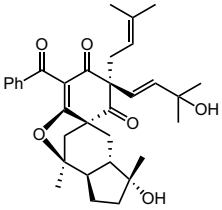
378 (sampbenzophenone E)



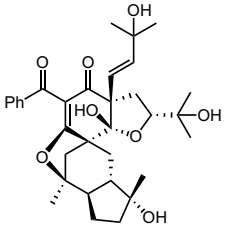
379 (sampbenzophenone F)



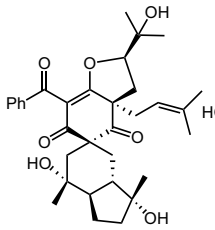
380 (sampbenzophenone G)



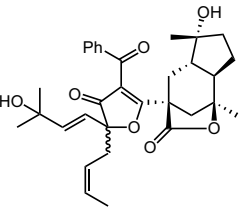
381 (hyperhenone J)



382 (hyperhenone K)



383 (hyperhenone L)



384 (hyperhenone M)

2.2.4 Simple Phloroglucinols

The simple phloroglucinols included in this class of phloroglucinol derivatives are biosynthesized by cyclization of a *C*-prenyl side chain with an *ortho*-phenolic hydroxy group of the phloroglucinol nucleus.

From the whole plant of *H. faberi*, faberiones A–D (**385**–**388**) were isolated. They share a rare styrene substituent and may be generated biosynthetically via further acylation of the acylphloroglucinols [123]. A chemical study of *H. erectum* resulted in two new compounds, otogirin (**389**) and otogirone (**390**) [124]. From the same species, six new simple phloroglucins, namely, adotogirin (**391**) and erecricins A–E (**392**–**396**), were also isolated [125].

In 2008, Tanaka et al. obtained takaneol A (**397**) from *H. sikokumontanum* [28], and soon afterwards the same research group isolated takaneol B (**398**), the takanechromones A (**399**) and B (**400**), and takanechromanones A–C (**401**–**403**) from this same species [126].

From *H. pseudopetiolatum* var. *kiusianum*, petiolins A (**404**) and B (**405**) (obtained as a keto-enol tautomeric mixture), together with petiolin C (**406**), were obtained [127]. Petiolin E (**407**) and the petiolins J–M (**408**–**411**) were also purified from this plant [128].

From *H. yojiroanum*, seven simple phloroglucinols, yojironins C–I (**412**–**418**), were acquired [129, 130]. From *H. prolificum*, prolificin A (**419**) [131], and from *H. densiflorum* 4-geranyloxy-1-(2-methylpropanoyl)-phloroglucinol (**420**), and 4-geranyloxy-1-(2-methylbutanoyl)-phloroglucinol (**421**) [107], were obtained.

In 2016, a new chromanone derivative, (2*R*,3*R*)-5,7-dihydroxy-2,3-dimethyl-6-(3-methylbut-2-en-1-yl)chroman-4-one (**422**), was isolated from *H. lissophloeus* by

Crockett et al. [132]. From *H. calycinum*, 1-(3,5-dihydroxy-1-((3-methylbut-2-enyl) oxy)phenyl)-2-methyl-1-methylbutan-1-one (**423**) has been isolated [133]. The same authors also described hypercalin A (**424**) from *H. calycinum* [94]. On investigation of *H. chinense*, chinesins I (**425**) and II (**426**) were obtained [134]. From *H. japonicum*, sarolactone (**427**) [135], 2-acetyl-3,5-dihydroxy-1-geranoxy-6-methyl-4-(2-methyl)-butyryl-benzene (**428**) [135], 5,7-dihydroxy-2-(1-methyl-propyl)-chromone-8-*β*-D-glucoside (**429**), 5,7-dihydroxy-2-isopropylchromone-8-*β*-D-glucoside (**430**), and 4,6-dimethyl-1-*O*-[α-L-rhamnopyranosyl-(1 → 6)-*β*-D-gluco-pyranosyl]multifidol (**431**) [136] were acquired.

Hypericum polyanthemum was found to produce the chromenes 6-isobutyryl-5,7-dimethoxy-2,2-dimethyl-benzopyran (**432**), 7-hydroxy-6-isobutyryl-5-methoxy-2, 2-dimethyl-benzopyran (**433**), and 5-hydroxy-6-isobutyryl-7-methoxy-2,2-dimethyl-benzopyran (**434**) [85, 137, 138]. In 2004, Gamiotea-Turro et al. found 3-geranyl-1-(3-methylbutanoyl)-phloroglucinol (**435**) in *H. styphelioides* [101]. Additionally, two compounds with the monomeric prenylated phloroglucinol pattern, laricifolins A (**436**) and B (**437**) were obtained from *H. laricifolium* [79]. From *H. foliosum*, 1-(3-((3,3-dimethyloxiran-2-yl)methyl)-2,4,6-trihydroxy-5-(3-methylbut-2-en-1-yl)phenyl)-2-methylbutan-1-one (**438**) was isolated [139]. Furthermore, eight simple phloroglucinols, madeleinols A (**439**) and B (**440**), empetriferdinol (**441**), empetrikarinols A (**442**) and B (**443**), 3-geranyl-2,4,6-trihydroxybenzophenone (**444**), 3-geranyl-1-(2′-methylpropanoyl)-phloroglucinol (**445**), and 3-geranyl-1-(2′-methylbutanoyl)-phloroglucinol (**446**) were isolated from *H. roeperianum* [140].

From *H. lanceolatum*, nine tricyclic acylphloroglucinol derivatives, selancins A–I (**447**–**455**), were isolated, and among them, selancin H (**454**) and I (**455**) are the first examples of natural products with a 6-acyl-2,2-dimethylchroman-4-one core fused with a dimethylpyran unit [50].

In 1987, Decosterd et al. reported four phloroglucinols, hypervoline (**456**), 2-methyl-1-(1,13,13a,13b-tetrahydro-5,8,10-trihydroxy-4-isobutyryl-2,2,6,9,13,12-hexamethyl-2*H*,7α-pyrano[3,2-*c*:4,5,6-*d*′*e*′]di[1]benzopyran-11-yl)-1-butanone (**457**), hyperevoline (**458**), and 1-((4*E*)-3,7-dimethylocta-2,6-dienyloxy)-2,6-dihydroxylphenyl)-2-methyl propan-1-one (**464**) in *H. revolutum* [141]. Subsequently, a phytochemical investigation of *H. jovis* and *H. empetrifolium* led to the isolation of hyperjovinols A (**459**) and B (**460**) [142] and empetrikathiforin (**461**) [143]. Winkelmann et al. reported in 2003 two analogues, hypercalyxones A (**462**) and B (**463**), from *H. amblycalyx* [144]. In addition, the antibacterial olympicins A–F (**465**–**469**) were identified from *H. olympicum* [145].

From *H. calycinum*, hypercalin C (**470**) was obtained, along with a mixture of the isomers of 3,5-dihydroxy-4-{[(1*R*,2*S*,5*S*)-2-hydroxy-2-methyl-5-(1-methyl-ethenyl) cyclopentyl]methyl}-2-(2-methylbutanoyl)-6,6-bis(3-methylbut-2-enyl)-cyclohexa-2,4-dien-l-one (**471a/b**) [49]. More recently, seven stereoisomeric phloroglucinol terpene adducts, hyperjaponols A (**472a/b**), B (**473a/b**), C (**474a/b**) (keto-enol tautomeric mixtures), and D–G (**475**–**478**), were isolated from *H. japonicum*. These compounds are characterized by the incorporation of sesquiterpenoid moieties to an acylated filicinic acid [146].

From the same species, Yang et al. reported a series of terpenoid polymethylated acylphloroglucinols, namely, hyperjapone A (**479a/b**) (keto-enol tautomeric mixture) and B–E (**480**–**483**) [58]. Additionally, hyperjapones F–I (**484**–**487**), the same type of terpenoid polymethylated acylphloroglucinols, with unusual carbon skeletons, were also found in this plant [147].

A study of *H. empetrifolium,* led to the isolation of empetrifelixins A–D (**488**–**491**), empetrikajaforin (**492**) [143], and empetrifranzinans A–D (**493**–**496**) [148].

From *H. henryi*, hyphenrones J (**497**) and K (**498**) [55] and the enantiomeric hyperhenones A–F (**499**–**504**) were also obtained [149]. Moreover, the enantiomers of japonicols E–G (**505a/b**–**507a/b**) and japonicols A–D (**508a/b**–**511a/b**) were isolated from the same species, and, among these, the enantiomers of japonicol E (**505a/b**) possess a previously unreported cyclopenta[*b*]chromene ring system [116].

Hyperjaponol H (**512**) [150] and hyperjapones B–E (**513**–**516**) were obtained from the same species, namely, *H. japonicum* [58].

The biological properties of the simple phloroglucinol derivatives **385**–**516** as isolated from *Hypericum* species are displayed in Table 6.

Table 6 Simple phloroglucinol derivatives

Compound name	Species	Biological activity	Ref.
Faberione A (**385**)	*H. faberi*		[123]
Faberione B (**386**)	*H. faberi*	Showed cytotoxicity for a pancreatic cell line (PANC-1; IC_{50} 6.2 μ*M*)	[123]
Faberione C (**387**)	*H. faberi*	Showed cytotoxicity for a pancreatic cell line (PANC-1) (IC_{50} 9.0 μ*M*)	[123]
Faberione D (**388**)	*H. faberi*		[123]
Otogirin (**389**)	*H. erectum*	Inhibitory action on thromboxane A2 and leukotriene D4 (50% at 10^{-4} mol/dm^3)	[124]
Otogirone (**390**)	*H. erectum*	1. Inhibitory action on thromboxane A2 (90% at 10^{-5} mol/dm^3) 2. Demonstrated in vitro antiplasmodial activity (IC_{50} 5.6 μ*M*).	[151, 124]
Adotogirin (**391**)	*H. erectum*	Exhibited antimicrobial activity against MRSA (*MIC* range 0.5–4.0 μg/cm^3; MIC_{50} 1.0 μg/cm^3)	[125]
Erecricin A (**392**)	*H. erectum*		[125]
Erecricin B (**393**)	*H. erectum*		[125]
Erecricin C (**394**)	*H. erectum*		[125]
Erecricin D (**395**)	*H. erectum*		[125]
Erecricin E (**396**)	*H. erectum*		[125]
Takaneol A (**397**)	*H. sikokumontanum*	Showed cytotoxic activity for K562/Adr multidrug-resistant (MDR) cancer cells (IC_{50} 10.0 μg/cm^3)	[28]
Takaneol B (**398**)	*H. sikokumontanum*		[126]

(continued)

Table 6 (continued)

Compound name	Species	Biological activity	Ref.
Takanechromone A (**399**)	*H. sikokumontanum*		[126]
Takanechromone B (**400**)	*H. sikokumontanum*		[126]
Takanechromanone A (**401**)	*H. sikokumontanum*		[126]
Takanechromanone B (**402**)	*H. sikokumontanum*		[126]
Takanechromanone C (**403**)	*H. sikokumontanum*		[126]
Petiolin A (**404**)	*H. pseudopetiolatum* var. *kiusianum*	Exhibited cytotoxic activity for murine lymphoma cells (L1210; IC_{50} 6.9 μM)	[127]
Petiolin B (**405**)	*H. pseudopetiolatum* var. *kiusianum*		[127]
Petiolin C (**406**)	*H. pseudopetiolatum* var. *kiusianum*	1. Exhibited cytotoxic activity against murine lymphoma cells (L1210; IC_{50} 6.9 μM) 2. Demonstrated antimicrobial activity against *Trichophyton mentagrophytes* (*MIC* 88 μM)	[127]
Petiolin E (**407**)	*H. pseudopetiolatum* var. *kiusianum*		[128]
Petiolin J (**408**)	*H. pseudopetiolatum* var. *kiusianum*	Exhibited antimicrobial activity against *Micrococcus luteus* (*MIC* 8 $\mu g/cm^3$), *Cryptococcus neoformans* (*MIC* 16 $\mu g/cm^3$), and *Trichophyton mentagrophytes* (*MIC* 16 $\mu g/cm^3$)	[128]
Petiolin K (**409**)	*H. pseudopetiolatum* var. *kiusianum*		[128]
Petiolin L (**410**)	*H. pseudopetiolatum* var. *kiusianum*		[128]
Petiolin M (**411**)	*H. pseudopetiolatum* var. *kiusianum*		[128]
Yojironin C (**412**)	*H. yojiroanum*		[130]
Yojironin D (**413**)	*H. yojiroanum*		[130]
Yojironin E (**414**)	*H. yojiroanum*	1. Exhibited activity against *Aspergillus niger* (IC_{50} 36 μM), *Candida albicans* (IC_{50} 9 μM), *Cryptococcus neoformans* (IC_{50} 9 μM), and *Trichophyton mentagrophytes* (IC_{50} 9 μM). 2. Displayed cytotoxicity against P388 murine lymphocytic leukemie cells (IC_{50} 8.3 μM) and KB human epidermoid carcinoma cells (IC_{50} 11.3 μM)	[130]
Yojironin F (**415**)	*H. yojiroanum*		[130]
Yojironin G (**416**)	*H. yojiroanum*		[130]
Yojironin H (**417**)	*H. yojiroanum*		[130]
Yojironin I (**418**)	*H. yojiroanum*		[130]
Prolificin A (**419**)	*H. prolificum*	Displayed in vitro growth inhibitory activity against human breast (MCF-7; IC_{50} 23.7 μM), lung (NCI-H460; IC_{50} 29.9 μM), stomach (AGS; IC_{50} 32.4 μM), and colon (HCT-116; IC_{50} 35.1 μM) cancer cell lines	[131]
4-Geranyloxy-1-(2-methylpropanoyl)-phloroglucinol (**420**)	*H. densiflorum*		[107]

(continued)

Table 6 (continued)

Compound name	Species	Biological activity	Ref.
4-Geranyloxy-1-(2-methylbutanoyl)-phloroglucinol (**421**)	*H. densiflorum*		[107]
(2*R*,3*R*)-5,7-Dihydroxy-2,3-dimethyl-6-(3-methylbut-2-en-1-yl)chroman-4-one (**422**)	*H. lissophloeus*	Acted as a potent stimulator of currents elicited by GABA in recombinant α1β2γ2 GABAA receptors	[132]
1-(3,5-Dihydroxy-1-((3-methylbut-2-enyl)oxy)phenyl)-2-methyl-1-methylbutan-1-one (**423**)	*H. calycinum*	Antifungal (against *Cladosporium cucumerinum*) and in vitro antimalarial (against *Plasmodium falciparum*; IC_{50} 3 μ*M*)	[133]
Hypercalin A (**424**)	*H. monogynum*		[49]
Chinesin I (**425**)	*H. chinense*		[134]
Chinesin II (**426**)	*H. chinense*		[134]
Sarolactone (**427**)	*H. japonicum*		[135]
2-Acetyl-3,5-dihydroxy-1-geranoxy-6-methyl-4-(2-methyl)-butyryl-benzene (**428**)	*H. japonicum*		[135]
5,7-Dihydroxy-2-(1-methylpropyl) chromone-8-*β*-D-glucoside (**429**)	*H. japonicum*		[136]
5,7-Dihydroxy-2-isopropylchromone-8-*β*-D-glucoside (**430**)	*H. japonicum*		[136]
4,6-Dimethyl-1-*O*-[α-L-rhamnopyranosyl-(1 → 6)-*β*-D-glucopyranosyl] multifidol (**431**)	*H. japonicum*		[136]
6-Isobutyryl-5,7-dimethoxy-2,2-dimethyl-benzopyran (**432**)	*H. polyanthemum*	1. Demonstrated antinociceptive effect in mice, through opioid system (30 mg/kg) 2. Anti-*Trichomonas vaginalis* activity (IC_{50} 215.5 μ*M*)	[85, 137, 138]
7-Hydroxy-6-isobutyryl-5-methoxy-2,2-dimethyl-benzopyran (**433**)	*H. polyanthemum*		[85, 137]
5-Hydroxy-6-isobutyryl-7-methoxy-2,2-dimethyl-benzopyran (**434**)	*H. polyanthemum*		[137]
3-Geranyl-1-(3-methylbutanoyl) phloroglucinol (**435**)	*H. styphelioides*		[101]
Laricifolin A (**436**)	*H. laricifolium*		[79]
Laricifolin B (**437**)	*H. laricifolium*		[79]
1-(3-((3,3-Dimethyloxiran-2-yl)methyl)-2,4,6-trihydroxy-5-(3-methylbut-2-en-1-yl)phenyl)-2-methylbutan-1-one (**438**)	*H. foliosum*	Anti-*Staphylococcus*-resistant strain growth inhibitory effect (*MIC* 44.2 μ*M*)	[139]
Madeleinol A (**439**)	*H. roeperianum*		[140]
Madeleinol B (**440**)	*H. roeperianum*		[140]
Empetriferdinol (**441**)	*H. roeperianum*		[140]
Empetrikarinol A (**442**)	*H. roeperianum*		[140]
Empetrikarinol B (**443**)	*H. roeperianum*		[140]
3-Geranyl-2,4,6-trihydroxybenzophenone (**444**)	*H. roeperianum*		[140]
3-Geranyl-1-(2′-methylpropanoyl)-phloroglucinol (**445**)	*H. roeperianum*		[140]

(continued)

Table 6 (continued)

Compound name	Species	Biological activity	Ref.
3-Geranyl-1-(2′-methylbutanoyl)-phloroglucinol (**446**)	*H. roeperianum*		[140]
Selancin A (**447**)	*H. lanceolatum*		[50]
Selancin B (**448**)	*H. lanceolatum*		[50]
Selancin C (**449**)	*H. lanceolatum*		[50]
Selancin D (**450**)	*H. lanceolatum*		[50]
Selancin E (**451**)	*H. lanceolatum*		[50]
Selancin F (**452**)	*H. lanceolatum*		[50]
Selancin G (**453**)	*H. lanceolatum*		[50]
Selancin H (**454**)	*H. lanceolatum*		[50]
Selancin I (**455**)	*H. lanceolatum*		[50]
Hypervoline (**456**)	*H. revolutum*		[141]
2-Methyl-1-(1,13,13a,13b-tetrahydro-5,8,10-trihydroxy-4-isobutyryl-2,2,6,9,13,12-hexamethyl-2*H*,7α-pyrano[3,2-*c*:4,5,6-*d*'*e*']di[1]benzopyran-11-yl)-1-butanone (**457**)	*H. revolutum*		[141]
Hyperevoline (**458**)	*H. revolutum*		[141]
Hyperjovinol A (**459**)	*H. jovis*		[142]
Hyperjovinol B (**460**)	*H. jovis*		[142]
Empetrikathiforin (**461**)	*H. empetrifolium*		[143]
Hypercalyxone A (**462**)	*H. amblycalyx*	Showed moderate cytotoxic activity for KB and Jurkat T cancer cells	[144]
Hypercalyxone B (**463**)	*H. amblycalyx*	Showed moderate cytotoxic activity for KB and Jurkat T cancer cells	[144]
1-(4*E*)-3,7-Dimethylocta-2,6-dienyloxy)-2,6-dihydroxylphenyl)-2-methyl propan-1-one (**464**)	*H. revolutum*		[141]
Olympicin A (**465**)	*H. olympicum*	Exhibited *MIC*s of 0.5–1 mg/dm^3 against *S. aureus* strains	[145]
Olympicin B (**466**)	*H. olympicum*	Exhibited *MIC*s of 64 to 128 mg/dm^3 against *S. aureus* strains	[145]
Olympicin C (**467**)	*H. olympicum*	Exhibited *MIC*s of 64 to 128 mg/dm^3 against *S. aureus* strains	[145]
Olympicin E (**468**)	*H. olympicum*	Exhibited *MIC*s of 64 to 128 mg/dm^3 against *S. aureus* strains	[145]
Olympicin F (**469**)	*H. olympicum*	Exhibited *MIC*s of 64 to 128 mg/dm^3 against *S. aureus* strains	[145]
Hypercalin C (**470**)	*H. calycinum*		[49]
3,5-Dihydroxy-4-{[(1*R*,2*S*,5*S*)-2-hydroxy-2-methyl-5-(1-methylethenyl) cyclopentyl]methyl}-2-(2-methylbutanoyl)-6,6-bis(3-methylbut-2-enyl) cyclohexa-2,4-dien-l-one (**471a**)	*H. calycinum*		[49]
3,5-Dihydroxy-4-{[(1*R*,2*S*,5*S*)-2-hydroxy-2-methyl-5-(1-methylethenyl)cyclopentyl]methyl}-2-(3-methylbutanoyl)-6,6-bis(3-methylbut-2-enyl)cyclohexa-2,4-dien-1-one (**471b**)	*H. calycinum*		[49]
Hyperjaponol A (**472a**)	*H. japonicum*		[146]
Hyperjaponol A (**472b**)	*H. japonicum*		[146]
Hyperjaponol B (**473a**)	*H. japonicum*	Demonstrated efficacy against Epstein-Barr virus (EC_{50} 0.57 μ*M*)	[146]

(continued)

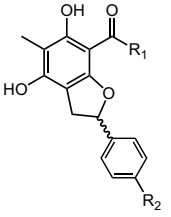
Table 6 (continued)

Compound name	Species	Biological activity	Ref.
Hyperjaponol B (**473b**)	*H. japonicum*	Demonstrated efficacy against Epstein-Barr virus (EC_{50} 6.60 μ*M*)	[146]
Hyperjaponol C (**474a**)	*H. japonicum*		[146]
Hyperjaponol C (**474b**)	*H. japonicum*		[146]
Hyperjaponol D (**475**)	*H. japonicum*	Demonstrated efficacy against Epstein-Barr virus (EC_{50} 0.49 μ*M*)	[146]
Hyperjaponol E (**476**)	*H. japonicum*		[146]
Hyperjaponol F (**477**)	*H. japonicum*		[146]
Hyperjaponol G (**478**)	*H. japonicum*		[146]
Hyperjapone A (**479a**)	*H. japonicum*		[58]
Hyperjapone A (**479b**)	*H. japonicum*		[58]
Hyperjapone B (**480**)	*H. japonicum*		[58]
Hyperjapone C (**481**)	*H. japonicum*		[58]
Hyperjapone D (**482**)	*H. japonicum*		[58]
Hyperjapone E (**483**)	*H. japonicum*		[58]
Hyperjapone F (**484**)	*H. japonicum*		[147]
Hyperjapone G (**485**)	*H. japonicum*		[147]
Hyperjapone H (**486**)	*H. japonicum*		[147]
Hyperjapone I (**487**)	*H. japonicum*		[147]
Empetrifelixin A (**488**)	*H. empetrifolium*		[143]
Empetrifelixin B (**489**)	*H. empetrifolium*		[143]
Empetrifelixin C (**490**)	*H. empetrifolium*		[143]
Empetrifelixin D (**491**)	*H. empetrifolium*		[143]
Empetrikajaforin (**492**)	*H. empetrifolium*		[143]
Empetrifranzinan A (**493**)	*H. empetrifolium*		[148]
Empetrifranzinan B (**494**)	*H. empetrifolium*		[148]
Empetrifranzinan C (**495**)	*H. empetrifolium*		[148]
Empetrifranzinan D (**496**)	*H. empetrifolium*		[148]
Hyphenrone J (**497**)	*H. henryi*	Exhibited cytotoxic effects for five human cancer cell lines (HL-60, myeloid leukemia, SMMC-7721, hepatocarcinoma, A549, lung cancer, MCF-7, breast cancer, and SW-480, colon cancer) (IC_{50} 1.7–7.0 μ*M*)	[55]
Hyphenrone K (**498**)	*H. henryi*		[55]
Hyperhenone A (**499**)	*H. henryi*		[149]
Hyperhenone B (**500**)	*H. henryi*		[149]
Hyperhenone C (**501**)	*H. henryi*		[149]
Hyperhenone D (**502**)	*H. henryi*		[149]
Hyperhenone E (**503**)	*H. henryi*	Exhibited cytotoxic activity for three cancer cell lines (NCI-H460, lung cancer HCT-15, colorectal cancer and MCF-7, breast cancer), (IC_{50} 2.4–7.0 μ*M*)	[149]
Hyperhenone F (**504**)	*H. henryi*		[149]
(+)-Japonicol E (**505a**)	*H. japonicum*	Exhibited inhibitory activity toward the lytic replication of KSHV in Vero cells (IC_{50} 8.30 μ*M*; selectivity index 23.49)	[116]
(–)-Japonicol E (**505b**)	*H. japonicum*		[116]

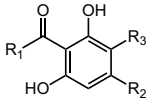
(continued)

Table 6 (continued)

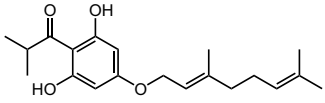
Compound name	Species	Biological activity	Ref.
(+)-Japonicol F (**506a**)	*H. japonicum*		[116]
(–)-Japonicol F (**506b**)	*H. japonicum*		[116]
(+)-Japonicol G (**507a**)	*H. japonicum*		[116]
(–)-Japonicol G (**507b**)	*H. japonicum*		[116]
(+)-Japonicol A (**508a**)	*H. japonicum*		[116]
(–)-Japonicol A (**508b**)	*H. japonicum*		[116]
(+)-Japonicol B (**509a**)	*H. japonicum*		[116]
(–)-Japonicol B (**509b**)	*H. japonicum*		[116]
(+)-Japonicol C (**501a**)	*H. japonicum*		[116]
(–)-Japonicol C (**510b**)	*H. japonicum*		[116]
(+)-Japonicol D (**511a**)	*H. japonicum*		[116]
(–)-Japonicol D (**511b**)	*H. japonicum*		[116]
Hyperjaponol H (**512**)	*H. japonicum*	Exhibited inhibitory activity towards lytic EBV DNA replication (EC_{50} 25 μ*M*)	[150]
Hyperjapone B (**513**)	*H. japonicum*	Showed cytotoxic activity for the AGS human gastric cancer cell line (IC_{50} 14.8 μ*M*)	[58]
Hyperjapone C (**514**)	*H. japonicum*		[58]
Hyperjapone D (**515**)	*H. japonicum*	1. Showed cytotoxic activity for the AGS human gastric cell line (IC_{50} 12.3 μ*M*) 2. Inhibited Hsp90 (IC_{50} 21.3 μ*M*)	[58]
Hyperjapone E (**516**)	*H. japonicum*		[58]



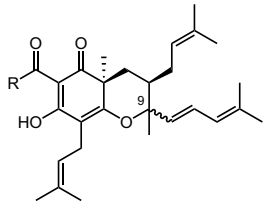
385 R^1 = *i*-Pr, R^2 = H (faberione A)
386 R^1 = *s*-Bu, R^2 = H (faberione B)
387 R^1 = *i*-Pr, R^2 = OH (faberione C)
388 R^1 = *s*-Bu, R^2 = OH (faberione D)



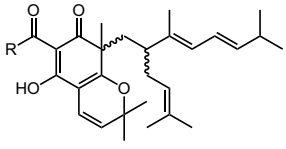
389 R^1 = $CH(CH_3)_2$,
R^2 = O-Ger, R^3 = CH_3 (otogirin)
391 R^1 = $CH(CH_3)CH_2CH_3$,
R^2 = O-Ger, R^3= CH_3(otogirone)



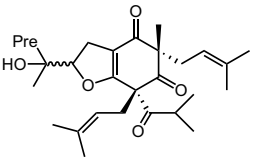
390 (adotogirin)



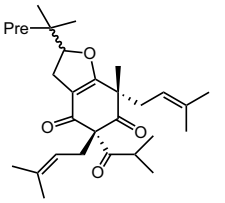
392 R = $CH(CH_3)_2$ (erecricin A)
393 R = $CH(CH_3)CH_2CH_3$, (9*R*) (erecricin B)
394 R = $CH(CH_3)CH_2CH_3$, (9*S*) (erecricin C)



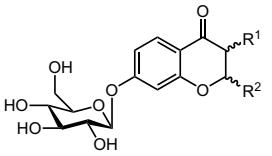
395 R = $CH(CH_3)_2$ (erecricin D)
396 R = $CH(CH_3)CH_2CH_3$ (erecricin E)



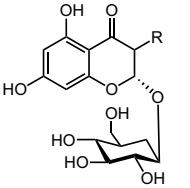
397 (takaneol A)



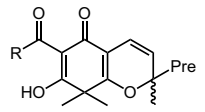
398 (takaneol B)



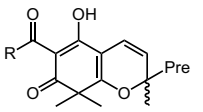
399 $R^1 = CH_3$, $R^2 = H$ (takanechromone A)
400 $R^1 = CH_2CH_3$, $R^2 = H$ (takanechromone B)
403 $R^1 = H$, $R^2 = CH(CH_3)_2$ (takanechromanone C)



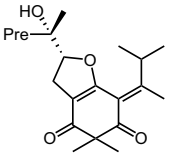
401 $R = CH_3$ (takanechromanone A)
402 $R = CH_2CH_3$ (takanechromanone B)



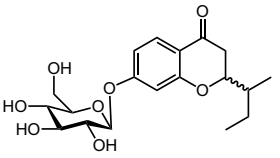
404a R = $CH(CH_3)_2$ (petiolin A)
405a R = $CH(CH_3)CH_2CH_3$ (petiolin B)



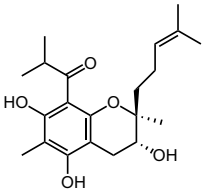
404b R = $CH(CH_3)_2$ (petiolin A)
405b R = $CH(CH_3)CH_2CH_3$ (petiolin B)



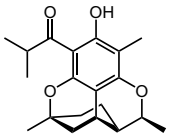
406 (petiolin C)



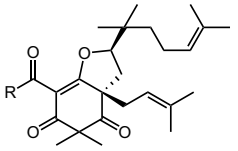
407 (petiolin E)



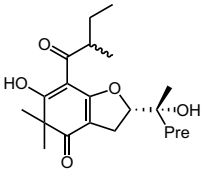
408 (petiolin J)



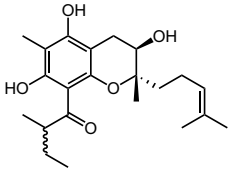
409 (petiolin K)



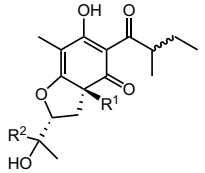
410 R = $CH(CH_3)CH_2CH_3$ (petiolin L)
411 R = $CH(CH_3)_2$ (petiolin M)



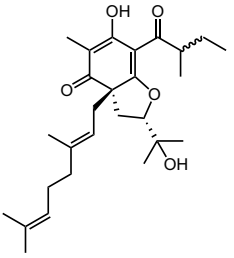
412 (yojironin C)



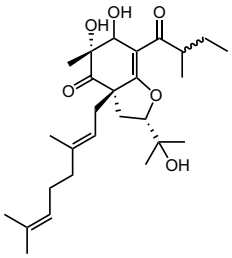
413 (yojironin D)



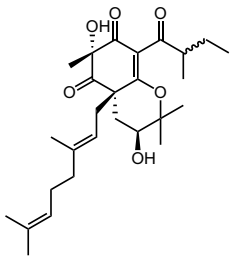
414 R^1 = Ger, R^2 = H (yojironin E)
415 R^1 = Per, R^2 = Per (yojironin CF)



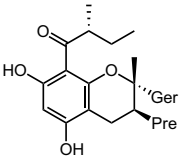
416 (yojironin G)



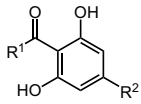
417 (yojironin H)



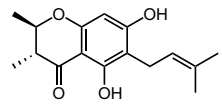
418 (yojironin I)



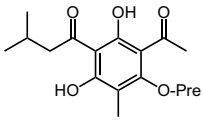
419 (prolificin A)



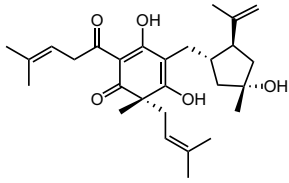
420 $R^1 = CH(CH_3)_2$, R^2 = O-Ger
(4-geranyloxy-1-(2-methylpropanoyl)-phloroglucinol)
421 $R^1 = CH(CH_3)CH_2CH_3$, R^2 = O-Ger
(4-geranyloxy-1-(2-methylbutanoyl)-phloroglucinol)



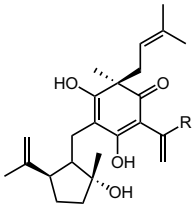
422 ((2*R*,3*R*)-5,7-dihydroxy-2,3-dimethyl-6-(3-methyl-but-2-en-1-yl)chroman-4-one)



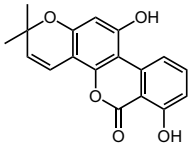
423 (1-(3,5-dihydroxy-1-((3-methyl-but-2-enyl)oxy)phenyl)-2-methyl-1-methylbutan-1-one)



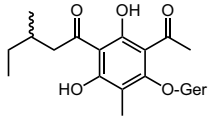
424 (hypercalin A)



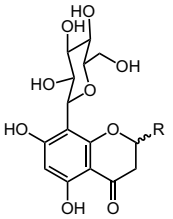
425 R = (2*R*)-CH(CH$_3$)CH$_2$CH$_3$
(chinesin I)
426 R = CH(CH$_3$)$_2$
(chinesin II)



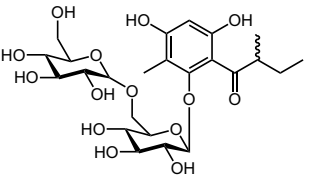
427 (sarolactone)



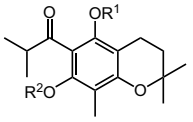
428 (2-acetyl-3,5-dihydroxy-1-geranoxy-6-methyl-4-(2-methyl)-butyryl-benzene)



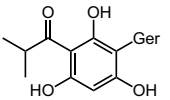
429 R = $CH(CH_3)_2$ (5,7-dihydroxy-2-(1-methyl-propyl)chromone-8-β-D-glucoside)
430 R = $CH(CH_3)CH_2CH_3$ (5,7-dihydroxy-2-isopropyl-chromone-8-β-D-glucoside)



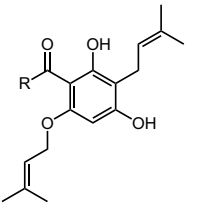
431 (4,6-dimethyl-1-O-[α-L-rhamno-pyranosyl-(1→6)-β-D-glucopyranosyl] multifidol)



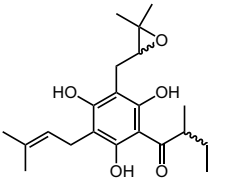
432 $R^1 = R^2 = CH_3$
433 $R^1 = CH_3$, $R^2 = H$
434 $R_1 = H$, $R_2 = CH_3$



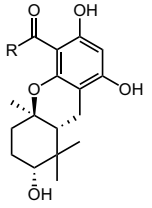
435



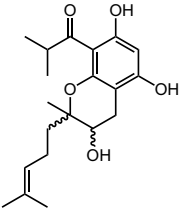
436 R = $CH(CH_3)_2$ $CH(CH_3)CH_2CH_3$ (laricifolin A)
437 R = $CH(CH_3)CH_2CH_3$ (laricifolin B)



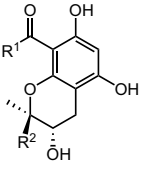
438 (1-(3-((3,3-dimethyloxiran-2-yl)methyl)-2,4,6-trihydroxy-5-(3-methyl-but-2-en-1-yl)phenyl)-2-methylbutan-1-one)



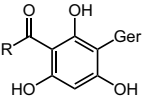
439 R = $CH(CH_3)_2$ (madeleinol A)
441 R = $CH(CH_3)CH_2CH_3$ (empetriferdinol)



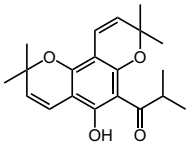
440 (madeleinol B)



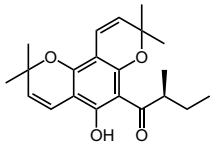
442 $R^1 = CH(CH_3)_2$, R^2 = Pre (empetrikarinol A)
443 $R^1 = CH(CH_3)CH_2CH_3$, R^2 = Pre (empetrikarinol B)



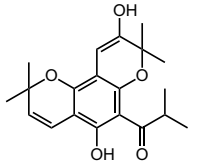
444 R = Pre,
445 R = $CH(CH_3)_2$
446 R = $CH(CH_3)CH_2CH_3$



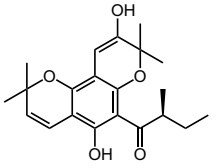
447 (selancin A)



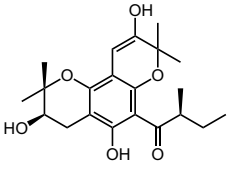
448 (selancin B)



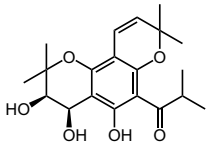
449 (selancin C)



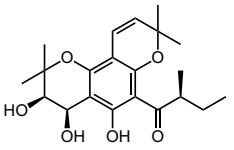
450 (selancin D)



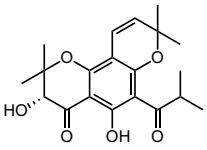
451 (selancin E)



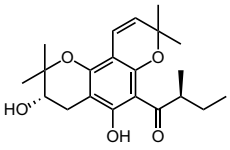
452 (selancin F)



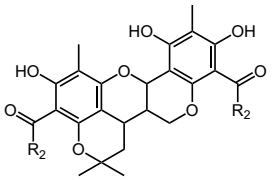
453 (selancin G)



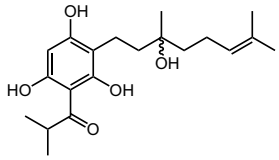
454 (selancin H)



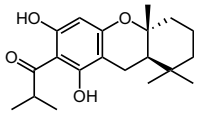
455 (selancin I)



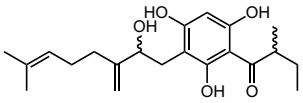
456 $R^1 = R^2 = CH(CH_3)_2$ (hypervoline)
457a $R^1 = CH(CH_3)_2$, $R^2 = CH(CH_3)CH_2CH_3$
457b $R^1 = CH(CH_3)CH_2CH_3$, $R^2 = CH(CH_3)_2$
458 $R^1 = R^2 = CH(CH_3)CH_2CH_3$ (hyperevoline)



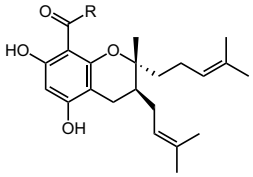
459 (hyperjovinol A)



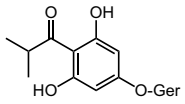
460 (hyperjovinol B)



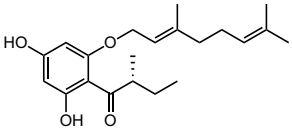
461 (empetrikathiforin)



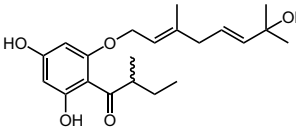
462 R = $CH(CH_3)_2$ (hypercalyxone A)
463 R = $CH(CH_3)CH_2CH_3$ (hypercalyxone B)



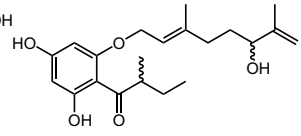
464 (1-((4E)-3,7-dimethylocta-2,6-dienyloxy)-2,6-dihydroxylphenyl)-2-methyl propan-1-one)



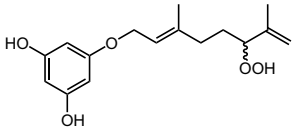
465 (olympicin A)



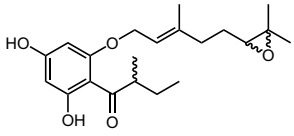
466 (olympicin B)



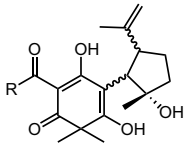
467 (olympicin C)



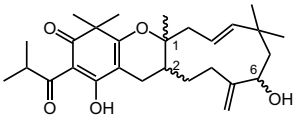
468 (olympicin E)



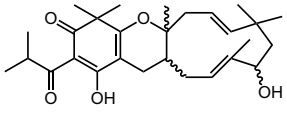
469 (olympicin F)



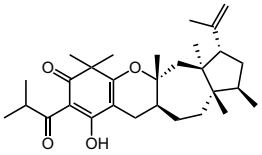
470 R = $CH(CH_3)_2$
471a R = $CH(CH_3)CH_2CH_3$
471b R = $CH_2CH(CH_3)_2$



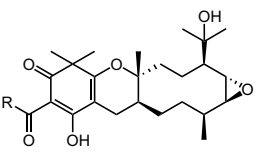
472a ((1*R*,2*S*,6*R*)-hyperjaponol A)
472b ((1*S*,2*R*,6*S*)-hyperjaponol A)



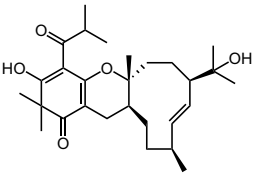
473a ((1*R*,2*S*,6*R*)-hyperjaponol B)
473b ((1*S*,2*R*,6*S*)-hyperjaponol B)



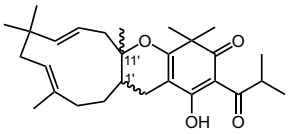
474a ((1*R*,2*S*,5*R*,6*R*,8*R*,9*S*)-hyperjaponol C)
474b ((1*S*,2*S*,5*R*,6*R*,8*R*,9*S*)-hyperjaponol A)



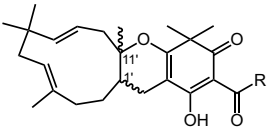
475 R = $CH(CH_3)_2$ (hyperjaponol D)
476 R = $CH(CH_3)CH_2CH_3$ (hyperjaponol D)
477 R = $CH(CH_3)CH_2CH_3$ (hyperjaponol F) (epimer of D)



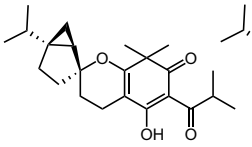
478 (hyperjaponol G)



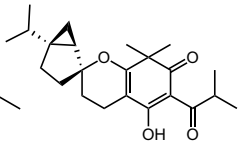
479a ((1′*S*,11′*R*)-hyperjapone A)
479b ((1′*S*,11′*R*)-hyperjapone A)



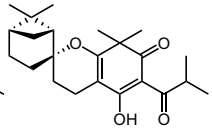
480 R = $CH(CH_3)_2$ ((1′*S*,11′*R*)-hyperjapone B)
481 R = $CH(CH_3)CH_2CH_3$ ((1′*S*,11′*R*)-hyperjapone C)
482 R = $CH(CH_3)_2$ ((1′*R*,11′*S*)-hyperjapone D)
483 R = $CH(CH_3)CH_2CH_3$ ((1′*R*,11′*S*)-hyperjapone E)



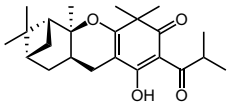
484 (hyperjapone F)



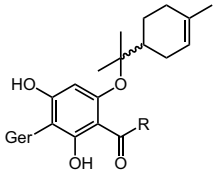
485 (hyperjapone G)



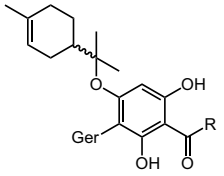
486 (hyperjapone H)



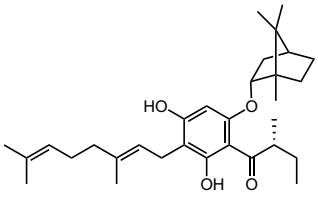
487 (hyperjapone I)



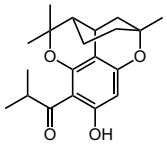
488 R = $CH(CH_3)_2$ (empetrifelixin A)
489 R = $CH(CH_3)CH_2CH_3$ (empetrifelixin B)



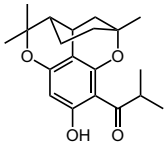
490 R = $CH(CH_3)_2$ (empetrifelixin C)
491 R = $CH(CH_3)CH_2CH_3$ (empetrifelixin D)



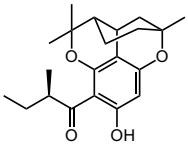
492 (empetrikajaforin)



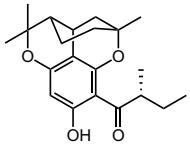
493 (empetrifranzinan A)



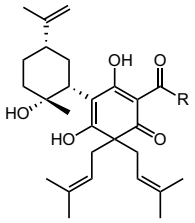
494 (empetrifranzinan B)



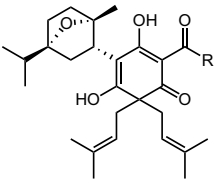
495 (empetrifranzinan C)



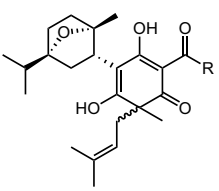
496 (empetrifranzinan D)



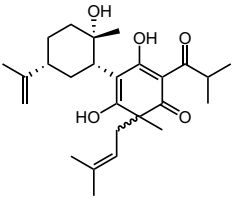
497 R = $CH(CH_3)_2$ (hyphenrone J)
498 R = $CH(CH_3)CH_2CH_3$ (hyphenrone K)



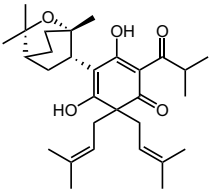
499 R = $CH(CH_3)_2$ (hyperhenone A)
500 R = $CH(CH_3)CH_2CH_3$ (hyperhenone B)



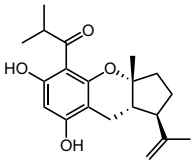
501 R = $CH(CH_3)_2$ (hyperhenone C)
502 R = $CH(CH_3)CH_2CH_3$ (hyperhenone D)



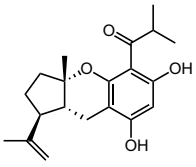
503 (hyperhenone E)



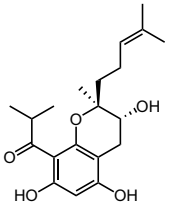
504 (hyperhenone F)



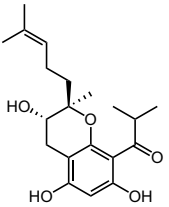
505a ((+)-japonicol E)



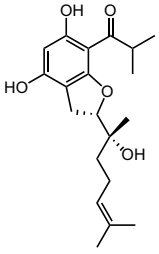
506b ((–)-japonicol E)



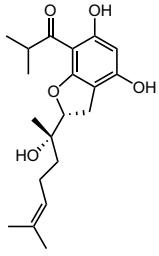
506a ((+)-japonicol F)



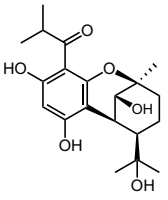
506b ((–)-japonicol F)



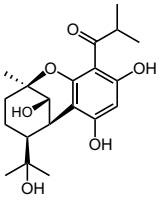
507a ((+)-japonicol G)



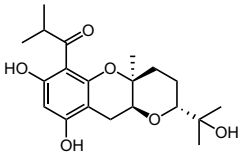
507b ((–)-japonicol G)



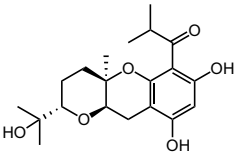
508a ((+)-japonicol A)



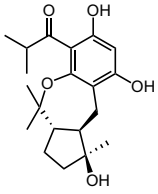
508b ((–)-japonicol A)



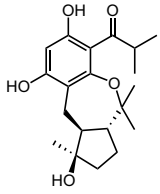
509a ((+)-japonicol B)



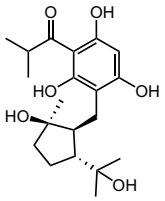
509b ((–)-japonicol B)



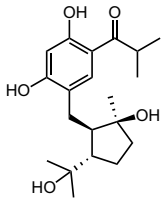
510a ((+)-japonicol C)



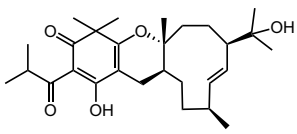
510ba ((–)-japonicol C)



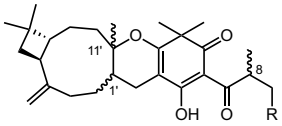
511a ((+)-japonicol D)



511b ((–)-japonicol D)



512 (hyperjaponol H)



513 R = H ((1'*S*,11'*R*)-hyperjapone B)
514 R = Me ((8*S*,1'*S*,11'*R*)-hyperjapone C)
515 R = H ((1'*R*,11'*S*)-hyperjapone D)
516 R = Me ((8*S*,1'*R*,11'*S*)-hyperjapone E)

2.3 Xanthones

Xanthones are a widespread and structurally diverse family of natural products found frequently in *Hypericum* species. The xanthone class has been studied for over a century since the early 1900s [152]. Xanthone chemistry is satisfyingly rich, with the conjugated donor–acceptor motif of the central B-ring ensuring that these compounds display a degree of scientific interest greater than their apparently simple core structure might suggest [153]. Many xanthones have been found to exhibit pronounced biological activities.

From the aerial parts of *H. ellipticum*, elliptoxanthone A (**517**), along with the three known xanthones, 1,6-dihydroxy-4-methoxy-9*H*-xanthen-9-one (**519**), 1,4,5-trihydroxy-9*H*-xanthen-9-one (**520**), and 1,3,7-trihydroxy-2-(2-hydroxy-3-methylbut-3-en-1-yl)-9*H*-xanthen-9-one (**539**) were isolated [108]. This plant species also contains elliptoxanthone B (**615**) [108]. From a phytochemical investigation of the xanthones from *H. chinense*, Tanaka et al. reported a series of new xanthones, namely, 2,6,8-trihydroxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**518**), 3,6-dihydroxy-1,7-dimethoxy-9*H*-xanthen-9-one (**527**), 3,7-dihydroxy-1-methoxy-9*H*-xanthen-9-one (**528**), 4,6-dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**529**), 2,6-dihydroxy-3,4-dimethoxy-9*H*-xanthen-9-one (**530**), 6-hydroxy-2,3,4-trimethoxy-9*H*-xanthen-9-one (**531**), 3,6-dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**532**), 4,7-dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**533**), 3,7-dihydroxy-2,4-dimethoxy-9*H*-xanthen-9-one (**534**), 1,3,7-trihydroxy-2-(2-hydroxy-3-methylbut-3-en-1-yl)-9*H*-xanthen-9-one (**539**), 1,3,7-trihydroxy-5-methoxy-9*H*-xanthen-9-one (**540**), 1,7-dihydroxy-5,6-dimethoxy-9*H*-xanthen-9-one (**541**), 4,5-dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**542**), 1,3-dihydroxy-2,4-dimethoxy-9*H*-xanthen-9-one (**543**), 4,7-dihydroxy-2-(2-hydroxy-

propan-2-yl)-2,3-dihydro-5*H*-furo[3,2-*b*]xanthen-5-one (**624**), the xanthonolignoid-2-*O*-demethylkielcorin (**629**), and the phenylxanthone chinexanthone A (**630**). In addition, four known xanthonolignoids, kielcorin (**631**), subalatin (**632**), 5′-demethoxycadensin G (**633**), cadensin G (**634**), together with a large number of known xanthones, 2-hydroxy-5-methoxy-9*H*-xanthen-9-one (**521**), 1,2,5-trihydroxy-9*H*-xanthen-9-one (**522**), 1,3-dihydroxy-5-methoxy-9*H*-xanthen-9-one (**523**), 3,5-dihydroxy-1-methoxy-9*H*-xanthen-9-one (**524**), 4-hydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**525**), 3,5,6-trihydroxy-1-methoxy-9*H*-xanthen-9-one (**526**), 3-hydroxy-2-methoxy-9*H*-xanthen-9-one (**535**), 1,5-dihydroxy-3-methoxy-9*H*-xanthen-9-one (**536**), 3,4-dihydroxy-2-methoxy-9*H*-xanthen-9-one (**537**), 1,5,6-trihydroxy-3-methoxy-9*H*-xanthen-9-one (**538**), 2-hydroxy-9*H*-xanthen-9-one (**544**), 2-hydroxy-1-methoxy-9*H*-xanthen-9-one (**545**), 1,7-dihydroxy-9*H*-xanthen-9-one (**546**), 2,5-dihydroxy-9*H*-xanthen-9-one (**547**), 2,7-dihydroxy-9*H*-xanthen-9-one (**548**), 1,3-dihydroxy-2-methoxy-9*H*-xanthen-9-one (**549**), 2,5-dihydroxy-1-methoxy-9*H*-xanthen-9-one (**550**), 3-hydroxy-2,4-dimethoxy-9*H*-xanthen-9-one (**551**), 1,3,5,6-tetrahydroxy-9*H*-xanthen-9-one (**552**), 1,3,5-trihydroxy-6-methoxy-9*H*-xanthen-9-one (**553**), 1,3,6-trihydroxy-5-methoxy-9*H*-xanthen-9-one (**554**), 1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one (**555**), 1,5-dihydroxy-6,7-dimethoxy-9*H*-xanthen-9-one (**556**), 3,8-dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**557**), 3,5-dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**558**), 1,3,5-trihydroxy-6,7-dimethoxy-9*H*-xanthen-9-one (**559**), 1,3,7-trihydroxy-5,6-dimethoxy-9*H*-xanthen-9-one (**560**), 1,7-dihydroxy-6-methoxy-9*H*-xanthen-9-one (**561**), and 1,3,7-trihydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**562**) were identified [154, 155]. From *H. canariensis*, 2,5-dihydroxy-9*H*-xanthen-9-one (**566**) was isolated [156].

From the aerial parts of *H. scabrum*, six new xanthones, hyperxanthones A–F (**608–613**), together with six known analogs, 2,3,6,8-tetrahydroxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**563**), 1,7-dihydroxy-9*H*-xanthen-9-one (**546**), 2,5-dihydroxy-9*H*-xanthen-9-one (**547**), 1,3,7-trihydroxy-9*H*-xanthen-9-one (**564**), 1,7-dihydroxy-4-methoxy-9*H*-xanthen-9-one (**565**), and toxyloxanthone B (**614**) [33] were obtained. From *H. hookerianum* 2-hydroxy-3-methoxy-9*H*-xanthen-9-one (**583**) could be isolated [157].

On investigating the roots of *H. geminiflorum*, Lin and coworkers found several xanthones, including the three new compounds, 6,7-dihydroxy-1,3-dimethoxy-9*H*-xanthen-9-one (**584**), 4-hydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**585**), and gemixanthone A (**639**), two new xanthonolignoids, hyperielliptone HC (**637**) and hyperielliptone HD (**638**), and the known xanthones, 1,3,8-trihydroxy-2-methoxy-9*H*-xanthen-9-one (**588**), 1,3,8-trihydroxy-4-methoxy-9*H*-xanthen-9-one (**589**), 1,5-dihydroxy-6-methoxy-9*H*-xanthen-9-one (**590**), 2,3-dimethoxy-9*H*-xanthen-9-one (**591**), 1,8-dihydroxy-3-methoxy-9*H*-xanthen-9-one (**592**), 10*H*-[1,3]dioxolo[4,5-*b*]xanthen-10-one (**607**), and cadensin D (**635**) [158, 159]. *H. canariensis* afforded 2,3,4-trihydroxy-9*H*-xanthen-9-one (**593**) and 7-hydroxy-2,3,4-trimethoxy-9*H*-xanthen-9-one (**594**) [156]. Investigating *H. geminiflorum* resulted in the isolation of 1,5,6-trihydroxy-3-methoxyxanthone (**586**), 3,8-dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**587**), 1,3,8-trihydroxy-2-methoxy-9*H*-xanthen-

9-one (**588**), 1,3,8-trihydroxy-4-methoxy-9*H*-xanthen-9-one (**589**), 1,5-dihydroxy-6-methoxy-9*H*-xanthen-9-one (**590**), 2,3-dimethoxy-9*H*-xanthen-9-one (**591**) and 1,8-dihydroxy-3-methoxy-9*H*-xanthen-9-one (**592**) [159].

From the aerial parts of *H. faberi*, two new isoprenylated xanthones, hyperfaberols A (**567**) and B (**568**), along with the known dulxanthone D (**572**) were isolated [155]. To find small-molecule regulators of RXRα (retinoid X receptor α), a phytochemical study of *H. elodeoides* was conducted and the new xanthone, 1,3,6-trihydroxy-7-*O*-(3-methylbut-2-enyl)xanthone (**569**), together with the known 1,3,6-trihydroxy-7-methoxyxanthone (**570**) and 5-hydroxy-3 methoxyxanthone (**571**) were obtained—with the first being found to exhibit the desired biological activity [160].

Calycinoxanthone D (**627**) was obtained from *H. acmosepalum* [161]. For the first time, sulfonated xanthonoids, namely, potassium 1,3-dihydroxy-5-methoxy-9-oxo-9*H*-xanthene-4-sulfonate (**599**) and potassium 1,3-dihydroxy-5-*O*-*β*-D-glycopyranosyl-xanthone-4-sulfonate (**600**), were obtained from *H. sampsonii* [162]. Additionally, five xanthones, 2,3,6,8-tetrahydroxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**563**), γ-mangostin (**581**), 1,3,5,6-tetrahydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**580**), 1,7-dihydroxy-9*H*-xanthen-9-one (**546**), and cudraxanthone K (**622**) were isolated [163].

From callus cultures of *H. perforatum* subsp. *perforatum,* two new xanthone derivatives, 1-hydroxy-5,6,7-trimethoxy-9*H*-xanthen-9-one (**573**) and 3-*O*-methylpaxanthone (**616**), together with eight known compounds, 1,3,5,6-tetrahydroxy-9*H*-xanthen-9-one (**552**), 1,3,6,7-tetrahydroxy-9*H*-xanthen-9-one (**555**), 1-hydroxy-6,7-dimethoxy-9*H*-xanthen-9-one (**574**), 1,3,5-trihydroxy-9*H*-xanthen-9-one (**576**), 1,3,5-trimethoxy-9*H*-xanthen-9-one (**577**), 2,6,8-trihydroxy-3-methoxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**578**), paxanthone (**617**), and cadensin G (**634**) were isolated [164]. From *H. perforatum*, 1,3,6,7-tetrahydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**575**) could be obtained [164]. Patulosides A (**602**) and B (**603**) together with paxanthonin (**604**) were obtained from *H. patulum* [165].

As a result of the study of the leaves of *H. styphelioides*, the new xanthone, 2-[(1*S*,4*S*)-2,2-dimethyl-4-(prop-1-en-2-yl)cyclopentyl]-1,3,5-trihydroxy-9*H*-xanthen-9-one (**605**), along with the known compound 5-*O*-demethylpaxanthonin (**606**), were obtained [101].

From the roots of *H. roeperianum,* the four new xanthones 5-*O*-demethylpaxanthonin (**606**), 5-*O*-methylisojacareubin (**619**), 5-*O*-methyl-2-deprenylrheediaxanthone B (**626**), and roeperanone (**628**) were obtained along with six known metabolites, 2-hydroxy-9*H*-xanthen-9-one (**544**), 1,5-dihydroxy-2-methoxy-9*H*-xanthen-9-one (**570**), 5-hydroxy-2-methoxy-9*H*-xanthen-9-one (**582**), isojacareubin (**618**), 2-deprenylrheediaxanthone B (**625**), and calycinoxanthone D (**627**) [166].

From the aerial parts of *H. japonicum*, the new xanthone glycoside, 4,8-dihydroxy-9-oxo-9*H*-xanthen-3-yl-*β*-D-glucopyranoside (**601**), the novel dimeric xanthone bijaponicaxanthone (**640**), the prenylated xanthone 1,3,5,6-tetrahydroxy-4-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**596**), two new

bisxanthones jacarelhyperols A (**641**) and B (**642**), 3,6,7-trihydroxy-1-methoxy-9*H*-xanthen-9-one (**595**), and 1,6-dihydroxyisojacereubin-5-*O*-*β*-D-glucoside (**621**) were isolated. In addition, the four known xanthones 1,5,6-trihydroxy-9*H*-xanthen-9-one (**597**), isojacareubin (**618**), 6-deoxyisojacareubin (**620**), and 5,9,10-trihydroxy-1,2,2-trimethyl-1,2-dihydro-6*H*-furo[2,3-*c*]xanthen-6-one (**623**) were obtained [167, 168].

From *H. oblongifolium*, hypericorin C (**643**) and D (**644**) and 3,4-dihydroxy-5-methoxyxanthone (**645**) were characterized [169]. In the CH_2Cl_2 extract of the stems and leaves of *H. henryi*, 1,5-dihydroxy-4-methoxy-9*H*-xanthen-9-one (**598**) and kielcorin (**631**) were found [170]. Ten new polyprenylated tetraoxygenated xanthones, the monogxanthones A–J (**646–655**) were isolated from the roots of *H. monogynum,* with such compounds being found rarely in plants of the genus *Hypericum* [171]. Finally, hyperixanthone (**656**) was characterized from *H. riparium* [92].

The biological properties of xanthones **517–656** isolated from *Hypericum* species are shown in Table 7 and their biosynthesis and synthesis aspects are covered in [172, 173].

Table 7 Xanthone derivatives

Compound name	Species	Biological activity	Ref.
Elliptoxanthone A (**517**)	*H. ellipticum*		[108]
2,6,8-Trihydroxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**518**)	*H. chinense*		[154, 155]
1,6-Dihydroxy-4-methoxy-9*H*-xanthen-9-one (**519**)	*H. ellipticum*		[108]
1,4,5-Trihydroxy-9*H*-xanthen-9-one (**520**)	*H. ellipticum*		[108]
2-Hydroxy-5-methoxy-9*H*-xanthen-9-one (**521**)	*H. chinense*		[154, 155]
1,2,5-Trihydroxy-9*H*-xanthen-9-one (**522**)	*H. chinense*		[154, 155]
1,3-Dihydroxy-5-methoxy-9*H*-xanthen-9-one (**523**)	*H. chinense*		[154, 155]
3,5-Dihydroxy-1-methoxy-9*H*-xanthen-9-one (**524**)	*H. chinense*		[154, 155]
4-Hydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**525**)	*H. chinense*		[154, 155]
3,5,6-Trihydroxy-1-methoxy-9*H*-xanthen-9-one (**526**)	*H. chinense*		[154, 155]
3,6-Dihydroxy-1,7-dimethoxy-9*H*-xanthen-9-one (**527**)	*H. chinense*		[154, 155]
3,7-Dihydroxy-1-methoxy-9*H*-xanthen-9-one (**528**)	*H. chinense*		[154, 155]
4,6-Dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**529**)	*H. chinense*		[154, 155]
2,6-Dihydroxy-3,4-dimethoxy-9*H*-xanthen-9-one (**530**)	*H. chinense*		[154, 155]
6-Hydroxy-2,3,4-trimethoxy-9*H*-xanthen-9-one (**531**)	*H. chinense*		[154, 155]
3,6-Dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**532**)	*H. chinense*		[154, 155]
4,7-Dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**533**)	*H. chinense*		[154, 155]
3,7-Dihydroxy-2,4-dimethoxy-9*H*-xanthen-9-one (**534**)	*H. chinense*		[154, 155]

(continued)

Table 7 (continued)

3-Hydroxy-2-methoxy-9*H*-xanthen-9-one (**535**)	*H. chinense*		[154, 155]
1,5-Dihydroxy-3-methoxy-9*H*-xanthen-9-one (**536**)	*H. chinense*		[154, 155]
3,4-Dihydroxy-2-methoxy-9*H*-xanthen-9-one (**537**)	*H. chinense*		[154, 155]
1,5,6-Trihydroxy-3-methoxy-9*H*-xanthen-9-one (**538**)	*H. chinense*		[154, 155]
1,3,7-Trihydroxy-2-(2-hydroxy-3-methylbut-3-en-1-yl)-9*H*-xanthen-9-one (**539**)	*H. ellipticum*		[154, 155]
1,3,7-Trihydroxy-5-methoxy-9*H*-xanthen-9-one (**540**)	*H. chinense*		[154, 155]
1,7-Dihydroxy-5,6-dimethoxy-9*H*-xanthen-9-one (**541**)	*H. chinense*		[154, 155]
4,5-Dihydroxy-2,3-dimethoxy-9*H*-xanthen-9-one (**542**)	*H. chinense*		[154, 155]
1,3-Dihydroxy-2,4-dimethoxy-9*H*-xanthen-9-one (**543**)	*H. chinense*		[154, 155]
2-Hydroxy-9*H*-xanthen-9-one (**544**)	*H. chinense*		[154, 155]
2-Hydroxy-1-methoxy-9*H*-xanthen-9-one (**545**)	*H. chinense*	Showed cytotoxicity for MCF-7 cells (IC_{50} 4.0 μg/cm^3) as well as less potent cytotoxic effects against the KB, K562, and COLO205 cell lines (IC_{50} 14.0–21.6 μg/cm^3)	[154, 155]
1,7-Dihydroxy-9*H*-xanthen-9-one (**546**)	*H. chinense*		[154]
2,5-Dihydroxy-9*H*-xanthen-9-one (**547**)	*H. chinense*		[154, 155]
2,7-Dihydroxy-9*H*-xanthen-9-one (**548**)	*H. chinense*		[154, 155]
1,3-Dihydroxy-2-methoxy-9*H*-xanthen-9-one (**549**)	*H. chinense*		[154, 155]
2,5-Dihydroxy-1-methoxy-9*H*-xanthen-9-one (**550**)	*H. chinense*		[154, 155]
3-Hydroxy-2,4-dimethoxy-9*H*-xanthen-9-one (**551**)	*H. chinense*		[154, 155]
1,3,5,6-Tetrahydroxy-9*H*-xanthen-9-one (**552**)	*H. chinense*		[154, 155]
1,3,5-Trihydroxy-6-methoxy-9*H*-xanthen-9-one (**553**)	*H. chinense*		[154, 155]
1,3,6-Trihydroxy-5-methoxy-9*H*-xanthen-9-one (**554**)	*H. chinense*		[154, 155]
1,3,6,7-Tetrahydroxy-9*H*-xanthen-9-one (**555**)	*H. chinense*		[154, 155]
1,5-Dihydroxy-6,7-dimethoxy-9*H*-xanthen-9-one (**556**)	*H. chinense*		[154, 155]
3,8-Dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**557**)	*H. chinense*		[154, 155]
3,5-Dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**558**)	*H. chinense*		[154, 155]
1,3,5-Trihydroxy-6,7-dimethoxy-9*H*-xanthen-9-one (**559**)	*H. chinense*		[154, 155]
1,3,7-Trihydroxy-5,6-dimethoxy-9*H*-xanthen-9-one (**560**)	*H. chinense*		[154, 155]
1,7-Dihydroxy-6-methoxy-9*H*-xanthen-9-one (**561**)	*H. chinense*		[154, 155]
1,3,7-Trihydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**562**)	*H. chinense*		[154, 155]
2,3,6,8-Tetrahydroxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**563**)	*H. scabrum*		[33]
1,3,7-Trihydroxy-9*H*-xanthen-9-one (**564**)	*H. scabrum*		[33]

(continued)

Table 7 (continued)

1,7-Dihydroxy-4-methoxy-9*H*-xanthen-9-one (**565**)	*H. scabrum*		[33]
2,5-Dihydroxy-9*H*-xanthen-9-one (**566**)	*H. canariensis*		[33]
Hyperfaberol A (**567**)	*H. faberi*		[155]
Hyperfaberol B (**568**)	*H. faberi*		[155]
1,3,6-Trihydroxy-7-*O*-(3-methylbut-2-enyl) xanthone (**569**)	*H. elodeoides*	Exhibited binding to the RXRα retinoid receptor (binding constant, K_D, 14.0 μ*M*)	[160]
1,3,6-Trihydroxy-7-methoxyxanthone (**570**)	*H. elodeoides*		[160]
5-Hydroxy-3-methoxyxanthone (**571**)	*H. elodeoides*		[160]
Dulxanthone D (**572**)	*H. faberi*		[155]
1-Hydroxy-5,6,7-trimethoxy-9*H*-xanthen-9-one (**573**)	*H. perforatum* subsp. *perforatum*		[164]
1-Hydroxy-6,7-dimethoxy-9*H*-xanthen-9-one (**574**)	*H. perforatum* subsp. *perforatum*		[164]
1,3,6,7-Tetrahydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**575**)	*H. perforatum* subsp. *perforatum*		[164]
1,3,5-Trihydroxy-9*H*-xanthen-9-one (**576**)	*H. perforatum* subsp. *perforatum*		[164]
1,3,5-Trimethoxy-9*H*-xanthen-9-one (**577**)	*H. perforatum* subsp. *perforatum*		[164]
2,6,8-Trihydroxy-3-methoxy-1-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**578**)	*H. perforatum* subsp. *perforatum*		[164]
2-Hydroxy-5-methoxy-9*H*-xanthen-9-one (**579**)	*H. chinense*		[154]
1,3,5,6-Tetrahydroxy-2-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**580**)	*H. androsaemum*		[163]
γ-Mangostin (**581**)	*H. androsaemum*		[163]
5-Hydroxy-2-methoxy-9*H*-xanthen-9-one (**582**)	*H. hookerianum* *H. roeperianum*		[166, 157]
2-Hydroxy-3-methoxy-9*H*-xanthen-9-one (**583**)	*H. hookerianum*		[157]
6,7-Dihydroxy-1,3-dimethoxy-9*H*-xanthen-9-one (**584**)	*H. geminiflorum*		[158, 159]
4-Hydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**585**)	*H. geminiflorum*		[158, 159]
1,5,6-Trihydroxy-3-methoxyxanthone (**586**)	*H. geminiflorum*		[159]
3,8-Dihydroxy-1,2-dimethoxy-9*H*-xanthen-9-one (**587**)	*H. geminiflorum*		[159]
1,3,8-Trihydroxy-2-methoxy-9*H*-xanthen-9-one (**588**)	*H. geminiflorum*		[159]
1,3,8-Trihydroxy-4-methoxy-9*H*-xanthen-9-one (**589**)	*H. geminiflorum*		[159]
1,5-Dihydroxy-6-methoxy-9*H*-xanthen-9-one (**590**)	*H. geminiflorum*		[159]
2,3-Dimethoxy-9*H*-xanthen-9-one (**591**)	*H. geminiflorum*		[159]
1,8-Dihydroxy-3-methoxy-9*H*-xanthen-9-one (**592**)	*H. geminiflorum*		[159]
2,3,4-Trihydroxy-9*H*-xanthen-9-one (**593**)	*H. canariensis*		[156]
7-Hydroxy-2,3,4-trimethoxy-9*H*-xanthen-9-one (**594**)	*H. canariensis*		[156]
3,6,7-Trihydroxy-1-methoxy-9*H*-xanthen-9-one (**595**)	*H. japonicum*		[168]
1,3,5,6-Tetrahydroxy-4-(3-methylbut-2-en-1-yl)-9*H*-xanthen-9-one (**596**)	*H. japonicum*		[167, 168]
1,5,6-Trihydroxy-9*H*-xanthen-9-one (**597**)	*H. japonicum*		[167, 168]
1,5-Dihydroxy-4-methoxy-9*H*-xanthen-9-one (**598**)	*H. henryi*		[170]

(continued)

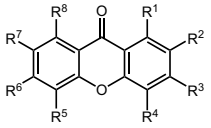
Table 7 (continued)

Potassium 1,3-dihydroxy-5-methoxy-9-oxo-9*H*-xanthene-4-sulfonate (**599**)	*H. sampsonii*	Exhibited cytotoxicity for P388 murine cancer cell line (ED_{50} 3.46 μ*M*)	[162]
Potassium1,3-dihydroxy-5-*O*-*β*-D-glycopyranosylxanthone-4-sulfonate (**600**)	*H. sampsonii*	Exhibited cytotoxicity for P388 murine cancer cell line (ED_{50} 15.69 μ*M*)	[162]
4,8-Dihydroxy-9-oxo-9*H*-xanthen-3-yl-*β*-D-glucopyranoside (**601**)	*H. japonicum*		[168]
Patuloside A (**602**)	*H. patulum*		[165]
Patuloside B (**603**)	*H. patulum*		[165]
Paxanthonin (**604**)	*H. patulum*		[165]
2-[(1*S*,4*S*)-2,2-Dimethyl-4-(prop-1-en-2-yl)cyclopentyl]-1,3,5-trihydroxy-9*H*-xanthen-9-one (**605**)	*H. styphelioides*		[101]
5-*O*-Demethylpaxanthonin (**606**)	*H. styphelioides*		[101, 166]
10*H*[1,3]Dioxolo[4,5-*b*]xanthen-10-one (**607**)	*H. geminiflorum*		[158]
Hyperxanthone A (**608**)	*H. scabrum*		[33]
Hyperxanthone B (**609**)	*H. scabrum*		[33]
Hyperxanthone C (**610**)	*H. scabrum*		[33]
Hyperxanthone D (**611**)	*H. scabrum*		[33]
Hyperxanthone E (**612**)	*H. scabrum*		[33]
Hyperxanthone F (**613**)	*H. scabrum*		[33]
Toxyloxanthone B (**614**)	*H. scabrum*		[33]
Elliptoxanthone B (**615**)	*H. ellipticum*		[108]
3-*O*-Methylpaxanthone (**616**)	*H. perforatum* subsp. *perforatum*		[164]
Paxanthone (**617**)	*H. perforatum* subsp. *perforatum*		[164]
Isojacareubin (**618**)	*H. japonicum*		[167, 168]
5-*O*-Methylisojacareubin (**619**)	*H. roeperianum*		[166]
6-Deoxyisojacareubin (**620**)	*H. japonicum*		[167, 168]
1,6-Dihydroxyisojacereubin-5-*O*-*β*-D-glucoside (**621**)	*H. japonicum*		[167, 168]
Cudraxanthone K (**622**)	*H. androsaemum*		[163]
5,9,10-Trihydroxy-1,2,2-trimethyl-1,2-dihydro-6*H*-furo[2,3-*c*]xanthen-6-one (**623**)	*H. japonicum*		[163]
2,3-Dihydro-4,7-dihydroxy-2-(1-hydroxy-1-methylethyl)-5*H*-furo[3,2-*b*]xanthen-5-one (**624**)	*H. chinense*	Exhibited cytotoxicity for the KB and MCF-7 cancer cell lines (IC_{50} 9.1 and 9.8 μg/cm^3)	[154]
2-Deprenylrheediaxanthone B (**625**)	*H. roeperianum*		[166]
5-*O*-Methyl-2-deprenylrheediaxanthone B (**626**)	*H. roeperianum*		[166]
Calycinoxanthone D (**627**)	*H. acmosepaium*		[161]
Roeperanone (**628**)	*H. roeperianum* *H. acmosepalum*		[166]
2-*O* Demethylkielcorin (**629**)	*H. chinense*	Displayed cytotoxicity (IC_{50} 15.8 μg/cm^3) for COLO205 cells	[154]
Chinexanthone A (**630**)	*H. chinense*		[154]
Kielcorin (**631**)	*H. chinense*	Demonstrated cytotoxicity for KB cells (IC_{50} 8.1 μg/cm^3), and activity against colchicine-resistant KB (KB-C2) cells (in the presence of colchicine, 2.5 μ*M*; IC_{50} 6.5 μg/cm^3), as compared to unmodified KB-C2 cells (IC_{50} 18.4 μg/cm^3)	[154]

(continued)

Table 7 (continued)

Subalatin (**632**)	*H. chinense*		[154]
5′-Demethoxycadensin G (**633**)	*H. chinense*		[154]
Cadensin G (**634**)	*H. perforatum* subsp. *perforatum*		[164]
Cadensin D (**635**)	*H. geminiflorum*		[158, 159]
Cadensin A (**636**)	*H. henryi*		[170]
Hyperielliptone HC (**637**)	*H. geminiflorum*		[158, 159]
Hyperielliptone HD (**638**)	*H. geminiflorum*		[158, 159]
Gemixanthone A (**639**)	*H. geminiflorum*		[158, 159]
Bijaponicaxanthone (**640**)	*H. japonicum*		[167, 168]
Jacarelhyperol A (**641**)	*H. japonicum*		[167, 168]
Jacarelhyperol B (**642**)	*H. japonicum*		[167, 168]
Hypericorin C (**643**)	*H. oblongifolium*		[169]
Hypericorin D (**644**)	*H. oblongifolium*		[169]
3,4-Dihydroxy-5-methoxyxanthone (**645**)	*H. oblongifolium*		[169]
Monogxanthone A (**646**)	*H. monogynum*	1. Exhibited neuroprotective effects against corticosterone (Cort)-induced lesions of PC12 cells at a concentration of 6.25 μ*M* 2. Showed cell viability of >75%, as well as inhibitory effects on nitric oxide production in lipopolysaccharide-induced BV2 microglia cells (IC_{50} 7.47 ± 0.65 μ*M*)	[171]
Monogxanthone B (**647**)	*H. monogynum*	1. Exhibited neuroprotective effects against corticosterone (Cort)-induced lesions of PC12 cells at concentration of 12.50 μ*M* 2. Showed cell viability of >75%, as well as inhibitory effects on nitric oxide production in lipopolysaccharide-induced BV2 microglia cells (IC_{50} 9.60 ± 0.12 μ*M*)	[171]
Monogxanthone C (**648**)	*H. monogynum*		[171]
Monogxanthone D (**649**)	*H. monogynum*		[171]
Monogxanthone E (**650**)	*H. monogynum*		[171]
Monogxanthone F (**651**)	*H. monogynum*		[171]
Monogxanthone G (**652**)	*H. monogynum*		[171]
Monogxanthone H (**653**)	*H. monogynum*		[171]
Monogxanthone I (**654**)	*H. monogynum*		[171]
Monogxanthone J (**655**)	*H. monogynum*		[171]
Hyperixanthone (**656**)	*H. riparium*		[92]



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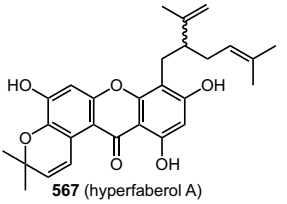
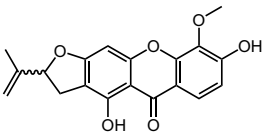
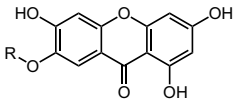
602 R^1 = OH R^2 = H R^3 = H R^4 = H R^5 = OH R^6 = OH R^7 = H R^8 = H
603 R^1 = OH R^2 = H R^3 = *O*-*ß*-D-Glc(2*R*,1) R^4 = H R^5 = *O*-*α*-L-Rha R^6 = OH R^7 = H R^8 = H



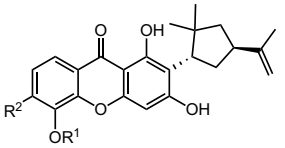
567 (hyperfaberol A)



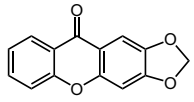
568 (hyperfaberol B)



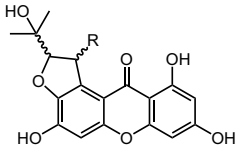
569 R = Pre (1,3,6-trihydroxy-7-*O*-(3-methylbut-2-enyl)xanthone)
570 R = Me (1,3,6-trihydroxy-7-methoxyxanthone)



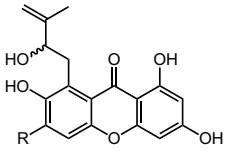
604 R^1 = Me, R^2 = OH (paxanthonin)
605 R^1 = H, R^2 = OH
606 R^1 = H, R^2 = H (5-*O*-demethylpaxanthonin)



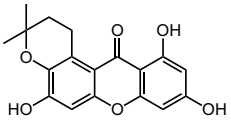
607 (10*H*-[1,3]dioxolo[4,5-*b*]xanthen-10-one)



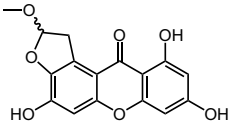
608 R = H (hyperxanthone A)
609 R = OH (hyperxanthone B)



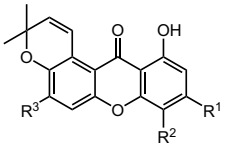
610 R = OH (hyperxanthone C)
611 R = H (hyperxanthone D)



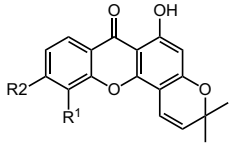
612 (hyperxanthone E)



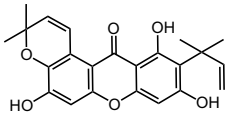
613 (hyperxanthone F)



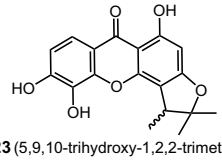
614 R^1 = OH, R^2 = H, R^3 = OH (toxyloxanthone B)
615 R^1 = H, R^2 = OH, R^3 = OH (elliptoxanthone B)
616 R^1 = OMe, R^2 = H, R^3 = OMe (3-*O*-methylpaxanthone)
617 R^1 = H, R^2 = H, R^3 = OMe (paxanthone)



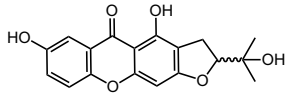
618 R^1 = OH, R^2 = OH (isojacareubin)
619 R^1 = OMe, R^2 = OH (5-*O*-methylisojacareubin)
620 R^1 = OH, R^2 = H (6-deoxyisojacareubin)
621 R^1 = β-D-Glc, R^2 = OH (1,6-dihydroxyisojacereubin-5-*O*-β-D-glucoside)



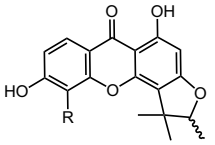
622 (cudraxanthone K)



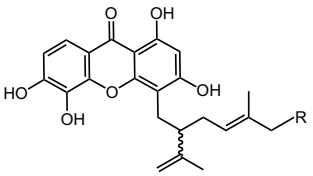
623 (5,9,10-trihydroxy-1,2,2-trimethyl-1,2-dihydro-6*H*-furo[2,3-*c*]xanthen-6-one)



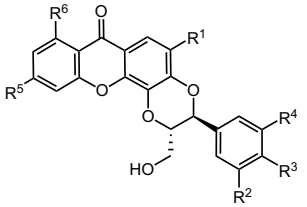
624 (4,7-dihydroxy-2-(2-hydroxypropan-2-yl)-2,3-dihydro-5*H*-furo[3,2-*b*]xanthen-5-one)



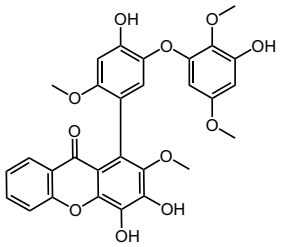
625 R = OH (2-deprenylrheediaxanthone B)
626 R = OMe (5-*O*-methyl-2-deprenyl-rheediaxanthone B)



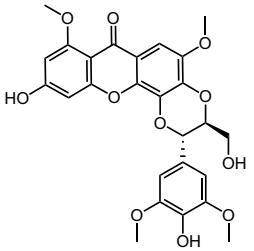
627 R = K (calycinoxanthone D)
628 R = $CH_2CH=C(CH_3)_2$ (roeperanone)



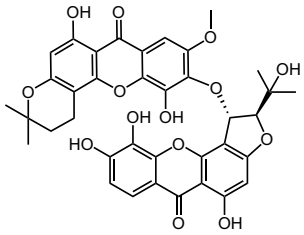
629 R^1 = OH, R^2 = H, R^3 = OH, R^4 = OMe, R^5 = H, R^6 = H (2-*O*-demethylkielcorin)
631 R^1 = OMe, R^2 = H, R^3 = OH, R^4 = OMe, R^5 = H, R^6 = H (kielcorin)
632 R^1 = OH, R^2 = H, R^3 = OOMe, R^4 = OMe, R^5 = H, R^6 = H (subalatin)
633 R^1 = H, R^2 = H, R^3 = OH, R^4 = OMe, R_5 = OH, R^6 = OH (5′-demethoxycadensin G)
634 R^1 = H, R^2 = OMe, R^3 = OH, R^4 = OMe, R^5 = OH, R^6 = OH (cadensin G)
635 R^1 = OMe, R^2 = OMe, R^3 = OH, R^4 = OMe, R^5 = H, R^6 = H (cadensin D)
636 R^1 = OMe, R^2 = OH, R^3 = OMe, R^4 = H, R^5 = H, R^6 = OH (cadensin D)
637 R^1 = H, R^2 = OMe, R^3 = OH, R^4 = OMe, R^5 = OMe, R^6 = OH (hyperielliptone HC)
638 R^1 = OMe, R^2 = H, R^3 = OMe, R^4 = OH, R^5 = H, R^6 = H (hyperielliptone HD)



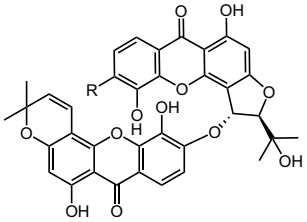
630 (chinexanthone A)



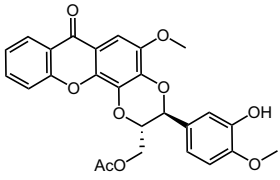
639 (gemixanthone A)



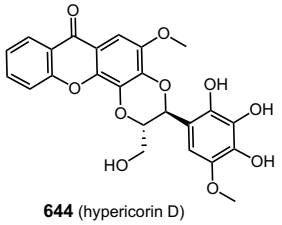
640 (bijaponicaxanthone)



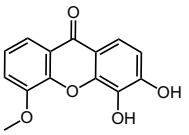
641 R = OH (jacarelhyperol A)
642 R = H (jacarelhyperol B)



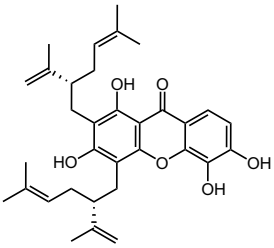
643 (hypericorin C)



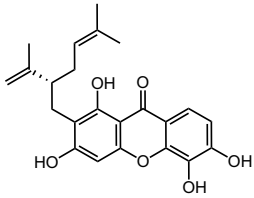
644 (hypericorin D)



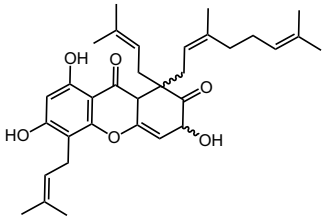
645 (3,4-dihydroxy-5-methoxyxanthone)



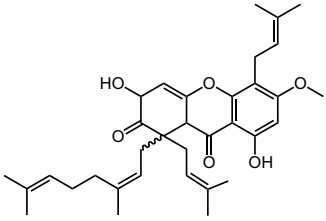
646 (monogxanthone A)



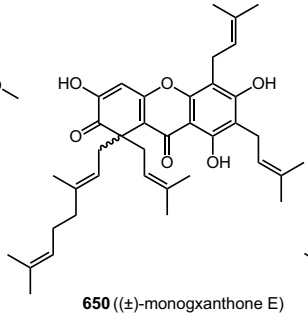
647 (monogxanthone B)



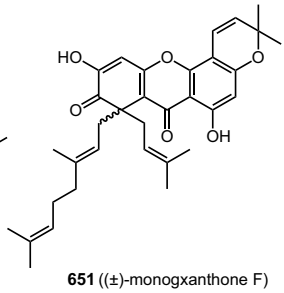
648 ((±)-monogxanthone C)



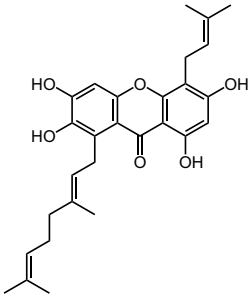
649 ((±)-monogxanthone D)



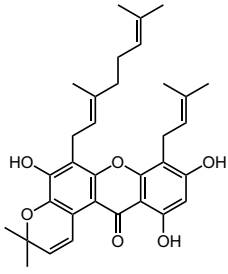
650 ((±)-monogxanthone E)



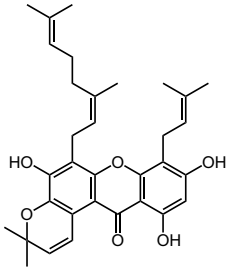
651 ((±)-monogxanthone F)



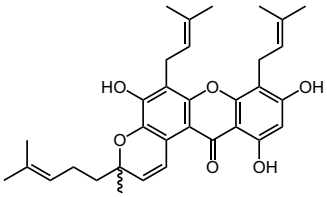
652 (monogxanthone G)



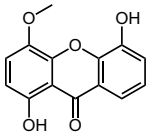
653 (monogxanthone H)



654 (monogxanthone I)



655 ((±)-monogxanthone J)



656 (hyperixanthone)

2.4 *Dianthrones and Phenanthroperylene Quinones*

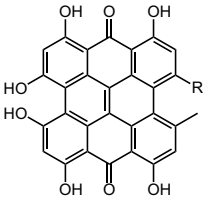
Dianthrones consist of two anthrone units, which are linked by a single bond or a double bond. Some dianthrones are also coupled to benzene rings to form fused aromatic hydrocarbon analogues (phenanthro[1,10,9,8-*opqra*]perylene-7,14-diones). Due to limited structural changes and difficulties in their separation, dianthrones and phenanthroperylene-quinones occur less frequently than other types of secondary metabolites from *Hypericum* species.

A phytochemical investigation of *H. perforatum* led to the detection and isolation of seven compounds: hypericin (**657**), pseudohypericin (**658**), protohypericin (**659**), protopseudohypericin (**660**), and cyclopseudohypericin (**663**) (due to their high condensation state should be referred as phenanthro[1,10,9,8-*opqra*]perylene-7,14-diones), and the dianthrones hypericodehydrodianthrone (**661**), and hydrodianthrone (**662**) [174]. From the same species, (+)-(*S*)-skyrin-6-*O*-*β*-D-glucopyranoside (**664**), (+)-(*S*)-skyrin-6-*O*-*β*-D-xylopyranoside (**665**), (+)-(*S*)-skyrin-6-*O*-α-L-arabinofuranoside (**666**), and (+)-(*R*)-*s*kyrin-6-*O*-*β*-D-glucopyranoside (**667**) were obtained [175]. Finally, the new bianthraquinone glycoside, (+)-(*R*)-skyrin-6-*O*-*β*-D-xylopyranoside (**668**) was isolated from *H. sampsonii* [103].

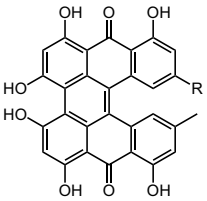
The biological properties of compounds **657**–**668** isolated from *Hypericum* species are shown in Table 8.

Table 8 Dianthrones

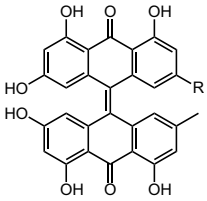
Compound name	Species	Biological activity	Ref.
Hypericin (**657**)	*H. perforatum*	1. Antidepressant effects by inhibiting monoaminooxidase (MAO) 2. Photodynamic activity	[174, 176]
Pseudohypericin (**658**)	*H. perforatum*		[174]
Protohypericin (**659**)	*H. perforatum*		[174]
Protopseudohypericin (**660**)	*H. perforatum*		[174]
Hypericodehydrodianthrone (**661**)	*H. perforatum*		[174]
Pseudohypericodehydrodianthrone (**662**)	*H. perforatum*		[174]
Cyclopseudohypericin (**663**)	*H. perforatum*		[174]
(+)-(*S*)-Skyrin-6-*O*-*β*-D-glucopyranoside (**664**)	*H. perforatum*		[175]
(+)-(*S*)-Skyrin 6-*O*-*β*-D-xylopyranoside (**665**)	*H. perforatum*		[175]
(+)-(*S*)-Skyrin-6-*O*-α-L-arabinofuranoside (**666**)	*H. perforatum*		[175]
(+)-(*R*)-Skyrin-6-*O*-*β*-D-glucopyranoside (**667**)	*H. perforatum*		[175]
(+)-(*R*)-Skyrin-6-*O*-*β*-D-xylopyranoside (**668**)	*H. sampsonii*		[103]



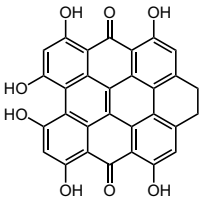
657 R = Me (hypericin)
658 R = CH_2OH (pseudohypericin)



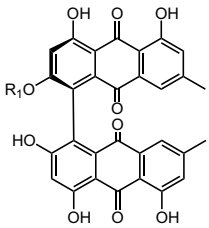
659 R = Me (protohypericin)
660 R = CH_2OH (protopseudohypericin)



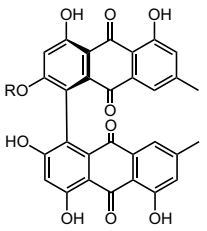
661 R = Me (hypericode hydrodianthrone)
662 R = CH_2OH (pseudohypericode hydrodianthrone)



663 (cyclopseudohypericin)



664 R = β-D-Glc ((+)-(*S*)-skyrin-6-*O*-β-D-glucopyranoside)
665 R = β-D-Xyl ((+)-(*S*)-skyrin 6-*O*-β-D-xylopyranoside)
666 R = α-L-Ara ((+)-(*S*)-skyrin-6-*O*-α-L-arabinofuranoside)



667 R = β-D-Glc ((+)-(*R*)-skyrin-6-*O*-β-D-glucopyranoside)
668 R = β-D-Xyl ((+)-(*R*)-skyrin-6-*O*-β-D-xylopyranoside)

2.5 *Flavonoids*

Flavonoids comprise a class of natural phenolic compounds that include a $C_6/C_3/C_6$ carbon framework. The fundamental flavonoid structure consists of a 2-phenyl-benzo[*c*]pyran nucleus comprising two benzene rings A and B linked through a heterocyclic pyran or pyrone ring C. Flavonoids are distributed widely among *Hypericum* species.

The two new flavonoids, 2-(3,4-dihydroxyphenyl)-5-hydroxy-3-methoxy-8,8-dimethyl-4*H*,8*H*-benzo[1,2-*b*:3,4-*b*′]dipyran-4-one (**685**) and (2*R*,3*R*)-dihydroquercetin-3,7-*O*-α-L-dirhamnoside (**681**) and the two novel chromone glycosides 8-(β-D-glucopyranosyloxy)-5,7-dihydroxy-2-(1-methylethyl)-4*H*-1-benzopyran-4-one (**694**) and 8-(β-D-glucopyranosyl-oxy)-5,7-dihydroxy-2-(1-methylpropyl)-4*H*-1-benzopyran-4-one (**695**), together with the nine known flavonoids quercetin (**669**), rutin (**671**), quercetin 3-*O*-α-L-rhamnosyl-(1 → 2)-*O*-α-L-rhamnoside (**677**), kaempferol (**678**), kaempferol-3-*O*-β-D-glucoside (**679**), kaempferol-7-*O*-α-L-rhamnoside (**680**), (2*R*,3*R*)-dihydroquercetin-7-*O*-α-L-rhamnoside (**682**), (2*R*,3*R*)-dihydroquercetin (**683**), and 2,3-*trans*-dihydro-3,5,4′-trihydroxyfavonol-7-*O*-α-L-rhamnoside (**684**) were isolated from *H. japonicum* [177]. The biaryl compound 3,8″-biapigenin (**686**) was obtained from *H. thasium* [96].

From the methanol extract of *H. sikokumontanum*, three chromone takanechromones A–C (**687**–**689**) and two chromanone glucosides takanechromanone A

(**690**) and B (**691**), together with the four known chromones, 5,7-dihydroxy-3-methyl-4*H*-1-benzopyran-4-one (**692**), 3-ethyl-5,7-dihydroxy-4*H*-1-benzopyran-4-one (**693**), 8-(*β*-D-glucopyranosyloxy)-5,7-dihydroxy-2-(1-methylethyl)-4*H*-1-benzopyran-4-one (**694**), and 8-(*β*-D-glucopyranosyloxy)-5,7-dihydroxy-2-(1-methylpropyl)-4*H*-1-benzopyran-4-one (**695**) were acquired [126].

From *H. lissophloeus,* the new chromanone derivative, 5,7-dihydroxy-2,3-dimethyl-6-(3-methyl-but-2-enyl)-chroman-4-one (**696**) [132] was isolated. A chemical investigation of *H. beanii* led to the isolation of isoastilbin (**697**) [114]. More recently, the flavone hypemonone E (**698**) was identified from *H. monogynum* [178]. Two structurally similar flavonoid glycosides, hyperoside (**699**) and isohyperoside (**700**) were found from *H. ascyron* [179]. Finally, 5,7-dihydroxy-2-isobutyl-4*H*-chromen-4-one (**701**) was obtained from *H. petiolulatum* [180].

The biological properties of flavonoids **669**–**701** isolated from *Hypericum* species are summarized in Table 9.

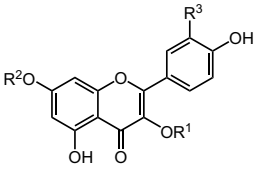
Table 9 Flavonoids

Compound name	Species	Biological activity	Ref.
Quercetin (**669**)	*H. japonicum*		[177]
Hyperin (**670**)	*H. sikokumontanum*		[126]
Rutin (**671**)	*H. sikokumontanum*		[126]
Quercitrin (**672**)	*H. sikokumontanum*		[126]
Isoquercetin (**673**)	*H. thasium*	1. Showed modulation of intracellular ROS production (IC_{50} 16.24 ± 3.97 μg/cm^3) 2. Showed protective effects against H_2O_2-induced injury in H9C2 cells (half-maximal inhibitory concentration 0.0017 μ*M*)	[96, 179]
Avicularin (**674**)	*H. sikokumontanum*		[126]
Quercetin-3-*O*-(2-acetyl)-*β*-D-galactoside (**675**)	*H. sikokumontanum*		[126]
Quercetin-7-*O*-α-L-rhamnoside (**676**)	*H. thasium*		[96]
Quercetin-3-*O*-α-L-rhamnosyl-(1 → 2)-*O*-α-L-rhamnoside (**677**)	*H. japonicum*		[177]
Kaempferol (**678**)	*H. japonicum*		[177]
Kaempferol-3-*O*-*β*-D-glucoside (**679**)	*H. japonicum*		[177]
Kaempferol-7-*O*-α-L-rhamnoside (**680**)	*H. japonicum*		[177]
(2*R*,3*R*)-Dihydroquercetin 3,7-*O*-α-L-dirhamnoside (**681**)	*H. japonicum*		[177]
(2*R*,3*R*)-Dihydroquercetin 7-*O*-α-L-rhamnoside (**682**)	*H. japonicum*		[177]
(2*R*,3*R*)-Dihydroquercetin (**683**)	*H. japonicum*		[177]
2,3-*trans*-Dihydro-3,5,4′-trihydroxyflavonol-7-*O*-α-L-rhamnoside (**684**)	*H. japonicum*		[177]
2-(3,4-Dihydroxyphenyl)-5-hydroxy-3-methoxy-8,8-dimethyl-4*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-4-one (**685**)	*H. japonicum*		[177]
3,8″-Biapigenin (**686**)	*H. thasium*		[96]
Takanechromone A (**687**)	*H. sikokumontanum*		[126]
Takanechromone B (**688**)	*H. sikokumontanum*		[126]
Takanechromone C (**689**)	*H. sikokumontanum*		[126]
Takanechromanone A (**690**)	*H. sikokumontanum*		[126]
Takanechromanone B (**691**)	*H. sikokumontanum*		[126]

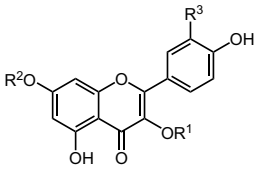
(continued)

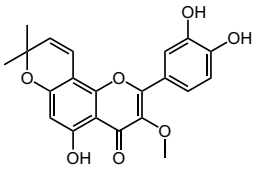
Table 9 (continued)

5,7-Dihydroxy-3-methyl-4*H*-1-benzopyran-4-one (**692**)	*H. sikokumontanum*		[126]
3-Ethyl-5,7-dihydroxy-4*H*-1-benzopyran-4-one (**693**)	*H. sikokumontanum*		[126]
8-(*β*-D-Glucopyranosyloxy)-5,7-dihydroxy-2-(1-methylethyl)-4*H*-1-benzopyran-4-one (**694**)	*H. japonicum*		[177]
8-(*β*-D-Glucopyranosyloxy)-5,7-dihydroxy-2-(1-methylpropyl)-4*H*-1-benzopyran-4-one (**695**)	*H. japonicum*		[177]
5,7-Dihydroxy-2,3-dimethyl-6-(3-methyl-but-2-enyl)-chroman-4-one (**696**)	*H. lissophloeus*	Demonstrated to act as a potent stimulator of currents elicited by GABA in recombinant $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptors (half-maximal potentiation observed at a concentration of about 4 μ*M* and a maximal potentiation of >4000%)	[132]
Isoastilbin (**697**)	*H. beanii*		[114]
Hypemonone E (**698**)	*H. monogynum*	Showed moderate inhibitory effect on α-glucosidase activities (IC_{50} value of 257.78 μg/cm^3)	[178]
Hyperoside (**699**)	*H. ascyron*	Protective effect against H_2O_2-induced injury in H9C2 cells (half maximal inhibitory concentration value 8 n*M*)	[179]
Isohyperoside (**700**)	*H. ascyron*	Protective effect against H_2O_2-induced injury in H9c2 cells (half maximal inhibitory concentration values 2 n*M*)	[179]
5,7-Dihydroxy-2-isobutyl-4*H*-chromen-4-one (**701**)	*H. petiolulatum*	Showed antioxidant activity (IC_{50} at 24.8 μ*M*)	[179]

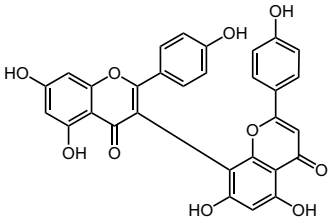


669 R^1 = H, R^2 = H, R^3 = OH (quercetin)
670 R^1 = *β*-D-Gal, R^2 = H, R^3 = OH (hyperin)
671 R^1 = Rut, R^2 = H, R^3 = OH (rutin)
672 R^1 = *α*-L-Rha, R^2 = H, R^3 = OH (quercitrin)
673 R^1 = *β*-D-Glc, R^2 = H, R^3 = OH (isoquercetin)
674 R^1 = *α*-L-Ara , R^2 = H, R^3 = OH (avicularin)
675 R^1 = 2-O-Ac-*β*-D-Gal, R^2 = H, R^3 = OH (quercetin-3-*O*-(2-acetyl)-*β*-D-galactoside)
676 R^1 = H, R^2 = *α*-L-Rha, R^3 = OH (quercetin-7-*O*-*α*-L-rhamnoside)
677 R^1 = *α*-L-Rha(2→1)*α*-L-Rha, R^2 = H, R^3 = OH (quercetin-3-*O*-*α*-L-rhamnosyl-(1→2)-*O*-*α*-L-rhamnoside)
678 R^1 = OH, R_2 = OH, R^3 = H (kaempferol)
679 R^1 = *β*-D-Glc, R_2 = H, R^3 = H (kaempferol-3-*O*-*β*-D-glucoside)

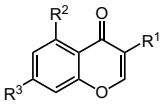




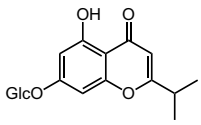
680 R^1 = H, R^2 = α-L-Rha, R^3 = H (kaempferol-7-O-α-L-rhamnoside)
681 R^1 = *α*-L-Rha, R^2 = *α*-L-Rha, R^3 = OH ((2*R*,3*R*)-dihydroquercetin 3,7-*O*-*α*-L-dirhamnoside)
682 R^1 = H, R^2 = *α*-L-Rha, R^3 = OH ((2*R*,3*R*)-dihydroquercetin 7-*O*-*α*-L-rhamnoside)
683 R^1 = H, R^2 = H, R^3 = OH ((2*R*,3*R*)-dihydroquercetin)
684 R^1 = H, R^2 = *α*-L-Rha, R^3 = H (2,3-*trans*-dihydro-3,5,4'-trihydroxy-favonol-7-*O*-*α*-L-rhamnoside)
685 (2-(3,4-dihydroxyphenyl)-5-hydroxy-3-methoxy-8,8-dimethyl-4H,8H-benzo[1,2-b:3,4-b']dipyran-4-one)



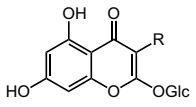
686 (3,8′′-biapigenin)



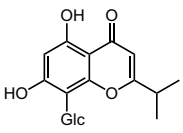
687 R^1 = Me R^2 = OH R^3 = OGlc (takanechromone A)
688 R^1 = Et R^2 = OH R^3 = OGlc (takanechromone B)
689 R^1 = Me R^2 = OH R^3 = OH (takanechromone C)
690 R^1 = Et R^2 = OH R^3 = OH (takanechromanone A)



691 (takanechromanone B)



692 R = Me
693 R = Et



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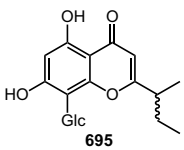

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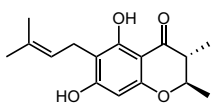

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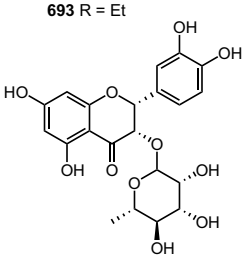
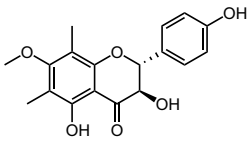
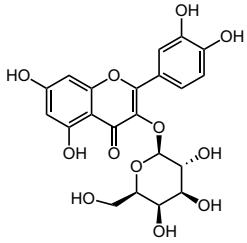


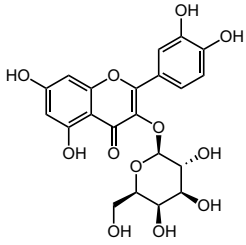
697 (isoastilbin)



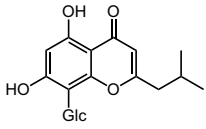
698 (hypemonone E)



699 (hyperoside)



700 (isohyperoside)



701

2.6 *Other Constituents*

Other constituents of *Hypericum* species are terpenoids (sesquiterpenes meroterpenoids, triterpenes), spiro-lactone-related derivatives, and phenylpropanoids.

Two new meroterpenoids, yojironins A (**702**) and B (**703**), were isolated from whole plants of *H. yojiroanum* [129, 181]. From the roots of *H. chinense,* three pentacyclic meroterpenoids, biyoulactones A–C (**704**–**706**) were isolated. These compounds have a unique dilactone structure containing C–C bonded bi- and tricyclic γ-lactone moieties [182]. In addition, eight novel spiro compounds, hyperolactones A–D (**707**–**710**) [183], biyouyanagin A (**711**), biyouyanagin B (**712**) [184], 5,6-dihydrohyperolactone D (**713**), and 4-hydroxyhyperolactone D (**714**) were purified and characterized from this species [90].

From *H. japonicum*, two pairs of enantiomeric japonones A (**715**, **716**) and B (**717**, **718**) were isolated [185]. Hyperenone A (**719**) was obtained from *H. acmosepalum* [113]. From *H. ascyron,* a new 3,4-*seco*-oleanane-type triterpenoid with an unusual enedione moiety, 3,4-*seco*-olean-13(18)-ene-12,19-dion-3-oic acid (**720**) and friedelin (**721**) were obtained [186].

Hyperdioxane A (**743**) and B (**744**) also were documented from this species, with **743** being a conjugate of dibenzo-1,4-dioxane and sesquiterpene moieties [187]. From investigation of the native Cameroonian medicinal plant *H. riparium*, hyperenone C (**722**) was reported [92]. In 2015, Yang et al. systematically studied the chemical constituents of *H. beanii*, and consequently hyperbeanol E (**723**), (*E*)-linalool-1-oic acid (**724**), (4*S*,5*R*)-4-hydroxy-5-methyl-5-(4-methylpent-3-en-1-yl) dihydrofuran-2(3*H*)-one (**725**), benzoic acid (**726**), 2,2-dimethyl-6-phenyl-4a,8a-dihydropyrano[3,4-*b*]pyran-8(2*H*)-one (**727**), (4*S*,4a*R*)-4-hydroxy-4a,8-dimethoxy-4,4a-dihydrodibenzo[*b*,*e*][1,4]dioxin-2(3*H*)-one (**728**), isoimperatorin (**729**), betulinic acid (**730**), and oleanolic acid 3β-caffeate (**731**) were found [114]. From *H. monogynum*, hypemonone F (**736**) and four chromanopyrones, hypemonones A–D (**732**–**735**), were obtained [178]. Two rearranged acylphloroglucinols with a 4,5-*seco*-3(2*H*)-furanone core, furanmonogones A (**741**) and B (**742**) were also reported from the same plant [188]. *Hypericum frondosum* afforded four short ketide–phenylketide conjugates, frondhyperins A–D (**737**–**740**) [189].

From *H. elatoides*, five biphenyl ether glycosides, hyperelatosides A–F (**745**–**750**) were obtained [190]. Four novel meroterpenes, merohyperins A–C (**751**–**753**) and hyperolactone A (**754**) were isolated from the leaves of *H. chinense* [191]. Two common phytochemicals, shikimic acid (**755**) and chlorogenic acid (**756**) were obtained from *H. androsaemum* [192].

Four novel compounds, peplidiforones A–D (**757**–**760**), representing prenylated phenyl polyketides, were isolated from *H. peplidifolium* [193]. Five rare biscoumarin derivatives, 7,7′-dihydroxy-6,6′-biscoumarin (**761**), 7,7′-dimethoxy-6,6′-biscoumarin (**762**), 7,7′-dihydroxy-8,8′-biscoumarin (**763**), 7-methoxy-6,7′-dicoumarinyl ether (**764**), and 2′-hydroxy-5′-(7″-methoxycoumarin-6″-yl)-4′-methoxyphenylpropanoic acid (**765**) were found in *H. riparium* [194]. The japopyrones A (**766**) and B (**767**), with an α-pyrone ring, were isolated from *H. japonicum* [195]. Finally, the precursor of the dianthrones and phenanthroperylene quinones, emodin anthrone (**768**) has been isolated from *Hypericum* species [196].

The biological properties of the above compounds **702**–**768** as isolated from *Hypericum* species are shown in Table 10.

Table 10 Other compounds

Compound name	Species	Biological activity	Ref.
Yojironin A (**702**)	*H. yojiroanum*		[129, 181]
Yojironin B (**703**)	*H. yojiroanum*		[129, 181]
Biyoulactone A (**704**)	*H. chinense*		[182]
Biyoulactone B (**705**)	*H. chinense*		[182]
Biyoulactone C (**706**)	*H. chinense*		[182]
Hyperolactone A (**707**)	*H. chinense*		[183]
Hyperolactone B (**708**)	*H. chinense*		[183]

(continued)

Table 10 (continued)

Compound name	Species	Biological activity	Ref.
Hyperolactone C (**709**)	*H. chinense*		[183]
Hyperolactone D (**710**)	*H. chinense*		[183]
Biyouyanagin A (**711**)	*H. chinense*		[184]
Biyouyanagin B (**712**)	*H. chinense*		[184]
5,6-Dihydrohyperolactone D (**713**)	*H. chinense*		[90]
4-Hydroxyhyperolactone D (**714**)	*H. chinense*		[90]
(+)-Japonone A (**715**)	*H. japonicum*	Exhibited inhibitory activity against Kaposi's sarcoma-associated herpesvirus (KSHV)	[185]
(–)-Japonone A (**716**)	*H. japonicum*	Exhibited inhibitory activity against Kaposi's sarcoma-associated herpesvirus (KSHV)	[185]
(+)-Japonone B (**717**)	*H. japonicum*	Exhibited inhibitory activity against Kaposi's sarcoma-associated herpesvirus (KSHV)	[185]
(–)-Japonone B (**718**)	*H. japonicum*	Exhibited inhibitory activity against Kaposi's sarcoma-associated herpesvirus (KSHV)	[185]
Hyperenone A (**719**)	*H. acmosepalum*	Exhibited antibacterial activity against multidrug-resistant strains of *S. aureus* (*MIC* 2–128 mg/dm^3 and 0.5–128 mg/dm^3) and *M. tuberculosis* H37Rv (*MIC* 75 mg/dm^3)	[113]
3,4-*seco*-Olean-13(18)-ene-12,19-dion-oic acid (**720**)	*H. ascyron*		[186]
Friedelin (**721**)	*H. ascyron*		[186]
Hyperenone C (**722**)	*H. riparium*	Showed antibacterial activity against *S. aureus* (IC_{50} 16.9 μM)	[92]
Hyperbeanol E (**723**)	*H. beanii*		[114]
(*E*)-Linalool-1-oic acid (**724**)	*H. beanii*		[114]
(4*S*,4a*R*)-4-Hydroxy-5-methyl-5-(4-methylpent-3-en-1-yl) dihydrofuran-2(3*H*)-one (**725**)	*H. beanii*		[114]
Benzoic acid (**726**)	*H. beanii*		[114]
(2,2-Dimethyl)-6-phenyl-4a,8a-dihydropyrano[3,4-*b*]-pyran-8 (2*H*)-one (**727**)	*H. beanii*		[114]
(4*S*,4a*R*)-4-Hydroxy-4a,8-dimethoxy-4,4a-dihydrodibenzo[*b*,*e*][1,4] dioxin-2(3*H*)-one (**728**)	*H. beanii*		[114]
Isoimperatorin (**729**)	*H. beanii*		[114]
Betulinic acid (**730**)	*H. beanii*		[114]
Oleanolic acid 3β-caffeate (**731**)	*H. beanii*		[114]
Hypemonone A (**732**)	*H. monogynum*	Showed an inhibitory effect on α-glucosidase activity (IC_{50} 161.46 μg/cm^3)	[178]
Hypemonone B (**733**)	*H. monogynum*		[178]
Hypemonone C (**734**)	*H. monogynum*		[178]
Hypemonone D (**735**)	*H. monogynum*		[178]
Hypemonone F (**736**)	*H. monogynum*		[178]

(continued)

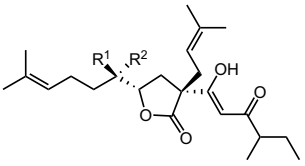
Table 10 (continued)

Compound name	Species	Biological activity	Ref.
Frondhyperin A (**737**)	*H. frondosum*		[189]
Frondhyperin B (**738**)	*H. frondosum*		[189]
Frondhyperin C (**739**)	*H. frondosum*		[189]
Frondhyperin D (**740**)	*H. frondosum*		[189]
Furanmonogone A (**741**)	*H. monogynm*		[188]
Furanmonogone B (**742**)	*H. monogynm*		[188]
Hyperdioxane A (**743**)	*H. ascyron*		[187]
Hyperdioxane B (**744**)	*H. ascyron*		[187]
Hyperelatoside A (**745**)	*H. elatoides*	Potentiation of activity of NGF to stimulate neurite outgrowth in PC12 cells (1 μ*M*)	[190]
Hyperelatoside B (**746**)	*H. elatoides*	Potentiation of activity of NGF to stimulate neurite outgrowth in PC12 cells (1 μ*M*)	[190]
Hyperelatoside C (**747**)	*H. elatoides*	Potentiation of activity of NGF to stimulate neurite outgrowth in PC12 cells (1 μ*M*)	[190]
Hyperelatoside D (**748**)	*H. elatoides*	Potentiation of activity of NGF to stimulate neurite outgrowth in PC12 cells (1 μ*M*)	[190]
Hyperelatoside E (**749**)	*H. elatoides*	Potentiation of activity of NGF to stimulate neurite outgrowth in PC12 cells (1 μ*M*)	[190]
Hyperelatoside F (**750**)	*H. elatoides*	Potentiation of activity of NGF to stimulate neurite outgrowth in PC12 cells (1 μ*M*)	[190]
Merohyperin A (**751**)	*H. chinense*		[191]
Merohyperin B (**752**)	*H. chinense*		[191]
Merohyperin C (**753**)	*H. chinense*		[191]
Hyperolactone A (**754**)	*H. chinense*		[191]
Shikimic acid (**755**)	*H. androsaemum*		[192]
Chlorogenic acid (**756**)	*H. androsaemum*		[193]
Peplidiforone A (**757**)	*H. peplidifolium*	Displayed antifungal activity (phytopathogenic *Botrytis cinerea* and *Septoria tritici*) (growth inhibition of 40 and 38% at 83.3 μ*M*, respectively)	[193]
Peplidiforone B (**758**)	*H. peplidifolium*		[193]
Peplidiforone C (**759**)	*H. peplidifolium*		[193]
Peplidiforone D (**760**)	*H. peplidifolium*		[193]
7,7′-Dihydroxy-6,6′-biscoumarin (**761**)	*H. riparium*		[194]
7,7′-Dimethoxy-6,6′-biscoumarin (**762**)	*H. riparium*		[194]
7,7′-Dihydroxy-8,8′-biscoumarin (**763**)	*H. riparium*		[194]
7-Methoxy-6,7′-dicoumarinyl ether (**764**)	*H. riparium*		[194]
2′-Hydroxy-5′-(7″-methoxycoumarin-6″-yl)-4′-methoxyphenylpropanoic acid (**765**)	*H. riparium*		[194]

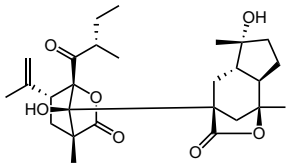
(continued)

Table 10 (continued)

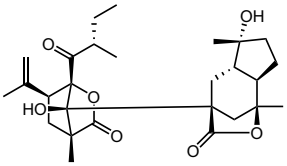
Compound name	Species	Biological activity	Ref.
Japopyrone A (**766**)	*H. japonicum*		[195]
Japopyrone B (**767**)	*H. japonicum*	Displayed inhibition of lytic replication of Kaposi's sarcoma-associated herpesvirus (KSHV) (IC_{50} 29.46 μ*M*; selectivity index > 6.79)	[195]
Emodin anthrone (**768**)	*Hypericum* sp.		[196]



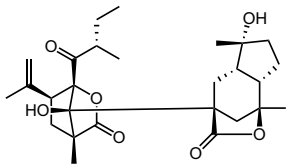
702 R^1 = OH R^2 = Me (yojironin A)
703 R^1 = Me R^2 = Me (yojironin B)



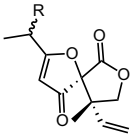
704 (biyoulactone A)



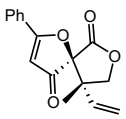
705 (biyoulactone B)



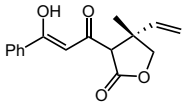
706 (biyoulactone C)



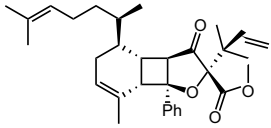
707 R = CH_3CH_2 (hyperolactone A)
708 R = CH_3 (hyperolactone B)



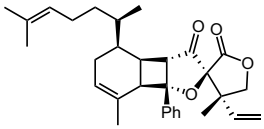
709 (hyperolactone C)



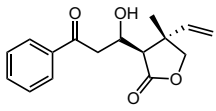
710 (hyperolactone D)



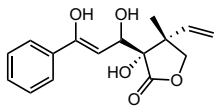
711 (biyouyanagin A)



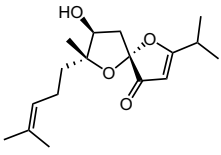
712 (biyouyanagin B)



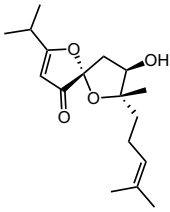
713 (5,6-dihydrohyperolactone D)



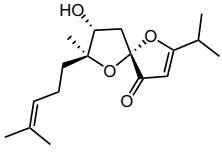
714 (4-hydroxyhyperolactone D)



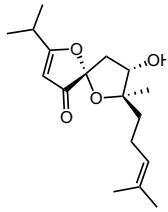
715 ((+)-japonone A)



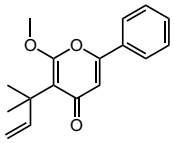
716 ((–)-japonone A)



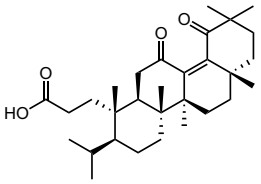
717 ((+)-japonone B)



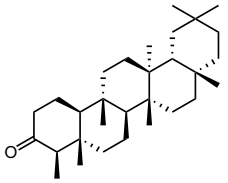
718 ((–)-japonone B



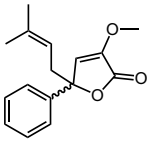
719 (hyperenone A)



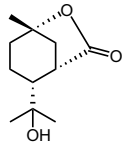
720 (3,4-*seco*-olean-13(18)-ene-12,19-dione-oic acid)



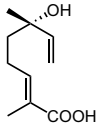
721 (friedelin)



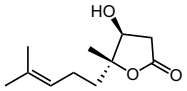
722 (hyperenone C)



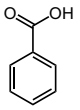
723 (hyperbeanol E)



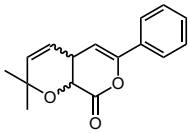
724 ((*E*)-linalool-1-oic acid)



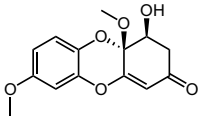
725 ((4*S*,5*R*)-4-hydroxy-5-methyl-5-(4-methylpent-3-en-1-yl)di-hydrofuran-2(3*H*)-one)



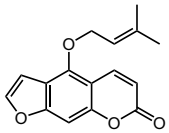
726 (benzoic acid)



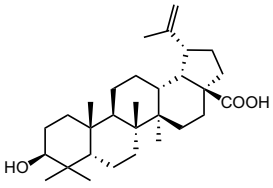
727 (2,2-dimethyl-6-phenyl-4a,8a-dihydro-pyrano[3,4-*b*]pyran-8(2*H*)-one)



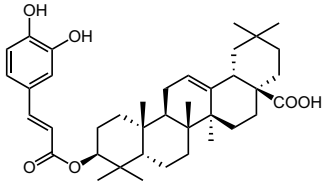
728 ((4*S*,4a*R*)-4-hydroxy-4a,8-dimethoxy-4,4a-dihydro-dibenzo[*b*,*e*][1,4]dioxin-2(3*H*)-one)



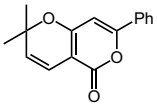
729 (isoimperatorin)



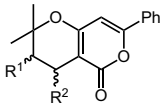
730 (betulinic acid)



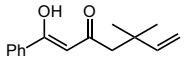
731 (oleanolic acid 3β-caffeate)



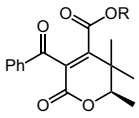
732 (hypemonone A)



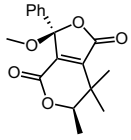
733 R^1 = α-OH, R_2 = α-OMe (hypemonone B)
734 R^1 = α-OH, R^2 = β-OH (hypemonone C)
735 R^1 = H, R^2 = OMe (hypemonone D)



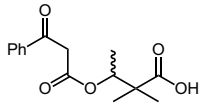
736 (hypemonone F)



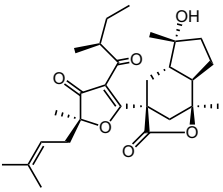
737 R = H (frondhyperin A)
739 R = Me (frondhyperin B)



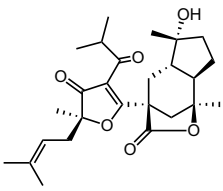
739 (frondhyperin C)



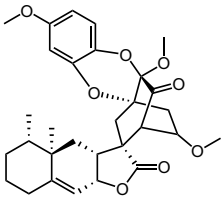
740 (frondhyperin D)



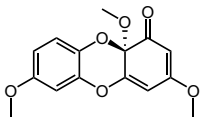
741 (furanmonogone A)



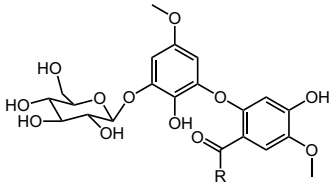
742 (furanmonogone B)



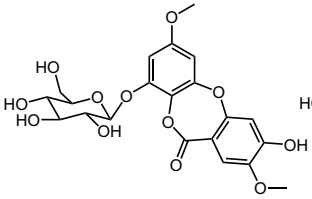
743 (hyperdioxane A)



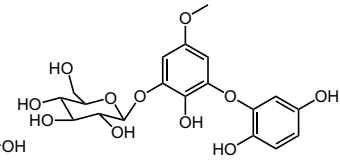
744 (hyperdioxane B)



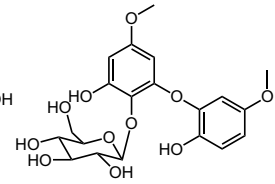
745 R = OMe (hyperelatoside A)
746 R = OH (hyperelatoside B)



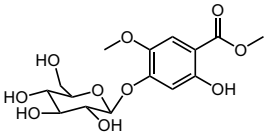
747 (hyperelatoside C)



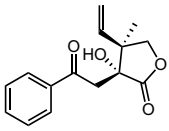
748 (hyperelatoside D)



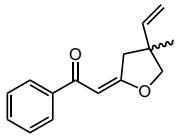
749 (hyperelatoside E)



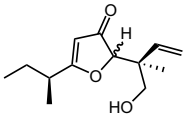
750 (hyperelatoside F)



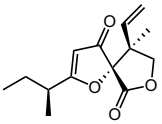
751 (merohyperin A)



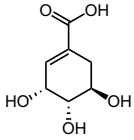
752 (merohyperin B)



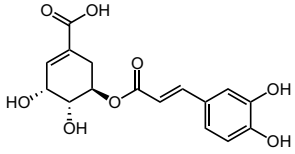
753 (merohyperin C)



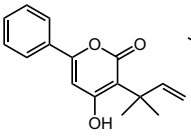
754 (hyperolactone A)



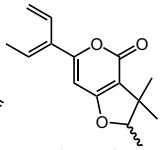
755 (shikimic acid)



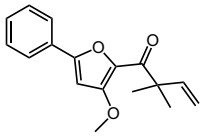
756 (chlorogenic acid)



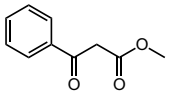
757 (peplidiforone A)



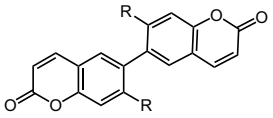
758 (peplidiforone B)



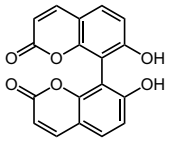
759 (peplidiforone C)



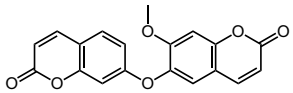
760 (peplidiforone D)



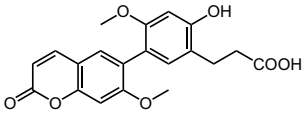
761 R = OH (7,7-dihydroxy-6,6-biscoumarin)
762 R = OMe (7,7-dimethoxy-6,6-biscoumarin)



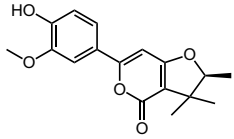
763 (7,7′-dihydroxy-8,8′-biscoumarin)



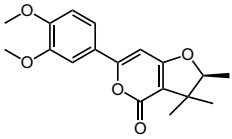
764 (7-methoxy-6,7-dicoumarinyl ether)



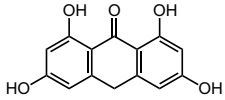
765 (2′-hydroxy-5′-(7′′-methoxy-coumarin-6′′-yl)-4′-methoxy-phenyl-propanoic acid)



766 (japopyrone A)



767 (japopyrone B)



768 (emodin anthrone)

3 Pharmacological Investigations

Of the 768 different types of compounds in *Hypericum* species, 160 of these have been reported in terms of their biological activities. A summary of the distribution of pharmacological activities in relation to the types of compound represented is shown in Fig. 2.

3.1 Antineoplastic Activity

Potential antineoplastic activity is one of the most well-studied biological properties of the constituents of species in the genus *Hypericum*, as investigated in the laboratory by the evaluation of cytotoxicity against various human and murine cancer cell lines. The particular compounds with potential antineoplastic activity that have been the most intensively investigated are hyperforin derivatives and sampsoniones.

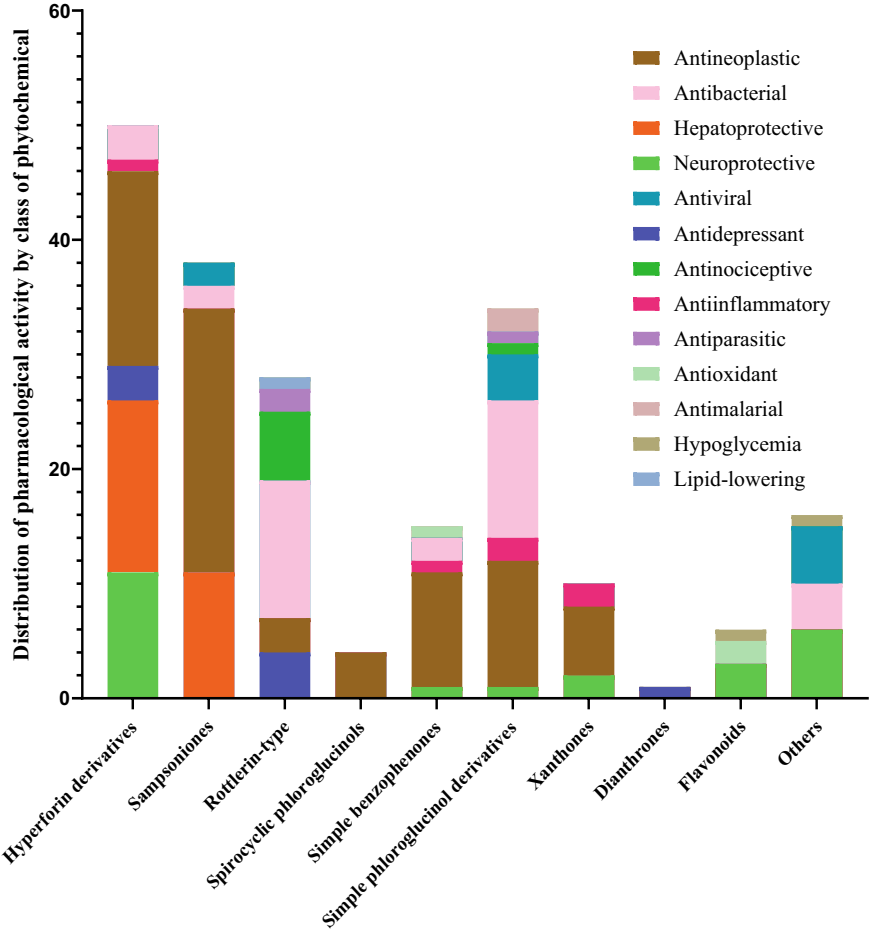


Fig. 2 Relationship of pharmacological activity to the classes of phytochemical constituents of the genus *Hypericum*

A summary of the types of tumor cell lines used to evaluate these compounds is shown in Fig. 3. Among them, breast cancer, lung cancer, leukemia, liver cancer, and colon cancer cells have been the most often utilized. The specific cell lines employed have been mainly MCF7, A549, HL-60, SMMC-7721, and SW480, respectively.

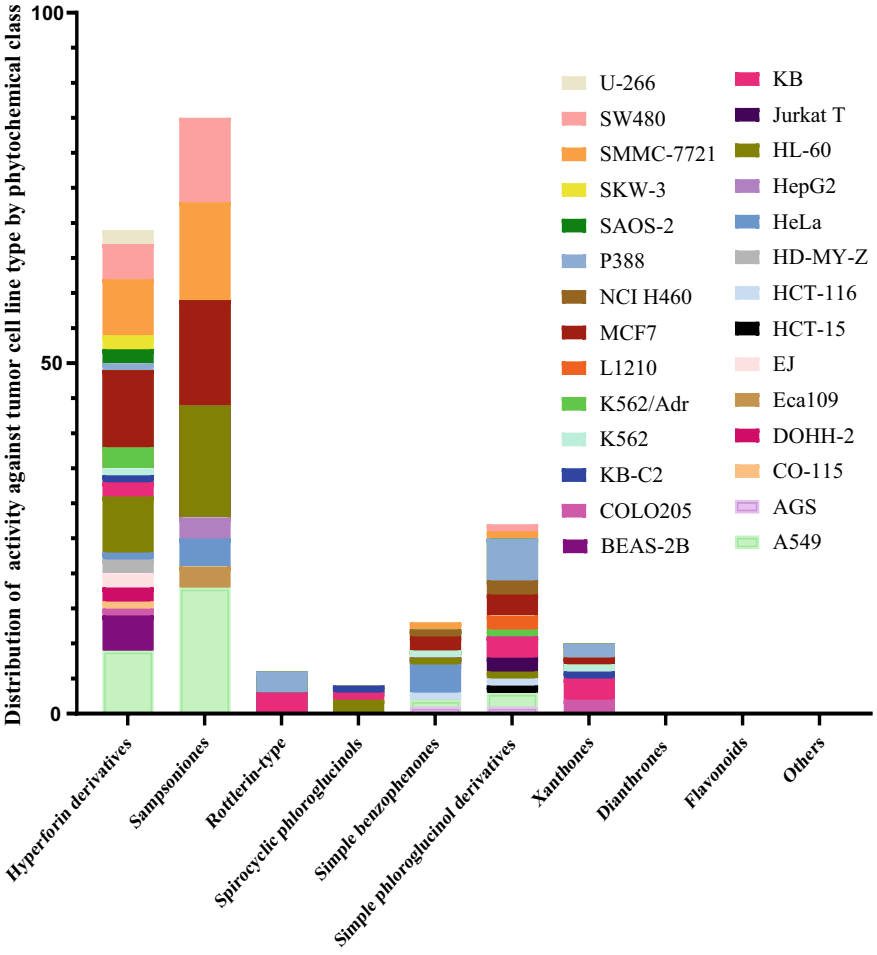


Fig. 3 Relationship of type of tumor cell cytotoxic activity to the classes of phytochemical constituents of the genus *Hypericum*

3.2 *Antimicrobial Activity*

Antimicrobial activity is another highly studied biological effect of the constituents of *Hypericum* species. Compounds with antibacterial activity have been found especially among the rottlerin and simple phloroglucinol derivatives. A summary of the relationship between antibacterial activity and the compound types represented is shown in Fig. 4. For the laboratory investigations concerned, *S. aureus*, *B. subtilis*, and *M. smegmatis* have been the most well-studied microorganisms.

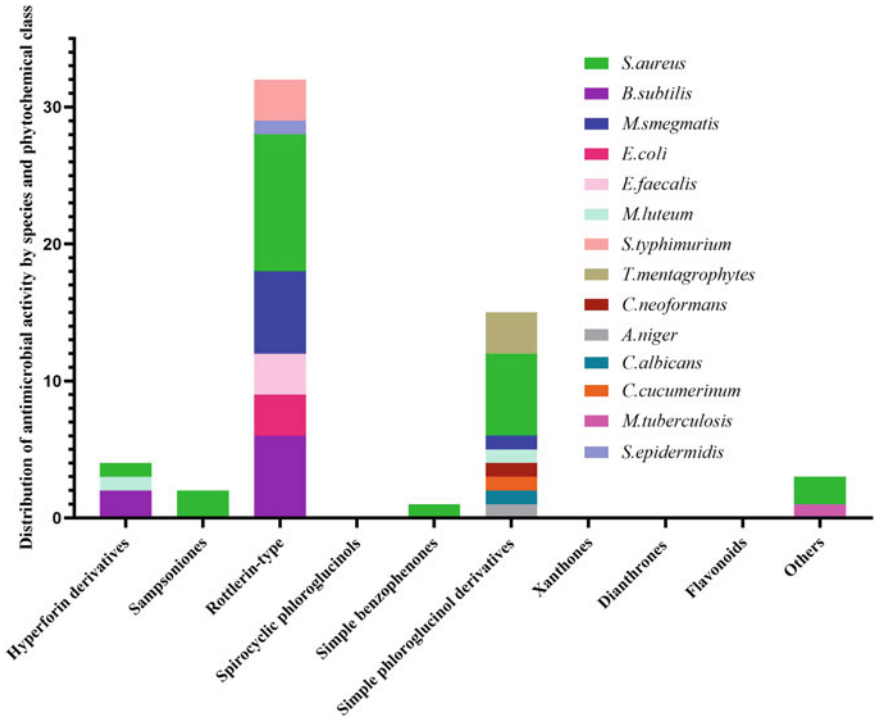


Fig. 4 Relationship of ntimicrobial activity and species to the phytochemical classes of the genus *Hypericum*

3.3 Hepatoprotective Activity

Compounds from *Hypericum* species demonstrating hepatoprotective activity that have been found primarily among the hyperforin and sampsonione derivatives have been examined. One means of investigating liver protection has been the inhibition of cytochrome P450 enzyme activity as, for example, in the case of compounds **14**–**16** [21].

3.4 Neuroprotective Activity

As with hepatoprotection, compounds from *Hypericum* species demonstrated to have neuroprotective activity are mostly hyperforin derivatives, with a few exceptions. Neuroprotection may be related to inhibition of acetylcholinesterase activity, with, for example, compounds **169–179** exhibiting such effects [55]. Compounds **745–750** [190] were shown to potentiate the activity of nerve growth factor to stimulate neurite outgrowth in PC12 cells.

3.5 Antiviral Activity

Compounds with antiviral activity have been found principally among the simple phloroglucinol derivatives. The antiviral effects of these *Hypericum* spp. constituents have been studied most frequently against HIV (human immunodeficiency virus), with compounds such as **224** and **227** being examples [53]. Other phytochemicals have proved to be active against Epstein Barr virus (EB), such as compounds **473** and **475** [146]. In turn, compound **512** displayed a moderate inhibitory effect on lytic EBV DNA replication [150]. Compound **505a** exhibited strong inhibitory activities toward the lytic replication of Kaposi's sarcoma-associated herpesvirus (KSHV) in Vero cells [116]. Also, compounds **715–718** showed some inhibitory activity against KSHV [185].

3.6 Antidepressant Activity

Compounds from *Hypericum* species with antidepressant activity include mainly the hyperforin and rottlerin derivatives. Antidepressant activity was found to be associated with inhibition of neuronal monoamines uptake, as observed with hyperfoliatin (**111**) [57]. Compound **696**, a chromanone derivative, was demonstrated to act as a potent stimulator of currents elicited by GABA in recombinant $\alpha_1\beta_2\gamma_2$ $GABA_A$ receptors [132].

3.7 Antinociceptive Activity

Compounds with antinociceptive activity are mainly rottlerins with, for example, the benzopyran HP1 **432** demonstrating an antinociceptive effect in mice through the opioid system [136].

3.8 Anti-inflammatory Activity

Compounds isolated from *Hypericum* species with potential anti-inflammatory activity have been found thus far among the simple phloroglucinol and xanthone classes. Their anti-inflammatory effects were indicated, for example, by inhibition of nitric oxide production, such as with **43** [29], and from inhibitory effects of thromboxane A2 and leukotriene D4, by compounds **389** and **390**, respectively [124].

3.9 Antiparasitic Activity

Compounds with antiparasitic activity are concentrated mainly in the rottlerin sub-class among the constituents of *Hypericum* species. The type of parasites that can be suppressed is exemplified by the protozoan *Trichomonas vaginalis*, which is inhibited by **235** and **236** [70].

3.10 Antioxidant Activity

Compounds with reported antioxidant activity from *Hypericum* species have been found mainly within the flavonoid group as, for example, compounds **334** and **701** [102, 180].

3.11 Antimalarial Activity

One compound from a member of the genus *Hypericum* spp. with antimalarial activity is otogistone (**390**), a simple phloroglucinol derivative, which exhibited an IC_{50} of 5.6 μ*M*, when evaluated against a chloroquine-sensitive strain of *Plasmodium falciparum* [151].

3.12 Hypoglycemic Activity

Some compounds with potential hypoglycemic activity, for example, both the flavonoid **698** and a further compound (**732**) from *H. monogynum* showed moderate inhibitory effects on α-glucosidase activities [178].

3.13 Lipid-Lowering Activity

Among the rottlerin-type compounds are some with lipid-lowering activity and, for example, hyperjaponical C (**272**) showed moderate lipase inhibitory activity [82].

3.14 Photodynamic Activity

The toxicology of *Hypericum* plants induced by sunlight or "hypericism", has been known for some time and is exemplified by ruminants grazing on these plants suffering death by edema [197]. The toxic compounds are phenanthroperylene quinones and are exemplified by the main compound hypericin (**657**). These are photosensitizers that generate reactive oxygen species in the presence of light, which can attack a range of biomolecules such as proteins and nucleic acids. In the absence of light they are "inactive".

For an overview of the chemistry of these interesting phytochemicals, the reader is directed to the comprehensive and superb review by Falk [176]. The attractiveness of photosensitizers is that they have potential utility in the treatment of an array of disease states ranging from cancer to microbial infections and in any tissue that can be accessed by light (generally in the form of a laser), such as the skin [198, 199] and even internally such as the stomach [200] and lungs [201]. Hypericin also preferentially accumulates in tumor tissue [202] and as it is a fluorescent molecule, this can be used in the so-called phytodynamic diagnosis [176].

Studies in this pharmacological area focus on *Hypericum perforatum* extracts and predominantly hypericin (**657**). Recent research on hypericin highlighted its activity as an antitumor agent and an inhibitor of viral replication by its ability to induce apoptosis and viral transcription, respectively [203]. Hypericin has also been shown to have activity against HIV by degrading the outer structure of the virus [204]. Photodynamic activity has also found utility in the removal of food contaminant bacteria such as *Listeria* and *Salmonella* species [205].

4 Conclusion

As an important group of herbal medicines worldwide, *Hypericum* species have been subjected to intensive phytochemical-related studies by several different research groups based in various countries over the last few decades. St. John's wort (*H. perforatum*) has been of great interest clinically for the treatment of mild-to-moderate depression, and is an established phytomedicine in countries of Western Europe [9, 10, 15].

In this contribution, 771 compounds have been documented as isolated constituents of *Hypericum* species, and their biological activities were tabulated. These secondary metabolites are dianthrones, flavonoids, phloroglucinols, xanthones, and members of other compound classes, with phloroglucinol and xanthone derivatives being the predominant phytochemical groups of the genus *Hypericum*. From the pharmacological investigations that have been presented, it is clear that the major biological activities documented are antinociceptive and antidepressant-like effects, cytotoxicity for cancer cell lines, and antimicrobial activity.

With respect to the wide diversity of chemical skeletons among the known constituents of *Hypericum* species, their chemical synthesis and biosynthesis aspects have not been addressed. For several of these classes, there exists an extensive literature on these topics [59, 172, 173, 196, 206–212].

Most of the phytochemistry and biological activities summarized in this chapter have been focused on only the six species, *H. ascyron*, *H. chinense*, *H. japonicum*, *H. perforatum*, *H. scabrum*, and *H. sampsonii*, which may be taken as indicative of the enormous potential for discovering interesting new structural types of biologically active secondary metabolites. Additionally, by considering the taxonomic sources of the compounds obtained to date, it was found that hyperforin derivatives and sampsoniones were reported mainly from *H. sampsonii*, while xanthones are typical for *H. chinense*.

Until to the present, only 14% of 469 known species in the genus *Hypericum* have been studied, so there are many unexamined taxa for which their constituents when determined structurally may attract the attention of pharmacologists. Given the high structural complexity and the diverse biological properties of its secondary metabolite constituents isolated to date, *Hypericum* is a promising genus that has great potential for new drug development. It is to be recommended highly that further chemical and biological studies are conducted on additional *Hypericum* species in the future.

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Chuan-Yun Xiao is a Ph.D. candidate in natural medicinal chemistry at the School of Pharmacy, Fudan University. Mr. Xiao obtained his Master's degree at Jiangxi University of Traditional Chinese Medicine. During his time of study there, he was a visiting scholar at the University of Adelaide, Adelaide, Australia. Mr. Xiao has summarized systematically the structures of geranyl- or prenyl group-bearing caged phytochemicals from plants of the genus *Hypericum*. Presently, he is focused on the isolation and structural elucidation of neolignans from *Piper* species, which inhibit drug-resistant *Staphylococcus aureus* in a synergistic manner, and is also exploring their primary mechanism of antibacterial activity.

Mu Qing is Professor of Pharmaceutical Chemistry at the School of Pharmacy, Fudan University, Shanghai, People's Republic of China. His research focuses on the synergism of Chinese traditional medicines and other herbs with activity against drug-resistant bacteria and cancer. Prof. Mu obtained his Master's and Ph.D. degrees in Phytochemistry from the Kunming Institute of Botany of the Chinese Academy of Sciences. He undertook postdoctoral fellowships at both the Shanghai Medical School and the Amorepacific R&D Centre in Korea. Prof. Mu has investigated geranyl- or prenyl group-bearing caged phytochemicals from *Hypericum* species. Recently, his team discovered several naturally occurring naphthoquinone, acetophenone, sesquiterpene, neolignan, and flavone constituents of selected medicinal plants, which inhibit antibiotic-resistance in *Staphylococcus aureus* in a synergistic manner. His interests also extend to chemical biology and include the development of a new method, OSR HSCCC (Online-Storage-Recycling High-Speed Counter-Current Chromatography) to purify natural compounds that are difficult to separate. Prof. Mu has worked also on the chemical synthesis of analogues of a cyclic nonapeptide that inhibits hepatic carcinoma. Prof. Mu has published 40 papers and holds ten Chinese innovation patents in the fields of natural products and pharmaceutical chemistry. He has served as an Editorial Board member for the journal "Phytochemistry Letters" since 2010 and been a member of an academic committee of natural products in Shanghai since 2005.

Simon Gibbons is Professor of Natural Product Chemistry and Head of The School of Pharmacy at the University of East Anglia, Norwich, United Kingdom. He is founding Editor-in-Chief of "Phytochemistry Letters" and Co-editor of "Progress in the Chemistry of Organic Natural Products" ("Zechmeister"). He has particular research interests in medicinal natural products, phytochemistry and antimicrobial natural products from plants and microbes. His group specializes in the isolation and structure elucidation of natural products that are active against drug-resistant bacteria. Prof. Gibbons is interested also in compounds that modify bacterial resistance, which may be plasmid transfer inhibitors or efflux inhibitors. A further focus of his research is on the characterization of new natural and synthetic psychoactive substances, which can be crude plant or fungal materials or single natural or synthetic chemical entities. He was formerly President of the Phytochemical Society of Europe (www.phytochemicalsociety.org) and has served on the Advisory Council on the Misuse of Drugs (ACMD) of the Government of the United Kingdom. Prof. Gibbons is a co-opted member of the Home Office's Cannabis-Based Prescription-Medicines Committee. Currently he is a member of the Editorial Boards of the "Journal of Natural Products", "Natural Products and Bioprospecting", "Phytochemical Analysis", "Phytochemistry Reviews", "Phytotherapy Research", "Fitoterapia", "The Chinese Journal of Natural Medicine", and "Scientia Pharmaceutica".

Taccalonolide Microtubule Stabilizers

Samantha S. Yee, Lin Du, and April L. Risinger

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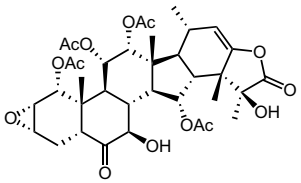
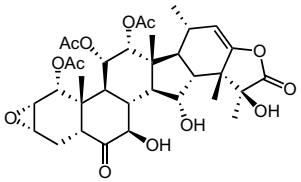
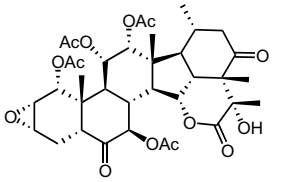
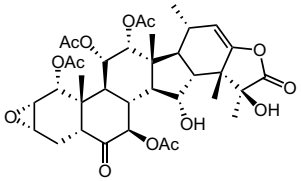
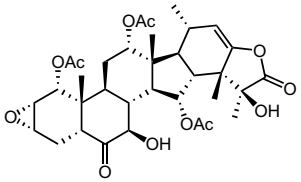
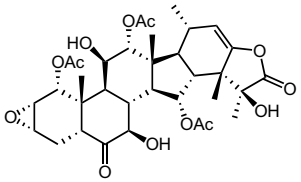
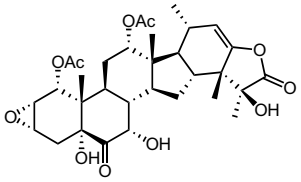
1 Introduction

The taccalonolides are a unique class of microtubule stabilizers that are produced by several *Tacca* species (Fig. 1). What we now know as the taccalonolides were first identified in the early 1960s by Dr. Paul Scheuer as the "bitter principle" of the tubers of *Tacca leontopetaloides*, a starchy food source. Scheuer and his colleagues purified a compound they named taccalin in 1963 as an intensely bitter, light yellow powder with a proposed tetracyclic structure [1]. While the actual structure of the taccalonolides was later found to be much larger than originally proposed, it laid the groundwork for the future study of this class of compounds. In 1987, Chen et al. [2] elucidated the structures of taccalonolides A (**1**) and B (**2**) isolated from the rhizomes of *Tacca plantaginea*. Taccalonolide A (**1**), the most abundant taccalonolide, demonstrated cytotoxic activity against P-388 leukemia in cell culture as well as antimalarial activity against *Plasmodium berghei*.

Over the following decades, two dozen additional taccalonolides were purified from *Tacca* species. Taccalonolides C–M (**3**–**13**) and W–Y (**23**–**25**) were first isolated from *Tacca plantaginea* [3–7], taccalonolides O–Q (**15**–**17**) from *Tacca subflabellata* [8], taccalonolides R–V (**18**–**22**) from *Tacca paxiana* [9], and taccalonolides Z (**26**) and AA (**27**) from *Tacca integrifolia* and *Tacca chantrieri*, respectively (Table 1) [10]. The discovery of the microtubule-stabilizing effects of the taccalonolides has sustained interest in these compounds as potential anticancer agents and will be the primary focus of this contribution. The taccalonolides and extracts from the leaves and tubers of *Tacca leontopetaloides* have also demonstrated antitrypanosomal activity [11] and the ability to control against snails [12] leading to a patent for their use as anthelmintic and molluscicidal agents [13].

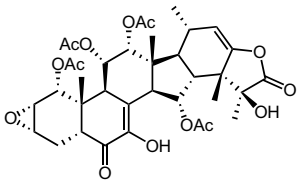
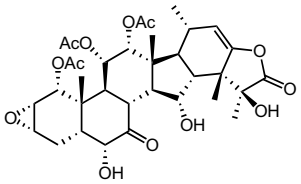
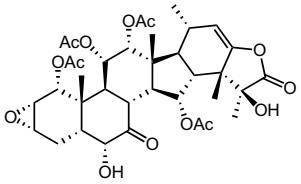
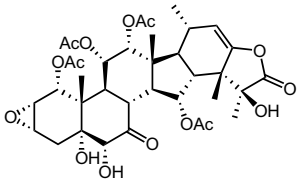
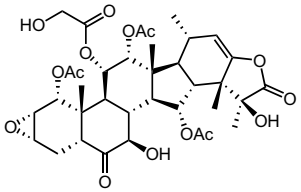
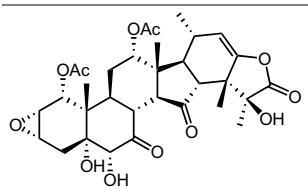
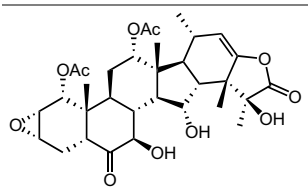
Fig. 1 *Tacca chantrieri*

Table 1 The structures and sources of taccalonolides

Structure	Name	Source	Ref.
	Taccalonolide A (**1**)	*Tacca plantaginea* *Tacca paxiana* *Tacca chantrieri*	[2] [9] [10]
	Taccalonolide B (**2**)	*Tacca plantaginea* *Tacca paxiana*	[2] [9]
	Taccalonolide C (**3**)	*Tacca plantaginea*	[3]
	Taccalonolide D (**4**)	*Tacca plantaginea*	[3]
	Taccalonolide E (**5**)	*Tacca plantaginea* *Tacca paxiana* *Tacca chantrieri*	[4] [9] [10]
	Taccalonolide F (**6**)	*Tacca plantaginea*	[4]
	Taccalonolide G (**7**)	*Tacca plantaginea*	[5]

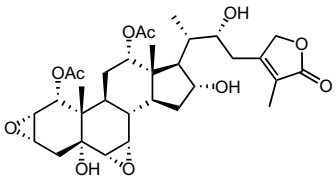
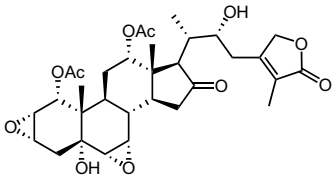
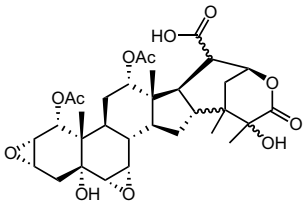
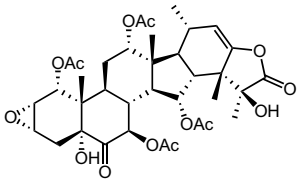
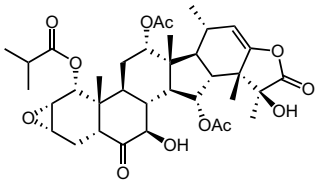
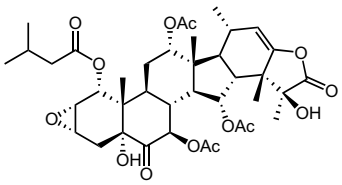
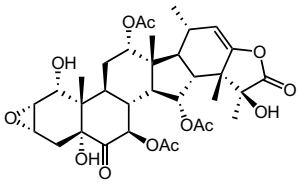
(continued)

Table 1 (continued)

Structure	Name	Source	Ref.
	Taccalonolide H (**8**)	*Tacca plantaginea*	[5]
	Taccalonolide I (**9**)	*Tacca plantaginea*	[5]
	Taccalonolide J (**10**)	*Tacca plantaginea*	[5]
	Taccalonolide K (**11**)	*Tacca plantaginea* *Tacca paxiana*	[5] [9]
	Taccalonolide L (**12**)	*Tacca plantaginea*	[6]
	Taccalonolide M (**13**)	*Tacca plantaginea*	[6]
	Taccalonolide N (**14**)	*Tacca paxiana*	[9]

(continued)

Table 1 (continued)

Structure	Name	Source	Ref.
	Taccalonolide O (**15**)	*Tacca subflabellata*	[8]
	Taccalonolide P (**16**)	*Tacca subflabellata*	[8]
	Taccalonolide Q (**17**)	*Tacca subflabellata*	[8]
	Taccalonolide R (**18**)	*Tacca paxiana* *Tacca chantrieri*	[9] [10]
	Taccalonolide S (**19**)	*Tacca paxiana*	[9]
	Taccalonolide T (**20**)	*Tacca paxiana* *Tacca chantrieri*	[9] [10]
	Taccalonolide U (**21**)	*Tacca paxiana*	[9]

(continued)

Table 1 (continued)

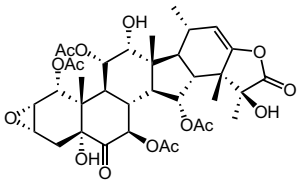
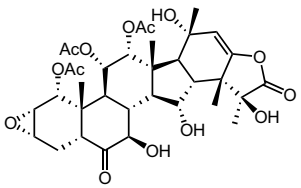
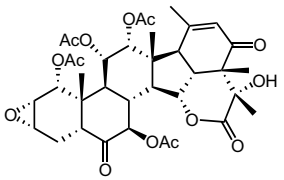
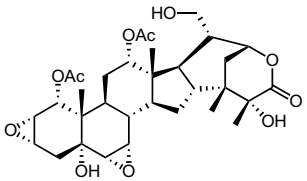
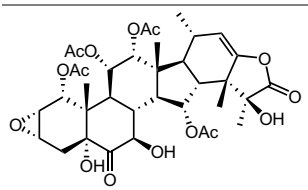
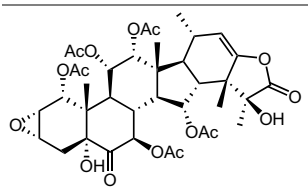
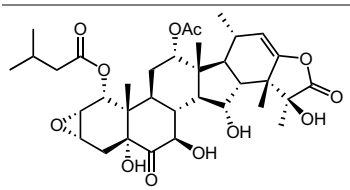
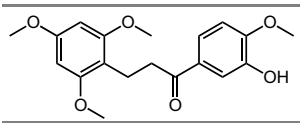
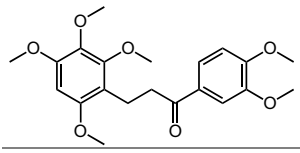
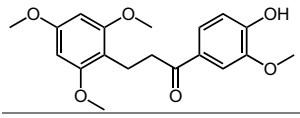
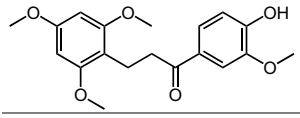
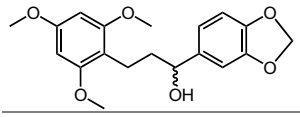
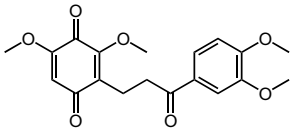
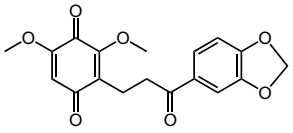
Structure	Name	Source	Ref.
	Taccalonolide V (**22**)	*Tacca paxiana*	[9]
	Taccalonolide W (**23**)	*Tacca plantaginea*	[7]
	Taccalonolide X (**24**)	*Tacca plantaginea*	[7]
	Taccalonolide Y (**25**)	*Tacca plantaginea*	[7]
	Taccalonolide Z (**26**)	*Tacca integrifolia*	[10]
	Taccalonolide AA (**27**)	*Tacca chantrieri*	[10]
	Taccalonolide AI (**30**)	*Tacca chantrieri*	[33]

Table 2 The structures of bioactive retro-dihydrochalcones isolated from *Tacca* sp.

Structure	Common name	Source	Ref.
	Taccabulin A (**31**)	*Tacca chantrieri* *Tacca integrifolia*	[36]
	Taccabulin B (**32**)	*Tacca chantrieri* *Tacca integrifolia*	[37]
	Taccabulin C (**33**)	*Tacca chantrieri* *Tacca integrifolia*	[37]
	Taccabulin D (**34**)	*Tacca chantrieri* *Tacca integrifolia*	[37]
	Taccabulin E (**35**)	*Tacca chantrieri* *Tacca integrifolia*	[37]
	Evelynin A (**36**)	*Tacca chantrieri* *Tacca integrifolia*	[37] [38]
	Evelynin B (**37**)	*Tacca chantrieri* *Tacca integrifolia*	[37]

2 Taccalonolides as Microtubule Stabilizers

The initial bioassays performed with purified taccalonolides were crude measures of cancer cell toxicity in vitro or antiparasitic and nematocidal activities that were not attributable to a specific mechanism of action. However, in 2003, the taccalonolides A (**1**) and E (**5**) (for structures see Table 1) were isolated as the bioactive components from *Tacca chantrieri* extracts that led to paclitaxel-like microtubule bundling and mitotic arrest with the formation of multiple spindle asters in cellular assays (Fig. 2) [14]. The antiproliferative potency of the taccalonolides A (**1**) and E (**5**) was found to be in the low micromolar range against human ovarian cancer (SK-OV-3, 1A9) cervical cancer (HeLa), and melanoma (MDA-MB-435 [15]) cell

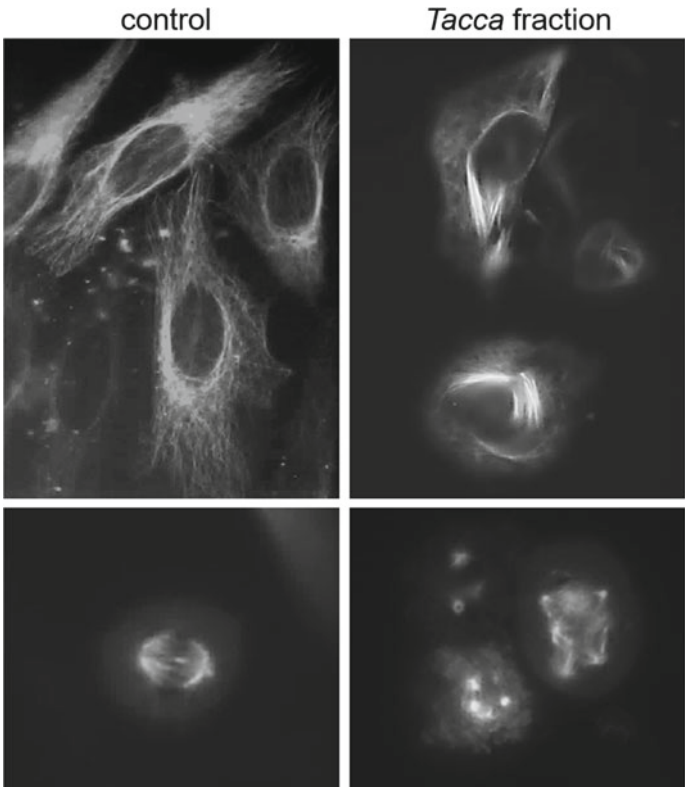


Fig. 2 The effect of taccalonolide-enriched *Tacca* fractions on microtubule structures in HeLa cervical cancer cells expressing GFP-tagged tubulin. The taccalonolides promote bundling of interphase microtubules (top panels) as well as the formation of multiple asters in mitotic cells that are markedly distinct from the microtubule spindle in normal mitotic cells (bottom panels)

lines, approximately 1000 times less potent than paclitaxel. However, the taccalonolides retained potency in the NCI/ADR-RES paclitaxel-resistant model that expresses high levels of the P-glycoprotein drug efflux pump, a major mechanism of taxane resistance in the clinic. The taccalonolides also retained potency in the 1A9 ovarian cancer cell line that contains mutations in paclitaxel (PTX 10 and PTX 22) binding sites in the human M40 β-tubulin isotype [16, 17].

The ability to circumvent these taxane resistance mechanisms was the first indication that their mechanism of action could be distinct from this other plant-derived class of microtubule stabilizers. Although the taccalonolides caused cellular microtubule bundling, mitotic arrest with multipolar spindles, and subsequent apoptosis similar to paclitaxel, the taccalonolides were also distinct in that they promoted the formation of spindle poles greater in number than paclitaxel, further suggesting the possibility of a distinct mechanism of action. Together, these findings first demonstrated that the taccalonolides were a structurally novel class of

microtubule stabilizers produced from a plant source with micromolar potency that were able to circumvent mechanisms of drug resistance to the taxanes potentially through a distinct mechanism.

The cellular microtubule-stabilizing activity of taccalonolides A (**1**) and E (**5**) was confirmed by Buey et al. [18] who demonstrated that 5 μ*M* taccalonolide A (**1**) and 10 μ*M* taccalonolide E (**5**) induced microtubule bundling, multipolar spindles, and multiple micronuclei in A549 adenocarcinomic human alveolar basal epithelial cells. However, these cellular microtubule effects could not be recapitulated in biochemical tubulin binding or polymerization assays. Furthermore, taccalonolides A (**1**) and E (**5**) did not promote tubulin assembly at concentrations as high as 66 μ*M* with 60 μ*M* GTP–tubulin when analyzed by either centrifugation or electron microscopy, and there was no evidence of taccalonolide binding to cross-linked or native microtubules. The taccalonolides only weakly displaced the paclitaxel-site probe Flutax-2, and the effect was not concentration dependent or observed in preincubation experiments leading to the conclusion that any observed Flutax-2 displacement was artifactual. Taccalonolide A (**1**) was also unable to promote microtubule polymerization even in non-denatured cytosolic extracts [19], further suggesting that the cellular microtubule-stabilizing activity of this taccalonolide was not the result of direct binding to microtubules or interactions with other soluble cellular factors that regulate microtubule polymer mass.

In spite of the inability to detect a direct interaction with microtubules and in being less potent than other classes of microtubule stabilizers, there was a continued interest in the taccalonolides due to their potential inability to interact with tubulin in biochemical preparations and their efficacy against taxane-resistant cancer cells. These studies were expanded by the evaluation of taccalonolides A (**1**), B (**2**), E (**5**), and N (**14**) as compared to other classes of microtubule-targeted drugs in cell lines representing clinical mechanisms of taxane resistance, including overexpression of P-glycoprotein, MRP7, and βIII-tubulin [20]. All four taccalonolides retained in vitro efficacy in taxane-resistant human ovarian cancer cell lines expressing P-glycoprotein, human embryonic kidney cell lines overexpressing MRP7, and HeLa cervical cancer cell lines expressing βIII-tubulin. Taccalonolides A (**1**) and E (**5**) were also found to be effective in vivo in a P-glycoprotein-expressing multidrug-resistant syngeneic murine mammary adenocarcinoma model Mam17/ADR that is resistant to both paclitaxel and doxorubicin [20].

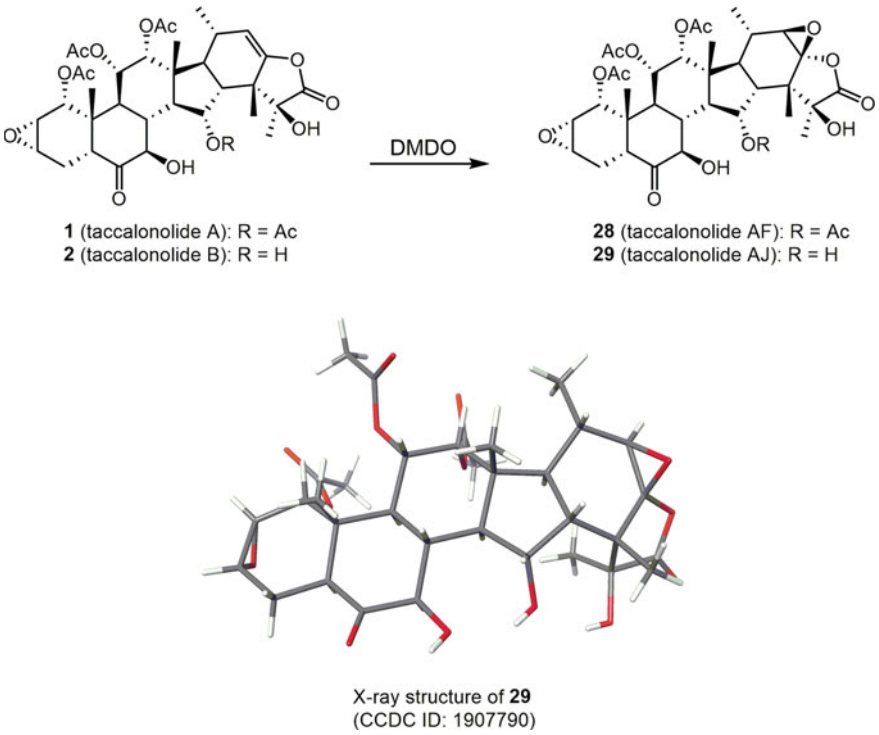
Surprisingly, although the taccalonolides were on average over 100-fold less potent than the taxanes in vitro, they demonstrated in vivo efficacy at concentrations comparable to or even lower than those used for paclitaxel. Further studies also demonstrated in vivo efficacy of taccalonolides A (**1**), E (**5**), N (**14**), and B (**2**) in the mammary 16/c syngeneic tumor model at total doses of 20–90 mg/kg, which were comparable to a total dose of 74 mg/kg paclitaxel [10]. These data not only confirmed that the taccalonolides were a novel class of microtubule stabilizers that can circumvent clinically relevant forms of drug resistance, but also demonstrated in vivo antitumor efficacy in paclitaxel-sensitive and -resistant tumor models at doses much lower than expected from studies based on their in vitro potency.

The lack of biochemical tubulin-polymerizing activity of the taccalonolides prompted additional cellular studies to elucidate the mechanism of cellular microtubule stabilization and how these effects were distinct from those of the taxanes. One intriguing finding was that gross bundling of interphase microtubules occurred at concentrations of taccalonolide A (**1**) that were equal to or less than those that promoted antiproliferative effects, whereas the concentration of paclitaxel required to observe cellular microtubule bundling was over 30-fold greater than its antiproliferative IC_{50} value, further suggesting a mechanistic difference between these two microtubule stabilizers [19]. This was particularly significant as it coincided with reports suggesting that the interphase effects of microtubule-targeting agents contribute to their antitumor efficacy in the clinic [21, 22]. It was also found that the cellular effects of the taccalonolides were highly persistent, providing long-term antiproliferative and cytotoxic efficacy even after only short periods of drug exposure and subsequent removal from the culture medium. This cellular persistence was not observed for other classes of microtubule stabilizers, including paclitaxel, further highlighting mechanistic differences between the taccalonolides and the taxanes. A high degree of cellular persistence has been associated with potent in vivo efficacy of the clinically approved microtubule destabilizer eribulin [23], providing a rationale for the unexpected in vivo potency of the taccalonolides.

3 Identification of Epoxidized Taccalonolides

Although early experiments demonstrated that taccalonolides A and E enriched preparations had microtubule stabilizing activity that was distinct from that of the taxanes, there were two issues that confounded a full understanding of their mechanism of action. One is the aforementioned lack of interaction with purified tubulin and the second was the inconsistent potency of different preparations of taccalonolides A (**1**) and E (**5**).

The original characterization of the microtubule-stabilizing effects of taccalonolide A (**1**) in 2004 demonstrated low micromolar potency, but follow-up studies by our same group in 2008 using a newly purified batch of taccalonolide A (**1**) were approximately 10-fold more potent. This inconsistency in the potency of our taccalonolide A (**1**) batches from preparation to preparation led to a rigorous evaluation of the chemical and biological properties of each of our HPLC fractions, including those before and after the prominent taccalonolide peak. To our surprise, we found that the microtubule-stabilizing potency did not comigrate perfectly with fractions that contained the highest taccalonolide A (**1**) levels. A careful chemical interrogation of the most potent HPLC fractions identified a sample containing compounds with the taccalonolide backbone possessing an unanticipated epoxide at positions C-22 and C-23 as opposed to the double bond in taccalonolide A (**1**). While this was a trace product that was not in sufficient quantity to purify fully from the natural product, the identification of the presence of this product led to its efficient semisynthesis from abundant 22,23-alkene taccalonolides (Scheme 1).



Scheme 1 Synthesis of taccalonolides AF (**28**) and AJ (**29**) via epoxidation of taccalonolides A (**1**) and B (**2**), respectively

Remarkably, the 22,23-epoxidation epoxidation of taccalonolides A (**1**) and B (**2**) to generate taccalonolides AF (**28**) and AJ (**29**), respectively, resulted in taccalonolide microtubule stabilizers with low nanomolar potency in cells. Additionally, these potent taccalonolides were able to effectively bind and polymerize tubulin in biochemical preparations, a property that was never observed for the non-22,23-epoxidized taccalonolides [24]. With this knowledge in hand, our group has revisited the activity of taccalonolides A (**1**) and B (**2**), in particular, and found that the microtubule-stabilizing activity of these compounds can be diminished by additional rounds of purification with highly purified material being completely devoid of any antiproliferative, cytotoxic, or cellular microtubule-stabilizing effects (unpublished observations).

Together, these data demonstrate that the previously reported micromolar potency biological activities of 22,23-alkene taccalonolides, including A (**1**), E (**5**), B (**2**), and N (**14**) among others, are likely a result of small amounts of material that was oxidized to generate a 22,23-epoxide. These formerly undetected trace amounts of nanomolar potency epoxidized taccalonolide were sufficient to promote cellular

efficacy in the micromolar range that was attributed to the more abundant 22,23-alkene taccalonolides. In contrast, the low quantities of epoxidized taccalonolides in these preparations were insufficient to promote biochemical tubulin polymerization, which requires near equimolar concentrations to tubulin, providing a rationale for why cellular but not biochemical microtubule polymerization could be observed in the early evaluations of taccalonolides A (**1**) and E (**5**). To provide further evidence for this rationale, Peng et al. demonstrated that the semisynthetic introduction of a 22,23-epoxide to ten additional purified taccalonolides was sufficient to improve their antiproliferative potency, some into the sub-nanomolar range. Furthermore, there has been minimal to no batch-to-batch variation in potency among preparations of the 22,23-epoxidized taccalonolides AF (**28**) and AJ (**29**) isolated from different plant sources by different laboratory groups, providing confidence that these are indeed the bioactive component of *Tacca* species that have been investigated for decades. Importantly, the potent taccalonolides, AF (**28**) and AJ (**29**), retain many of the same biological properties that were previously ascribed to taccalonolides A (**1**) and B (**2**), including the ability to circumvent clinically relevant drug resistance mechanisms, a high degree of cellular persistence, and in vivo antitumor efficacy [25, 26].

4 Identification of a Direct Interaction Between the Taccalonolides and Tubulin

Equipped with an understanding of the role of the 22,23-epoxide in the microtubule-stabilizing activity of the taccalonolides and semisynthetic strategies to convert the naturally abundant 22,23-alkene into the potent 22,23-epoxy-taccalonolides, there was a renewed approach in understanding the molecular interactions between the taccalonolides and tubulin/microtubules. Unlike the 22,23-alkene taccalonolides A (**1**) and E (**5**), the 22,23-epoxy-taccalonolides were indeed sufficient to polymerize purified tubulin in a similar manner to other microtubule-stabilizing agents. However, there was a significant lag time associated with taccalonolide-induced tubulin polymerization in contrast to the almost immediate polymerization induced by the taxanes (Fig. 3) [26].

Additionally, the microtubules formed in the presence of taccalonolide AJ (**29**) were highly resistant to cold-induced depolymerization as determined both turbidometrically and by electron microscopy [26]. This was markedly distinct from microtubules induced by other stabilizers, including paclitaxel and laulimalide (also named fijianolide B), which were subject to cold-induced depolymerization. Together, these results suggested that the taccalonolides promoted a distinct mechanism of microtubule polymerization from other classes of microtubule stabilizers.

To address whether the taccalonolides bind to the same site as paclitaxel and laulimalide on microtubules, synergism and displacement studies were employed.

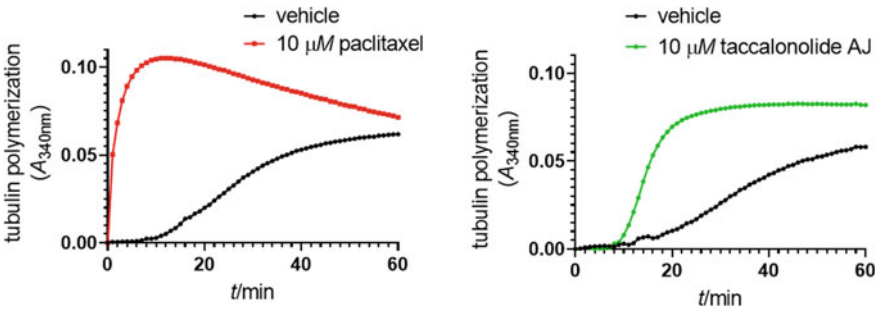


Fig. 3 Comparison of the biochemical tubulin polymerization activities of paclitaxel and taccalonolide AJ. Left: paclitaxel (10 μ*M*) promotes the immediate polymerization of purified tubulin (20 μM) as compared to a vehicle control. Right: in contrast, taccalonolide AJ (10 μ*M*) dependent polymerization of purified tubulin (20 μ*M*) is associated with a lag time of 8–10 min

Synergistic effects were observed between taccalonolide AF (**28**) and either paclitaxel or laulimalide [26], further indicating that the taccalonolides bind to a site pharmacologically distinct from the two major stabilizer-binding sites on tubulin. Displacement studies using equimolar concentrations of taccalonolide AJ (**29**) with either laulimalide or paclitaxel with purified tubulin demonstrated some competition between taccalonolide AJ (**29**) and paclitaxel [26]. However, it was notable that prior addition of taccalonolide AJ (**29**) before paclitaxel was required to observe decreased paclitaxel binding. This temporal effect on taxane displacement was the first indication that the taccalonolides might be interacting in an irreversible manner with tubulin. Indeed, after interaction with purified tubulin, the taccalonolides could not be extracted from either the supernatant or the microtubule pellet [26].

Mass spectrometric analysis confirmed that the *m*/*z* 212–230 peptic fragment of β-tubulin was lost after incubation with taccalonolide AJ (**29**) and replaced by a peptide that was increased by the molecular weight of **29** [26]. Together, these results demonstrated that the 22,23-epoxy-taccanolides covalently bound β-tubulin within the β212–230 region, which includes the βHis229 residue that is the covalent binding site of the cyclostreptin and zampanolide microtubule stabilizers. Additional hydrogen–deuterium exchange mass spectrometry was employed to determine that taccalonolide AJ-induced microtubule stabilization did not involve profound stabilization of the M-loop of tubulin, which is associated with taxane and zampanolide-induced microtubule stabilization, but instead promoted dramatic inter-protofilament stability as a mechanism of microtubule stabilization [26].

These biochemical studies were confirmed by Wang et al., who reported the first crystal structure of tubulin complexed with taccalonolide AJ (**29**) (Fig. 4), demonstrating that the 22,23-epoxide of **29** binds covalently to the Asp226 residue on β-tubulin [27]. Their data suggested that this covalent interaction promotes a conformation shift in the M-loop of tubulin that favors the binding of GTP in the E-site of tubulin. While the authors suggested in the supplemental data that the previously assigned stereochemistry of the 22,23-epoxide may need to be revisited, they did not ultimately promote this adjustment in configuration. However,

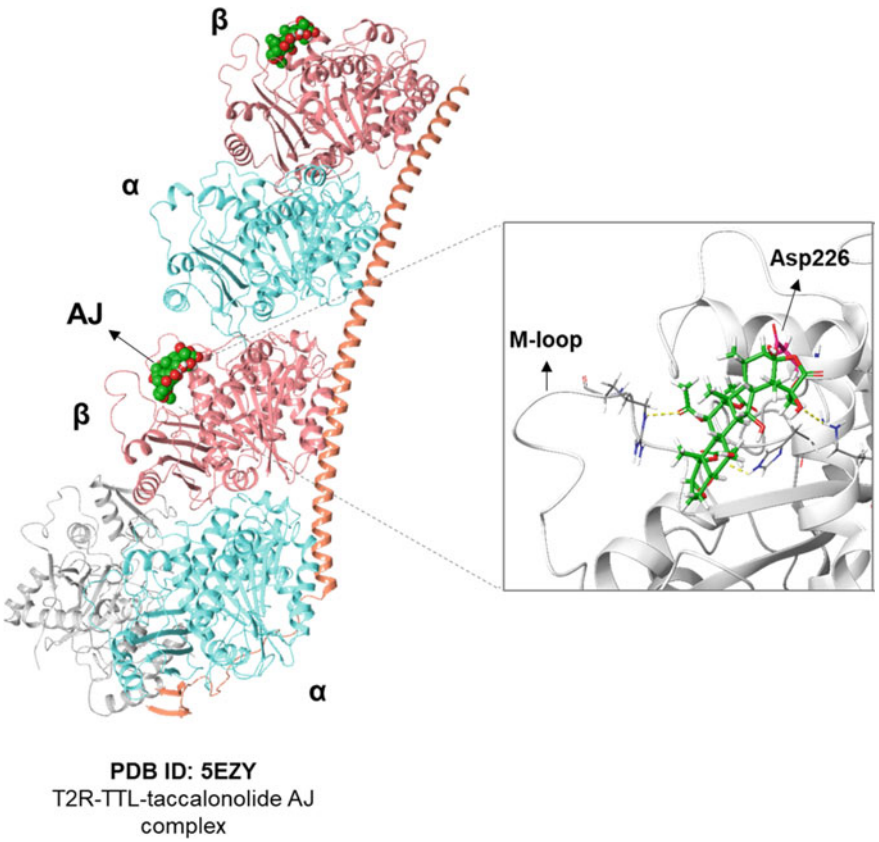
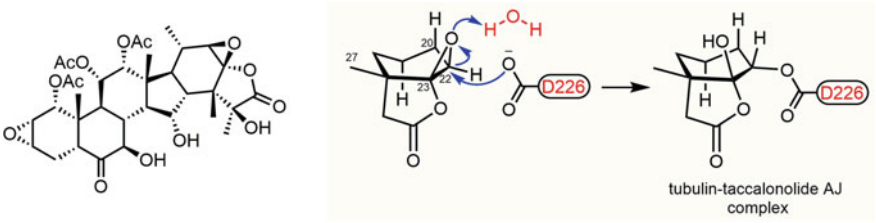


Fig. 4 Taccalonolide AJ binding covalently to Asp226 on β-tubulin as determined by X-ray crystallography of the T2R-TTL-taccalonolide AJ complex

additional crystallographic data of taccalonolide AJ (**29**) in the absence of tubulin and elucidation of the reaction mechanism (Scheme 2) confirmed that the stereochemistry of the 22,23-epoxide originally described by Li et al. needed to be revised [28, 29].

Based on these data, Sanchez-Murcia et al. undertook extensive in silico modeling and molecular dynamics simulations to elucidate further the unique interaction between the 22,23-epoxy-tacconolides and β-tubulin [30]. They proposed that the nucleophilic attack on C-22 by the OD1/OD2 carboxylate of βAsp226 and opening of the 22,23-epoxide is facilitated by the long-lived hydrogen bond interaction of the carboxylate with the side-chain hydroxy of Thr223 and enhanced stabilization mediated via water-bridged hydrogen bonds. The C-22 carbon was suggested to undergo initial addition, indicating that the epoxide is non-protonated prior to nucleophilic attack. They further emphasize that the 22,23-epoxide is essential for covalent bond formation between the taccalonolide and tubulin. Their detailed molecular analysis of the putative interactions provides an important framework for



Scheme 2 Reaction mechanism of the covalent binding of taccalonolide AJ to β-tubulin Asp226

additional biochemical and molecular biological studies exploring their functional importance.

The discrepancy between the lack of taccalonolide-induced M-loop stabilization detected by hydrogen–deuterium exchange mass spectrometry and the observed conformational shift of the M-loop in the taccalonolide AJ-tubulin crystal structure [27] was clarified by Balaguer et al. [25]. This elegant study compared the binding, allosteric effects, and tubulin polymerization dynamics of the three known covalent microtubule stabilizers: zampanolide, cyclostreptin, and the potent 22,23-epoxy-taccanolides.

The crystal structure of cyclostreptin bound to β-tubulin corrected previous literature suggesting covalent interactions with βThr220 and βAsn228 and instead confirmed that cyclostreptin and zampanolide both bind covalently to βHis229 [25]. Furthermore, they demonstrated that cyclostreptin-dependent tubulin polymerization was associated with a similar lag period that had been observed with taccalonolide AJ (**29**). In contrast, zampanolide rapidly induced tubulin polymerization in a manner similar to taxane microtubule stabilizers. Superimposition of the crystal structures of each of these compounds with tubulin demonstrated that extensive M-loop interactions and helical stabilization were correlated with stabilizers that promoted a strong initial rate of assembly [25]. In contrast, stabilizers such as taccalonolide AJ (**29**) that only promote partial M-loop structuring without inducing a helical confirmation were associated with a significant lag time prior to the initiation of tubulin polymerization. Together, these data demonstrate that while the taccalonolides do promote some structuring of the M-loop of β-tubulin, these interactions are not as significant as those promoted by the taxanes, which result in a delay in the initiation of microtubule stabilization by the taccalonolides.

5 Cellular Effects of Taccalonolide-Induced Microtubule Stabilization

Given the distinct biochemical interaction of the taccalonolides with tubulin, studies were undertaken to evaluate the effects of the 22,23-epoxy-tacconolides as compared to taxanes on microtubule dynamics in biochemical preparations and in live cells [31]. While paclitaxel and taccalonolide AJ (**29**) had similar overall effects on the microtubule dynamics of purified tubulin that promoted overall stabilization,

taccalonolide AJ (**29**) demonstrated a greater suppression of catastrophe frequency likely as a result of its irreversible binding. In contrast, paclitaxel had a greater effect on microtubule rescue frequency than taccalonolide AJ (**29**). Similar effects were observed when microtubule dynamicity was evaluated in live cells with **29** having a greater impact on microtubule catastrophe and paclitaxel affecting rescue frequency to a larger extent. These differences in cellular microtubule dynamics were found to underlie the distinct microtubule aster morphology observed in cells treated with the taccalonolides as compared to the taxanes [14, 32].

Real-time spindle formation was evaluated in live cells expressing GFP-tagged tubulin upon treatment with the taccalonolides or paclitaxel compared to vehicle controls. While cells entered mitosis at similar rates with similar effects on aster formation, differences were noted in the consolidation of these asters by paclitaxel but not the taccalonolides during extended mitotic arrest. This aster consolidation in paclitaxel-treated cells led to the previously described phenotype of 2–3 asters per cell in contrast to the taccalonolides that result in an average over five asters per cell (Fig. 5). The finding that the taccalonolides suppress microtubule catastrophe and inhibit aster consolidation to a greater extent than paclitaxel demonstrates that these distinct effects on microtubule dynamicity between the test compounds can lead to the formation of different cellular microtubule structures that could contribute toward distinct biological readouts.

Rohena et al. [32] investigated the microtubule-associated mitotic effects initiated by three structurally and functionally diverse microtubule-stabilizing agents: taccalonolide AJ (**29**), laulilamide, and paclitaxel. Each microtubule stabilizer initiated distinct mitotic defects and differentially dysregulated the expression of key mitotic kinases. Taccalonolide AJ (**29**) produced the most profound defects in centrosome maturation, separation, and disjunction as observed by indirect immunofluorescence of the centrosomal-associated proteins rootletin, Nek2, and γ-tubulin [32]. However, taccalonolide AJ-treated cells also contained the more peripheral centrosomal protein pericentrin at every spindle aster, suggesting these structures facilitated the maintenance and stability of the multiple, highly focused asters observed in taccalonolide-treated cells as compared to the other two microtubule stabilizers, which only contained two pericentrin foci [32]. Not surprisingly, these defects in centrosomal structures were accompanied by mitotic signaling

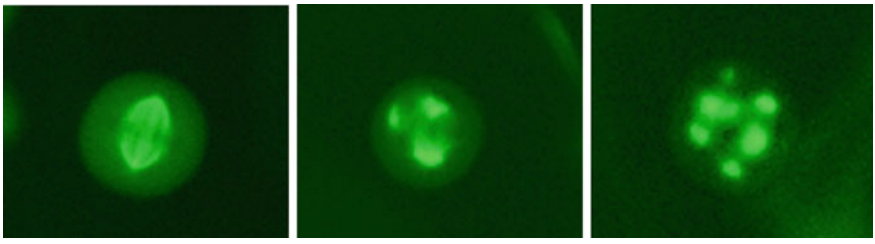


Fig. 5 Distinct mitotic spindle structures in normal cells (left), paclitaxel-treated cells (middle), and taccalonolide-treated cells (right)

defects, including enhanced Eg5 phosphorylation by taccalonolide AJ-treated cells as compared to those treated with the other stabilizers [32].

6 In Vivo Antitumor Efficacy of 22,23-Epoxy-tacconolides

The antitumor efficacy of the epoxy-taccalonolides AF (**28**) and AJ (**29**) was evaluated initially in a MDA-MB-231 flank triple-negative breast cancer xenograft murine model. Taccalonolide AF (**28**) exhibited antitumor efficacy at a total dose of 5 mg/kg that produced a greater degree of tumor regression than 40 mg/kg paclitaxel [26]. Additional antitumor studies with the potent 22,23-epoxidation products of taccalonolides T (**20**) and AI (**30**) also demonstrated antitumor efficacy in a MDA-MB-231 xenograft model [33]. However, taccalonolide AJ (**29**) did not demonstrate antitumor effects even at the LD_{40} dose of 2 mg/kg [26]. These results suggested that taccalonolides AF and AJ, with similar biochemical and cellular microtubule-stabilizing activities, may have distinct pharmacokinetic properties.

Initial efforts to characterize differences in the chemical stability of taccalonolides AF (**28**) and AJ (**29**) demonstrated that the C-15 acetoxy group of taccalonolide AF (**28**) was hydrolyzed in aqueous solutions to generate AJ (**29**) [26]. In vivo pharmacokinetic properties were evaluated for both taccalonolides AJ (**29**) and AF (**29**) in the same strain of nude mice that were utilized for xenograft studies. AJ (**29**) was demonstrated to have an elimination half-life of 8.1 min, when administered systemically, while the half time of AF (**28**) was 44.1 min [34]. AJ (**29**) had excellent and persistent antitumor efficacy when administered directly into the tumor, suggesting that the lack of antitumor efficacy demonstrated with systemic administration of AJ (**29**) was likely due to its short half-life in vivo [34].

Given the fact that the C-15 acetyl group on taccalonolide AF (**28**), which demonstrated in vivo efficacy, was effectively hydrolyzed in aqueous solution to generate taccalonolide AJ (**29**), which does not have a therapeutic window for systemic administration in vivo, we hypothesized that semisynthesis of taccalonolides with C-15 substitutions could provide increased stability of an active antitumor drug to provide an increased therapeutic window. The in vitro biological activities of 28 novel taccalonolides with mono substitutions at C-7 or C-15 or disubstitutions at C-7 and C-25 ranged in antiproliferative potency from 2.4 n*M* to >20 μ*M* [29]. However, no improved stability or therapeutic window was observed with isovalerate, cyclopropyl, isobutyrate, or formate substituents at C-7 or C-15. Additionally, substitutions at C-25 completely abrogated in vitro activity, likely due to interference with the covalent binding of the 22,23-epoxide to β226 of tubulin. The two most potent taccalonolides in vitro, isovalerate modifications at C-7 or C-15, were evaluated for in vivo antitumor efficacy by intratumoral injection in the drug-resistant human NCI/ADR-RES xenograft murine model. Similarly to taccalonolide AJ (**29**), the isovalerate-modified taccalonolides demonstrated potent in vivo efficacy when directly administered to the tumor and notably caused long-term antineoplastic efficacy for over a month after the final

dose was administered [29]. These results demonstrate that targeted delivery of the taccalonolides provides for long-term efficacy in drug-resistant tumor models and led to studies to identify a handle on the taccalonolides that could be used for tumor targeting strategies.

7 Taccalonolide Conjugates Provide Evidence of Specificity and a Handle for the Generation of Targeted Agents

Data from previous semisynthetic efforts as well as an interrogation of the taccalonolide AJ-tubulin crystal structure led to the identification of C-6 as a possible handle amenable to functionalization. Indeed, modification of this site provided a stable fluorescein-tagged taccalonolide that retained microtubule-stabilizing activity and could be visualized colocalizing with microtubules (Fig. 6) [35].

These efforts were expanded to eventually generate a C-6-fluorescein taccalonolide conjugate that retained in vitro potency in the low nanomolar range and provided the stability to perform detailed imaging and cellular binding studies [28]. Optimization of the taccalonolide–fluorescein probe included the addition of pivaloyl-protected groups on fluorescein to quench fluorescence of the probe prior to cellular import, which provided the ability to monitor uptake and binding in live cells with no need to remove excess probe from the surrounding medium (Fig. 7).

Serendipitously, the C-6 fluorescein modification actually improved the biochemical tubulin-polymerizing activity of the taccalonolides by making additional contacts with tubulin [28]. However, the pivalate protective groups prevented a direct interaction with tubulin in biochemical assays, demonstrating that the pivalate

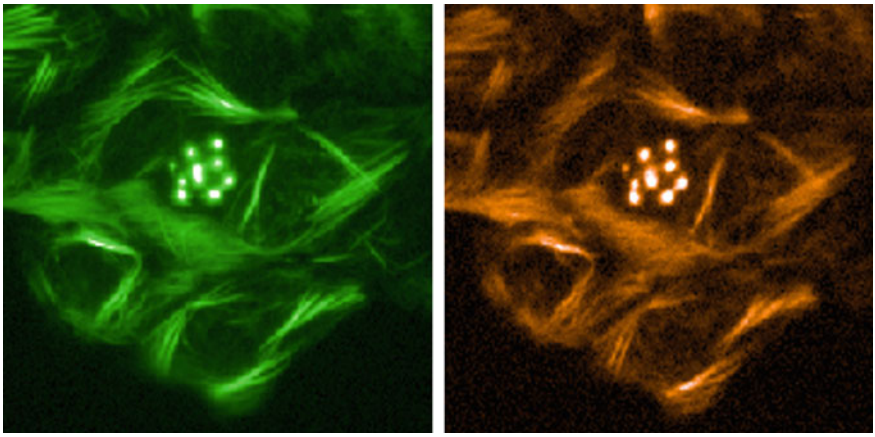


Fig. 6 Fluorescein-tagged taccalonolide (green) colocalized with β-tubulin immunofluorescence (orange) in fixed HCC1937 triple-negative breast cancer cells after 24 h treatment

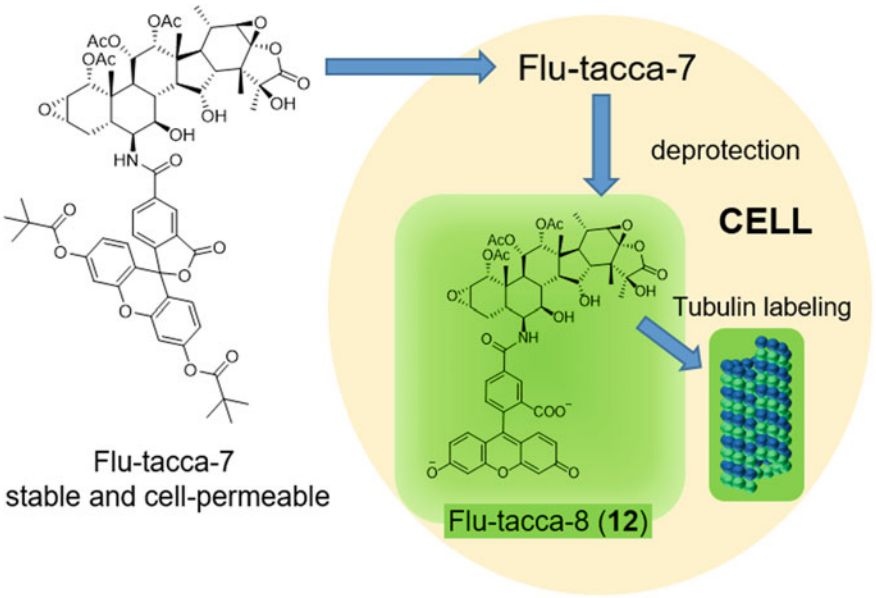


Fig. 7 Flu-tacca-7 is a cell-permeable fluorescent taccalonolide containing pivalate protective groups on the fluorophore that prevent fluorescence as well as target engagement prior to intracellular esterase cleavage. Upon cellular entry and pivalate deprotection to generate flu-tacca-8, the probe can directly bind tubulin and fluorescently label intracellular microtubules. The quenching provided by the pivalate groups permits live cellular imaging without the need to remove excess probe from the medium, providing a no-wash, irreversible fluorogenic labeling system for cellular microtubules

modification simultaneously prevented fluorescence and target engagement prior to cellular hydrolysis. The taccalonolide–fluorescein probe was found to be superior to commercially available taxane probes with regard to its microtubule staining without the addition of carrier molecules or removing excess probe from the medium [28]. It also provided microtubule staining under conditions that are not amenable to visualization with reversible taxane-based probes, including chilled conditions where microtubules are sensitive to depolymerization or in cells with high expression of drug efflux transporters [28].

The fluorescent taccalonolide probe strikingly colocalized with β-tubulin by immunofluorescence in human cancer cells, and the interaction was retained throughout immunoblotting to demonstrate a specific interaction between tubulin and the labeled taccalonolide [28]. A taccalonolide probe lacking the 22,23-epoxide completely abrogated this colocalization and binding, providing the first direct evidence of the exquisite specificity of the covalent interaction between the 22,23-epoxide of the taccalonolides and tubulin. This provided an unprecedented opportunity to use mutational analysis of an ectopically expressed form of tubulin to systematically evaluate the relative contribution of β-tubulin residues to taccalonolide binding with a focus on those that would be predicted to facilitate this

interaction based on the crystallographic and modeling data [27, 30]. Consistent with these data, βAsp226 was critical for the covalent interaction between the taccalonolides and tubulin [28]. Additionally, βLys19 and βLeu219 were also critical for taccalonolide binding, βHis229 and βThr223A had a moderate effect on binding, and βArg278 did not influence binding [28]. These data provide critical insight into the taccalonolide pharmacophore that will be highly valuable in strategies to optimize target binding and, potentially, to facilitate the synthesis of new classes of taccalonolide-like small molecules. Overall, this study provided insight into the target specificity and detailed drug–target interactions of the taccalonolides and strategies to further develop targeted taccalonolides.

8 Other Bioactive Compounds Isolated from *Tacca* Species

In addition to the taccalonolides, other bioactive compounds have been isolated from *Tacca* species. Most intriguingly, a microtubule destabilizer, taccabulin A (**31**) (Table 2), was isolated from the roots and rhizomes of *Tacca* species [36], which was the first study reporting the isolation of both a microtubule stabilizer and microtubule destabilizer from the same natural product source. Taccabulin A (**31**) effectively displaced colchicine binding to tubulin, suggesting that it binds within the colchicine pharmacophore, and demonstrated synergistic effects when combined with the taccalonolides [36]. Similar to the taccalonolides and other colchicine site-binding agents, taccabulin A (**31**) retained efficacy in drug-resistant models, including those that express elevated levels of the P-glycoprotein drug efflux pump or the β-III isotype of tubulin [36]. Six additional retro-chalcones, taccabulins B–E (**32**–**35**) and evelynins A (**36**) and B (**37**), were also isolated from *Tacca* extracts. Evelynin A (**36**) and B (**37**), as well as taccabulin D (**34**) demonstrated some cytotoxic activity toward cancer cells in vitro but with no evidence of microtubule stabilizing or destabilizing activities [37, 38]. Other classes of compounds isolated from *Tacca* species include withanolides, glucosides, steroidal glycosides, diarylheptanoids, and diarylheptanoid glycosides [39–49].

9 Conclusion

In the 60 years since the taccalonolides were first identified as the bitter principle of *Tacca* tubers, they have continually provided interesting and often unanticipated discoveries. These include the finding in 1987 that the structure of the taccalonolides was more complicated than initially proposed, the elucidation of their mechanism of action as microtubule stabilizers in 2003, and the critical nature of the 22,23-epoxide for direct tubulin binding in 2013. This last finding is somewhat

of a cautionary tale in natural products research that describes how a potent minor constituent, in this case 22,23-epoxy-tacconolides, could be responsible for the activity originally ascribed to more naturally abundant compounds. We now know that taccalonolides without a 22,23-epoxide lack the ability to bind and polymerize tubulin and have no detectable antiproliferative activity against cancer cell lines in culture. In contrast, potent 22,23-epoxy-taccanolides, including AJ (**29**) and AF (**28**), have the ability to covalently and irreversibly bind the Asp226 residue of β-tubulin to promote a distinct profile of microtubule stability as compared to other classes of clinically approved microtubule stabilizers. Most notably, some of these taccalonolides have demonstrated in vivo antitumor efficacy in drug-resistant breast and ovarian cancer models that persists for extended periods after drug treatment due to their covalent binding. Continued efforts to improve the therapeutic window for systemic administration and/or promote localized drug delivery based on the recent identification of a drug handle on the taccalonolide backbone may provide for their development as novel anticancer agents for the treatment of drug-resistant disease.

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