Phytochemicals from fern species: potential for medicine applications

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Abstract Ferns are an important phytogenetic bridge between lower and higher plants. Historically they have been used in many ways by humans, including as ornamental plants, domestic utensils, foods, and in handicrafts. In addition, they have found uses as medicinal herbs. Ferns produce a wide array of secondary metabolites endowed with different bioactivities that could potentially be useful in the treatment of many diseases. However, there is currently relatively little information in the literature on the phytochemicals present in ferns and their pharmacological applications, and the most recent review of the literature on the occurrence, chemotaxonomy and physiological activity of fern secondary metabolites was published over 20 years ago, by Soeder (Bot Rev 51:442–536, 1985). Here, we provide an updated review of this field, covering recent findings concerning the bioactive phytochemicals and pharmacology of fern species.

Keywords Ferns · Phytochemicals · Pharmacology · Medicine · Food

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Introduction

It is well established that chemicals extracted from plants have a wide range of pharmacological applications (Lanzotti 2014; Xiao 2015, 2016a, b, c; Zheng et al. 2016). However, studies on the pharmacology of phytochemicals have mainly focused on angiosperms rather than pteridophytes in general. This may be because angiosperms exhibit greater biodiversity, more varied adaptations, and are more widely distributed, making them accessible to a greater number of research groups.

Although pteridophytes (Fig. 1) are less widely distributed than angiosperms, they are reportedly used for medicinal purposes in places where they do occur, suggesting that they produce secondary metabolites with specialized ecological functions relating to herbivore defence (Morais-Braga et al. 2012a). The pteridophytes are a group of vascular plants that is divided into two monophyletic lineages, the lycophytes and the ferns, which differ phylogenetically: the ferns more closely resemble the seed-bearing plants (Prado and Sylvestre 2010).

In the botanical kingdom, ferns represent an important phylogenetic bridge between lower and higher plants. Because of their unique evolutionary history and biology, they produce a distinct set of secondary metabolites, many of which are not found in other plants. There are almost 12,000 species of ferns around the world, most of which are native to tropical and subtropical areas. Around 2600 of these species are found in China, over 300 of which are used in traditional Chinese medicine (Ching 1988).

Phytochemical studies on ferns have revealed that they contain a wide range of alkaloids (Dong et al. 2012), flavonoids (Xia et al. 2014), polyphenols (Socolsky et al. 2012), terpenoids (Socolsky et al. 2007), and steroids (Ho et al. 2012). The structures of these compounds usually differ from those of related secondary metabolites produced by other higher plants, making them a potentially valuable source of chemical diversity.

Several reviews on the ferns have been published since 2012: Liu et al. (2012b) reviewed ferns eaten in China, Christenhusz and Chase (2014) highlighted recent trends and concepts in fern classification, and Plackett et al. (2015) discussed missing links in shoot evolution and the development of ferns. However, there have been no review articles covering studies on the phytochemistry and pharmacology since 1985, when Soeder (1985) summarized the occurrence, chemotaxonomy and physiological activity of ferns' chemical constituents. Since then, the number of known phytochemicals from ferns has increased dramatically, as has their range of potential pharmacological applications. This review summarizes current knowledge regarding the phytochemistry and pharmacology of fern species.

Overview of fern species used in medicinal applications

Ferns have historically been used extensively by humans as ornamental plants, in domestic utensils, in handicrafts, as components of cosmetic formulations

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Fig. 1 Different species of ferns identified on the Araripe Plateau, Crato, CE, Brazil. (Courtesy of Flaviana Morais-Braga)

and foodstuffs, and for medicinal purposes (Morais-Braga et al. 2012a). Reports of therapeutic effectiveness, as well as scientific curiosity and the need for new drugs have prompted several groups to conduct pharmacological research on ferns and related plants. Pharmacological and ethnopharmacological studies have revealed that substances in ferns exhibit diverse pharmacological effects such as cytotoxicity (Radhika et al. 2010), hepatoprotective activity (Wills and Asha 2006), antihyperglycemic activity (Zheng et al. 2011a, b), leishmanicidal activity (Socolsky et al. 2015), trypanocidal activity (Morais-Braga et al. 2013a, b), anti-nociceptive activity, anti-inflammatory activity (Yonathan et al. 2006), immunomodulatory activity (Wu et al. 2005), and chemopreventive effects (Wills and Asha 2009). Because of the need for new medicines with such activities, pteridophytes and their secondary metabolites could potentially be of great medicinal value.

Phytochemicals from fern species

Huperziaceae

The Huperziaceae comprise two genera, *Huperzia* and *Phlegmariurus*. The former produces a wide range of secondary metabolites including lycopodium alkaloids, triterpenes, flavones and phenolic acids (Lu et al. 2001; Tong et al. 2003b; Ma and Gang 2004; Zhou et al. 2003a, b; Shi et al. 2005). *Huperzia serrata* (Thunb.) Trev. is a typical member of the lycophytes, and is synonymous with *Lycopodium serratum* (Thunb.). Alkaloids from *H. serrata* have been investigated by Chinese phytochemists since the mid-1980s, resulting in the identification of huperzine A, which has been proposed to have anti-Alzheimer's activity (Liu et al. 1986a, b). More than 200 alkaloids had been indentified from *H. serrata* and related genera by 2004 (Ma and Gang 2004). To date, over 100 Lycopodium alkaloids have been identified in *H. serrata*, around 80 of which were previously unknown (Table 1). Based on their structures and proposed biogenesis, these compounds can be classified as lycodine, lycopodine, fawcettimine, or phlegmarine alkaloids (Fig. 2). Lycopodine and fawcettimine alkaloids are the major lycopodium alkaloids found in *H. serrata*.

Lycopodium alkaloids

Lycopodium alkaloids (Fig. 2) have been isolated and reported from 13 Huperziaceae species and varieties (Table 1): *H. serrata*, *H. serrata* (Thunb.) Trev.f. *longipetiolata* (Spring) Ching, *H. selago* (L.) Bernh. ex Schrank et Mart., *H. lucidula* (Michx.) Ching, *H. chinensis* (Christ) Ching, *H. miyoshiana* (Makino)

Table 1 80 New lycopodium alkaloids from *H. serrata*

Chemical name	Source (references)
I. Lycopodium class	
12-Epilycodoline	*H. miyoshiana* (Tong et al. 2003b)
12-Epilycodoline *N*-oxide	*H. serrata* (Tan and Zhu 2004)
4,6-Dihydroxyserratidine	*H. serrata* (Tan et al. 2002d)
4-Hydroxyserratidine	*H. serrata* (Tan et al. 2002d)
4,6-Dihydroxylycopodine	*H. serrata* (Tan and Zhu 2004)
6-Hydroxylycopodine	*H. serrata* (Yuan et al. 1995)
6-Hydroxyserratidine	*H. serrata* (Tan et al. 2002d)
7-Hydroxylycopodine	*H. serrata* (Tan and Zhu 2004)

Table 1 continued

Chemical name	Source (references)
Clavolonine	*H. miyoshiana* (Tong et al. 2003b)
Flabelliformine	*H. miyoshiana* (Tong et al. 2003b)
Gnidioidine	*H. carinata* (Thorroad et al. 2014)
Huperzine E	*H. serrata* (Zhu et al. 1996; Wang et al. 2001)
Huperzine F	*H. serrata* (Zhu et al. 1996; Wang et al. 2001)
Huperzine G	*H. serrata* (Wang et al. 1998, 2000)
Huperzine O	*H. serrata* (Wang et al. 2000)
Lucidioline	*H. serrata* (Zhou et al. 1993; Ma et al. 1998)
Lycocarinatine A	*H. carinata* (Thorroad et al. 2014)
Lycodoline	*H. miyoshiana* (Tong et al. 2003b), *H. serrata* (Yuan et al. 1995), *H. carinata* (Thorroad et al. 2014)
Lycopodine	*H. miyoshiana* (Tong et al. 2003b), *H. serrata* (Yuan et al. 1995)
Lycoposerramine K	*H. carinata* (Thorroad et al. 2014)
Lycoposerramine U *N*-oxide	*H. squarrosa* (Thorroad et al. 2014)
Miyoshianine A	*H. miyoshiana* (Tong et al. 2003b)
Miyoshianine B	*H. miyoshiana* (Tong et al. 2003b)
Phlegmariurine B	*H. carinata* (Thorroad et al. 2014), *H. squarrosa* (Thorroad et al. 2014)
Sauroine	*H. saururus* (Ortega et al. 2004)
Selagoline	*H. selago* (Staerk et al. 2004)
Serratidine	*H. serrata* (Tan et al. 2002d), *H. selago* (Staerk et al. 2004)
II. Lycodine class	
12-Epilycodine *N*-oxide	*H. squarrosa* (Thorroad et al. 2014)
6-Hydroxyhuperzine A	*H. serrata* (Yuan and Zhao 2000)
8,15-Dihydrohuperzine A	*H. carinata* (Thorroad et al. 2014)
Des-*N*-methyl–obscurine	*H. serrata* (Yuan et al. 1995)
Huperserine E	*H. serrata* (Jiang et al. 2014)
Huperzine A	*H. serrata* (Liu et al. 1986a, b), *H. selago* (Staerk et al. 2004), *H. carinata* (Thorroad et al. 2014), *Huperzia squarrosa* (Thorroad et al. 2014)
Huperzine B	*H. serrata* (Liu et al. 1986a, b)
Huperzine C	*H. serrata* (Liu and Huang 1994)
Huperzine D	*H. serrata* (Liu and Huang 1994)
Huperzine U	*H. serrata* (Tan et al. 2003)
Huperzinine	*H. serrata* (Yuan and Wei 1988; Jiang et al. 2014)
Lycodine	*H. serrata* (Yuan et al. 1994)
Lycoflexine *N*-oxide	*H. squarrosa* (Thorroad et al. 2014)
N,N-Dimethylhuperzine A	*H. serrata* (Hu et al. 1992)
N-Demethyl-sauroxine	*H. saururus* (Vallejo et al. 2013)
N-Methyl-huperzine B	*H. serrata* (Yuan and Wei 1988; Southon and Buckingham 1989)
III. Fawcettimine class	
11-Hydroperoxyphlegmariurine B	*H. serrata* (Tan et al. 2003)
11-Hydroxyphlegmariurine B	*H. serrata* (Tan et al. 2002e)
11-Oxophlegmariurine B	*H. serrata* (Tan et al. 2002b)
2-Hydroxyphlegmariurine B	*H. serrata* (Tan et al. 2002b)
2-Oxophlegmariurine B	*H. serrata* (Tan et al. 2002b)
7,11-Dihydroxy-phlegmariurine B	*H. serrata* (Tan et al. 2002e)

Table 1 continued

Chemical name	Source (references)
7-Hydroxyphlegmariurine B	*H. serrata* (Tan et al. 2002e)
7-Hydroperoxyphlegmariurine B	*H. serrata* (Tan et al. 2003)
8-Hydroxyphlegmariurine B	*H. serrata* (Tan et al. 2000b)
8-Hydroxyphlegmariurine B	*H. serrata* (Yuan and Zhao 2003)
Fawcettimine	*H. serrata* (Tan et al. 2000a), *H. carinata* (Thorroad et al. 2014)
Huperserines A	*H. serrata* (Jiang et al. 2014)
Huperserines B	*H. serrata* (Jiang et al. 2014)
Huperserines C	*H. serrata* (Jiang et al. 2014)
Huperserines D	*H. serrata* (Jiang et al. 2014)
Huperserratinine	*H. serrata* (Zhu et al. 1994)
Huperzine H	*H. serrata* (Gao et al. 1999)
Huperzine I	*H. serrata* (Gao et al. 2000b)
Huperzine P	*H. serrata* (Tan et al. 2000a)
Huperzine Q	*H. serrata* (Tan et al. 2002c)
Huperzine R	*H. serrata* (Tan et al. 2002a)
Huperzine S	*H. serrata* (Tan et al. 2003)
Huperzine T	*H. serrata* (Tan et al. 2003)
Huperzine W	*H. serrata* (Tan et al. 2002d)
Neohuperzinine	*H. serrata* (Yuan et al. 2002)
N-Oxyhuperzine Q	*H. serrata* (Tan et al. 2002c)
Phlegmariurine A	*H. serrata* (Tan et al. 2000b)
Phlegmariurine B	*H. serrata* (Yuan et al. 1994; Tan et al. 2000a, b)
Serratine	*H. serrata* (Zhang et al. 1990)
Serratinine	*H. serrata* (Zhou et al. 1993; Ma et al. 1998)
IV. Miscellaneous group	
Huperzine J	*H. serrata* (Gao et al. 2000a)
Huperzine K	*H. serrata* (Gao et al. 2000a)
Huperzine L	*H. serrata* (Gao et al. 2000a)
Huperzine V	*H. serrata* (Liu et al. 2004)
Huperzinine B	*H. serrata* (Yuan et al. 2001)
Phlegmariurine N	*H. serrata* (Miao et al. 1989; Yuan and Zhao 2000)
Lycobeline A	*H. goebelii* (Hirasawa et al. 2012)
Lycobeline B	*H. goebelii* (Hirasawa et al. 2012)
Lycobeline C	*H. goebelii* (Hirasawa et al. 2012)
Lycotetrastine A	*H. tetrasticha* (Hirasawa et al. 2011)
Huperminone A	*H. phlegmaria* (Hirasawa et al. 2013)
Hupermine A	*H. phlegmaria* (Hirasawa et al. 2014)

Ching, *H. saururus* (Lam.) Trevis, *H. kunmingensis* Ching, *H. goebelii*, *H. tetrasticha*, *H. phlegmaria*, *H. carinata* (Desv. Ex. Poir.) Trevis, and *H. squarrosa* (G. Forst) Trevis (Hirasawa et al. 2012, 2013). A

novel $C_{20}N$-type Lycopodium alkaloid, lycotetrastine A, with an unprecedented fused-hexacyclic ring system featuring lactone, aza-cycloheptene, aza-cyclohexane, cyclohexane, cyclopentane, and
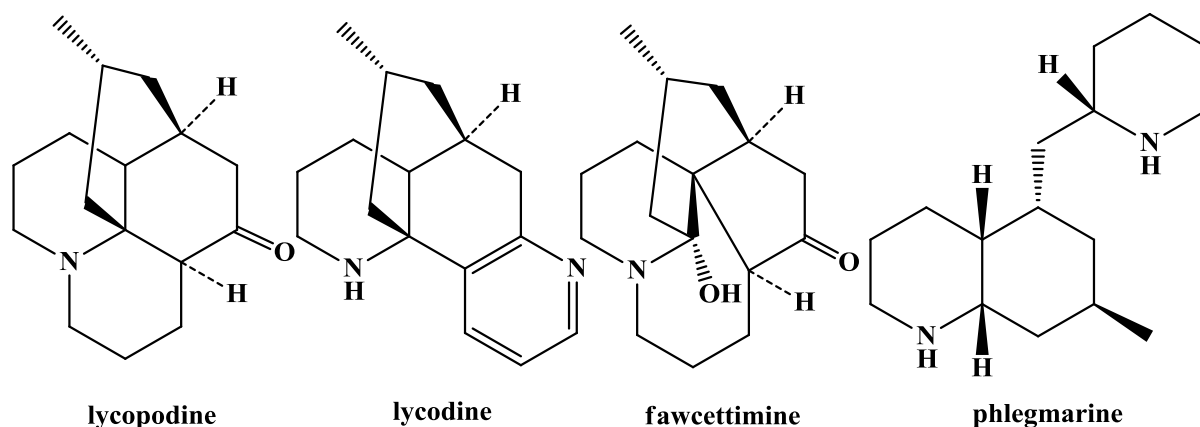
Fig. 2 Representative skeletons of Lycopodium alkaloids from Huperzia

tetrahydrofuran rings, has been isolated from the club moss *H. tetrasticha* (Hirasawa et al. 2011). Lycobelines A–c alkaloids featuring a decahydroquinoline ring system with an aminohexyl side chain, have been isolated from the club moss *H. goebelii* (Hirasawa et al. 2011). A novel C_{16}N-type Lycopodium alkaloid known as huperminone A featuring a decahydroquinoline and a cyclohexanone has been isolated from the club moss *H. phlegmaria* (Hirasawa et al. 2013) along with hupermine A, a new alkaloid with a novel skeleton consisting of a quinolizidine with a 6-dimethylaminohexyl side chain (Hirasawa et al. 2014). Huperminone A has a unique C_{16}N-type skeleton with one fewer nitrogen atom than its closest structural relatives, and may be derived from the $C_{16}N_2$ phlegmarane skeleton. *N*-demethyl-sauroxine, a novel Lycopodium alkaloid, has been obtained from *H. saururus* (Lam.) Trevis. Eleven Lycopodium alkaloids including three new alkaloids—8,15-dihydrohuperzine A, lycocarinatine A, and lycoposerramine U N-oxide—have been isolated from whole plants of *H. carinata* (Desv. Ex. Poir.) Trevis and *H. squarrosa* (G. Forst) Trevis. *Huperzia* and *Lycopodium* species continue to be rich sources of novel heterocyclic alkaloids with C_{11}N, C_{16}N, $C_{16}N_2$, $C_{22}N_2$ and $C_{27}N_3$ skeletons, many of which represent challenging targets for total synthesis. All the Lycopodium alkaloids have complex polycyclic carbon skeletons, albeit with variable levels of oxidation. The most prominent compound in this group is huperzine A, although lycopodine was the first Lycopodium alkaloid to be identified and appears

to be the most widely distributed (Ma and Gang 2004).

Lycodine alkaloids

Members of the lycodine alkaloid family found in the Huperziaceae include huperzine A and lycodine derivatives with an opened C-ring such as huperzines B–U and huperserine E (Jiang et al. 2014; Liu et al. 1986a, b; Tan et al. 2003). Lycodine alkaloids typically feature four fused six-membered rings (Jiang et al. 2010; Tan et al. 2002a; Wang et al. 1998, 2000; Wang et al. 2007; Yang et al. 2010; Zhu et al. 1996), and sometimes exhibit N-oxidation (Takayama et al. 2003; Tan and Zhu 2004; Wang et al. 2009a, b; Ying et al. 2014).

Fawcettimine alkaloids

Of the *Huperzia* species, that which produces the largest number of known fawcettimine alkaloids is *H. serrata*. The fawcettimine alkaloids differ from the lycopodine alkaloids in that the carbon–carbon single bond between C-4 and C-13 found in the lycopodine alkaloids is replaced by a C-13 to C-12 bond, yielding a fused tetracyclic structure (Ayer et al. 1994; Gao et al. 2000a, b; Jiang et al. 2014; Katakawa et al. 2007, 2011; Takayama et al. 2001). Surprisingly, N-oxidized variants of these alkaloids have been identified, such as *N*-oxyhuperzine Q (Tan et al. 2002b). The chemical bond between C-12 and C-13 in the fawcettimine alkaloids can be broken,

expanding the heterocyclic ring to yield the isoforms known as the phlegmariurine B alkaloids (Tan et al. 2000a, b, c, d, 2003). In addition, the single bond between the N atom and C-13 can be broken to yield derivatives with nine-membered heterocyclic rings such as lycoposerramines A, B and T (Takayama et al. 2001; Katakawa et al. 2005, 2009). A variety of phlegmarine-type alkaloids have been isolated from *H. serrata*, including N-oxides such as huperzines J–N, lycoposerramines X–Z, and hupserramine A (Gao et al. 2000a, 2008a, b; Katakawa et al. 2006; Ying et al. 2014). Derivatives featuring a single bond between C-4 and C-12 of the phlegmarine skeleton have also been identified; this modification introduces a new five-membered ring and is observed in phlegmarine alkaloids from *H. serrata* such as lycoposerramine R and huperzimine (Katakawa et al. 2009; Yu et al. 2014). Finally, a simple alkaloid designated huperzine W has been isolated from *H. serrata* (Tan et al. 2002e).

Triterpenoids

Studies on the non-alkaloidal fraction of *Huperzia* species have revealed the presence of serratene-type triterpenoids in addition to alkaloids (Shi et al. 2005; Zhou et al. 2003a, b) (Table 2). Serratenes are a group of naturally occurring pentacyclic triterpenoids with seven tertiary methyl groups and a seven-membered C ring (instead of eight methyl groups and a six-membered C ring as found in common pentacyclic triterpenoids), usually with a double bond between C-14 and C-15, and oxygen functionalities at both C-3 and C-21. They have been detected in fern allies and conifers (Pinaceae) (Wittayalai et al. 2012; Tanaka et al. 2004; Zhou et al. 2003a, b).

Serratenediol, a representative serratene-type triterpenoid with a seven-membered C ring and seven tertiary methyl groups (Fig. 3), was first isolated from the Japanese club moss *Lycopodium serratum* (or *H. serrata*) in 1964 (Tong et al. 2003b). Subsequent

Table 2 Serratene-type triterpenoids from *Huperzia* plants

Chemical name	Source (references)
14β,15β-Epoxyserratan-3β,21β,29-triol	*H. serrata* (Zhou et al. 2004)
14β,15β-Epoxy-3-hydroxyserratan-21α-ol	*H. serrata* (Zhou et al. 2003b)
14β,15β-epoxy-3-hydroxyserratan-21α-ol-3β-*O*-acetate	*H. serrata* (Zhou et al. 2003b)
14β,15β-epoxy-3-hydroxyserratan-21β-ol	*H. serrata* (Zhou et al. 2003b)
16-oxo-21β-hydroxyserrat-14-en-yl acetate	*H. serrata* (Zhou et al. 2003a)
16-oxo-3α,21β-dihydroxy-serrat-14-en-24-al	*H. serrata* (Zhou et al. 2013)
16-oxo-3α,21β-dihydroxy-serrat-14-en-24-oic acid	*H. serrata* (Zhou et al. 2013)
16-oxo-3α-hydroxyserrat-14-en-21β-ol	*H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011)
16-oxodiepiserratenediol	*H. serrata* (Zhou et al. 2013; Li et al. 1988; Zou et al. 2004)
16-oxoserratriol	*H. serrata* (Zhou et al. 2013)
21-epi-serratenediol	*H. serrata* (Zhou et al. 2003a), *H. kunmingensis* (Li et al. 2013), *H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011)
21-episerratenediol-3- acetate	*H. serrata* (Zhou et al. 2003a), *H. kunmingensis* (Li et al. 2013), *H. miyoshiana* (Tong et al. 2003b)
21α-hydroxy-serrat-14-en-3β-yl dihydrocoumarate	*H. serrata* (Zhou et al. 2003a)
21α-hydroxy-serrat-14-en-3β-yl *p*-dihydrocaffeate	*H. serrata* (Zhou et al. 2003a)
21α-hydroxy-serrat-14-en-3β-yl propanedioic acid monoester	*H. serrata* (Zhou et al. 2003a)
21β-hydroxyserrat-14-en-3α-ol	*H. serrata* (Zhou et al. 2003a), *H. phlegmaria* (=*L. phlegmaria*) (Wittayalai et al. 2012)
2lα-hydroxy-serrat-14-en-3β-yl-acetate	*H. miyoshiana* (Tong et al. 2003b)
2lβ-hydroxy-serrat-14-en-3β-yl-acetate	*H. miyoshiana* (Tong et al. 2003b), *H. phlegmaria* (Wittayalai et al. 2012)
3-*O*-acetyltohogenol	*H. miyoshiana* (Tong et al. 2003a, b)
3α,21β,24-trihydroxy-serrat-14-en-16-one	*H. serrata* (Zhou et al. 2003a), *H. kunmingensis* (Li, et al. 2013), *H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011)
3α,2lα-dihydroxy-serrat-14-en-24-oic acid	*H. serrata* (Zhou et al. 2003a)
3α,2lβ-dihydroxy-serrat-14-en-24,29-diol	*H. serrata* (Zhou et al. 2003a)
3α,2lβ-dihydroxy-serrat-14-en-24-ol	*H. serrata* (Zhou et al. 2003a), *H. miyoshiana* (Tong et al. 2003b)

Table 2 continued

Chemical name	Source (references)
3β,14β,21α,24-Serratanetetrol (tohogeninol)	*H. serrata* (Sano et al. 1970)
3β,14β,21α-Serratanetriol (tohogenol)	*H. miyoshiana* (Tong et al. 2003a)
3β,21β-Dihydroxy-serrat-14-en-16-one	*H. serrata* (Zhou et al. 2003a), *H. miyoshiana* (Tong et al. 2003b)
3β,2lα-Dihydroxy-serrat-14-en (serratenediol)	*H. serrata* (Zhou et al. 2003a, 2004; Li et al. 1988), *H. crispate* Ching (Pei et al. 2004), *H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011), *H. kunmingensis* (Li et al. 2013)
3β,2lα-Dihydroxy-serrat-14-en-24-ol	*H. serrata* (Zhou et al. 2003a)
3β,2lβ-Dihydroxy-serrat-14-en-24-ol	*H. serrata* (Zhou et al. 2003a), *H. miyoshiana* (Tong et al. 2003b)
3β,2lβ-Dihydroxy-serrat-14-en-29-ol	*H. serrata* (Zhou et al. 2003a), *H. kunmingensis* (Li, et al. 2013), *H. miyoshiana* (Tong et al. 2003b)
3β-Hydroxy-serrat-14-en-21-one	*H. serrata* (Zhou et al. 2003a)
Lycoclavanol	*H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011)
Lycophlegmarin	*H. phlegmaria* (Shi et al. 2005)
Lycophlegmariol A	*H. phlegmaria* (Wittayalai et al. 2012)
Lycophlegmariol B	*H. phlegmaria* (Wittayalai et al. 2012)
Lycophlegmariol C	*H. phlegmaria* (Wittayalai et al. 2012)
Lycophlegmariol D	*H. phlegmaria* (Wittayalai et al. 2012)
Miyoshianois A	*H. miyoshiana* (Tong et al. 2003b)
Miyoshianois B	*H. miyoshiana* (Tong et al. 2003b)
Miyoshianois C	*H. miyoshiana* (Tong et al. 2003b)
Tohogenin	*H. serrata* (Zhou et al. 2003a)
Miyoshianol A	*H. miyoshiana* (Tong et al. 2003a)
Serrat-14-en-3,21β,24,29-tetraol	*H. serrata* (Zhou et al. 2004)
Serrat-14-en-3α,21β,24,29-tetraol	*H. serrata* (Zhou et al. 2003a)
Serrat-14-en-3β,21α,24-triol	*H. serrata* (Zhou et al. 2003a)
Serrat-14-en-3β,21α-diyl-acetate	*H. miyoshiana* (Tong et al. 2003b)
Serrat-14-en-3β,21β,24-triol	*H. serrata* (Zhou et al. 2003a)
Serrat-14-en-3β,21β,29-triol	*H. serrata* (Zhou et al. 2004)
Serrat-14-en-3β,2lβ,29-triol	*H. serrata* (Zhou et al. 2003a)
Serratenediol (3β-hydroxyserrat-14-en-21α-ol)	*H. serrata* (Zhou et al. 2004; Li et al. 1988), *H. crispate* Ching (Pei et al. 2004), *H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011)
Serratenediol-21-acetate	*H. serrata* (Zhou et al. 2003a)
Serratenediol-3-acetate	*H. serrata* (Zhou et al. 2003a), *H. kunmingensis* (Li, et al. 2013), *H. crispate* Ching (Pei et al. 2004), *H. serrata* (thunb.) Trev.f. *longipetiolata* (Spring) Ching (Pei et al. 2011)

studies in this field led to the discovery of several related triterpenoids in *Huperzia* plants, particularly *H. serrata*. For example, Zhou and co-workers reported the isolation of many serratane-type triterpenoids from this species (Zhou et al. 2003a, b, 2004). In addition, thirteen triterpenoids, including the previously unknown miyoshianois A–C, were isolated from *H. miyoshiana* (Tong et al. 2003b). Serratene-type triterpenoids have also been isolated from *H. kunmingensis* and *H. serrata* (Thunb.) Trev.f. *longipetiolata* (Spring) Ching (Li et al. 2013). Finally, five new serratene-type triterpenes, lycophlegmarin (Shi et al. 2005) and

lycophlegmariol A–D, along with an abietane-type diterpene have been isolated from the methanol extract of the club moss *H. phlegmaria* (=*L. phlegmaria* L.) (Wittayalai et al. 2012).

Other secondary metabolites

In addition to alkaloids and triterpenoids, *H. serrata* also produces phenols and flavonoids (Gao et al. 2000b; Lu et al. 2001; Sano et al. 1970; Zhou et al. 2004). For example, a new flavone glycoside, identified as 5,5′-dihydroxy-2′,4′-dimethoxy-flavone-7-O-β-D-(6″-O-Z-p-coumaroyl)- glucopyranoside was
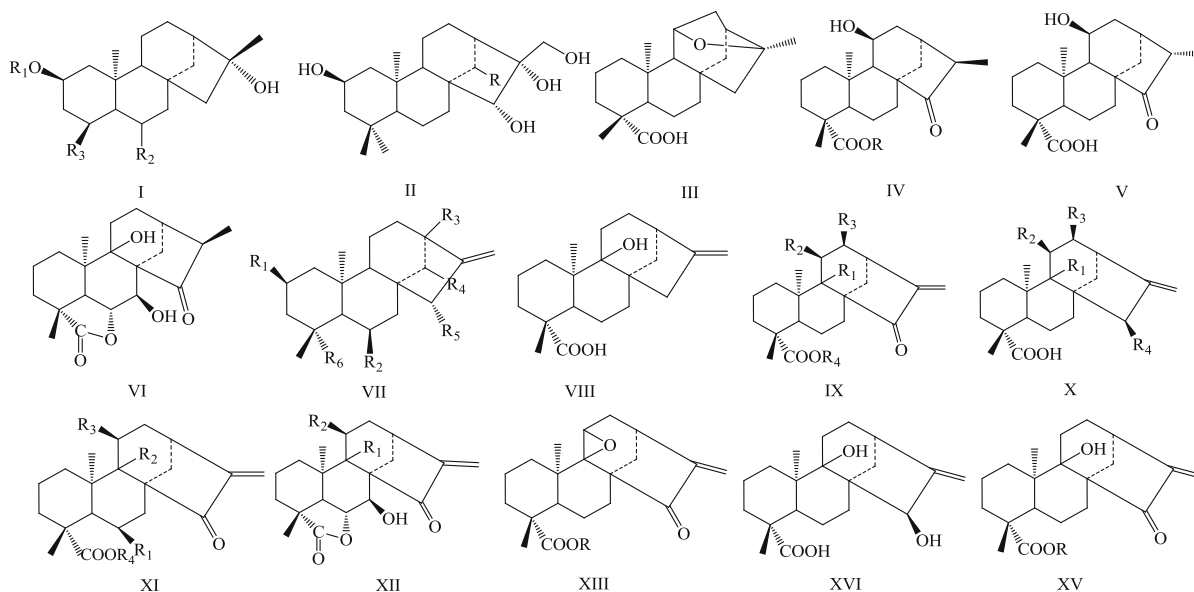
Fig. 3 Skeleton of serratene-type triterpenoids from Huperzia

recently isolated from *H. serrata* (Thunb.) (Yang et al. 2008).

Pteridaceae

Phytochemical studies on the genus *Pteris* (Pteridaceae) have yielded a variety of secondary metabolites including *ent*-kaurane diterpenoids and pterosin-sesquiterpenes (Wang et al. 2011a, b, c; Liu et al. 2011a, b, c; Shu et al. 2012; Murakami et al. 1980; Tanaka et al. 1982), flavonoids (Chen et al. 2007; Lu et al. 1999), benzenoids, and benzenoid derivatives (Chen et al. 2007, 2013a, b). Pterosins and *ent*-kaurane diterpenoids are the characteristic constituents of the fern family Pteridaceae.

Diterpenoids

All of the diterpenoid secondary metabolites isolated from the Pteridaceae to date have either an *ent*-kaurane or an *ent*-kaurene skeleton (Table 3) with hydroxyl groups at some or all of the C-2, 6, 7, 9, 11, and 15 positions. In addition, a minority bear hydroxyl groups at C-16, 17, and/or C-18. In some cases, the C-15 hydroxyl is further oxidized to yield 15-oxygenated *ent*-kaurane or *ent*-kaurene derivatives. Glycosidic linkages are usually formed via the C-2 or C-4 hydroxyl groups, and the sugar moieties are mainly glucopyranosyl and/or allopyranosyl (Fig. 4) (Chen et al. 2007, 2013a, b).

The novel tetrahydroxylated *ent*-kaurane pterokaurane M_2 (which is hydroxylated at C-2, C-14, C-15, and C-18) was isolated from *Pteris multifida* (Ge et al. 2008). Although C-15 hydroxylated kaurenes had previously been isolated from *P. cretica* (Harinantenaina et al. 2009), this 2,15-dihydroxy-*ent*-kaur-16-ane 2-*O*-D-glucopyranoside is the first *ent*-kaurene derivative with an α-oriented hydroxyl group at C-15 to be isolated from any *Pteris* species (Wang et al. 2011a, b, c). In addition, *ent*-atisane type diterpenes, which represent a small proportion of the diterpenoids in *Pteris*, were isolated from the fronds of *P. purpureorachis* COPEL (Fig. 5) (Tanaka et al. 1981; Murakami et al. 1983).

P. semipinnata L. is a member of the genus *Pteris* that grows in northern China. Phytochemical studies on this species have led to the isolation of over thirty terpenoids, including diterpenoids and sesquiterpenoids. Most of the novel diterpenoids from *P. semipinnata* are *ent*-kaurane derivatives such as 6β,11α-dihydroxy- 15-oxo-*ent*-kaur-16-en-19-oic acid and 7α,11α-dihydroxy-15-oxo-*ent*-kaur-16-en-19-oic acid (Bai et al. 2013), 7 β-hydroxy-11β,16β-epoxy-*ent*-kauran-19-oic acid (Zhan et al. 2009), and pterisolic acids A–F (Wang et al. 2011a, b, c). In addition, a new *ent*-kaurane diterpenoid glucoside known as pteriside has been obtained from *P. semipinnata* (Shi and Bai

Table 3 *ent*-Kaurane diterpenoids from Pteridaceae species

Name	Source	References
2β,16α-Dihydroxy-*ent*-kaurane	*P. angustipinna, P. cretica, P. dactylina, P. multifida*	Murakami et al. ([1985a, b](#)), Murakami and Tanaka ([1988](#))
2β,16α-Dihydroxy-*ent*-kaurane 2-*O*-β-D-glucoside	*P. angustipinna, P. cretica, P. dactylina, P. multifida*	Murakami et al. ([1985a, b](#)), Murakami and Tanaka ([1988](#))
2β,6β,16α-Trihydroxy-*ent*-kaurane	*P. cretica*	Murakami et al. ([1985a, b](#)), Murakami and Tanaka ([1988](#))
2β,6β,16α-Trihydroxy-*ent*-kaurane 2-*O*-β-D-glucoside	*P. cretica*	Murakami and Tanaka ([1988](#))
2β,16α,18-Trihydroxy-*ent*-kaurane	*P. ryukyuensis*	Tanaka et al. ([1978](#))
2β,15α,16α,17-Tetrahydroxy-*ent*-kaurane	*P. cretica*	Murakami and Tanaka ([1988](#))
2β,14β,15α,16α,17-pentahydroxy-*ent*-kaurane	*P. cretica*	Murakami and Tanaka ([1988](#))
11β,16β-Epoxy-*ent*-kauran-19-oic acid	*P. longipes*	Murakami et al. ([1981](#))
(16*R*)-11β-Hydroxy-15-oxo-*ent*-kauran-19-oic acid	*P. dispar, P. semipinncta*	Murakami et al. ([1976a, b](#)), Aoyama et al. ([1977](#))
(16*R*)-11β-Hydroxy-15-oxo-*ent*-kauran-19-oic acid 19-β-D-glucoside	*P. dispar, P. semipinncta*	Murakami et al. ([1976a, b](#)), Aoyama et al. ([1977](#))
(16*S*)-11β-Hydroxy-15-oxo-*ent*-kauran-19-oic acid	*P. dispar, P. semipinncta*	Murakami et al. ([1976a, b](#)), Aoyama et al. ([1977](#))
(16*R*)-7β,9-Dihydroxy-15-oxo-*ent*-kauran-19,6β-olide (6F)	*P. dispar, P. semipinncta*	Murakami et al. ([1976a, b](#)), Aoyama et al. ([1977](#))
2β,15α-Dihydroxy-*ent*-kaur-16-ene	*P. angustipinna, P. cretica, P. dactylina, P. multifida*	Murakami et al. ([1985a, b](#)), Murakami and Tanaka ([1988](#)), Liu and Qin ([2002](#))
2β,15α-Dihydmxy-*ent*-kant-16-ene 2-*O*-β-D-glucoside	*P. angustipinna, P. cretica, P. dactylina, P. multifida, P. plumbaea*	Murakami et al. ([1985a, b](#)), Murakami and Tanaka ([1988](#))
2β,16β,15α-Trihydroxy-*ent*-kaur-16-ene	*P. cretica, P. multifida*	Murakami and Tanaka ([1988](#)), Liu and Qin ([2002](#))
2β,6β,15α-trihydroxy-*ent*-kaur-16-ene 2-*O*-β-D-glucoside	*P. cretica*	Murakami and Tanaka ([1988](#))
2β,14β,15α-Trihydroxy-*ent*-kaur-16-ene	*P. plumbaea*	Murakami and Tanaka ([1988](#))
2β,14β,15α-Trihydroxy-*ent*-kaur-16-ene 2-*O*-β-D-glucoside	*P. plumbaea*	Murakami and Tanaka ([1988](#))
2β,6β,14β,15α-Tetrahydroxy-*ent*-kaur-16-ene	*P. plumbaea*	Murakami and Tanaka ([1988](#))
2β,13,14β,15α-Tetrahydroxy-*ent*-kaur-16-ene	*P. plumbaea*	Murakami and Tanaka ([1988](#))
2β,14β,15α,19-Tetrahydroxy-*ent*-kaur-16-ene	*P. plumbaea*	Murakami and Tanaka ([1988](#))
9-Hydroxy-*ent*-kaur-16-en-19-oic acid	*P. longipes*	Murakami et al. ([1981](#))
15-Oxo-*ent*-kaur-16-en-19-oic acid	*P. longipes*	Murakami et al. ([1981](#))
9-Hydroxy-15-oxo-*ent*-kaur-16-en-19-oic acid	*P. livida, P. longipes*	Murakami et al. ([1981](#)), Tanaka et al. ([1981](#))
9-Hydroxy-15-oxo-*ent*-kaur-16-en-19-oic acid19-β-D-glueoside	*P. altissima, P. livida*	Tanaka et al. ([1981](#))
11β-Hydroxy 15-oxo-*ent*-kaur-16-en-19-oic acid (5F)	*P. dispar, P. livida, P. semipinncta*	Murakami et al. ([1976a, b, 1983](#)), Aoyama et al. ([1977](#)), Tanaka et al. ([1981](#))
11β-Hydroxy 15-oxo-*ent*-kaur-16-en-19-oic acid19-β-D-glueoside	*P. altissima, P. dispar, P. livida, P. semipinncta, P. tremula*	Murakami et al. ([1985a, b](#)), Tanaka et al. ([1981](#))
12β-Hydroxy15-oxo-*ent*-kaur-16-en-19-oic acid19-β-D-glueoside	*P. tremula*	Murakami et al. ([1985a, b](#))

Table 3 continued

Name	Source	References
9,15β-Dihydroxy-*ent*-kaur-16-en-19-oic acid	*P. longipes*	Murakami et al. ([1981](#))
11β,15β-Dihydroxy-*ent*-kaur-16-en-19-oic acid	*P. longipes*	Murakami et al. ([1981](#))
12β,15β-Dihydroxy-*ent*-kaur-16-en-19-oic acid	*P. longipes*	Murakami et al. ([1981](#))
6β,9-Dihydroxy-15-oxo-*ent*-kaur-16-en-19-oic acid 19-β-D-glucoside	*P. livida*	Tanaka et al. ([1981](#))
6β,11-Dihydroxy-15-oxo-*ent*-kaur-16-en-19-oic acid 19-β-D-glucoside	*P. altissima*, *P. livida*	Tanaka et al. ([1981](#))
7β,9-Dihydroxy-15-oxo-*ent*-kaur-16-en-19,6β-olide	*P. dispar*, *P. purpureorachis*	Murakami et al. ([1976a](#), [b](#)), Li et al. ([1998](#))
7β,11β-Dihydroxy-15-oxo-*ent*-kaur-16-en-19,6β-olid (A)	*P. semipinncta*	Li et al. ([1998](#))
9,11β-Epoxy-15-oxo-*ent*-kaur-16-en-19-oic acid	*P. purpureorachis*	Murakami et al. ([1983](#))
9,11β-Epoxy-15-oxo-*ent*-kaur-16-en-19-oic acid 19-β-D-glucoside	*P. purpureorachis*	Murakami et al. ([1983](#))
9,15β-Dihydroxy-*ent*-kaur-16-en-19-oic acid	*P. purpureorachis*	Tanaka et al. ([1981](#))
9-Hydroxy-*ent*-kaur-16-en-19-oic acid	*P. purpureorachis*	Tanaka et al. ([1981](#))
9-Hydroxy-*ent*-kaur-16-en-19-oic acid 19-β-D-glucoside	*P. purpureorachis*	Tanaka et al. ([1981](#))
16-Hydroxy-*ent*-kaurane-2-β-D-glucoside (creticoside B)	*P. multifida*	Liu and Qin ([2002](#))
Pterokaurane M1	*P. multifida*	Ge et al. ([2008](#))
Pterokaurane M2	*P. multifida*	Ge et al. ([2008](#))
Pterokaurane M3	*P. multifida*	Ge et al. ([2008](#))
2β,15β-Dihydroxy-ent-kaur-16-ene 2-*O*-β-D-glucopyranoside	*P. cretica* Linn.	Harinantenaina et al. ([2009](#))
5,11β,12β-Trihydroxy-15-oxo-ent-kuar-16-en-19-oic acid	*P. dispar*	Gou et al. [2011](#)
Pterisolic acid A	*P. semipinnata*	Liu et al. ([2011a](#), [b](#), [c](#))
Pterisolic acid B	*P. semipinnata*	Liu et al. ([2011a](#), [b](#), [c](#))
Pterisolic acid C	*P. semipinnata*	Liu et al. ([2011a](#), [b](#), [c](#))
Pterisolic acid D	*P. semipinnata*	Liu et al. ([2011a](#), [b](#), [c](#))
Pterisolic acid E	*P. semipinnata*	Liu et al. ([2011a](#), [b](#), [c](#))
Pterisolic acid F	*P. semipinnata*	Liu et al. ([2011a](#), [b](#), [c](#))

[2010](#)). In addition to *ent*-kaurane ditertenoids, a novel labdane diterpenoid glucoside, 15-*O*-β-D-glucopyranosyl-labda-8(17), 13E-diene-3β,7β-diol has been identified (Jin et al. [2010](#)).

Flavonoids

Many flavonoids, especially flavonols, have been isolated from ferns and characterized (Harborne and Williams [1988](#); Cao et al. [2013a](#), [b](#)). Flavonoids are abundant in *Pteris* species, and epidemiological and medical data suggest that they play key roles in preventing and managing diseases (Chen et al. [2017](#); Xiao and Kai [2012](#); Xia et al. [2014](#); Xiao et al. [2016](#); Chen et al. [2017](#); Xiao [2016c](#)). Flavonoids from 20 fern species belonging to the genus *Pteris* have been studied (Gong et al. [2007](#); Chen et al. [2007](#)). Most flavonoids from this genus are α- or β-glycosides such as flavonoid glucosides, galactosides, rhamnosides, or arabinosides. The most numerous glycosylated
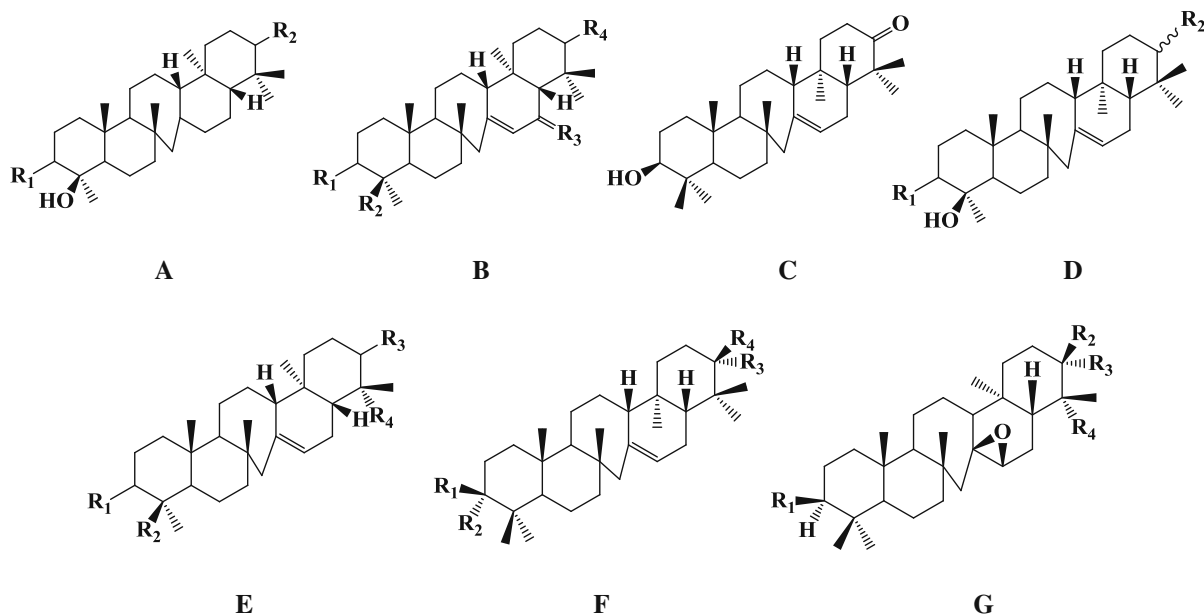
Fig. 4 Ent-kaurane-type diterpenoids from genus Pteris (Chen et al. 2007, 2013a, b)
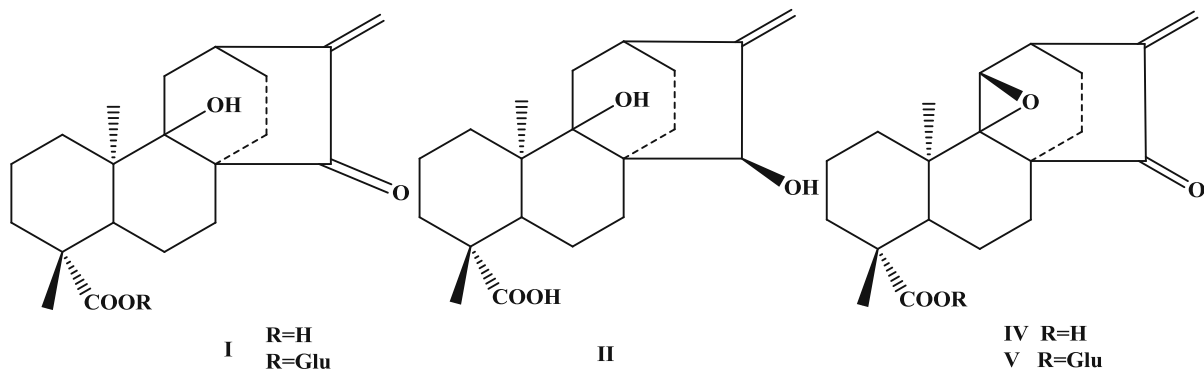

Fig. 5 Atisane-type diterpenoids from genus Pteris

flavonoids are flavonol *O*-glycosides. Most of the flavonoid glycosides are 3- or 7-*O*-glycosides, but the hydroxyl groups at C-5, 4, and 8 positions are sometimes glycosylated as well (Gong et al. 2007; Imperato 2003, 2006; Cai et al. 2000; Cao et al. 2012). In addition, some C-glycosylflavones have been isolated from *Pteris* (Imperato 2004, 2006). The basic flavonoid aglycones in this genus are apigenin, kaempferol, quercetin, and luteolin. For example, two known flavonoids, apigenin 7-*O*-α-D-glucoside and apigenin 7-*O*-α-D-glucuronide, have been obtained from *P. semipinnata* (Zhan et al. 2010).

New flavonoids are still being isolated from *Pteris*. For example, 3,8-di-*C*-arabinosylluteolin, 3-*O*-(2,3-di-*O*-*p*-coumaroyl)-glucosides, 7-*O*-rhamnoside, 7-*O*-*p*-

hydroxybenzoate and three di-*C*-glycosylflavones have been isolated from *P. vittata* (Fig. 6) (Imperato 2003, 2004, 2006). The main flavonoids in *P. multifida* are rutin, luteolin, apigenin, and their glycosides (Lu et al. 1999). The Sword Brake fern (*P. ensiformis* Burm.) is used extensively in traditional Taiwanese herbal drinks. Chen et al. (2007) reported the isolation of three new phenolic compounds in aqueous extracts of this species: kaempferol 3-*O*-L-rhamnopyranoside-7-*O*-[-D-apio-furanosyl-(1-2)-*O*-D-glucopyranoside], 7-*O*-caffeoylhydroxymaltol 3-*O*-D-glucopyranoside and hispidin 4-*O*-D-glucopyranoside, along with the known compounds kaempferol 3-*O*-L-rhamnopyranoside-7-*O*-D-glucopyranoside, caffeic acid, 5-caffeoylquinic acid, 3,5-di-caffeoylquinic acid, and 4,5-di-caffeoylquinic acid.

Fig. 6 *Pteris vittata* L. (Courtesy of Jianguo Cao)

Fig. 7 Aerial parts of the fern *Pityrogramma calomelanos*. (Courtesy of Flaviana Morais-Braga)

A novel bihomoflavanonol with an unprecedented skeleton, designated pteridium III, was recently isolated from *P. aquilinum*, and glycosides with *O*-D-xylopyranosyl and *O*-D-glucopyranoside moieties have been isolated from *P. esculentum*. This represents the second time that unusual disaccharide analogues of this kind have been found in this family.

The species *Pityrogramma calomelanos* (Fig. 7), syn. *Acrostichum calomelanos,* belongs to the family Pteridaceae and is distributed across tropical America, where it is very often found on the edges of paths and roads and in disturbed areas at either high or low altitude (Moran and Davidse 1995; Prado 2005b). Dihydrochalcone was evaluated in India by Sukumaran and Kuttan (1991). The complex flavonoids, calomelanols A-J, were isolated from the farinose exudate of *Pityrogramma calomelanos* in early 1990s (Asai et al. 1991, 1992a, b).

Sesquiterpenes

Phytochemical investigations on *Pteris* have revealed that the C_{14} and C_{15} illudane-type sesquiterpenoids known as pterosins (Fig. 8), are key chemotaxonomical constituents of the genus (Wang et al. 2011a, b, c; Liu et al. 2011a, b, c; Shu et al. 2012; Murakami et al. 1980; Tanaka et al. 1982). The pterosins are a large group of naturally occurring sesquiterpenes with an indanone skeleton.

Bracken (*Pteridium* spp.) is a ubiquitous fern that has been described as one of the five most common plants on earth; it has a long history of poisoning grazing livestock. *P. aquilinum* is the most widespread species within the family Pteridaceae, with 11 subspecies occurring predominantly in the northern hemisphere (Yamada et al. 2007; Vetter 2009). In the 1970s, several indanone-type sesquiterpenes (Table 4), such as pterosin B, were isolated as characteristic constituents of bracken (Fukuoka et al. 1978; Hikino et al. 1970, 1971, 1972; Kuroyanagi et al. 1974a, 1979). In addition to diterpenoids, several new sesquiterpenoid indanone derivatives including pterisemipol, (2R)-norpterosin B, (2R)-12-*O*-β-D-glucopyranosylnorpterosin B and semipterosin A (Fig. 9) have been found in *P. semipinnata* (Zhang and Xuan 2007; Zhan et al. 2010). Pterosin sesquiterpenoids (Table 4) were first isolated from bracken, *P. aquilinum* var. *latiusculum* (Pteridaceae) (Hikino et al. 1970), and proved to be the long-sought bracken carcinogens (Hirono 1987). To date, over 60 pterosin sesquiterpenoids, all 2,5,7-trimethyl-indan-1-one derivatives, have been isolated from *Pteris* (Fig. 9) (Wang et al. 2011a, b, c; Liu et al. 2011a, b, c; Shu et al. 2012; Murakami et al. 1980; Tanaka et al. 1982). Several of them, including pterosin Z and acetyl-Δ^2-dehydropterosin B have proven to be cytotoxic (Chen et al. 2008a, b).

New chemicals related to the pterosins continue to be discovered. For example, a novel pterisane skeleton sesquiterpenoid, pterisemipol (Fig. 10), was isolated from *P. semipinnata* L. (Fig. 11). Its skeleton appears to be formed via a rearrangement of protoilludane, which was isolated from the mycelia of *Fomitopsis insularis*. Interestingly, its biosynthesis does not appear to follow the isoprene rule (Zhang
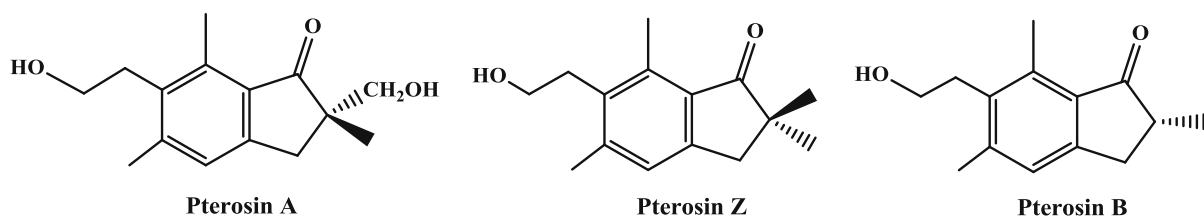
Pterosin A   **Pterosin Z**   **Pterosin B**

Fig. 8 Typical pterosins found in genus Pteris

et al. 2007). Recently, two novel isomeric C_{14} pterosin dimers designated bimutipterosins A and B were isolated from a whole *P. multifida* plant (Fig. 10). This novel type of pterosin dimer was reported for the first time (Liu et al. 2011a, b, c). From a biogenetic point of view, these compounds, which have a central cyclobutene motif, could be regarded as [2 + 2] dimerization products of dehydropterosin Q, a known compound that has also been isolated from this plant.

Terpene glycosides

After the discovery of ptaquiloside, more ptaquiloside-related terpene glycosides were isolated. Two new ptaquiloside-related compounds, isoptaquiloside and caudatoside were isolated from fresh fronds of *P. aquilinum* var. *caudatum* in 1997 (Castillo et al. 1997). Isoptaquiloside is a C-8 epimer of ptaquiloside. Subsequently, a bioassay-guided separation of an aqueous extract of fresh fronds of the Neotropical bracken *P. aquilinum* var. *caudatum* yielded ptaquiloside Z. Studies on the biogenesis of illudane sesquiterpene glucosides such as ptaquiloside resulted in the discovery of a proto-illudane sesquiterpene glucoside, pteridanoside, which was first isolated from the bracken *P. aquilinum* var. *caudatum* (Castillo et al. 1999). More recently, a novel norsesquiterpene glucoside ptesculentoside was isolated from the Australian bracken *P.*

Table 4 1H-indan-1-one sesquiterpenoids from *Pteridaceae* species

| Chemical name	Type	Source	References
Pterosin A	I	*P. aqullinum* var. Latiusculum; *D. seabra* (wall) Moore; *P. cretica* L; *M. substrigosa* Tagawa; *D. wilfordii* (Moore) Christ;	Yoshihira et al. (1972, 1978), Murakami et al. (1976a), Kuraishi et al. (1985), Tanaka et al. (1981)
Pterosin B	I	*P. aqullinum* var. *Latiusculum*; *P. bella* Tagawa; *J. scammanae* Tryon; *P. tremula* Br; *P. dactylina* Hook; *P. multifida* Poir; *P. grevilleana* Wall; *P. cretica* L; *P. ryukyuensis* Tagawa;	Yoshihira et al. (1978), Murakami et al. (1974, 1975, 1976a), Kuroyanagi et al. (1974b), Satake et al. (1984), Kuraishi et al. (1985), Tanaka et al. (1981)
Pterosin C	I	*P. aqullinum* var. *Latiusculum*; *P. wallichiana* Agardh; *P. bella* Tagawa; *P. aqullinum* subsp *wightianum* (Wall) Shich; *P. ashimensis* Hieron; *H. incise* (Thunb) Smith; *P. multifida* Poir; *P. cretica* L; *P. ryukyuensis* Tagawa; *P. livida* Mett; *P. podophylla*	Yoshihira et al. (1978), Murakami et al. (1974, 1975, 1976a), Kuroyanagi et al. (1974a), Hikino et al. (1972), Kuraishi et al. (1985), Tanaka et al. (1981)
Pterosin D	I	*P. aqullinum* var. *Latiusculum*; *P. aqullinum subsp wightianum* (Wall) Shich; *H. punctata* (Thunb) Mett; *J. scammanae* Tryon; *M. speluncae* (L.) Moore; *M. strigosa* (Thunb) Presl; *D. wilfordii* (Moore) Christ	Yoshihira et al. (1978), Kuroyanagi et al. (1974a, 1979), Murakami et al. (1980), Tanaka et al. (1978, 1981)
Pterosin E	I	*P. aqullinum* var. *Latiusculum*	Yoshihira et al. (1978)
Pterosin F	I	*P. aqullinum* var. Latiusculum; *P. aqullinum subsp wightianum* (Wall) Shich; *P. tremula* Br; *P. dactylina* Hook; *P. multifida* Poir; *Pteris cretica* L	Yoshihira et al. (1978), Kuroyanagi et al. (1974a), Murakami et al. (1974, 1976a), Satake et al. (1984), Kuraishi et al. (1985)

Table 4 continued

Chemical name	Type	Source	References
Pterosin G	I	*P. aqullinum* var. *Latiusculum*; *P. podophylla* Swartz	Yoshihira et al. (1978), Tanaka et al. (1981)
Pterosin H	I	*P. aqullinum* var. *Latiusculum*; *P. aqullinum subsp wightianum* (Wall) Shich; *M. speluncae* (L.) Moore; *M. Trepeziformis* (Boxb.) Kuhn; *M. obtusiloba Hayata; M. substrigosa* Tagawa	Yoshihira et al. (1972, 1978), Kuroyanagi et al. (1974a, 1979), Murakami et al. (1980)
Pterosin I	I	*P. aqullinum* var. *Latiusculum*; *P. aqullinum* subsp *wightianum* (Wall) Shich; *M. speluncae* (L.) Moore; *M. obtusiloba* Hayata	Yoshihira et al. (1978), Kuroyanagi et al. (1974a, 1979), Murakami et al. (1980)
Pterosin J	I	*P. aqullinum* var. *Latiusculum*; *P. tremula* Br; *P. dactylina* Hook	Yoshihira et al. (1978), Murakami et al. (1976a, b), Tanaka et al. (1981)
Pterosin K	I	*P. aqullinum* var. *Latiusculum*;	Yoshihira et al. (1978)
Pterosin L	I	*P. aqullinum* var. *Latiusculum*; *H. punctata* (Thunb) Mett; *J. scammanae* Tryon; *M. speluncae* (L.) Moore; *M. strigosa* (Thunb) Presl; *D. wilfordii* (Moore) Christ	Yoshihira et al. (1978), Kuroyanagi et al. (1974a, 1979), Murakami et al. (1980), Tanaka et al. (1978, 1981)
Pterosin M	II	*O. japonicum*	Yoshihira et al. (1978)
Pterosin N	I	*P. aqullinum* var. *Latiusculum*; *P. ashimensis* Hieron; *H. incise* (Thunb) Smith	Yoshihira et al. (1978), Hikino et al. (1972), Murakami et al. (1976a, b), Kuroyanagi et al. (1974a)
Pterosin O	I	*P. aqullinum* var. *Latiusculum*; *P. dactylina* Hook; *P. multifida* Poir	Yoshihira et al. (1978), Satake et al. (1984), Murakami et al. (1974), Kuroyanagi et al. (1974a)
Pterosin P	II	*P. aquilinum*	Kuroyanagi et al. (1974a, 1979)
Pterosin Q	II	*P. kiuschiuensis* Hieron; *P. bella* Tagawa; *P. oshimensis* Hieron; *H. incise* (Thunb) Smith; *P. dactylina* Hook; *P. ryukyuensis* Tagawa	Fukuoka et al. 1978, Murakami et al. (1974, 1975, 1976a), Hikino et al. (1972), Satake et al. (1984), Kuroyanagi et al. (1974a)
Pterosin R	II	*C. barometz*	Murakami et al. (1980)
Pterosin S	II	*P. kiuschiuensis* Hieron; *J. scammanae* Tryon; *P. multifida* Poir; *P. cretica* L; *P. livida* Mett	Fukuoka et al. (1978), Kuroyanagi et al. (1974a), Murakami et al. (1974), Kuraishi et al. (1985), Tanaka et al. (1981)
Pterosin T	II	*P. kiuschiuensis* Hieron; *P. bella* Tagawa	Fukuoka et al. (1978), Murakami et al. (1975)
Pterosin U	II	*P. kiuschiuensis* Hieron;	Fukuoka et al. (1978)
Pterosin V	II	*D. seabra* (wall) Moore	Murakami et al. (1976b)
Pterosin W	II	*P. fauriei* Hieron; *P. inaqualis Baker* var. *Aequata (Miq)* Tagawa;	Tanaka et al. (1982), Hikino et al. (1971)
Pterosin X	II	*P. fauriei* Hieron; *P. inaqualis Baker* var. *Aequata (Miq)* Tagawa	Tanaka et al. (1982), Hikino et al. 1971
Pterosin Y	II	*C. japonica*	Murakami et al. (1980)
Pterosin Z	I	*P. aqullinum* var. *Latiusculum*; *P. aqullinum* subsp *wightianum* (Wall) Shich	Yoshihira et al. (1978), Kuroyanagi et al. (1974a)
(2R)-Norpterosin B	I	*P. semipinnata*	Zhan et al. (2010)
(2S, 3S)-Pterosin C	I	*P. semipinnata*	Zhan et al. (2010)

Table 4 continued

Chemical name	Type	Source	References
Norpterosin C	I	*P. semipinnata*	Zhan et al. ([2010](#))
(2S)-13-Hydroxypterosin A	I	*P. ensiformis*	Chen et al. ([2013a, b](#))
(2S,3S)-12-Hydroxypterosin Q	I	*P. ensiformis*	Chen et al. ([2013a, b](#))
1α,3β-Dihydroxylnorpterosin C	I	*P. dispar*	Gou et al. ([2011](#))
2R,3S-Acetylpterosin C	I	*P. multifida* Poir	Shu et al. ([2012](#))
(2S,3S)-Acetylpterosin C	I	*P. multifida* Poir	Shu et al. ([2012](#))
Acetylpterosin B	I	*P. multifida* Poir	Wang et al. ([2013](#))
Acetylpterosin C	I	*P. aqullinum* var. *Latiusculum*; *P. ashimensis* Hieron; *H. incise* (Thunb) Smith	Yoshihira et al. ([1978](#)), Hikino et al. ([1972](#)), Murakami et al. ([1976a, b](#))
Benzoylpterosin B	I	*P. aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Bimutipterosins A	II	*P. multifida* Poir	Liu et al. ([2011a, b, c](#))
Bimutipterosins B	II	*P. multifida* Poir	Liu et al. ([2011a, b, c](#))
Isocrotonylptersin B	I	*P. aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Palmitylpterosin A	I	*P. aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Palmitylpterosin B	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Palmitylpterosin C	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Phenylacetylpterosin C	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#)), Kuroyanagi et al. ([1974a](#))
Pterisemipol	III	*Pteris semipinnata L.*	Zhang and Xuan [2007](#)
Semipterosin A	I	*Pteris semipinnata* L.	Zhan et al. ([2010](#))
Pteroside A	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Pteroside B	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Pteroside C	I	*Pteridium aqullinum* var. Latiusculum; *Pteris bella* Tagawa; *Pteris grevilleana* Wall	Yoshihira et al. ([1978](#)), Murakami et al. ([1975, 1985](#))
Pteroside D	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Pteroside K	I	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#))
Pteroside M	II	*Pteridium aqullinum* var. *Latiusculum*; *Onychium japonicum*	Kuroyanagi et al. ([1974a](#))
Pteroside P	II	*Pteridium aqullinum* var. *Latiusculum*	Yoshihira et al. ([1978](#)), Kuroyanagi et al. ([1974a](#))
Pteroside Q	II	*Pteris bella* Tagawa; *Pteris ashimensis* Hieron; *Histiopteris incise* (Thunb) Smith	Murakami et al. ([1974, 1975, 1976a](#)), Hikino et al. ([1972](#))
Pteroside S	II	*Pteris fauriei* Hieron; *Pteris inaqualis* Baker var. *Aequata (Miq)* Tagawa; *Pteris tremula* Br	Tanaka et al. ([1982](#)), Hikino et al. ([1971](#)), Murakami et al. ([1976a, b](#))
Pteroside T	II	*Pteris fauriei* Hieron; *Pteris inaqualis* Baker var. *Aequata (Miq)* Tagawa	Tanaka et al. ([1982](#)), Hikino et al. [1971](#)
Pteroside U	II	*Pteris fauriei* Hieron; *Pteris inaqualis* Baker var. *Aequata (Miq)* Tagawa	Tanaka et al. ([1982](#)), Hikino et al. ([1971](#))
Pteroside W	II	*Pteris fauriei* Hieron; *Pteris inaqualis* Baker var. *Aequata (Miq)* Tagawa	Tanaka et al. ([1982](#)), Hikino et al. ([1971](#))
Pteroside X	II	*Pteris fauriei* Hieron; *Pteris inaqualis* Baker var. *Aequata (Miq)* Tagawa	Tanaka et al. ([1982](#)), Hikino et al. ([1971](#))

Table 4 continued

Chemical name	Type	Source	References
Pteroside Z	I	*Pteridium aqullinum* var. *Latiusculum*; *Microlepia speluncae* (L.) Moore; *Miaolepia Trepeziformis* (Boxb.) Kuhn; *Microlepia substrigosa* Tagawa	Yoshihira et al. (1972, 1978), Murakami et al. (1980)
Wallichoside	I	*Pteridium aqullinum* var. *Latiusculum*;	Yoshihira et al. (1978)
(2*R*)-12-*O*-β-D-Glucopyranosylnorpterosin B	I	*Pteris semipinnata*	Zhan et al. (2010)
2*R*,3*R*-13-Hydroxy-pterosin L 3-*O*-β-D-glucopyranoside	I	*Pteris multifida* Poir	Shu et al. (2012)
Multifidoside A	I	*Pteris multifida* Poir	Ge et al. (2008)
Multifidoside B	I	*Pteris multifida* Poir	Ge et al. (2008)
Multifidoside C	I	*Pteris multifida* Poir	Ge et al. (2008)
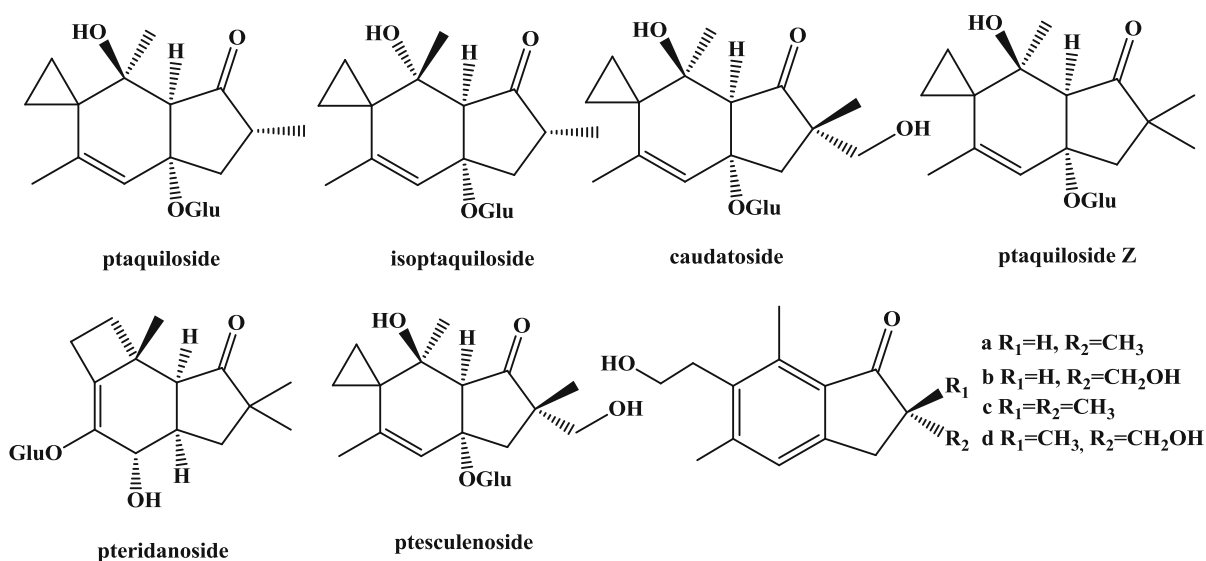
Fig. 9 Illudane glycosides and some pterosins found in Bracken (*Pteridium* spp.)

esculentum (Fletcher et al. 2010). Finally, two spiro-cyclic polyketide natural products, pteridic acids A and B, were isolated by Igarashi group from the fermentation broth of *Streptomyces hygroscopicus* TP-A0451 obtained from the stems of the bracken *P. aquilinum*, collected in Toyama, Japan (Igarashi et al. 2002).

Triterpenoids

Adiantum is another genus in the family Pteridaceae; it comprises 150–200 species (Brahmachari et al. 2003; Pan et al. 2011). Phytochemical analyses have revealed a variety of chemical compounds derived from various *Adiantum* species, primarily triterpenoid compounds

with a variety of structural motifs (Ibraheim et al. 2011; Reddy et al. 2001; Shiojima et al. 1993). In addition, *Adiantum* extracts reportedly contain flavonoids, phenyl-propanoids, and sterols (Pan et al. 2011). The list of *Adiantum*-derived phytochemicals continues to expand; the latest additions include 30-normethyl fernen-22-one and hopan-3β-ol, two new triterpenoids isolated from the ethanol extract of *A. capillus-veneris* L. fronds (Haider et al. 2013).

Sitosterols

β-Sitosterol has been isolated from *P. multifida*. To date, *P. multifida* is the only *Pteris* species shown to contain large amounts of quinic acid derivatives
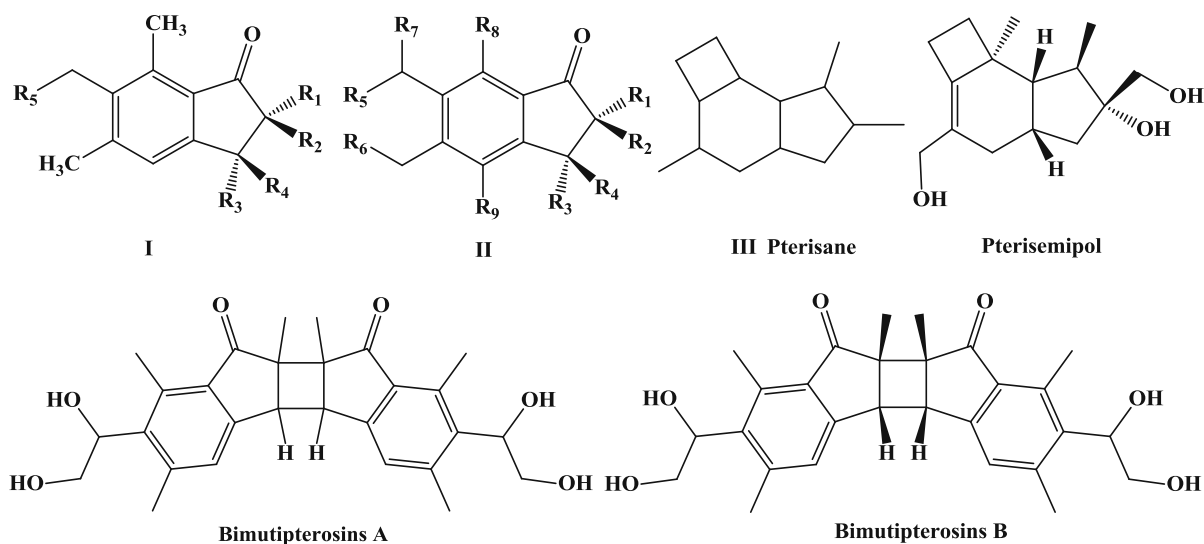
Fig. 10 Skeleton of 1H-indan-1-one sesquiterpenoids from Pteridaceae

Fig. 11 *Pteris semipinnata*. (Courtesy of Jianguo Cao)

(Harinantenaina et al. 2009). New benzoyl glucosides have been isolated from *P. ensiformis* Burm. (Chen et al. 2008a, b). In addition, an analysis of the "volatile oils" from *P. semipinnata* revealed 30 distinct compounds that accounted for 97.35% of their mass, including 3-methoxy-1,2-propanediol, 3-hexen-1-ol, 1-hexanol, 4-hydroxy-2-butanone, and 3-methyl pentanol (Gong et al. 2005).

Dryopteridaceae

The major constituents that have been identified with in *Dryopteris* plants are flavonoids, polyphenols, and terpenoids (Harborne 1966, 1988; Hiraoka 1978; Gao et al. 2003). Ten flavonol *O*-glycosides (based on kaempferol and quercetin), two flavanone *O*-glycosides (based on naringenin and eriodictyol), and three *C*-glycosylflavones (vitexin, vitexin 7-*O*-glucoside and orientin) have been identified with in 18 *Dryopteris* species by Hiraoka (1978). Harborne (1966) found 3-desoxyanthocyanins in *D. erythrosora*. In addition, kaempferol 7-*O*-(6″-succinyl-glucoside) was found in four *Dryopteris* species and an unusual flavan was isolated from *D. filix-mas* (L.) Schott. (Harborne 1988). Three new kaempferol glycosides, namely kaempferol 3-α-L-(2,4-di-*O*-acetyl) rhamnopyranoside-7-α-L-rhamnopyranoside, kaempferol 3-α-L-(3,4-di-*O*-acetyl) rhamnopyranoside-7-α-L-rhamnopyranoside, and kaempferol 3-α-L-(2,3-di-*O*-acetyl) rhamnopyranosside-7-α-L-rhamnopyranoside were isolated from the rhizome of *D. crassirhizoma* (Aspidiaceae) (Min et al. 2001). Ten flavonoids (seven flavonol glycosides based on kaempferol and quercetin including a new compound identified as kaempferol 3-*O*-(acetylrutinoside) and

three flavonoid aglycones (apigenin, kaempferol and quercetin) were found in *D. villarii* (Bell.) Woynar by Imperato ([2006](#)). More recently, the same group found five new flavonoids, quercetin 3-*O*-(X″- acetyl-X″-cinnamoyl-glucoside), quercetin 3-*O*-(glucosyl-rhamnoside), kaempferol 3-*O*-(caffeoylrhamnoside), apigenin 4′-*O*-(caffeoylglucoside) and 4′-*O*-(feruloyl-glucoside) in *D. villarii* (Imperato [2007a](#), [b](#)).

The Autumn Fern (*D. erythrosora*) (Fig. [12](#)) is native to China and Japan and is widely known as the Japanese Red Shield Fern because its youngest leaves have a coppery red, bronze, or pink coloration during spring, as shown in the third photo below (as shown in June). Chang et al. ([2005](#)) reported that the total flavonoid content of *D. erythrosora* leaves is around 0.89%, while Cao et al. ([2013a](#)) reported the total flavonoid content in whole *D. erythrosora* plants to be around 14.33%. The main flavonoids in *D. erythrosora* were identified as gliricidin 7-*O*-hexoside, apigenin 7-*O*-glucoside, quercetin 7-*O*-rutinoside, quercetin 7-*O*-galactoside, kaempferol 7-*O*-gentiobioside, kaempferol-3-*O*-rutinoside, myricetin 3-*O*-rhamnoside and quercitrin by means of HPLC–DAD–ESI–MS analysis.

Phytochemical investigations have revealed the presence of phloroglucinols (e.g. flavaspidic acids PB and AB), triterpenes (e.g. dryopteric acids A and B), flavonoids and other phenolic analogs in *D. crassirhizoma* (Chang et al. [2006](#); Gao et al. [2008b](#); Min et al. [2001](#); Noro et al. [1973](#); Shiojima et al. [1990](#)). Interestingly, such secondary metabolites were not detected by gas chromatography-mass spectrometry (GC–MS) analysis of a methanol extract of the fern (Ban et al. [2012](#)). Rather, GC–MS analysis of the fern

Fig. 12 *Dryopteris erythrosora* (Courtesy of Jianguo Cao)

extract revealed mainly primary metabolites, including monosaccharides and disaccharides (e.g. fructose, glucose and sucrose), fatty acids (e.g. palmitic, linoleic and oleic acids) and sugar alcohols (e.g. glycerol, xylitol and mannitol) (Ban et al. [2012](#)).

Thelypteridaceae

Macrothelypteris (H. Ito) Ching is a fern species of intermediate size. Protoapigenone, 5,7-dihydroxy-2-(1,2-isopropyldioxy-4-oxo-cyclohex-5-enyl)-chromen-4-one, and 5,7-dihydroxy-2-(1-hydroxy-2,6-dimethoxy-cyclohex-4-oxo)-chromen-4-one, were isolated from *M. viridifrons* (Tagawa) Ching (Wei et al. [2011a](#)). Protoapigenone was also isolated from *M. oligophlebia* (Wu et al. [2011a](#)).

Extracts of *Abacopteris penangiana* (Hook.) Ching contain many flavonoids, including novel flavan-4-ol derivatives such as abacopterins A-K, (2S,4R)-4,5,7-trihydroxy-4′-methoxy-6,8-dimethylflavan-5-*O*-β-D-6-acetylglucopyranoside-7-*O*-β-D-glucopyranoside, (2S, 4R)-5,7-dihydroxy-4,4′-dimethoxy-6,8-dimethylflavan-5-*O*-β-D-6-acetylglucopyranoside-7-*O*-β-D-glucopyrano-side, (2R,4S)-6,8-dimethyl-7-hydroxy-4′-methoxy-4,2″-oxidoflavan- 5-*O*-β-D-6″-*O*-acetyl-glucopyranoside and (2R,4S)-5,7-*O*-β-D-diglucopyranosyloxy-4′-methoxy-6, 8-dimethyl-4,2″-oxidoflavane (Zhao et al. [2006](#), [2007a](#), [b](#), [2010a](#), [b](#), [2011](#); Lei et al. [2011](#)). In addition, new flavanoids, (2S)-5,2′,5′-trihydroxy-7-methoxyfla-vanone and abacopterin L together with (7′Z)-3-*O*-(3,4-dihydroxyphenylethenyl)-caffeic acid were identified from the rhizomes of *A. penangiana* (Zhao et al. [2011](#); Wei et al. [2011a](#), [b](#); Fu et al. [2013](#)).

M. torresiana (Gaud.) Ching is another fern whose phytochemistry and pharmacology have been studied in some detail. This plant grows in southern China and is rich in flavonoids including some that were previously unknown such as protoapigenone, 5,6-dihydroxy-6-methoxyprotoapigenone, protoapigenin, flavotorresin, multiflorin C, (2S)-5,7,2′,5′- tetrahydroxyflavanone 2′-*O*-β-D-6″-*O*-acetylglucopyrano-side, (2S)-5,7,2′,5′- tetrahydroxyflavanone 2′-*O*-β-D-glucopyranoside, 5,7-dihydroxy-2-(1,2-isopropyl-dioxy- 4-oxocyclohex-5-enyl)-chromen-4-one, 5,7-dihydroxy-2-(1-hydroxy-2,6-dimethoxy-4- oxo-cy-clohex)-chromen-4-one, 2-(*cis*-1,2-dihydroxy-4-oxo-cyclohex-5-enyl)-5,7- dihydroxy-chromone, and 2-(*trans*-1,4-dihydroxy-cyclohexyl)-5,7-dihydroxy-chro-

mone, along with a sesquiterpene, a steroid and two phenols (Lin et al. 2005a, 2007; Fu et al. 2009; Tang et al. 2009, 2010; Lei et al. 2011).

Polypodiaceae

Fernblock® is a polyphenol-enriched hydrophilic extract of the aerial part of *Polypodium leucotomos* (Choudhry et al. 2014) that is widely used in the formulation of topical gels, creams, sprays, and makeup powder as well as oral dietary supplement capsules marketed for their photoprotective effects. However, the phytochemical composition of *P. leucotomos* and Fernblock® has not been fully characterised. LC–MS analysis revealed the presence of 3,4-dihydroxybenzoic acid, 4-hydroxybenzoic acid, vanillic acid, caffeic acid, *p*-coumaric acid, 4-hydroxycinnamoyl-quinic acid, ferulic acid, and five chlorogenic acid isomers in Fernblock® (García et al. 2006). Studies on the transepithelial transport of caffeic, *p*-coumaric, ferulic, vanillic and chlorogenic acids across a Caco-2 cell monolayer suggested that such phenolics may be fully absorbed in humans following oral administration (Gombau et al. 2006). This implies that the bioactivity of Fernblock® when taken orally may be attributable at least in part to such phenolics. Oral administration of *P. leucotomos* extract apparently has no mutagenic or other toxic side effects, enabling repeated use (Choudhry et al. 2014; Gonzalez 2009).

The significance of *P. leucotomos* extract as a photoprotective nutraceutical as well as the molecular and cellular mechanisms underlying its effects have been discussed in recent reviews (Gonzalez 2009; Gonzalez et al. 2011; Parrado et al. 2014).

The bioactive constituents isolated and identified from *P. hastata* include flavonol glycosides (e.g. kaempferol 3,7-di-*O*-α-L-rhamnopyranoside and kaempferol 3-*O*-α-L- arabinofuranosyl 7-*O*-α-L-rhamnopyranoside), phenolic acids (e.g. *trans*-caffeic acid and protocatechuic acid), and their derivatives (e.g. *trans*-caffeic acid 3-*O*-D-glucopyranoside) (Duan et al. 2012a, b). Protocatechuic acid and myricetin were detected in both leaf and rhizome aqueous extracts of *P. triloba*. Sinapic acid was found in the leaf, but not in the rhizome extract (Chai et al. 2013b). Conversely, *p*-hydroxybenzoic and gallic acids were detected in the rhizome were undetectable in the leaf extract (Chai et al. 2013b).

Selaginellaceae

Selaginella is a genus including more than 700 species that has a wide global distribution (Weng and Noel 2013). It is frequently regarded as one of the oldest lineages of surviving vascular plants (Banks 2009; Weng and Noel 2013) and new *Selaginella* species are continually being identified and reported, including *S. wangpeishanii* (Zhang et al. 2014), *S. longistrobilina* (Zhang et al. 2012a, b, c, d), and *S. amasrae* (Šimunek and Thomas 2012). Studies on different *Selaginella* species have resulted in the identification of over 100 natural products, including flavonoids, lignans, selaginellins, phenolics, alkaloids and terpenoids (Weng and Noel 2013). Weng and Noel (2013) have summarized the chemodiversity of *Selaginella*, which continues to expand as more powerful and advanced analytical techniques are applied.

Biflavonoids

Selaginella-derived biflavonoids are particularly noteworthy because they exhibit a range of interesting pharmacological properties. They are typically dimeric, being linked by a C–O–C or C–C bond. Amentoflavone, hinokiflavone, heveaflavone, neocryptomerin, pulvinatabiflavone and 7″-*O*-methylamentoflavone were isolated from *S. tamariscina* (Cheng et al. 2008; Zhang et al. 2012a, b, c, d). New biflavonoids continue to be reported, a recent example being 2,3-dihydrorobustaflavone 7,7″-dimethyl ether, isolated from *S. doederleinii* Hieron (Han et al. 2013). In addition, an unusual macrocyclic biflavone with an unprecedented methylene bridge, selacyclicbiflavone A, was recently isolated from *S. uncinata* (Zou et al. 2016a, b).

Involvenflavones

Six new flavonoids, involvenflavones A–F (Fig. 13), were isolated from *S. involven*. All six are apigenin derivatives with 3′-aryl substituents; this is the first time apigenin derivatives with this substitution pattern have been isolated from a natural source (Long et al. 2015). Two other new flavonoids, uncinataflavones A and B were isolated from *S. uncinata* (Desv.) Spring. Both are apigenin derivatives with 6-aryl substituents (Zou et al. 2016a, b).
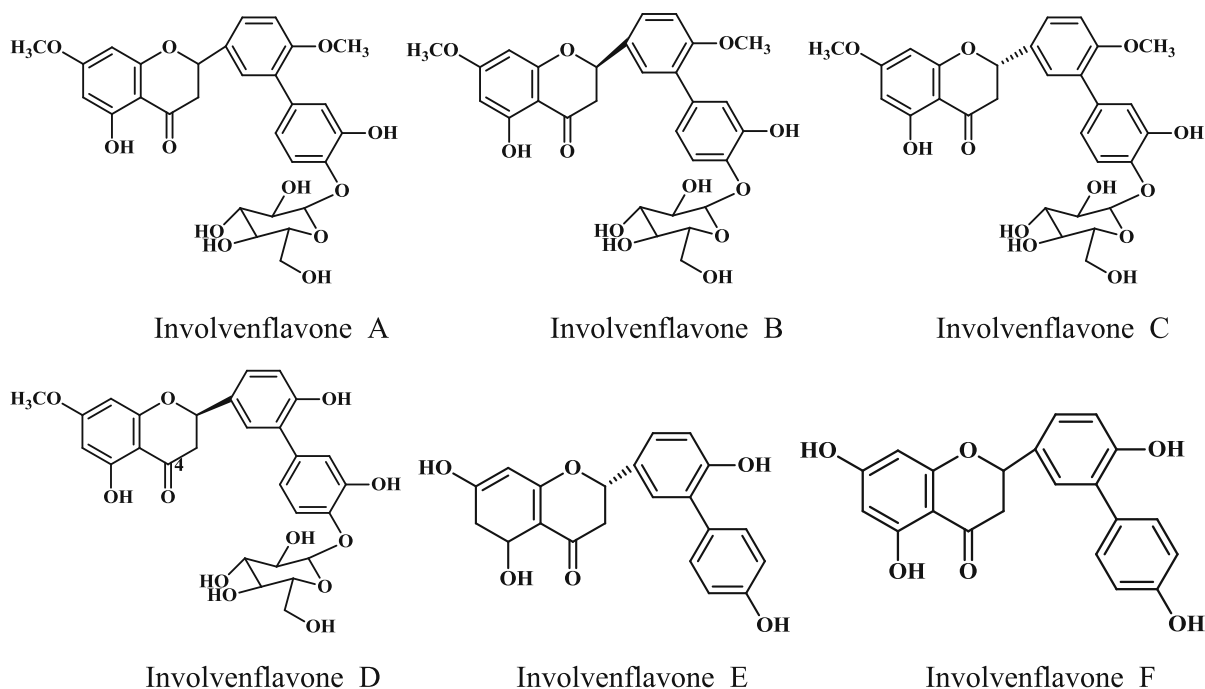
Fig. 13 Involvenflavones from *S. involven* (Long et al. 2015)

Alkaloids

Alkaloids were isolated from *S. tamariscina* (Beauv.) Spring and *S. moellendorfii* Hieron (Zheng et al. 2004; Wang et al. 2009a, b; Zou et al. 2013). In addition, eight new pyrrolidinoindoline alkaloids (selaginellic acid, 5-hydroxyselaginellic acid, 5-hydroxy-N_8,N_8-dimethylpseudophrynaminol, *N*-selaginelloyl-L-phenylalanine, *N*-(5-hydroxyselaginelloyl)-L-phenylalanine, neoselaginellic acid, *N*-neoselaginelloyl-L-phenylalanine, and *N*-(5-hydroxyneoselaginelloyl)-L-phenylalanine) were isolated from whole plants of *S. moellendorfii* Hieron (Wang et al. 2009a, b). These alkaloids have a 3-carboxybut-2-enyl group at C-3a and two methyl groups at N-8. More recently, another new pyrrole alkaloid was isolated from this plant (Zou et al. 2013).
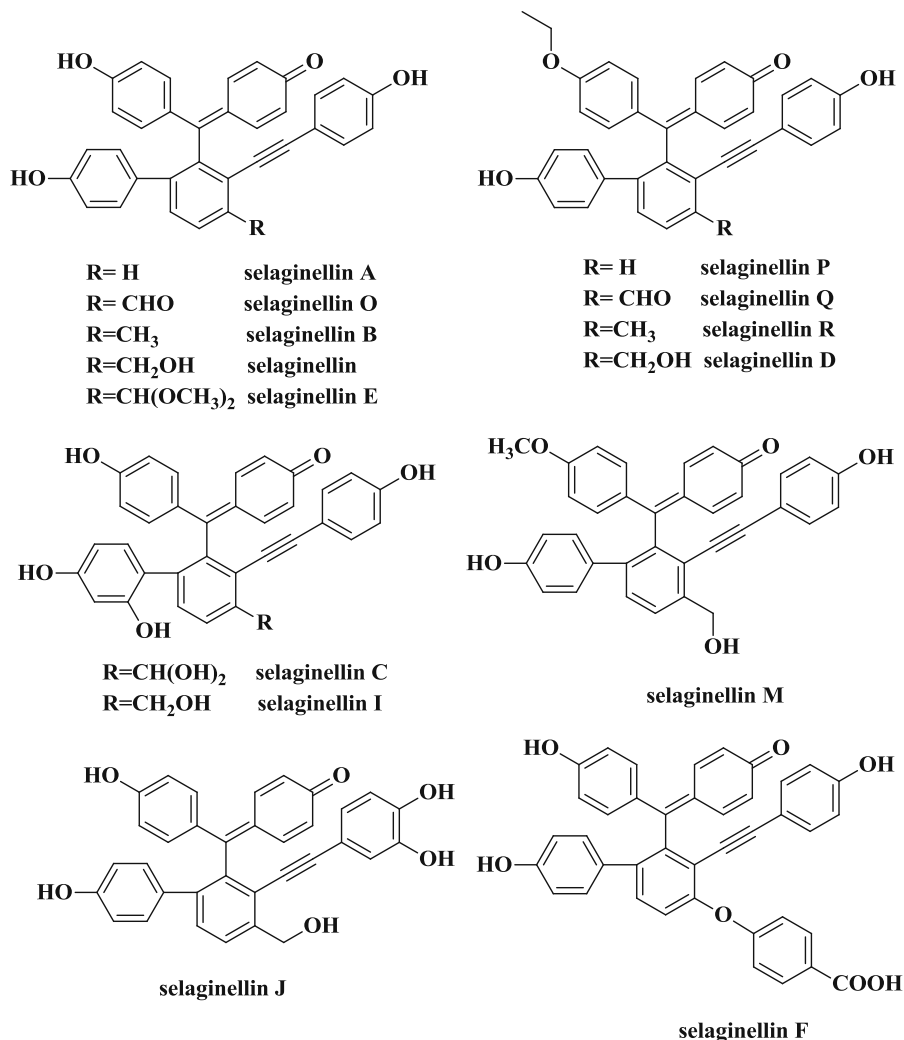
Selaginellins

The selaginellins are a group of phenols with a unique alkynylphenol carbon skeleton that have only been found in the genus *Selaginella* to date. The first member of this compound class, selaginellin, was isolated from *S. sinensis* as a racemic mixture. It features a *p*-quinone methide unit and an alkynylphenol moiety. Since 2007, several related compounds, selaginellins A–S (Fig. 14) have been isolated from a range of *Selaginella* species. Thus, selaginellin along with selaginellins A–C and I–Q were found in *S. tamariscina*, while selaginellins C-H, M, and P-S were found in *S. pulvinata*. Most recently, selaginellin S was isolated from *S. moellendorffii* (Zhu et al. 2016). A novel isoquinoline-type selaginellin, selaginisoquinoline A, was isolated from *S. pulvinata* (Cao et al. 2015a, b), it was isolated as a racemate because of quinone methide-phenol tautomerism. Selariscinins A–D (Fig. 15) from *S. tamariscina* are also selaginellin derivatives via tautomerism (Nguyen et al. 2015a, b).

Others

A new sesquilignan was isolated from *S. sinensis* (Desv.) Spring (Wang et al. 2007). Other recently identified natural products from the Selaginellaceae

Fig. 14 Selaginellins A–S from several *Selaginella* species

R= H   selaginellin A
R= CHO   selaginellin O
R=CH₃   selaginellin B
R=CH₂OH   selaginellin
R=CH(OCH₃)₂   selaginellin E

R= H   selaginellin P
R= CHO   selaginellin Q
R=CH₃   selaginellin R
R=CH₂OH   selaginellin D

R=CH(OH)₂   selaginellin C
R=CH₂OH   selaginellin I

selaginellin M

selaginellin J

selaginellin F

include four new phenols with unprecedented 9H-fluorene skeletons (selaginpulvilins A–D, isolated from *S. pulvinata*) (Liu et al. 2013b) and a new sesquilignan glycoside, sinensioside A, isolated from *S. sinensis* (Chen et al. 2014a, b). Additionally, the first abietane diterpenoid from the genus *Selaginella* (isolated from *S. involven* Spring) was reported in 2014 (Long et al. 2014). Two novel C-28 spirostene monosides, chrysocauloside A (1β,3β-dihydroxy-20S,22R-spirost-5-ene-1-yl-β-D-glucopyranoside) and chrysocauloside B (1β,3β-dihydroxy-20S,22R-spirost-5-ene-1-yl-β-D-galactopyranoside), were identified from *S. ehrysocaulos*; both compounds are *O*-glycosylated at C-1 and bear a methyl group at C-24 and C-25 (Kunert et al. 2015).

Gleicheniaceae

Terpenoids

Terpenoids including labdane-type and clerodane-type diterpenoids, diterpenoid glycosides, and triterpenoids are the major phytochemicals produced by the family Gleicheniaceae (Li et al. 2006, 2008; Hu et al. 2011; Socolsky et al. 2007). Fifteen new diterpenoid glycosides (Fig. 16) were isolated from an Argentine collection of the bitter fern *G. quadripartita* (Socolsky et al. 2007). *Dicranopteris dichotoma* Bernb is a very common fern belonging to the genus *Dicranopteris* that grows in most provinces of northern China and is sometimes known

Fig. 15 Selariscinins A-D and selaginisoquinoline A

Selariscinin A

Selariscinin B

Selariscinin C

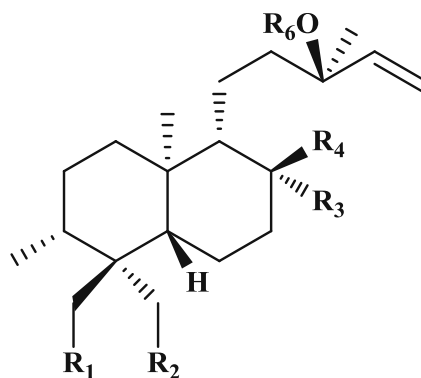Selariscinin D

selaginisoquinoline A
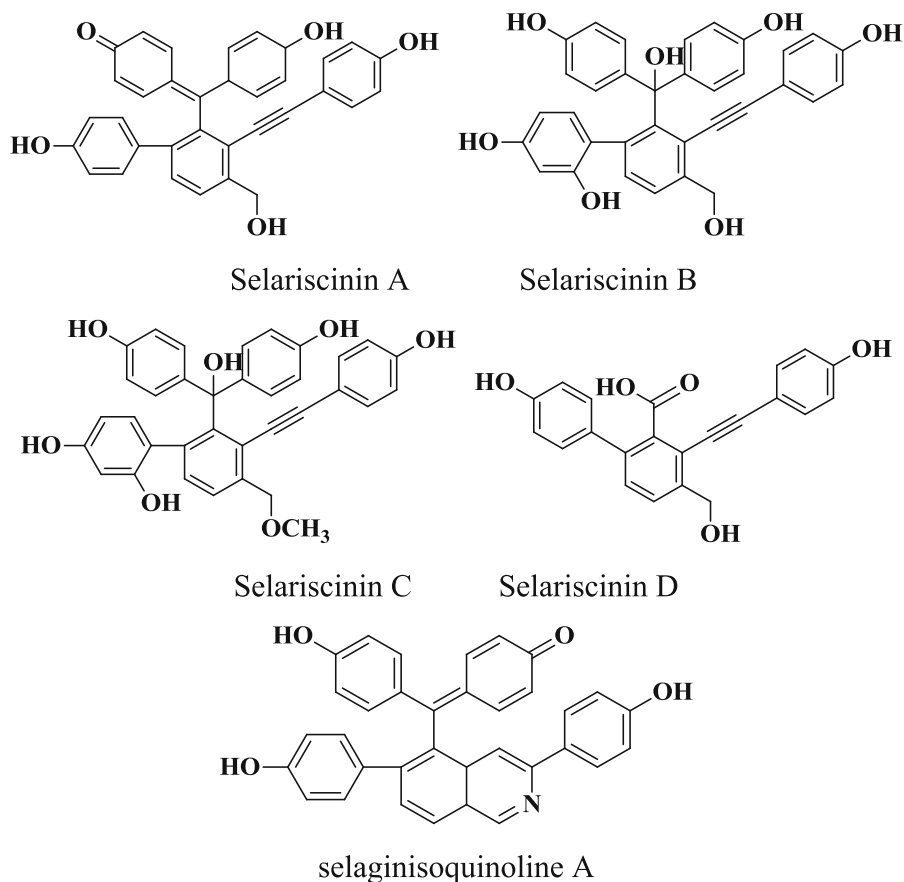
as *D. pedata*. Phytochemical studies on its fronds led to the identification of eleven clerodane-type diterpenes including nine new ones and two unprecedented phenolic derivatives (Aoki et al. 1997; Li et al. 2006, 2007). In addition, there were four phenolic glycosides, two of which had previously been found by Japanese phytochemists (Kuraishi et al. 1983). Another fern from the family Gleicheniaceae is *Hicriopteris glauca* (Thunb.) Ching, which belongs to the genus *Diplopterygium* and is distributed across southern China. Recent phytochemical studies have shown that it produces *ent*-kaurane diterpenoids as well as flavonoids and phytoecdysones (Fang et al. 2013; Takemoto et al. 1973; Zhang et al. 2009). One of its diterpenoids, *ent*-2-β-hydroxyl-16-ene-kauran-19-oic acid, was previously unknown.

Five ecdysteroids, (22R,24R,25S,26S)-2β,3β,14α,20R-tetrahydroxy-26α-methoxy-6-oxo-stigmast-7-ene-22,26-lactone (1), (22R,24R,25S)-2β,3β,14α,20R,26S-pentahydroxy-6-oxo-stigmast-7-ene-22,26-lactone (2), (22R,25S)-2β,3β,14α,20R,24S-pentahydroxy-6,26-di-oxo-stigmast-7-ene-22,26-lactone (3), (22R,25S)-2β,3β,14α,20R,24S,26S-hexahydroxy-6-oxo-stigmast-7-ene-22,26-lactone (4), and capitasterone (5) (Fig. 17) (Hu et al. 2014), as well as two new diterpenoids, (3#,13S)-3-*O*-[6-*O*-acetyl-beta-D-glucopyranosyl]-13-*O*-alpha-L-rhamnopyranosyl-labda-8(17),14-diene and (4R,13S)-18-*O*-beta-D-glucopyranosyllabda-8(17),14-dien-13-ol (Hu et al. 2011), were detected in a 95% EtOH extract of *D. rufopilosum* from Yunnan province in China.

Flavonoids

Favonol glycosides are also present in the family Gleicheniaceae. *G. hirta* Bl., *G. microphylla* R. Br., *G. longissima* Bl. and *G. blotiana* C. Chr. produce kaempferol and quercetin, while genkwanin and luteolin are present in *G. blotiana* C. Chr. and *G.*

	R$_1$	R$_2$		R$_3$	R$_4$	R$_5$	R$_6$
1	H	H		OH	CH$_3$	OH	β-D-quinovopyranosyl-(1→2)- α-L-rhamnopyranosyl
2	H	H		OH	CH$_3$	H	β-D-glucopyranosyl
3	H	OH		OH	CH$_3$	H	β-D-glucopyranosyl
4	H	OH		CH$_3$	OH	H	β-D-glucopyranosyl
5	OH	H		OH	CH$_3$	H	β-D-glucopyranosyl
6	OH	H		CH$_3$	OH	H	β-D-glucopyranosyl
7	H	OH		OH	CH$_3$	H	α-L-rhamnopyranosyl
8	H	OH		OH	CH$_3$	H	β-D-quinovopyranosyl-(1→2)- α-L-rhamnopyranosyl
9	H	O-β-D-glucopyranosyl		CH$_3$	OH	H	H
10	H	O-α-L-rhamnopyranosyl		OH	CH$_3$	H	H
11	H	O-α-L-rhamnopyranosyl		OH	CH$_3$	H	β-D-glucopyranosyl
12	H	O-α-L-rhamnopyranosyl		OH	CH$_3$	H	α-L-rhamnopyranosyl
13	H	O-α-L-rhamnopyranosyl		OH	CH$_3$	H	β-D-quinovopyranosyl-(1→2)- α-L-rhamnopyranosyl
14	H	O-α-L-rhamnopyranosyl		OH	CH$_3$	H	β-D-quinovopyranosyl-(1→2)- 3'-O-acetyl-α-L-rhamnopyranosyl
15	H	OAc		OH	CH$_3$	H	2'',3'',4''-tri-O-acetyl-β-D-quinovopyranosyl-(1→2)- 3'-O-acetyl-α-L-rhamnopyranosyl

Fig. 16 Diterpenoid glycosides from *G. quadripartita* (Socolsky et al. 2007)

hirta Bl, and acacetin in *G. microphylla* R. Br. (Yusuf et al. 2003). The flavonols in *Gleichenia* leaves were found to be present as 3-glucosides, 3-rhamnosides, 3-rutinosides, 3,4'-diglucosides, 7-glucosides and 7-arabinoside. Quercetin-3-glucoside was identified as a major flavonoid component of all species studied (Yusuf et al. 2003).

Equisetaceae

The Equisetaceae are bushy perennial herbs native to the northern hemisphere that are commonly known as horsetails. They are represented by a single extant genus, *Equisetum*, which comprises around 30 species (Fig. 18). The content of inorganic substances
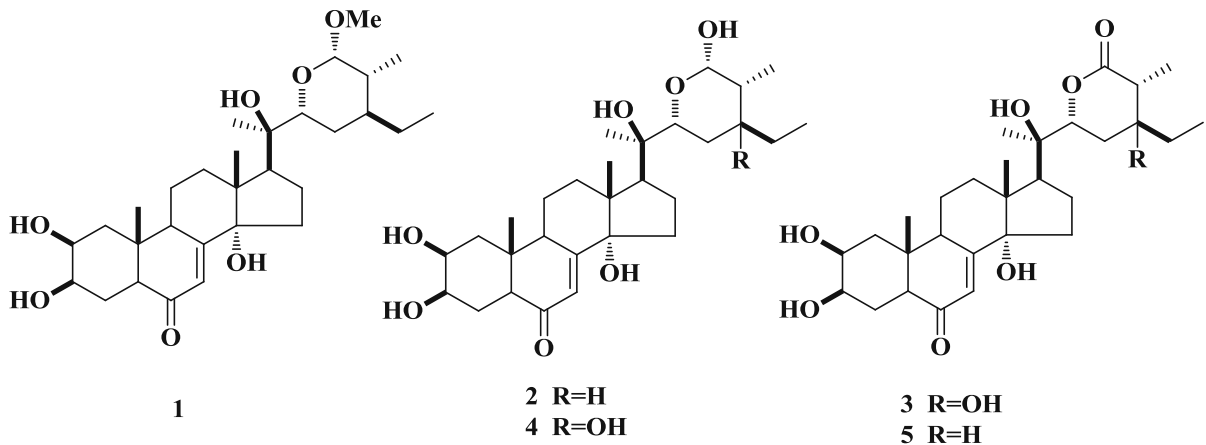
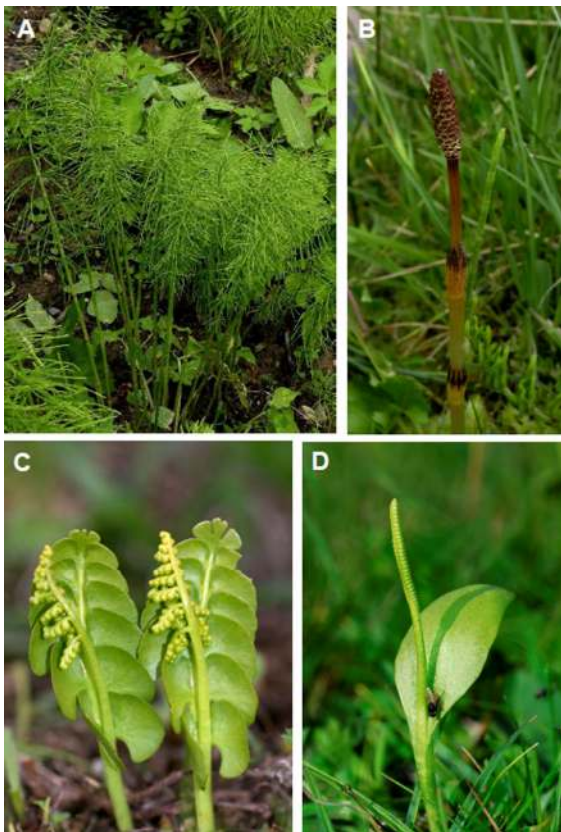**Fig. 17** Ecdysteroids from *D. rufopilosum* of China (Hu et al. 2014)

Fig. 18 Representative plants of Equisetaceae (**a**, **b**) and Ophioglossaceae (**c**, **d**). A. *E. arvense* L., sterile stems. B. *E. arvense*, fertile stem. C. *Botrychium lunaria* (L.) Sw. D. *Ophioglossum vulgatum* L. (Courtesy of Remo Bernardello)

(mainly silicic acid and potassium salts) in *E. arvense* is over 10%. *E. arvense* is also rich in sterols (β-sitosterol, campesterol, and isofucosterol) (D'Agostino et al. 1984), ascorbic acid, polienic acids, rare dicarboxylic acids (including equisetolic acid), flavonoids (Wichtl 1994; Veit et al. 1990; Oh et al. 2004), styrylpyrones (Veit et al. 1995a), and phenolic acids (cinnamic acids, caffeic acid, di-E-caffeoyl-*meso*-tartaric acid, and 5-*O*-caffeoylshikimic acids) (Veit et al. 1995b; Mimica-Dukic et al. 2008). The methanol extract of *E. arvense* L. was found to contain two phenolic petrosins, onitin and onitin 9-*O*-glucoside, along with four flavonoids, apigenin, luteolin, kaempferol 3-*O*-glucoside, and quercetin 3-*O*-glucoside (Oh et al. 2004).

A series of alkaloids have been isolated from *E. palustre*, namely palustrine, N^5-formylpalustrine, N^5-acetylpalustrine, palustridiene, and N^5-formyl-palustridiene, to which the toxicity of the plant is ascribed (Cramer et al. 2015).

Helminthostachyaceae

It was previously reported that four flavonoids, ugonins A–D, were isolated from the rhizomes of *Helminthostachys zeylanica* (Murakami et al. 1973a, b). Eight flavonoids, ugonins E–L, were isolated from the rhizomes of *H. zeylanica* (Huang et al. 2003).
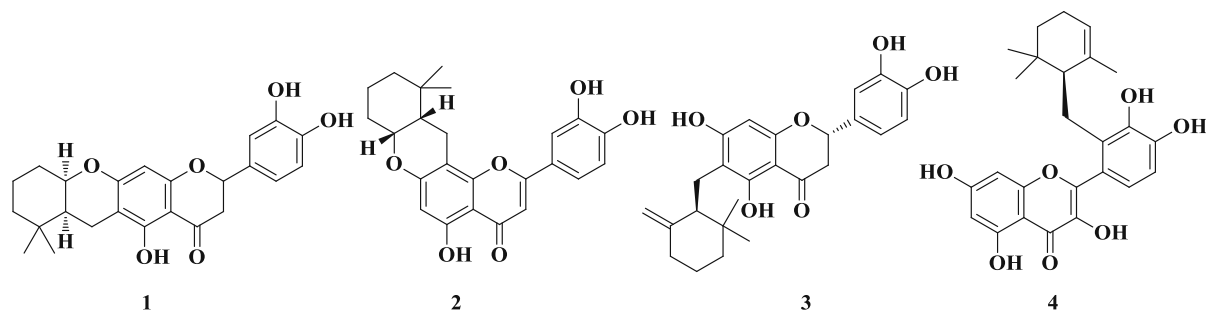
Fig. 19 Prenylated flavonoids from *Helminthostachys zeylanica* (Huang et al. 2010a, b, c)

Three new cyclized geranyl stilbenes, ugonstilbenes A–C were isolated from the dried rhizomes of *H. zeylanica* (Chen et al. 2003). Four new prenylated flavonoids, 4″a,5″,6″,7″,8″,8″a-hexahydro-5, 3′, 4′-trihydroxy-5″, 5″, 8″a-trimethyl-4H-chromeno[2″, 3″:7, 6]flavone (1), 4″a,5″,6″,7″,8″,8″a-hexahydro-5,3′,4′,-trihydroxy-5″,5″,8″a-trimethyl-4H-chromeno[2″,3″:7,8]flavone (2), 2-(3,4-dihydroxyphenyl) 6-((2,2-dimethyl-6-methylenecyclohexyl)methyl)-5, 7-dihydroxy-chroman-4-one (3), and 2-(3,4-dihydroxy-2-[(2,6,6-trimethylcyclohex-2-enyl)methyl] phenyl)-3,5,7-trihydroxy-4H-chromen-4-one (4) (Fig. 19), were isolated from *H. zeylanica* (Huang et al. 2010a, b, c).

Recently, two novel quercetin glucosides, namely 4′-O-β-D-glucopyranosyl-quercetin 3-O-β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranoside and 4′-O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranosyl-quercetin 3-O-β-D-glucopyranosyl-(1 → 4)-β-D-glucopyranoside were isolated from *H. zeylanica* roots (Yamauchi et al. 2013).

Ophiolossaceae

Botrychium ternatum is a member of the Ophiolossaceae family that is distributed across China, Korea, and Japan. It is used in folk medicine to treat dizziness, headache, cough, and fevers. Twenty-six kaempferol glycosides, and four quercetin glycosides were identified from its methanol extracts (Warashina et al. 2012), including the new kaempferol glycosides ternatumosides I-XVII (Fig. 20).

Ophioglossaceae

To date, only a few flavonoids have been identified from *Ophioglossum* species. However, these species are rich in homoflavonoids. Seven new homoflavonoid glucosides, pedunculosumosides A–G, were isolated from ethanolic extracts of whole *O. pedunculosum* plants (Wan et al. 2012). Six homoflavonoids, ophioglonin, ophioglonin 7-O-β-D-glucopyranoside, ophioglonol, ophioglonol prenyl ether, ophioglonol 4′-O-β-D-glucopyranoside, and isoophioglonin 7-O-β-D-glucopyranoside, quercetin, luteolin, kaempferol, 3,5,7,3′,4′-pentahydroxy-8-prenylflavone, and quercetin 3-O-methyl ether, were isolated from *O. petiolatum* (Lin et al. 2005a, b). Homoflavonoids were also found in *O. vulgatum* and *O. thermale* (Wan et al. 2013). These compounds can be divided to two groups: type I homoflavonoids, which have an additional carbon atom attached to the C-3 position of ring C, and undergo competing losses of H_2O and CH_2O from their aglycone ions; and type II homoflavonoids, which bear an additional carbon atom at the C-2′ position of ring B, forming a new ring (Wan et al. 2013; Lin et al. 2005a, b; Wan et al. 2012).

In addition, several flavonoids were isolated from the aerial parts of the fern *O. vulgatum* L., including 3-O-methylquercetin and its glucosides, 5′-isoprenyl-3-O-methylquercetin 4′,7-di-β-D-glucopyranoside, 3-O-methylquercetin 4′-β-D-glucopyranoside 7-[O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside], and 3-O-methylquercetin 7-[O-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside], were isolated from *O. pedunculosum* (Wan et al. 2012). 3-Methylquercetin, quercetin 3-O-[(6-caffeoyl)-β-glucopyranosyl(1 → 3)α-rhamnopyranoside]-7-O-α-rhamnopyranoside and kaempferol 3-O-[(6-caffeoyl)-β-glucopyranosyl(1 → 3)α-rhamnopyranoside]-7-O-α-rhamnopyranoside were isolated from *O. pedunculosum* (Clericuzio et al. 2012).

Different prenylated flavonoids have been isolated from *Helminthostachys zeylanica* (L.) Hook.,
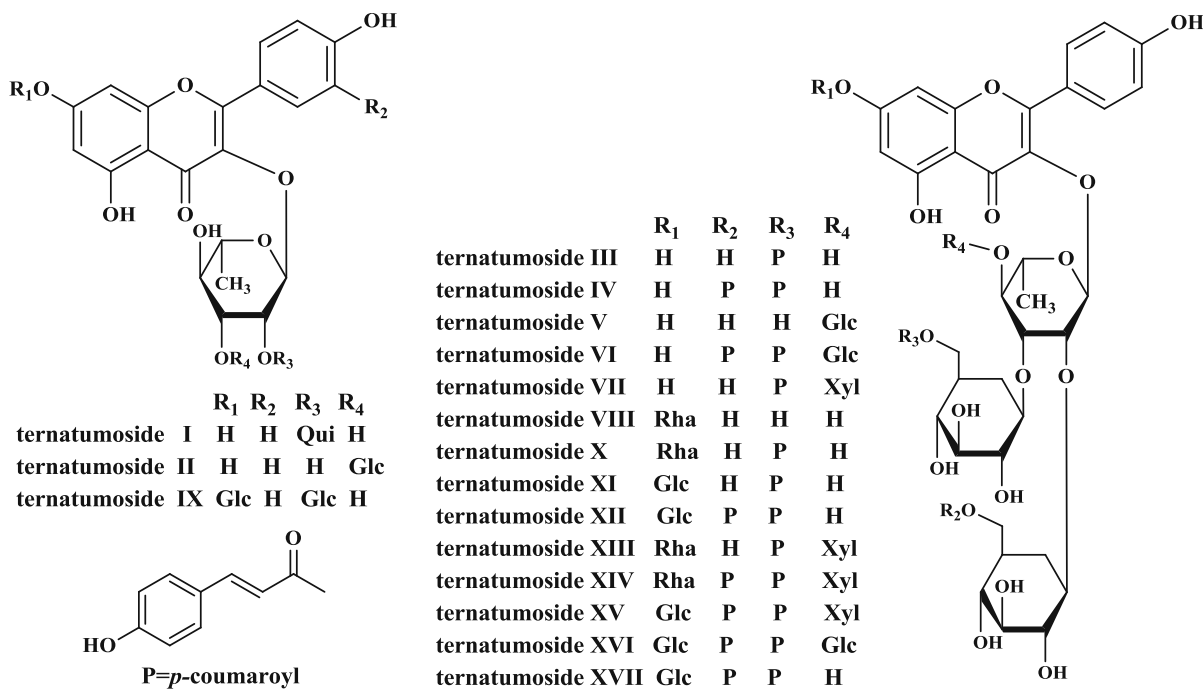
Fig. 20 Ternatumosides I-XVII from *B. ternanum* (Warashina et al. 2012)

including the new molecules neougonins A and B, and the previously-described ugonin D, 2-(3,4-dihydroxyphenyl)-6-((2,2-dimethyl-6-methylene cyclohexyl) methyl)-5,7-dihydroxy-chroman-4-one, ugonins E, J, L, and S, 4″a,5″,6″,7″,8″,8″a-hexahydro-5,3′,4′-trihydroxy-5″,5″,8″a-trimethyl-4H-chromeno [2″,3″:7,6]flavone, 4″a,5″,6″,7″,8″,8″a-hexahydro-5, 3′,4′-trihydroxy-5″,5″,8″atrimethyl-4H-chromeno[2″, 3″:7,8] flavone, and ugonin N (Su et al. 2016). Besides flavonoids, the new peroxy fatty acids thermalic acids A, and B, have been isolated from *O. thermal* (Dong et al. 2016).

Lygodiaceae

Lygodium venustum (Fig. 21), a cosmopolitan fern belonging to the family Lygodiaceae is widely distributed across Latin America, from Mexico to Paraguay and islands of the Caribbean, where it grows at altitudes of up to 1100 m above sea level (Costa and Pietrobon 2007; Mehltreter 2006; Prado 2005a). *L. venustum* is rich in flavonoids, including kaempferol 3-*O*-B-D-glucopyranoside, acacetin, acacetin 7-*O*-β-D-glucopyranoside, acacetin 7-*O*-rutinoside, diosmetin 7-*O*-rutinoside, 7-*O*-(6″-*O*-α-L-rhamnopyranosy1)-β-sophoroside, and kaempferol 3-*O*-rutinoside (Wang

et al. 2011a, b, c). *L. japonicum* (Fig. 22) is another fern species from the same family that is used in traditional Chinese medicine (Chinese name 海金沙). Its main bioactive constituents are phenolic and flavonoid glycosides. Phenylpropanoid glucosides including 4-*O*-caffeoyl-D-glucopyranose, 3-*O*-caffeoyl-D-glucopyranose, 2-*O*-caffeoyl-D-glucopyranose, 6-*O*-caffeoyl-D-glucopyranose, 4-*O*-*p*-coumaroyl-D-glucopyranose, 6-*O*-*p*-coumaroyl-D-glucopyranose were isolated from the roots of *L. japonicum* (Duan et al. 2012a, b). 3,4-Dihydroxybenzoic acid 4-*O*-(4′-*O*-methyl)-β-D-glucopyranoside (Ye et al. 2007) and a new ecdysteroside, 2,3,14,20R,22R-pentahydroxy-24R-methyl-5-cholest-7-en-6-one-3-*O*-D-glucopyranoside were isolated from the roots of *L. japonicum* (Thunb.) (Fig. 23) (Zhu et al. 2009). 1,4-Naphthoquinone (Chen et al. 2010) and two new tetracyclic triterpenoids, lygodipenoids A and B, with a new 9,19: 24,32-dicyclopropane skeleton, were also isolated from whole plants of *L. japonicum* (Han et al. 2012).

Lindsaeaceae

Stenoloma chusanum (L.) Ching (Fig. 24) belongs to the family Lindsaeaceae and is widely distributed in southern China. It has a very high total flavonoid

Fig. 21 Aerial parts of the lianescent fern *Lygodium venustum*. (Courtesy of Flaviana Morais-Braga)

content (up to 30% w/w) and shows strong antioxidant and antibacterial activities (Xia et al. 2014). The total flavonoid content of *S. chusanum* exhibits clear seasonal dynamics, peaking at 24.63 ± 1.34% in February (Wu et al. 2016). Two new phenolic compounds, 4-*O*-β-D-(6-*O*-gentisoylglucopyranosyl) vanillic acid, 2-*O*-β-D-(6-*O*-gentisoylglucopyranosyl) gentisic acid, vanillic acid, syringic acid, and gentisic

acid, were isolated from whole *S. chusanum* plants (Ren et al. 2009).

Athyriaceae and Aspleniaceae

Umikalsom et al. (1994) compared the flavonoid contents of 18 Athyriaceae species and 15 Aspleniaceae of Malaysian origin. Flavonol 3-*O*-glycosides (quercetin and kaempferol) were the main flavonoids in the Athyriaceae, with some *Diplazium* and *Deparia* species also having appreciable contents of flavone *C*-glycosides (apigenin *C*-glycosides). The flavonoid profiles of the Aspleniaceae are much more complex. Kaempferol 3,7-glycosides predominate, but kaempferol 3,4′-diglycosides and 3,7,4′-triglycosides were also found. *O*-Methylated kaempferol glycosides were found in *A. marinum*. Luteolin and apigenin *C*-glycosides, sometimes with *O*-glycosylated *C*-sugars were detected in Aspleniaceae species (Umikalsom et al. 1994).

The profiles and bioactivities of flavonoids extracted from *Dryoathyrium boryanum* (Willd.) Ching were investigated by Cao et al. (2013b). Based on HPLC–DAD–ESI–MS analyses, the main flavonoids in *D. boryanum* were tentatively identified as 3-hydroxyphloretin 6′-*O*-hexoside, quercetin-7-hexoside, apigenin7-*O*-glucoside, luteolin 7-*O*-glucoside,

Fig. 22 *Lygodium japonicum* (Thunb.) Sw (Courtesy of Jianguo Cao)

Fig. 23 *Lycopodium japonicum* Thunb (Courtesy of Jianguo Cao)

Fig. 24 *Stenoloma chusanum* Ching (Courtesy of Jianguo Cao)

apigenin 7-*O*-galactoside, acacetin 7-*O*-(α-D-apio-furanosyl)(1 → 6)-β-D-glucoside, 3-hydroxy phloretin 6-*O*-hexoside, and luteolin 6-*C*-glucoside (Cao et al. 2013b).

Davalliaceae

Some species of the genus *Davallia*, such as *Davallia divaricata*, *D. mariesii*, *D. solida*, *D. formosana*, *Drynaria fortunei* (Kunze) J.Sm., *D. cylindrica* (Fig. 25) are used in Gusuibu (Chinese name 骨碎补), a famous traditional Chinese Medicine used to treat inflammation, cancers, aging, bone injuries, and osteoporosis (Chang et al. 2007). The main bioactive constituents of *Davallia* species are flavanones, flavan-3-ols, procyanidins, and proanthocyanidins (Chen et al. 2008a, b; Cui et al. 1990; Ko et al. 2012; Cheng et al. 2012) (Tables 5, 6). The total flavonoid content of *D. cylindrica* Ching was determined to be around 164.41 mg/g (w/w) (Cao et al. 2014), and flavan-3-ol dimers, trimers and tetramers are particularly abundant in these species. Thus, procyanidin B-2 (dimer), epicatechin-(−(4β → 8)-epicatechin-(4β → 6)-epicat-echin (trimer), epiafzelechin-(4β → 6)-epicatechin-(4β → 8)-epicatechin-(4β → 6)-epicatechin (tetramer) have all been isolated from *D. mariesii* MOORE and *D. divaricata* Blume (Hwang et al. 1989, 1990; Cui et al. 1990, 1993). Additionally, (−)-epiafzelechin-(4β → 8)-4β-carboxymethyl-(−)-epicatechin methyl ester, (−)-epiafzelechin-(4β → 8)-4α-carboxymethyl-(−)epiafzelechin ethyl ester, (−)-epiafzelechin-(4β → 8)-(−)-epiafzelechin-(4β → 8)-4β-carboxy-methyl-(−)-epiafzelechin methyl ester were isolated from the rhizomes of *D. fortunei* (Liang et al. 2011).

The genus *Elaphoglossum*, recently relocated in the family Dryopteridaceae, comprises around 600 species and is widely spread in South America. The acylphloroglucinols (Fig. 26) are found in *E. lindbergii* (Socolsky et al. 2011a, 2016), *E. yungense* (Socolsky et al. 2010a, b), *E. piloselloides* (Socolsky et al. 2009) and *E. gayanum* (Socolsky et al. 2010b). Specially, the prenylated acylphloroglucinols, ela-phogayanin A-B, elaphopilosin C- E, lindbergins A-F and yungensins A-F were identified from *E. gayanum* (Socolsky et al. 2010b), *E. piloselloides* (Socolsky et al. 2010b), *E. lindbergii* (Socolsky et al. 2011a, 2015) and *E. yungense* (Socolsky et al. 2010a).

Diphasiastrum

The genus *Diphasiastrum* includes more than 23 species, 11 of which have been reported to produce lycopodium alkaloids; the distribution of these alkaloids across this genus was recently reviewed by Halldorsdottir et al. (2015). Most lycopodium alkaloids identified in the *Diphasiastrum* to date belong to the lycopodine, lycodine, or fawcettimine families.

Fig. 25 *Davallia cylindrica* (Courtesy of Jianguo Cao)

Table 5 New kaempferol glycosides from *B. ternanum* (Warashina et al. 2012)

Name	Structure
Ternatumoside I	Kaempferol 3-*O*-β-D-quinovopyranosyl-(1 → 2)-α-L-rhamnopyranoside
Ternatumoside II	Kaempferol 3-*O*-β-D-glucopyranosyl-(1 → 3)-α-L-rhamnopyranoside
Ternatumosides III	Kaempferol 3-*O*-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside
Ternatumosides IV	Kaempferol 3-*O*-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside
Ternatumoside V	kaempferol 3-*O*-(2,3,4-tri-*O*-β-D-glucopyranosyl)-α-L-rhamnopyranoside
Ternatumoside VI	Kaempferol 3-*O*-[β-Dglucopyranosyl-(1 → 4)]-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside
Ternatumoside VII	Kaempferol 3-*O*-[β-D-xylopyranosyl-(1 → 4)]-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside
Ternatumoside VIII	Kaempferol 3-*O*-(2,3-di-*O*-β-D-glucopyranosyl)-α-L-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside
Ternatumoside IX	Kaempferol 3-*O*-β-D-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside-7-*O*-β-D-glucopyranosyl-(1 → 2)-β-D-glucopyranoside
Ternatumoside X	Kaempferol 3-*O*-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside
Ternatumoside XI	Kaempferol 3-*O*-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 2)-α-Lrhamnopyranoside-7-*O*-β-D-glucopyranoside
Ternatumoside XII	Kaempferol 3-*O*-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside-7-*O*-β-D-glucopyranoside
Ternatumoside III	Kaempferol 3-*O*-[β-Dxylopyranosyl-(1 → 4)]-[β-D-6-*O*-[4-hydroxy- (*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-glucopyranosyl-(1 → 2)-α-Lrhamnopyranoside-7-*O*-α-L-rhamnopyranoside
Ternatumoside XIV	Kaempferol 3-*O*-[β-D-xylopyranosyl-(1 → 4)]-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside-7-*O*-α-L-rhamnopyranoside
Ternatumoside XV	Kaempferol 3-*O*-[β-D-xylopyranosyl-(1 → 4)]-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-Lrhamnopyranoside-7-*O*-β-D-glucopyranoside
Ternatumoside XVI	Kaempferol 3-*O*-[β-D-glucopyranosyl-(1 → 4)]-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside-7-*O*-β-D-glucopyranoside
Ternatumoside XVII	Kaempferol 3-*O*-[β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 3)]-β-D-6-*O*-[4-hydroxy-(*E*)-cinnamoyl]-glucopyranosyl-(1 → 2)-α-L-rhamnopyranoside-7-*O*-α-D-glucopyranosyl-(1 → 6)-β-D-glucopyranoside

Biological activity of fern species

Pteridaceae

Pteris is one of the largest and most economically important fern genera, comprising some 200–250 species that are distributed across all the world's continents bar Antarctica. Its species diversity is greatest in the tropical and subtropical regions (Zhang et al. 2014). Many species belonging to this genus have significant value as medicines and spices (Jiang Su New College of Medicine 1985). The most important and intensively studied by far are *P. semipinnata* L. and *P. multifida*, both of which are

discussed in traditional Chinese medicine texts and used extensively to treat various symptoms (Jiang Su New College of Medicine 1985). *P. multifida* Poiret, also known as Fong-Wei-Cao, is not only one of the most widely used vegetables and herbs in China but also is a popular component of herbal beverages in Taiwan (Lu et al. 1999; Harinantenaina et al. 2008). *P. semipinnata* L. is widely distributed in China and is used in folk medicine to treat toothache, diarrhoea, jaundices, and viper bites (Zhang et al. 1999, 2007). *Pteris vittata* L. is the first reported arsenic-hyperaccumulating fern. Traditionally, it is used to treat abdominal pains, diarrhoea, and flu (Li 2006). There is also preliminary evidence that aqueous extracts of

Table 6 Flavan-3-ols, procyanidins and phenolic acids in Davallia species

Source	Polyphenols and phenolic acids	References
D. formosana	6,8-Dihydroxychromone 7-*C*-β-D-glucopyranoside, 6,8,3′,4′-tetrahydroxyflavanone-7-*C*-β-D-glucopyranoside, 6,8,4′-Trihydroxyflavanone 7-*C*-β-D-glucopyranoside, 8-(2-pyrrolidinone-5-yl)-catechin 3-*O*-β-D-allopyranoside, epiphyllocoumarin 3-*O*-β-D-allopyranoside, (−)-epicatech-3-*O*-β-D-allopyranoside, (−)-epicatech-3-*O*-β-D-(2″-*O*-vanillyl)-allopyranoside, (−)-epicatech-3-*O*-β-D-(3″-*O*-vanillyl)-allopyranoside, eriodictyol-8-*C*-β-D-glucopyranoside, davallioside A, davallioside B, caffeic acid-4-*O*-β-D-glucopyranoside, *p*-coumaric acid 4-*O*-β-D-glucopyranoside, protocatehuic acid, 4-hydroxy-3,5-dimethylbenzoic acid, vanillic acid	Chen et al. (2014a, b), Cui et al. (1990, 1992), Hsu and Chen (1993)
D. fortunei (Kunze) J. Sm.	4α-Carboxymethyl-(+)-catechin methyl ester, (+)-afzelechin 3-*O*-β-allopyranoside, (+)-afzelechin 6-*C*-β-glucopyranoside, (−)-epiafzelechin-(4β → 8)-4β-carboxymethyl-(−)-epicatechin methyl ester, -(−)-epiafzelechin-(4β → 8)-4α-carboxymethyl-(−)epiafzelechin ethyl ester, (−)-epiafzelechin-(4β → 8)-(−)-epiafzelechin-(4β → 8)-4β-carboxymethyl-(−)-epiafzelechin methyl ester	Liang et al. (2011)
D. solida (Forst.) Sw	Mangiferin, 3′-*O*-*p*-hydroxybenzoylmangiferin, 4′-*O*-*p*-hydroxybenzoylmangiferin, 4β-carboxymethyl-(−)-epicatechin methyl ester, 6′-*O*-*p*-hydroxybenzoylmangiferin, icariside E-3, 3-*O*-*p*-hydroxybenzoylmangiferin, eriodictyol, eriodictyol 8-*C*-β-D-glucopyranoside, 2-*C*-β-D-4β-carboxymethyl-(−)-epicatechin, icariside E-5, xylopyranosyl-1,3,6,7-tetrahydroxyxanthone, 2-*C*-β-D-xylopyranosyl-1,3,6,7-tetrahydroxyxanthone	Chen et al. (2008a, b), Rancon et al. (1999)
D. mariesii MOORE	Davallin, 5-*O*-beta-D-(6-*O*-vanilloylglucopyranosyl)gentisic acid, 4-*O*-beta-D-(6-*O*-vanilloylglucopyranosyl)vanillic acid, procyanidin B-2 and B-5, epicatechin-(-(4β → 8)-epicatechin-(4β → 6)-epicatechin, epicatechin-(4β → 6)–epicatechin-(4β → 8)-epicatechin-(4β → 6)-epicatechin, protocatechuic acid, 1-naphthol-β-D-glucopyranoside, davallialactone, (±)-eriodictyol 7-*O*-beta-D-glucuronide, caffeic acid, 4-*O*-beta-D-glucopyranosylcaffeic acid, 4-*O*-beta-D-glucopyranosyl-*p*-coumaric acid	Cui et al. (1990, 1993)
D. divaricata Blume	Davallic acid, (+)-catechin 3-*O*-β-D-allopyranoside, (−)epicatechin 3-*O*-β-D-allopyranoside, procyanidins B-1 and B-2, trimeric procyanidin, β-carboxymethyl-(−)-epicatechin, and epiafzelechin-(4β → 6)-epicatechin-(4β → 8)-epicatechin-(4β → 6)-epicatechin	Hwang et al. (1989, 1990)

this species are cytotoxic towards K562 leukaemic cells (Chai et al. 2015a). *P. multifida* is another arsenic hyperaccumulator that is widely distributed in China and other Asian countries. It has been used to treat enteritis, hepatitis, bacterial dysentery, hematemesis, hematuria, tonsillitis, parotitis and eczema (Cao et al. 2004; Srivastava et al. 2005; Rahman 2008; Rahman et al. 2014; Jiang Su New College of Medicine 1985).

There are also reports discussing the use of *Pityrogramma calomelanos* as a medicinal plant. It appears to be very versatile: its parts are used to treat renal, urinary and circulatory disturbances, digestive problems related to biliary calculi, cough, cold, chills, pains, fever, arterial hypertension, and bleeding, among other things (Barros and Andrade 1997; Cheryl 2006; May 1978).

Adiantum is another important genus within the family Pteridaceae (Brahmachari et al. 2003; Pan et al. 2011), whose members are distributed across tropical, sub-tropical, and temperate regions. Many species in this genus have ethnopharmacological applications. For instance, *A. capillus-veneris* Linn. is used to treat skin diseases and measles in Northwestern Pakistan (Abbasi et al. 2010), and to treat inflammatory diseases (Haider et al. 2011). In
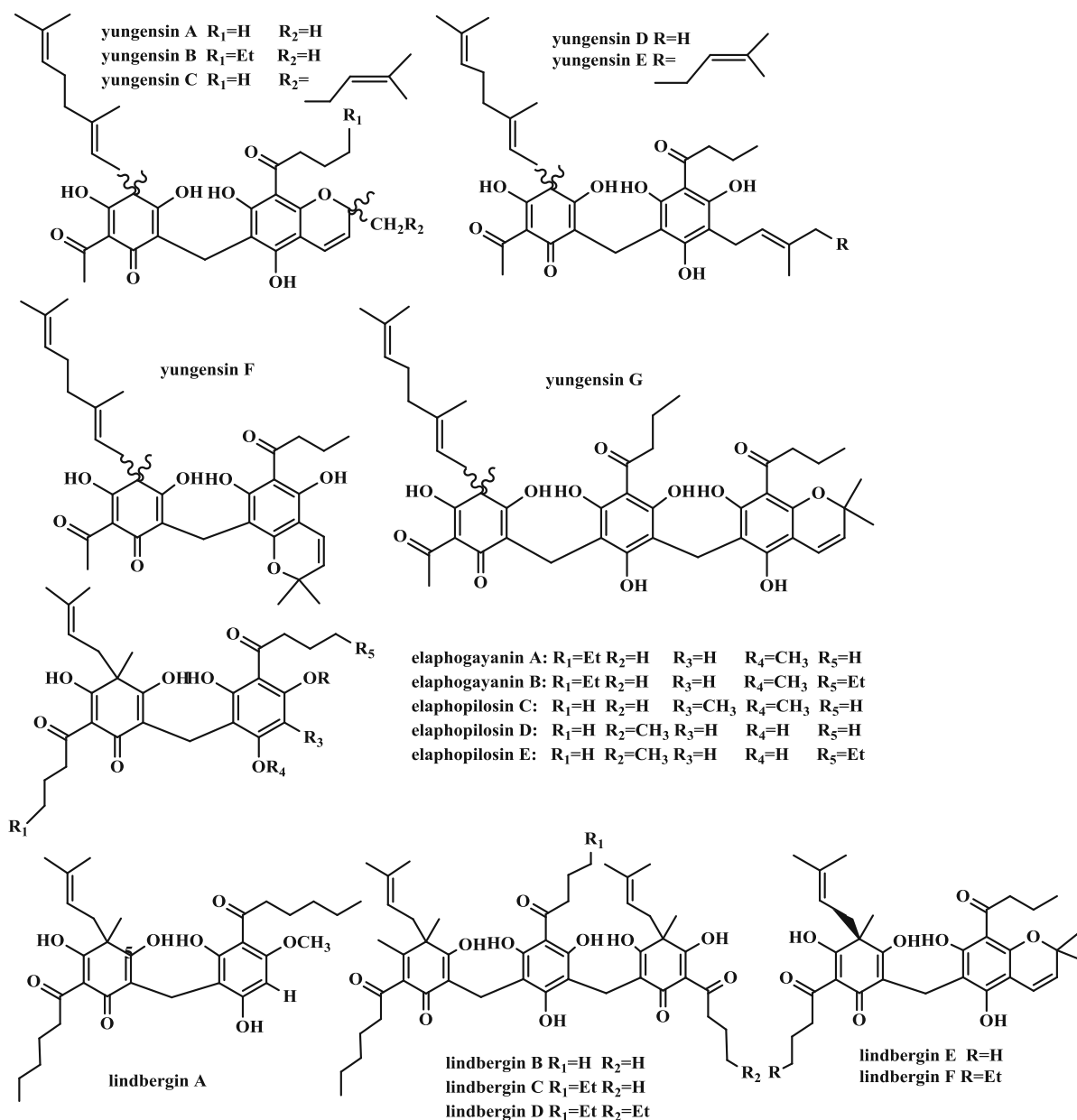
Fig. 26 New prenylated phloroglucinols from genus Elaphoglossum (Socolsky et al. 2010a, b, 2016)

traditional Chinese medicine, members of this genus have been used to treat fevers, promote urination, and relieve swelling (Pan et al. 2011).

Anticancer activity

The genus *Pteris* is a rich source of bioactive *ent*-kaurane diterpenoids. Many compounds in this class exhibit very good anticancer activity (Liu et al.

2011a, b, c; Shu et al. 2012; Qin and Zhu 2004), and it has been reported that the Michael-accepting capability of their α,β-unsaturated ketone moieties is essential for this cytotoxicity (Sun et al. 2006; Ge et al. 2008).

Pteris semipinnata L. is used as a medicinal plant for the treatment of venomous snake bites in Chinese folk medicine. In recent years, pharmacological investigations on this species have primarily focused

on the *ent*-kaurane diterpenoid *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid, which was shown to exhibit significant cytotoxicity and anticancer activity by Zhang et al. (1996, 1999, 2007). *ent*-11α-Hydroxy-15-oxo-kaur-16-en-19-oic-acid has inhibitory effects in various cancer cell lines: it induces apoptosis in human colon cancer HT-29 cells by increasing the abundance of p38 and iNOS. However, this effect can be mitigated by overexpression of Bcl-2 or Bcl-xL, which upregulates NF-κB activity and leads to apoptotic offset (Chen et al. 2004, 2008a, b). Interestingly, *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid exhibited stronger cytotoxicity in the gastric cancer cell line MKN-45, which expresses the wild-type p53 protein, than in the related gastric cancer line MKN-28, which expresses a p53 variant with a missense mutation. Further investigations revealed that *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid induces apoptosis in MNK-45 (in the presence of wild-type p53) by causing the translocation of Bax into mitochondria, leading to a reduction in ΔΨm and DNA fragmentation (Liu et al. 2005a). In addition, the release of cytochrome *c* and apoptosis inducing factor from mitochondria into the cytosol was also observed during the apoptosis of anaplastic thyroid carcinoma cells treated with *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid (Liu et al. 2005b). In vitro experiments showed *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid inhibits the proliferation of the human lung cancer cell lines A549, NCI-H23 and CRL-2066, arrested the cell cycle in the G2 phase, and induced apoptosis through a mitochondria-mediated pathway. In keeping with previous results, mechanistic investigations indicated that *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid induces apoptosis by triggering the overexpression and translocation of Bax into the mitochondria, leading to the release of cytochrome *c* into cytosol, activation of caspase-3, and translocation of AIF from mitochondria into the nucleus (Li et al. 2010, 2012). In addition, *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid significantly inhibited the development of NNK-induced mouse lung cancer in vivo by inducing apoptosis and exerting anti-proliferation effects with minimal side effects (Li et al. 2010). In vivo and in vitro investigations confirmed that *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid effectively inhibits hepatocellular carcinoma (HCC), significantly reducing the number of

tumor foci and the size of tumors in a diethylnitrosamine-induced mouse HCC model with minimal side effects. It also induced the death of HCC cells by stabilizing IkBα to inhibit NF-κB (Chen et al. 2012a). In tests against CNE-2Z nasopharyngeal carcinoma (NPC) cells, *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid exhibits significant inhibitory effects, causing cell cycle arrest in G2 phase and apoptosis by increasing the Bax/Bcl-2 ratio and the level of cytochrome c in the cytosol while reducing levels of NF-κB-p65 and increasing those of IκB (Wu et al. 2013). Finally, *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid sensitised A549 cells to cisplatin despite reducing cisplatin-induced ROS production (Li et al. 2012).

In addition to *ent*-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid, 7,9-dihydroxy-15-oxo-ent-kaur-16-en-19,6-olide and 7,11-dihydroxy-15-oxo-ent-kaur-16-en-19,6-olide from *P. semipinnata* can inhibit lung adenocarcinoma cells by acting as inhibitors of DNA topoisomerases (TOPO) and tyrosine protein kinase (TPK) (Tomšík 2014). 7,9-Dihydroxy-15-oxo-*ent*-kaur-16-en-19,6-olide inhibited TOPO II at a concentration of 0.01 mg/L, while 7,11-dihydroxy-15-oxo-*ent*-kaur-16-en-19,6-olide was a moderately potent inhibitor of membrane TPK and also reduced the expression of the oncogene *c-myc* (Li et al. 2001).

Bracken (*Pteridium spp.*) illudane glycosidess are labile biologically active terpenoids that undergo decomposition under mildly acidic or alkaline conditions, under heating, or in the presence of degradative enzymes (Cáceres-Peña et al. 2013). The novel bihomoflavanonol pteridium III, which has an unprecedented skeleton, was isolated from *P. aquilinum* and exhibits in vitro antitumor activity against NCI-H46 lung cancer cells, A375 melanoma cells, and U-7MG glioma cells with IC_{50} values of 22.9, 106.7, and 1540.5 μmol/L, respectively (Chen et al. 2013a, b).

The pterosins (Fig. 8) are a large group of naturally occurring sesquiterpenes with indanone skeletons. They are widely distributed among the Pteridophyte and exhibit both cytotoxicity and smooth muscle relaxant activity. Pterosin Z and acetyl-Δ^2-dehydropterosin B were found to be particularly cytotoxic (Chen et al. 2008a, b). Pterosin Z was later isolated from *Microlepia speluncae* (L.) Moore, *M. trapeziformis* (Roxb. ex Griff.) Kuhn and *M. substrigosa* Tagawa (Tomšík 2014). In addition,

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bimutipterosins A and B, isolated from *Pteris mul-tifida*, exhibited cytotoxicity against the HL$_{60}$ human leukemia cell line (Liu et al. 2011a, b, c).

Pterosin C and other C$_{14}$ and C$_{15}$ sesquiterpenoids, along with C$_{20}$-monoxygenated *ent*-kaurane diterpenoids and 4, 5-dicaffeoylquinic acid, were identified as the cytotoxic constituents of *P. multifida* Poir. (Ge et al. 2008; Harinantenaina et al. 2008; Ouyang et al. 2010). The pterosin sesquiterpenes 2*R*,3*R*-13-hydroxy-pterosin L 3-*O*–D–glucopyranoside, 2*R*,3*S*-acetylpter-osin C, and 2*S*,3*S*-acetylpterosin C also showed cytotoxicity against HL$_{60}$ cells with IC$_{50}$ values of 14.6, 48.3 and 35.7 mM, respectively (Shu et al. 2012). The new C$_{14}$ pterosin-sesquiterpenoids multifidosides A and B showed cytotoxicity against the HepG2 tumor cell line, with IC$_{50}$ values below 10 µM, and also displayed inhibitory effects on K562 cells with IC$_{50}$ values of 10.63 and 9.57 µM, respectively (Ge et al. 2008). The new diterpene 5,11,12-trihydroxy-15-oxo-*ent*-kuar-16-en-19-oic acid and the sesquiterpene 1, 3-dihydroxyl-norpterosin C from *Pteris dispar* showed potent cytotoxicity against KB cells in vitro, with IC$_{50}$ values of 59.8 and 36.5 mol/L by the MTT method (Gou et al. 2011)..

Pterosin B, one of the main pterosins found in the genus *Pteris*, exhibits potent cytotoxic activity against HL$_{60}$ (human leukemia) cells (Qin and Zhu 2004; McMorris et al. 1992). While searching for the carcinogenic constituent of bracken, Yoshihira et al. (1978) monitored the development of cytotoxicity-related morphological changes in HeLa cells upon incubation with bracken components. These studies failed to detect the potent carcinogen ptaquiloside, but did lead to the isolation of several indanone-type sesquiterpenoidspterosins and their glycosides, the pterosides.

The in vitro antitumor activity of *P. calomelanos* and its isolated dihydrochalcones (DHCs) was evaluated in India by Sukumaran and Kuttan (1991) using the trypan blue exclusion assay with Dalton's lymphoma ascites tumor cells (DLA cells) and Ehrlich ascites tumor cells (EA cells). The extract concentrations leading to 50% cytotoxicity in these cell lines were 16 and 18 µg/mL, respectively. The isolated DHCs exhibited greater cytotoxicity against these cell lines, with IC$_{50}$ values of 6.1 and 11.5 µg/mL, respectively. They also exerted cytotoxic effects in human myelogenous leukemia K562 cells and human nasopharyngeal KB cells, with IC$_{50}$ values of 1.1 and

8 µg/mL, respectively. A liposome preparation of the isolated DHCs was also tested in vivo in female Swiss albino mice to evaluate its effect on their survival after injection with Ehrlich ascites tumor cells. The treatment increased the animals' lifespan by 52 and 57% when applied at doses of 5 and 25 mg/kg, respectively. Because tumors are characterized by rapid cell division, the capacity of DHC to inhibit DNA synthesis was investigated by monitoring the incorporation of labelled thymidine in tumor cells, yielding an estimated IC$_{50}$ of 8 µg/mL. These results indicate that *P. calomelanos* has antitumor activity and is cytotoxic because of its DHC content.

In addition to the promising results discussed above, an ethanol extract of *Adiantum venustum* Don. was shown to increase the mean survival time in carcinoma-bearing mice relative to a positive control group treated with the established drug vincristine (Viral et al. 2011).

Antiprotozoal activity

As part of an ethnopharmacological screening program seeking medicinal plants with antiprotozoal activity, the fern *P. calomelanos* was investigated by Valadeau et al. (2009). Tests for antiplasmodial activity were conducted utilizing erythrocytes infected with *Plasmodium falciparum* FCR3, and an ethanolic extract of this plant exhibited an IC$_{50}$ of 49.9 µg/mL in the assay. While promising, this result did not satisfy the study's predefined activity criterion, under which an extract was considered to have good activity if its assayed IC$_{50}$ was below 10 µg/mL. The investigators also examined the extract's antileishmanial activity against axenic amastigotes of *Leishmania amazonensis* (strain MHOM/BR/76/LTB-012), obtaining an IC$_{50}$ of 88 µg/mL. When studying the antiprotozoal activity of ethanolic extracts of *P. calomelanos* and extract subfractions against *L. braziliensis*, Souza et al. (2013a) observed 100% inhibition of the promastigote forms upon treatment with either the ethanolic extract or the ethyl acetate fraction at a concentration of 500 µg/mL. However, these extract concentrations induced significant cytotoxicity in tests using mammalian fibroblasts from the NCTC929 cell line. Consequently, there is a need for further investigations to determine whether the compounds responsible for the

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extracts' leishmanicidal activity are also the ones that are harmful to mammalian cells.

Souza et al. (2012a) also conducted a similar screening campaign to identify plant extracts with trypanocidal activity against the epimastigote forms of the *Trypanosoma cruzi* CL-B5 strain. They observed that the hexane fraction of the ethanolic extract of *P. calomelanos* achieved 73.57% trypanosomal growth inhibition at a concentration of 50 µg/mL, and that this treatment had no detectable adverse effect on mammalian fibroblasts. However, the ethanolic extract exhibited complete cytotoxicity at a concentration of 500 µg/mL, with only 55.26% inhibition of epimastigotes. It thus appears that a detailed analysis of the hexane fraction may reveal promising trypanocidal compounds.

Antidiabetic activity

Pterosin A is a low-molecular-weight natural product that has been isolated from several different ferns (Qin and Zhu 2004). Its antidiabetic activity has been studied in several diabetic mouse models, in which it effectively alleviates hyperglycemia, glucose intolerance, insulin resistance, dyslipidemia, and islet hypertrophy. Pterosin A can suppress the reduction of body weight in diabetic mice as well as increases in body weight in fed mice and *db/db* diabetic mice. Moreover, it reverses the diabetes-associated reduction in GLUT-4 translocation from the cytosol to the membrane in the skeletal muscles of diabetic mice, and the increased PEPCK expression in their livers. An AMPK-regulated signalling pathway is involved in the activation of muscle GLUT-4 and inhibition of liver PEPCK expression by pterosin A. Pterosin A also increases GSK3 phosphorylation, further enhancing intracellular glycogen synthesis in liver cells. In addition, pterosin A treatment effectively reversed islet hypertrophy in *db/db* mic. Its antidiabetic activity is associated with inhibition of gluconeogenesis in the liver and enhanced glucose consumption in peripheral tissues. These findings indicate that pterosin A may be a viable therapeutic option for diabetes (Hsu et al. 2013).

Chai et al. (2015a) reported that an aqueous extract of *P. vittata* fronds exhibited moderate, dose-dependent antiglucosidase activity (EC_{50} 87 µg/mL) when compared to myricetin (EC_{50} 53 µg/mL). The identity of the alpha-glucosidase inhibitors in the extract is unknown.

Antitubercular activity

P. ensiformis Burm. was shown to exhibit antitubercular activity in vitro when screened against the *M. tuberculosis* H37Rv strain. (2S)-13-Hydroxypterosin A, (2S, 3S)-12-hydroxypterosin Q, pterosin B, and alpha-tocopheryl quinone from *P. ensiformis* exhibited antitubercular activity (MIC = 40 g/ml) against *M. tuberculosis* H_{37}Rv in vitro. (2S)-13-Hydroxypterosin A was the most effective of the tested antitubercular compounds, with an MIC value of 6.25 g/ml against *M. tuberculosis* H_{37}Rv (Chen et al. 2013a).

Antimicrobial activity

Extracts of many different ferns have been tested for activity against bacteria, fungi and viruses (Zhou and Li 1998; Xu et al. 2005). Water extracts of *P. multifida* showed remarkable antibacterial activity against *Shigella sp.*, *Escherichia coli*, *Proleus vulgaris*, *Staphylococcus aureus*, and *Bacterium pyocyaneum* (Zhou and Li 1998; Kubo et al. 1992). In addition, water extracts and alcohol extracts from 20 species of medicinal pteridophytes were tested for bacteriostatic activity against *S. aureus*, *E. coli*, *S. lutea*, *P. vulgaris*, *B. subtilis* and *S. cerevisiae*. Water and alcohol extracts of *P. ensiformis* Burm. and *P. semipinnata* exhibited particularly strong activity in these experiments (Cai et al. 2003). The inhibitory effects of polysaccharides from eight species of pteridophytes against eight species of microorganisms (*E. coli*, *P. vulgaris*, *S. aureus*, *R. solanacearum*, *A. flavus*, *P. sp.*, *S. cerevisiae*, *M. grisea*.) were tested using the disk agar diffusion method, revealing that polysaccharide extracts of *P. aquilinum*, *P. vittata*, *P. multifida* exhibited clear inhibitory effects against bacteria and fungi including *E. coli*, *P. vulgaris*, *S. aureus*, *S. cerevisiae*, and *Penicillium sp.* (Xu et al. 2005).

The antibacterial activity of fern extracts has also been studied extensively by Souza et al. (2012b, 2013b). This group determined the MIC values of the ethanolic extract and various fractions of *P. calomelanos* by the microdilution method but did not detect any clinically relevant activity,

obtaining MIC values above 1024 µg/mL for both bacteria and fungi (genus *Candida*). However, interesting results were obtained in drug-modifying assays where the natural product extracts were combined with conventional drugs. In these studies, the ethanolic extract as well as the hexane and methanolic fractions potentiated the action of antifungals against the yeasts *C. albicans, C. krusei* and *C. tropicalis*. Against bacteria, the extract and fractions exhibited drug-modifying potential in conjunction with some aminoglycoside antibiotics when tested against *E. coli* and *S. aureus*. Subsequent experiments (Souza et al. 2013c) demonstrated that the interaction between the natural products (i.e. the ethanolic extract and the ethyl acetate fraction) and the tested drugs (amikacin, gentamicin, and neomycin) was additive.

A flavonoid isolated from the ethyl acetate fraction of a *P. calomelanos* extract was evaluated for antibacterial activity. The isolated compound was 2′, 6′-di-hydroxy-4′-methoxydihydrochalcone, and it was tested against Gram-positive and Gram-negative bacteria by the disk diffusion method. It exhibited an intermediate level of antimicrobial activity, forming inhibition halos of 18.43 mm against *S. aureus* and 18.70 mm against *E. coli*. Luciano-Montalvo et al. (2013) conducted a separate ethnopharmacological antimicrobial screening using the disk diffusion method (with some modifications) with extracts from 13 plant species, revealing that a decoction of *P. calomelanos* leaves inhibited bacterial growth in the order *P. aeruginosa > S. aureus > S. saprophyticus*, with inhibition percentages above 20% relative to a positive control (streptomycin).

Extracts of several *Adiantum* species have also demonstrated potent antimicrobial activity. *A. venustum* is especially noteworthy, as its methanol extract was found to inhibit a broad range of Gram-positive and Gram-negative bacteria. In addition, an extract of *A. capillus-veneris* L. had a very low MIC value (0.48 µg/mL) against *E. coli*; for comparative purposes, the corresponding value for the reference antibiotic gantamicin is 7.81 µg/mL (Singh et al. 2008).

Antioxidant activity

Ferns are widely used as traditional medicinal herbs in part because of their content of phenolic compounds. These substances are potent antioxidants that play an important role in human nutrition as protective agents against several diseases. Many flavonoids, especially flavonols, have been isolated and characterized from ferns (Harborne and Williams 1988; Cao et al. 2012), and the DPPH radical scavenging activity of fern extracts has been shown to increase with their total flavonoid concentrations (Xia et al. 2014). An extract of *D. boryanum* (Willd.) Ching (Cao et al. 2013a, b) with a total flavonoid content of around 145.8 mg/g exhibited very strong superoxide anion radical scavenging potential at a concentration of 0.21 mg/ml, which is higher than that of rutin (0.25 mg/mL). Poudel (2011) reported that the polyphenol content of the ethyl acetate fraction of *D. boryanum* is 266 µg GAE/mg and that it exhibits potent antioxidative activity based on its DPPH free radical scavenging activity and hydrogen peroxide scavenging activity. The ethyl acetate fraction of *D. boryanum* also reduced lipid oxidation by 35% when applied to the 3T3-L1 cell line at 100 µg/mL.

Phytochemical investigations on the *Pteris* genus have identified various phenolic compounds (Lu et al. 1999; Gong et al. 2007). Aqueous extracts of the Sword Brake fern (*P. ensiformis* Burm.), a common ingredient in traditional Taiwanese herbal drinks, showed strong antioxidant activity in DPPH assay. Moreover, caffeic acid and its derivatives 7-*O*-caffeoylhydroxymaltol 3-*O*-β-D-glucopyranoside, 5-*O*-caffeoyl-quinic acid, 3,5-di-*O*-caffeoylquinic acid and 4,5-di-*O*-caffeoylquinic acid as well as hispidin glucoside (hispidin 4-*O*-β-D-glucopyranoside) were found to have similar or superior DPPH scavenging activities to the common antioxidant supplement alpha-tocopherol. This suggests that a catechol moiety facilitates DPPH scavenging. Yung-Husan Chen et al. (2007) reported that 3,5-di-*O*-caffeoylquinic acid and 4,5-di-*O*-caffeoylquinic acid (both of which are present in the Sword Brake fern) have strong DPPH scavenging potential, with IC_{50} values of around 10 µM and a TEAC of around 2 mM. *P. multifida* Poiret is another fern that is commonly used in Taiwanese herbal beverages, and is also widely eaten as a vegetable in mainland China. An aqueous extract of *P. multifida* Poiret showed high antioxidant activities in a conjugated diene assay. Moreover, at a concentration of 20 mg/mL, it exhibited high radical scavenging activity towards

DPPH, hydroxyl, and ferrous radicals (82.5, 80.1 and 85.4 mg/mL, respectively) as well as a high level of reducing power based on absorbance at 700 nm. Its antioxidant activity is somewhat variable, presumably because of variation in the distribution and relative abundance of its naturally occurring antioxidant components (Lan et al. 2011).

Antioxidant tests in vitro showed that the purified polysaccharide prepared from *P. aquilinum* is a powerful scavenger of superoxide radicals and the DPPH radical, as well as an effective inhibitor of 1,2,3-phentriol self-oxidation. In addition, the lipopolysaccharides had a high FRAP value (827.6 mol/L) comparable to that of vitamin C. These results suggest that water-soluble polysaccharides warrant further exploration as potential natural antioxidants (Xu et al. 2009).

Lai and Lim (2011) investigated the capacity of methanolic extracts of 15 pteridophyte species, including *P. calomelanos,* to sequester free radicals. Three radical scavenging assays were used—DPPH assay, FRAP assay, and bleaching assays. The extracts' overall activity was moderate and correlated with their total phenol content, which was also moderate. Morais-Braga et al. (2012a) utilized the DPPH assay to study the antioxidant capacity of the hexane, chloroform, ethyl acetate and methanolic fractions of *P. calomelanos*, revealing that the ethanolic extract and methanolic fraction showed the best results, with IC_{50} values of 43.4 and 123.57 µg/mL, respectively. The activity was attributed to presence of polar compounds in the extracts such as phenolic acids and flavonoids, which have known antioxidant activity.

Toxicity and carcinogenic activity

Ptaquiloside is a norsesquiterpene glucoside of the illudane type that was shown to be responsible for many conditions associated with bracken consumption by livestock, including acute haemorrhagic disease in cattle (bracken poisoning), bright blindness in sheep, bovine enzootic haematuria, and upper alimentary carcinoma. The biological activity of this reactive glycoside has been attributed to the facile elimination of glucose to form an unstable conjugated dieneone intermediate that acts as a powerful alkylating agent of amino acids and DNA (Yamada et al. 2007).

A new toxic unstable sesquiterpene glycoside, ptaquiloside Z, from the neotropical bracken fern *P. aquilinum* var. *caudatum* showed toxicity toward brine shrimp (LC_{50} 62.5 g/mL at 24 h and LC_{50} 7.8 g/mL at 48 h) (Castillo et al. 1998).

The only vascular plant known to cause cancer in humans is the bracken fern *P. aquilinum* (L.) Kuhn. Bracken is currently the most common fern worldwide and one of the most aggressive and most widely distributed weeds of all; the only regions where it is not found are those with polar or desert climates (Vetter 2009). The toxicity of bracken, its mutagenic, carcinogenic and teratogenic effects in animals and humans, and its assumed mechanism of action have been described at length (Yamada et al. 2007; Vetter 2009). Ptaquiloside was discovered in 1983, and its carcinogenicity was clearly demonstrated in 1984: intragastric administration of ptaquiloside to rats induced mammary cancer (100%) and ileal tumours (91%) (Yamada et al. 2007). The unstable nor-esquiterpene glucoside ptaquiloside has been conclusively identified as the main mutagenic, clastogenic and carcinogenic constituent of bracken. However, the carcinogenic potential of bracken is enhanced by its co-occurrence with other closely related illudane glycosides (IG) that are less well characterized. In particular, isoptaquiloside and caudatoside from the Venezuelan species *P. caudatum* (L. Maxon) (Castillo et al. 1997) and ptesculenoside from the Australian species *P. esculentum* (G. Forst.) (Fletcher et al. 2010) have been observed in quantities comparable to those ptaquiloside, with lesser amounts of ptaquiloside Z also being found in *P. caudatumthus*.

Insecticidal activity

Many methanol fern extracts were recently reported to possess insecticidal activity against houseflies (*Musca domestica*) and mosquitoes (*Aedes albopictus*). For example, an extensive screening study showed that methanolic extracts of whole *Onychium japonicum* plants exhibit potent insecticidal activity, suggesting that these plants could be used as botanical insecticides. *M. domestica* adults treated for 48 h with extracts of *P. vittata* leaves and roots exhibited mortalities above 90% (Huang et al. 2010a, b, c).

Immunomodulatory activity

The Sword Brake fern (*P. ensiformis* Burm.) is widely used in traditional Chinese herbal medicine. Aqueous extracts of the Sword Brake fern exert immunomodulatory effects by inhibiting the release of TNF-α, IL-1β, IL-6, NO, and PGE2 in LPS-activated RAW264.7 cells (Wu et al. 2005).

Anti-inflammatory activity

The hexane fraction of *A. capillus-veneris* L. showed anti-inflammatory effects against croton oil-induced and formalin-induced inflammation in mice (Ibraheim et al. 2011). A recent work evaluated the anti-inflammatory effect of an *A. capillus-veneris* L. ethanol extract at the transcriptional and translational levels using a luciferase gene reporter assay and Western blotting, revealing a potential link between the *Adiantum*-mediated anti-inflammatory effect and inhibition of the transcription factor (NF-κB) pathway (Yuan et al. 2013a, b).

Other bioactivities

Ali et al. (2013) reported that methanol extracts of *A. philippense* L. leaves exhibited thrombolytic activity in a blood clot lysis study. Additionally, Ibraheim et al. (2011) reported that *A. capillus-veneris* extracts possess hypoglycemic activity.

Huperziaceae

Huperzia is a famous source of Lycopodium alkaloids with acetylcholinesterase (AChE) inhibiting activity (Liu et al. 1986a; Ma and Gang 2004), particularly huperzine A (Ma et al. 2007). Huperzine A was isolated from whole plants of *H. serrata* (Thunb. ex Murray) Trev. (Liu et al. 1986b), which is used in traditional medicine to treat contusions, strain, swelling, and schizophrenia (Jiang et al. 2014). As a potent AChE inhibitor, huperzine A has potential applications in the treatment of mild to moderate Alzheimer's disease and was examined in a phase II trial to evaluate its safety, tolerability, and efficacy (Zhang et al. 2004; Yang et al. 2003; Rafii et al. 2011). Treatment with this alkaloid can improve learning and reduce memory impairment in patients, and has neuroprotective effects in rats as a result of

modulating the oxidative stress, apoptosis, mitochondrial dysfunction and inflammatory responses, and ameliorate Aβ$_{25-35}$ induced apoptosis of rat cortical neurons via inhibition of reactive oxygen species production and activation of caspase-3 (Xiao et al. 2002; Zhang et al. 2008).

Because of these promising results, huperzine A has become an important lead compound for the development of new anti-Alzheimer's drugs (Wu et al. 2011a, b). Huperzine A itself has been marketed in China as a new drug for Alzheimer Disease (AD) treatment, and a derivative known as ZT-1 is being developed as a new anti-AD drug candidate in China and Europe (Ma et al. 2007; Zhang 2012).

In addition to the activities described above, huperzine A promotes hippocampal neurogenesis in vitro and in vivo by stimulating the proliferation of neural stem cells, and attenuates hippocampal cognitive deficits in rats exposed to acute hypobaric hypoxia (Ma et al. 2013a, b; Shi et al. 2012). It can also alleviate chronic pain in rats induced by spinal cord compression injury (Yu et al. 2013).

Huperzine A is a more powerful AChE inhibitor with higher oral bioavailability than some approved AChE-inhibiting drugs, is more capable of penetrating the blood–brain barrier, and has a longer half-life (Wang and Yan 2006).

2α,11α-Dihydroxyfawcettidine and lycoposerramine H also inhibit AChE, with IC$_{50}$ values of 27.9 and 16.7 μM, respectively (Katakawa et al. 2007), and the known compound lycopodine-6α,11α-diol inhibited α-glucosidase more potently (IC$_{50}$ = 148 ± 5.5 μM) than the approved anti-diabetes drug acarbose (IC$_{50}$ 376.3 ± 2.7 μM) (Ying et al. 2014). Additionally, 12-deoxyhuperzine O antagonizes the *N*-methyl-*D*-aspartate receptor with an IC$_{50}$ of 0.92 μM (Yang et al. 2010). Alcohol extracts of *H. serrata* and specific triterpenoids within those extracts can inhibit the proliferation of HL-60 human leukemia cells and induce their apoptosis (Ham et al. 2012).

A novel Lycopodium alkaloid was obtained from *H. saururus* (Lam.) Trevis and its AChE inhibitory activity was evaluated (IC$_{50}$ = 209.6 ± 1.1 μM) (Vallejo et al. 2013). Lycopodium alkaloids have attracted considerable research interest in recent years, with many in vitro and in vivo studies having been conducted to study their AChE-inhibiting activity. For example, lycotetrastine A isolated from

H. tetrasticha inhibited AChE from bovine erythrocytes with an IC_{50} of 85 µM; for comparative purposes, the IC_{50} of (−)-huperzine A for this enzyme is 53 µM (Hirasawa et al. 2011). A separate in vitro AChE inhibition assay showed that the new lycodine-type alkaloid huperserine E exhibited moderate anti-AChE activity with an IC_{50} value of 6.71 µM (Jiang et al. 2014).

H. saururus is a native Argentine species used in ethnomedicine as aphrodisiac and memory improver (Vallejo et al. 2007). In experiments with male Wistar rats, treatment with its main alkaloid component sauroine improved memory retention in the step-down test while significantly increasing hippocampal plasticity as determined by electrophysiological experiments and behavioral tests (Vallejo et al. 2008). A purified alkaloid extract of *H. saururus* strongly inhibited AChE ($IC_{50} = 0.58$ µg/mL) based on a slight modification of Ellman's method, but the most abundant alkaloids present in the extract had much weaker inhibitory effects when isolated and purified: sauroxine has an IC_{50} of 8.9 ± 0.4 µg/mL and was present at a concentration of 32.3 µM, 6-hydroxylycopodine has an IC_{50} 78.1 ± 3.5 µg/mL (present at 298.8 ± 13.3 µM), and the new alkaloid *N*-demethyl-sauroxine has an IC_{50} of 54.5 µg/mL (209.6 ± 1.1 µM). The inhibitory activities of all three compounds are several orders of magnitude weaker than that of the extract, suggesting a possible synergistic effect between the different alkaloids (Vallejo et al. 2013). As demonstrated by the results presented above, none of the Lycopodium alkaloids identified to date have exhibited comparable in vitro AChE inhibitory activity to huperzine A (Konrath et al. 2013).

The Lycopodium serratene triterpenoids lycophlegmariol B, D and 21β-hydroxyserrat-14-en-3α-ol from *H. phlegmaria* (=*L. phlegmaria* L.) showed inhibitory effects against MOLT-3 acute lymphoblastic leukemia (T-lymphoblast) with IC_{50} values of 14.7, 3.0 and 2.9 µM, respectively (Wittayalai et al. 2012). Lycophlegmarin also showed modest growth-inhibitory activity against BEL 7402 human hepatoma cells (Shi et al. 2005).

Selaginellaceae

Selaginella-based treatments were first documented in the traditional Chinese medicine textbook Shen Nong Ben Cao Jing in 2737 BC (Yang and Flaws 1998). Many of the *Selaginella* species have been used in traditional ethnomedicines for different purposes, including analgesia and the treatment of depression (*S. convoluta*, northern Brazil) (de Sá et al. 2012), the treatment of chronic tracheitis (*S. sinensis*, Traditional Chinese Medicine) (Chen et al. 2014a, b), 'Sanjeevani' or resurrection (*S. bryopteris*, Indian Ayurvedic Medicine) (Mishra et al. 2011), or for treatment of renal disorders (*S. lepidophylla*, Mexico) (Aguilar et al. 2013).

As a genus, *Selaginella* is medicinally significant because many of its species exhibit pharmacologically relevant properties including anti-carcinogenic, anti-hyperglycemic, anti-nociceptive, antioxidative and neuroprotective activity (Chai and Wong 2012; de Sá et al. 2012; Girish and Muralidhara 2012; Weng and Noel 2013). Several studies have been conducted to characterize the mechanisms of action of *Selaginella*-derived natural products and to identify the phytochemicals responsible for specific observed activities.

Anticancer activity

Ethyl acetate extracts of *S. doederleinii* Hieron exhibit pronounced antitumor activity in vitro and in vivo without obvious toxicity towards normal cells, and efficiently induce apoptosis (Wang et al. 2015). The mechanisms of anti-tumor activity and cell apoptosis induced by *S. doederleinii* extracts may be associated with reductions in the ratio of mRNAs from tumor suppressor genes, caspase-3 activation, the suppression of survivin, and reduced expression of the COX-2, 5-LOX, FLAP, and 12-LOX mRNAs (Wang et al. 2015). The main active components in *S. doederleinii* extracts are bioflavonoids, and two biflavonoids (biapigenin and binaringenin derivatives) isolated from *S. doederleinii* Hieron have been linked to cytotoxicity towards human cancer cell lines (Li et al. 2014). In addition, an extract of *S. tamariscina* (Beauv.) Spring was shown to exhibit anti-metastatic properties that resulted from the down-regulation of metalloproteinases and reduced activation of an Akt kinase (Yang et al. 2013). In this context, it is interesting that an earlier report had suggested that caspase-3 plays a functional role in *S. tamariscina*-induced apoptosis in leukemia cells (Ahn et al. 2006).

Antidiabetic activity

S. tamariscina extracts have also been shown to exert anti-hyperglycemic effects in diabetic rats and HepG2 cells (Zheng et al. 2011a). Specifically, total flavonoids of *S. tamariscina* were found to increase the expression of PPAR-γ and IRS-1, two protein mediators with functional roles in insulin-stimulated signalling and glucose metabolism (Zheng et al. 2011b). A later study using a diabetic mouse model validated the proposed connection between antioxidative and antidiabetic activities by showing that treatment with *S. tamariscina* total flavonoids reduced levels of nitric oxide and nitric oxide synthase while increasing levels of superoxide dismutase and other antioxidative enzymes (Zheng et al. 2013).

Biflavonoids from *S. tamariscina* (amentoflavone, robustaflavone, cupressuflavone, taiwaniaflavone, and 3,8″-biapigenin) potently inhibited protein tyrosine phosphatase 1B, with IC_{50} values ranging from 4.5 ± 0.1 to 13.2 ± 0.8 μM, and also had significant stimulatory effects on the glycose uptake in 3T3-L1 adipocyte cells (Nguyen et al. 2015a). Selaginellins (selaginellin, selariscinin A, selariscinin B, selariscinin C, selariscinin E, selaginellin M) isolated from *S. tamariscina* strongly stimulated glucose uptake in 3T3-L1 adipocyte cells and also significantly inhibited the PTP1B enzyme, with IC_{50} values ranging from 4.6 ± 0.1 to 21.6 ± 1.5 μM (Nguyen et al. 2015a, b).

Neuroprotective and phosphodiesterase inhibitory activities

Recent publications have discussed the neuroprotective and phosphodiesterase-inhibiting properties of *Selaginella* extracts, suggesting that they may have applications in the treatment of Parkinson's disease and pulmonary conditions (Chandran 2014; Liu et al. 2013b).

Lygodiaceae

Lygodium venustum, which has been used as a medicinal plant by indigenous populations in Mesoamerica, reportedly exhibits antiseptic, fungicidal and trichomonacidal activities, and is indicated for the treatment of dermatoses, mycoses and

infections (Duke 2008). It is also used to treat gastrointestinal and gyneco-obstetric disorders, and as a postpartum anti-inflammatory agent (Argueta Villamar et al. 1994). Traditionally, it is used to prepare the hallucinogenic drink ayahuasca by the Sharanahua and indigenous peoples of the upper Purus River in the Peruvian Amazon (Rivier and Lindgren 1972). In Brazil, this fern is utilized by mystical Afro-Brazilian cults in cleansing baths and to treat nervousness and emotional instability (Albuquerque et al. 1997; Rahman 2008).

The pharmacological activities of *L. venustum* have been investigated in various places, particularly Brazil and Mexico. These studies have mainly adopted an ethno-directed approach, although other approaches have also been utilized. Because *L. venustum* is rich in flavonoids, much of its bioactivity is attributed to these secondary metabolites. However, further studies will be needed to confirm this assumption and identify the precise compounds responsible for specific effects.

Antimicrobial activity

The first report on the bioactivity of *L. venustum* was published in 2005: Alanis et al. conducted a screening study in which 26 Mexican medicinal plants were tested for activity against eight bacterial strains using the disk-diffusion method. Methanolic and aqueous extracts of *L. venustum* achieved less than 50% inhibition in all tested cases, indicating that the plant has only weak inhibitory effects on bacterial growth. Microbiological tests were also performed by Morais-Braga et al. (2012a, b, 2013a, b), who determined the plant's MIC using the broth microdilution method and showed that extracts of the whole plant and subfractions of *L. venustum* had no clinically relevant effects, with a MIC ≥ 1024 μg/mL against the bacteria *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and the yeasts *Candida albicans, Candida tropicalis*, and *Candida krusei.* Tests of these extracts and fractions at subinhibitory concentrations (MIC/8) in combination with conventional drugs revealed no potentiation of antifungal activity. However, the authors did observe an interesting effect whereby the extracts and fractions enhanced the activity of aminoglycoside antibiotics (amikacin, kanamycin, neomycin and gentamicin) against *E. coli* and *S. aureus*. This effect was

especially pronounced for the ethyl acetate fraction, which potentiated all of the tested aminoglycosides. The interactions between the antibiotics and the extract or the ethyl acetate fraction were evaluated using the checkerboard method, which demonstrated that the natural products had additive or synergistic effects when combined with the conventional drugs, clearly demonstrating their antibiotic-modifying ability (Morais-Braga et al. 2012a).

Antidiarrheal activity

Because of its use in treating gastrointestinal disorders such as diarrhoea, *L. venustum* was tested for anti-secretory activity by Velázquez et al. (2006) in an in vivo model with induction by the cholera toxin. Methanolic and aqueous extracts of *L. venustum* were evaluated at a concentration of 300 mg/kg; the aqueous extract had no effect but the methanolic extract achieved 51.6% inhibition, indicating interesting antidiarrheal activity. A methanolic extract of the same concentration was investigated by Calzada et al. (2010) to assess its inhibition of peristalsis of the intestinal tract in rats. The effect observed was moderate (42%) but superior to that of the drug used as the positive control, loperamide, which achieved 34% inhibition at a dose of 10 mg/kg.

Antiprotozoal activity

The antiprotozoal activity of pteridophytes in general and *L. venustum* in particular was investigated by Calzada et al. (2007) in a study where 22 plants were tested for trichomonacidal effects. *L. venustum* exhibited moderate activity, with an IC_{50} of 60.9 µg/mL. The same group conducted an in vitro screening of plants based on ethnomedicinal use for treatment of giardiasis and amebiasis, in which methanolic extracts of 26 plants were tested, including *L. venustum*. The IC_{50} of the *L. venustum* extract against *Entamoeba histolytica* was 178.4 µg/mL, which was much higher than that found for *Giardia lamblia* (74.3 µg/mL). The effect against *Giardia* was classified as being of intermediate strength (Calzada et al. 2006).

Morais-Braga et al. (2013a) examined the antileishmanial activity of an ethanolic extract of *L. venustum* and its hexane, ethyl acetate, dichloromethane and methanolic fractions against the promastigote forms of protozoa of the family Kinetoplastida. With the exception of the methanolic fraction, all of the tests indicated insignificant activity; the methanolic fraction exhibited a moderate effect, achieving 68% inhibition at a concentration of 500 µg/mL. This fraction also exhibited antiepimastigote activity against *Trypanosoma cruzi*, achieving 63% inhibition at a concentration of 500 µg/mL. The hexane fraction similarly achieved 63% inhibition of the epimastigote forms, but at twice the concentration.

Antioxidant activity

The antioxidant effect of *L. venustum* was evaluated by Morais-Braga et al. (2012a) in a study using a photocolorimetric method based on the reduction of the 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical. The ethanolic extract of the fern exhibited antioxidant activity with an IC_{50} of 67.58 µg/mL. The ethyl acetate fraction exhibited still lower antioxidant activity, with an EC_{50} of 82.70 µg/mL.

Cytotoxicity

In view of the bioactivities shown by the fern *L. venustum*, it was tested for cytotoxicity in vitro using mammalian fibroblasts (NCTC-929). The ethanolic extract and the hexane, ethyl acetate and methanolic fractions exhibited varied cytotoxicities at a concentration of 100 µg/mL but the dichloromethane fraction showed no cytotoxicity at this concentration (Morais-Braga et al. 2013a, b). However, an interesting and beneficial cytotoxic effect was observed when the extracts and fractions of *L. venustum* were combined with a heavy metal such as mercury in prokaryotic cells (*E. coli*).

Equisetaceae

Extracts of *E. arvense*, the common horsetail, are widely used for pain relief and to relieve inflammation in treatments for diseases such as tuberculosis, kidney and bladder disorders, dysmenorrhea and hemorrhages, rheumatic diseases, gout, swellings and traumas, problematic wounds, ulcers, and frostbite (Asgarpanah and Roohi 2012; Sandhu et al. 2010). In addition, *E. arvense* extracts are used in various cosmetics such as anti-aging, moisturizer,

anti-wrinkle, anti-acne, and hair conditioning products (Sandhu et al. 2010).

Diverse bioactivities of E. arvense

Investigations on *E. arvense* have revealed antioxidant, anti-inflammatory, analgesic, antibacterial, antifungal, antitumor and neurotropic effects. Alcoholic extracts of the plant's stem reportedly induce anticonvulsant, sedative, anxiolytic, and neuroprotective effects in rodents (Santos et al. 2005; Santos-Junior et al. 2005; Samura and Dovzhenok 2002; Singh et al. 2011), while methanolic extracts have shown antidiabetic activity in streptozotocin-induced diabetic rats (Soleimani et al. 2007); and the ethyl acetate extract reportedly exerts antiproliferative effect in tumor cell lines (Četojević-Simin et al. 2010). The only clinical data for such extracts relates to the induction of diuretic effects by a standardized dried extract (Carneiro et al. 2014). It has been suggested that *E. arvense* extracts could be beneficial silicon supplements, but this has been questioned based on the limited quantities of water-extractable silicon in the plant's tissues (Bey et al. 2010).

Hepatoprotective activities of E. arvense

Hepatoprotective activity-guided fractionation of the MeOH extract of *Equisetum arvense* L. resulted in the isolation of two phenolic petrosins, onitin and onitin-9-*O*-glucoside (Oh et al. 2004). Onitin exhibited hepatoprotective activities against tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, with EC_{50} value of 85.8 ± 9.3 μM. For comparative purposes, the positive control agent silybin achieved an EC_{50} value of 69.0 ± 3.3 μM. Onitin also showed superoxide and DPPH free radical scavenging activity. These results support the use of this plant for the treatment of hepatitis in oriental traditional medicine.

Bioactivities of other Equisetum species

Secondary metabolites from various other horsetail species have also been reported to have interesting bioactivity. For example, a kaempferol diglucoside from *E. palustre* has been proposed as an antiulcerogenic agent (Yesilada and Gurbuz 2010), and ointments prepared from *E. pyramidale* and *E.*

arvense promoted the healing of cutaneous wounds in diabetic rats (Corrêa et al. 2013; Ozay et al. 2013). An extract from *E. hiemale* inhibited platelet aggregation and thrombosis in rats, suggesting a potential use in stroke prevention (Qi and Wang 2004). Finally, an alkaloid preparation from *E. pratense* exerted a sedative effect in rats by reducing the levels of central monoamine neurotransmitters (Ji and Gao 2005). A study on various polar and nonpolar extracts from *E. ramosissimum* has revealed antimelanoma and antimelanogenesis effects (Li et al. 2016).

Helminthostachyaceae

The rhizome of *Helminthostachys zeylanica* is used in traditional medicine in China, India and Sri Lanka as an aperient, analgesic, anti-inflammatory, antipyretic, and hepatoprotective principle, and to treat malaria, jaundice, syphilis, and impotence (Huang et al. 2003; Suja et al. 2003). Its liver-protecting activity was confirmed in a study on CCl_4-induced liver damage in Wistar rats (Suja et al. 2004), while acetogenin and prenylated flavonoids from the rhizome have been shown to inhibit superoxide and elastase release by neutrophils (Huang et al. 2010a, b, c). In addition, novel quercetin glucosides from the rhizome were found to stimulate melanin biosynthesis in murine B16 melanoma cells (Yamauchi et al. 2013).

Ugonins E–L (1–8) were evaluated for their antioxidative activity in DPPH assay. Ugonins J, K and L were more active than Trolox, with IC_{50} values of 5.29, 7.23, and 7.93 mg/mL, respectively (Huang et al. 2003).

Botrychiaceae

Botrychium (=*Sceptridium*) *ternanum* is used in China and Japan as a folk remedy for dizziness, headache, cough, asthma, and fever (Wang et al. 2001; Warashina et al. 2012). A study on its anti-asthma activity in a mouse model revealed effects on the regulation of Th1/Th2 balance and leukotriene receptors (Yuan et al. 2013a, b). An extract from *B. virginianum* induced keratinocyte proliferation and inhibited melanin biosynthesis, suggesting possible cosmetic uses (Koshimizu et al. 2004).

Small, eusporangiate ferns produce a single leaf divided into a sporophore, bearing sporangia, and a trophophore. Ethnobotanical surveys have reported

several uses of these ferns as folk remedies, and the therapeutic properties of some species have been explored using experimental approaches (Azaizeh et al. 2006; Kao 1985; Srivastava 2007).

Ophioglossaceae

The fern *Ophioglossum vulgatum*, known as the adder's tongue, is frequently used in folk medicine for dermatological, hemostatic, antiparasitic, and alimentary purposes (Kala et al. 2011; Nwosu 2002; Sarker and Hossain 2009). An ointment known in England as ''Green Oil of Charity'' has long had a reputation as a vulnerary. Accordingly, galactoglycerolipids and flavonol derivatives from aerial parts of *O. vulgatum* have been shown to promote in vitro keratinocyte scratch-wound healing (Clericuzio et al. 2012, 2014). In addition, the fern's aqueous extract has been found to counteract bovine viral diarrhoea virus (BVDV) (Herrmann et al. 2011).

Homoflavonoids from *O. petiolatum* have anti-hepatitis B virus activity (Lin et al. 2005b; Wan et al. 2013). *O. pedunculosum* contains 3-*O*-methyl-quercetin glucosides that inhibit lipopolysaccharide-induced NO production in macrophages (Wan et al. 2012), and a mannan-specific lectin with antifungal activity (He et al. 2011). An alcohol-ethyl acetate fraction from *O. thermale* has shown anti-inflammatory effects on carrageenan-induced inflammation, which may be related to the extract's antioxidant properties (Zhang et al. 2012d).

Gleicheniaceae

In Chinese folk medicine, *Dicranopteris dichotoma* Bernb. is used to treat urinary disease, trauma, and fevers in children, while *Hicriopteris glauca* (Thunb.) Ching. is used to treat bleeding and trauma. The most abundant phytochemicals in the family Gleicheniaceae are terpenoids, many of which exhibit distinct pharmacologically relevant activities (Kamisan et al. 2014). For example, the diterpene (6S, 13S)-cleroda-3, 14-diene-6, 13-diol exhibits moderate anti-HIV activity (Li et al. 2007). In a study of highland ferns in Malaysia, two species occurring at high altitude (1495 m), *Gleichenia truncata* and *Dicranopteris curranni*, were found to be potential sources of natural antiglucosidase, antibacterial, and antioxidant agents (Chai et al. 2013a).

Antiglucosidase activity

Aqueous extracts of *G. truncata* and *D. curranii* were found to have alpha-glucosidase inhibitory activity, suggesting their potential as sources of natural antidiabetic or antihyperglycaemic agents (Chai et al. 2013b). The EC_{50} values of the leaf and rhizome extracts of *G. truncata* in these assays were 408 and 175 μg/mL, respectively, while the corresponding values for *D. curranii* were 143 and 179 μg/mL, respectively (Chai et al. 2013a).

Antibacterial activity

MIC assays performed with extracts at concentrations of up to 50 mg/mL revealed that a *G. truncata* leaf extract inhibited the growth of both Gram-positive (*Staphylococcus aureus*; *Micrococcus luteus*) and Gram-negative (*Escherichia coli*; *Pseudomonas aeruginosa*) bacteria (Chai et al. 2013a). This suggests that *G. truncata* may be a potential source of broad-spectrum antibacterial agents that warrants further investigation. Leaf and rhizome extracts of *D. curranii* and the rhizome extract of *G. truncata* only inhibited the growth of Gram-positive bacteria (Chai et al. 2013b).

Lindsaeaceae

The activities of the compounds isolated from whole *S. chusanum* (L.) Ching plants against *Candida albicans*, *Cryptococcus neoformans*, *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporum canis*, *Epidermophyton floccosum*, and *Aspergillus niger* were determined, yielding minimal inhibitory concentrations (MIC) of 25–100 μg/mL (Ren et al. 2009). Extracts from this species also exhibited inhibitory activity against tyrosinase and the proliferation and apoptosis of K562 cells (Wu et al. 2016).

In addition to the studies described above, four *S. chusanum* extracts were tested to determine their antidotal effects in mice suffering from acute poisoning with arsenic and ammonium chloride. Two of the extracts (B and C) dramatically reduced mortality in arsenic-poisoned mice, and extract C increased tolerance of arsenic, raising the LD_{50} from 31.1 ± 4.3 to 38.2 ± 5.9 mg/kg. In the case of mice poisoned with ammonium chloride, the four extracts also reduced mortality but not in a statistically significant

fashion when compared to a control group at the $P < 0.05$ level (Yang et al. 1989).

Thelypteridaceae

Parathelypteris nipponica (Franch.et Say.) Ching is widely used to treat burns, scale, hematemesis and dysentery in Chinese folk medicine (Editorial Board of China Herba 1998). To explore the origins of its putative beneficial health effects, the antioxidant, free radical scavenging, anti-inflammatory and hepato-protective potential of its extracts have been studied (Fu et al. 2010).

Another investigation showed that methanolic extracts of *Pronephrium megacuspe* (Bak.) Holtt. exhibited toxicity towards *Musca domestica* adults and the 4th instar larva of *Aedes albopictus* and *Myzus persicae*, while also having antifeedant effects on 3rd instar larvae of *Plutella xylostella*, *Ostrinia furnacalic* and *P. rapae* (Huang et al. 2012).

Abacopteris penangiana (Hook.) Ching. is commonly used in traditional medicine to treat acute or chronic pharyngitis, dysentery, upper respiratory infections and other conditions (Ding 1982; Zhao et al. 2006). Because of its diverse biological activities, the pharmacological properties of its extracts and phytochemicals have been studied extensively. Compounds isolated from *A. penangiana* were found to possess cytotoxic activity (Zhao et al. 2006, 2008). Specifically, biological evaluations of flavonoids from this species revealed cytotoxicity towards the HepG2, HeLa and L929 human cell lines (Zhao et al. 2006, 2010b; Fang et al. 2010), antioxidative activity (Zhao et al. 2007a, b), and dopamine-induced neurotoxicity in PC12 cells (Wei et al. 2013).

Further pharmacological investigations on *A. penangiana* have clarified the diverse activities of its extracts and phytochemicals. Total flavonoids extracted from this species and their hydrolysates can prevent testosterone-induced benign prostatic hyperplasia in rats via their anti-inflammatory, antioxidant and anti-proliferative effects (Wei et al. 2012; Yang et al. 2014a). Such mixtures also exert anti-prostatitis effects on carrageenan-induced rats, again as a result of their antioxidative and anti-inflammatory activities (Yang et al. 2014b).

Metabolic syndrome is usually characterized by hyperglycemia, hyperlipidemia, and vascular injury.

Total flavonoids from *A. penangiana* effectively ameliorate these symptoms in diabetic rats when induced by high fat diet and streptozotocin, and the *A. penangiana*-derived flavonoid abacopterin A exhibited hypolipidemic and anti-inflammatory activity in C57BL/6J mice fed on a high fat diet. These effects have been linked to the modulation of oxidative stress and the mitigation of inflammatory responses associated with metabolic disorder (Chen et al. 2011; Lei et al. 2011). Many other studies on the bioactivities of phytochemicals from *A. penangiana* have focused on their neuroprotective effects in vitro and in vivo. Three other flavonoids from this species—5,2′,5′-trihydroxy-7-methoxyflavone (TMF), abacopterin E—significantly attenuated H_2O_2-induced damage in PC12 cells and neurotoxicity in mice induced by D-galactose (Wei et al. 2011a, b; Lei et al. 2011; Wei et al. 2013; Fu et al. 2013).

The genus *Macrothelypteris* (H. Ito) Ching consists of around ten species of moderately large terrestrial ferns (Xing 1991), many of which are used in traditional medicine. Ethanolic extracts of *M. torresiana*, which is distributed across southern China (Chang and Wu 1999), exhibited strong cytotoxicity (An et al. 2005, 2007), and the flavonoid compound protoapigenone isolated from *M. torresiana* (Gaud.) Ching proved to be highly cytotoxic to various tumor cells, with potential pro-apoptotic activity (Chang et al. 2008a, b). This compound and another flavonoid isolated from *M. torresiana* (Gaud.) Ching, 2-(cis-1, 2-dihydroxy 4-oxo-cyclohex-5-enyl)-5, 7-dihydroxy-chromone (DEDC), was identified as being potentially useful in cancer chemoprevention (Liu et al. 2011a, b, c). In a separate study, protoapigenone, 5,7-dihydroxy-2-(1,2-isopropyldioxy-4-oxo-cyclohex-5-enyl)-chromen-4-one, and 5,7-dihydroxy-2-(1-hydroxy-2,6-dimethoxy-cyclohex-4-oxo)-chromen-4-one isolated from *M. viridifrons* (Tagawa) Ching showed strong concentration-dependent anti-proliferative effects on six tumor cell types (Wei et al. 2011a, b). Protoapigenone was also isolated from *M. oligophlebia*, and exhibited clear antitumor activity in vitro and in vivo (Wu et al. 2011a, b).

Total polyphenols from *M. torresiana* were shown to have potential in the treatment of chronic nephrotic syndrome in puromycin aminonucleoside-induced hyperlipidemic mice (Chen et al. 2012a, b). In addition to this renal protective effect, extracts and phytochemicals from *M. torresiana* have various anti-

cancer effects. Total flavonoids from *M. torresiana* showed significant antitumor activity relative to 5-fluorouracil and low acute/subacute oral toxicity in BALB/c mice (Huang et al. 2010a, b, c). In vitro evaluations have shown that protoapigenone possesses significant cytotoxic activity against the cancer cell lines Hep G2, Hep 3B, Tca-8113, MCF-7, A549, MDA-MB-231, M5 and K562, with its lowest IC_{50} value being 0.23 μg/ml towards M5 cancer cells (Huang et al. 2010a, b, c; Lin et al. 2005a, b). Although DEDC (2-(*cis*-1,2-dihydroxy-4-oxo-cyclohex-5-enyl)-5,7-dihydroxy-chromone) exhibited only weak cytotoxicity towards HepG2, MCF-7 and K562 cells, it can induce apoptosis of human neuroblastoma SH-SY5Y cells by triggering the production of ROS and activation of NF-κB (Liu et al. 2012a, b). DICO (5,7-Dihydroxy-2-(1,2-isopropyldioxy-4-oxo-cyclohex-5-enyl)-chromen-4-one) is a novel flavonoid with a nonaromatic B-ring that inhibits the growth of Hep G2 cells, causes arrest at the G2/M phase of the cell cycle, and, induces apoptosis via a ROS-mediated mitochondrial pathway (Zhou et al. 2013).

Aqueous extracts of *Christella arida*, *C. dendata* and *Cyclosorus interruptus* were cytotoxic towards the K562 cell line (Chai et al. 2015b), achieving EC_{50} values of 478.62, 194.50, and 314.52 μg/mL, respectively; for comparative purposes, that of the anticancer drug 5-fluorouracil was 212.86 μg/mL. These results suggest that *C. dendata* may be a valuable source of potent cytotoxic agents with potential applications in cancer therapy (Chai et al. 2015b). Aqueous extracts of *C. arida* and *C. dendata* also exhibit antiglucosidase activity, with EC_{50} values of 559.87 and 87.48 μg/mL, respectively. However, the aqueous extract of *C. interruptus* had no detectable antiglucosidase activity (Chai et al. 2015b). Extracts of *C. dendata* thus contain both cytotoxic and antiglucosidase agents, indicating that further studies on the phytochemistry and pharmacology of this species are warranted.

Dryopteridaceae

The Dryopteridaceae are a family of ferns comprising around 1400 species around the world, many of which have been identified as medicinal herbs (Wu 1991). The rhizomes of *Arachniodes exilis* (Hance)

Ching have been used in folk medicine to treat acute icterus hepatitis, inflammation, dysentery and burn scalds (Chinese Materia Medica Editorial Board 1999). *D. filix-mas* (L.) Schott had been used to treat parasitic diseases in Europe since 1750; its use has been recorded in pharmacopeias from England, Germany, Switzerland, Japan, and America (Zuo and Chen 2005). *D. crassirhizoma* Nakai is another fern in this family that occurs in Korea, Japan, and northern China (Han et al. 1998). Its rhizomes are traditionally used as a vermicide (Han et al. 1998), and it has also been used to treat viral diseases including severe acute respiratory syndrome (SARS) (Zhao et al. 2007b).

Anti-tumor activity

A *n*-hexane extract of *D. fragrans* was tested in an in vitro short-term assay for anti-tumor promoting agents. Flavonoids extracted from *D. erythrosora* showed clear cytotoxic effects on A549 cells and exhibited dose-dependent inhibition of acetylcholinesterase (Zhang et al. 2012a, b, c, d). Moreover, the anticancer activity of fern flavonoids was shown to correlate weakly but positively with their antioxidant potential (Cao et al. 2013a, b). The ethanol extract of *D. crassirhizoma* was reported to have anti-cancer activity and to inhibit the proliferation of human prostate cancer cell lines in a dose- and time-dependent manner (Chang et al. 2010). Flow cytometry and Western blot experiments indicated that its anti-proliferative activity were due to the induction of cell cycle arrest in the G0/G1 phase and apoptosis. The extract's active anti-proliferative components were not identified, but it exhibited no cytotoxicity towards normal spleen cells, suggesting the potential for development as an anti-cancer agent with minimal side effects (Chang et al. 2010).

Fatty acid synthase (FAS) is an important therapeutic target for anti-cancer drug discovery (Flavin et al. 2010). Ten phloroglucinol derivatives with anti-FAS activity were isolated from a methanol extract of the *D. crassirhizoma* rhizome. Among these, flavaspidic acid PB and methylene-bis-methylphlorobutyrophenone exhibited the strongest inhibition of FAS (Na et al. 2006). These results highlight the potential value of *D. crassirhizoma* as a source of lead compounds for anti-cancer drug development.

Antiviral activity

Human immunodeficiency virus (HIV)-1 protease and reverse transcriptase are important therapeutic targets for the development of anti-HIV chemotherapies. Three kaempferol acetylrhamnosides isolated from methanol extracts of *D. crassirhizoma* (crassirhizomoside A, crassirhizomoside C, and sutchuenoside A) were found to be potent inhibitors of both the RNA-dependent and the DNA-dependent DNA polymerase activities of the HIV-1 reverse transcriptase (Min et al. 2001). In addition, four HIV-1 protease inhibitors were isolated from the fern's methanol extract: two triterpenes (dryopteric acids A and B), ursolic acid, and 3,4-dihydroxybenzaldehyde. All four compounds had only moderate HIV-1 protease inhibitory activity compared to the positive control agent acetyl-pepstatin. However, acetylation of dryopteric acid A drastically improved its protease inhibitor activity, yielding an IC_{50} value only 19-fold greater than that of acetyl-pepstatin (Lee et al. 2003).

Antibacterial activity

The antibacterial properties of *Polystichum tussimense*, *P. neolobatum*, *Cyrtomium fortune*, *C. falcatum*, *D. uniformis* and *D. cycadina* have been investigated, revealing that species from the genus *Polystichum* showed more promising antibacterial activity than the others that were tested (Song et al. 2008).

Flavaspidic acids PB and AB from *D. crassirhizoma* were also found to have activity against Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, *Streptococcus mutans*, and *Bacillus subtilis* (Lee et al. 2009). In keeping with this result, the hexane fraction of a methanol extract of *D. crassirhizoma* exhibited good antibacterial activity against clinical isolates and the standard ATCC strain of methicillin-resistant *S. aureus* (Kwon et al. 2007).

The potential of *D. crassirhizoma* as a source of antimicrobial agents for the prevention of dental caries has been highlighted in the literature. Ban et al. (2012) reported that the methanol extract of the fern had bactericidal and bacteriostatic effects on *Streptococcus mutans*, a cariogenic dental pathogen. At concentrations below the minimum inhibitory concentration, the extract attenuated the pathogen's virulence potential by inhibiting its acid production,

acid tolerance, water-insoluble glucan formation, and sucrose-dependent adherence in a dose-dependent manner (Ban et al. 2012). A more recent study confirmed the effectiveness of the hexane fraction of a methanol extract of *D. crassirhizoma* in controlling *S. mutans* biofilm formation, and identified linoleic acid as a key component of the hexane fraction in this context (Jung et al. 2014). Both the hexane fraction and linoleic acid could thus be used in anti-biofilm agents for topical application (Jung et al. 2014).

Antioxidant activity

An ethanol extract of *A. exilis* exhibited anti-oxidant activity in vitro and hepatoprotective activity in vivo against CCl_4-induced hepatotoxicity (Zhou et al. 2010). Flavaspidic acids PB and AB isolated from the *D. crassirhizoma* rhizome exhibited lipid peroxidation inhibitory activity comparable to that of alpha-tocopherol and the synthetic antioxidant butylated hydroxyanisole. The two compounds also showed moderate free radical scavenging activity (Lee et al. 2003).

Zhang et al. (2012a, b, c, d) investigated the total flavonoid contents and free radical scavenging activity of extracts from the leaves, stems, rachis and roots of *D. erythrosora*. Their results indicated that the total flavonoid content of the different plant parts declined in the order stems > roots > rachis > leaves, while the DPPH free radical scavenging abilities (IC_{50}) of 50% ethanol extracts of the different parts declined in the order stems > root > rachis ≫ leaves (Zhang et al. 2012a, b, c, d). The free radical scavenging ability of the different plant parts thus appears to be proportional to their total flavonoid content.

Molluscicidal activity

Socolsky et al. (2011a) evaluated the molluscicidal activity of 12 phloroglucinol derivatives isolated from *E. piloselloides*, *E. gayanum*, *E. yungense*, and *E. lindbergii* against the schistosomiasis vector snail *Biomphalaria peregrina*. The prenylated desaspidins elaphopilosins A and B showed the greatest activity in these assays, and a QSAR analysis showed that there is an optimum molecular volume for high activity, which is probably related to the size of the

active site of the receptor(s) that these compounds interact with.

Other relevant biological activities

Water and ethanol extracts of *D. fragrans* both reportedly help relieve the symptoms of psoriasis (Shen et al. 2002). Flavon-3-ol glycosides from *D. filix-mas* (L.) Schott can be used as histidine decarboxylase inhibitors for the treatment of peptic ulcers and atopic dermatitis (Minoru et al. 1996). In vitro and in vivo results suggest that water extracts of *D. crassirhizoma* can mitigate bone loss by suppressing osteoclast differentiation and function (Ha et al. 2013). The active components responsible for these effects were not identified, but the results suggest that the fern may be useful in the treatment of bone diseases (Ha et al. 2013). In addition, an ethanol extract of *D. crassirhizoma* suppressed inflammatory reactions in macrophages and protected against acute inflammatory lesions of the stomach in mice, suggesting that this fern (or compounds derived from it) could be useful as an anti-inflammatory agent. These effects have been attributed to the presence of kaempferol, quercetin and resveratrol in the extract (Yang et al. 2013).

Polypodiaceae

Two *Phymatopteris* species (Family Polypodiaceae) are used in traditional medicine. *P. hastata* is used in China as a remedy for various diseases including diarrhoea, bronchitis, and influenza, as well as conditions such as carbuncles, furunculosis, and viper bites (Su et al. 2011). On the other hand, in Nepal, *P. quasidivaricata* is used as a traditional treatment for musculo-skeletal problems and dermatological infections (Uprety et al. 2010). Such uses imply that the *Phymatopteris* genus is a promising source of phytochemicals with therapeutically-relevant bioactivities. However, its phytochemistry and pharmacology/bioactivity remain underexplored; the only *Phymatopteris* that have been studied in this context are *P. hastata* and *P. triloba*. A tropical fern from the same family, *Polypodium leucotomos*, which is native to Central and South America is traditionally used as an antiphlogistic, anti-tumor, and anti-inflammatory agent, as well as a general tonic and psoriasis remedy (Ho et al. 2011; Horvath et al. 1967).

Anticancer activity

Several lines of evidence indicate that fern extracts can protect against the development of UV-induced skin cancer. For instance, fern extracts inhibited skin tumor formation in mice exposed to UVB (Alcaraz et al. 1999). Oral aministration of *P. leucotomos* extracts also reduced the formation of mutagenic cyclobutane pyrimidine dimers in human subjects (Middelkamp-Hup et al. 2004) and mice (Zattra et al. 2009) following exposure to UV radiation. The antioxidant activity of *P. leucotomos* extracts is considered central to their ability to mitigate UV-induced DNA damage (Gonzalez et al. 2011). In mice, the fern extract also inhibited UV-induced cyclooxygenase-2 expression and activated tumor suppressor p53 (Zattra et al. 2009), both potentially contributing to the extract's chemopreventive activity against skin cancer (Parrado et al. 2014).

Anti-inflammatory activity

The beneficial actions of *P. leucotomos* extracts as an adjuvant treatment for vitiligo, psoriasis, melasma, and atopic dermatitis have recently been reviewed (Choudhry et al. 2014; Nestor et al. 2014). Oral *P. leucotomos* extract supplementation has been shown to enhance repigmentation in patients with vitiligo undergoing NB-UVB (narrowband ultraviolet B) (Middelkamp-Hup et al. 2007) and PUVA (psoralen plus ultraviolet A) (Reyes et al. 2006) phototherapies. This may be due to the antioxidant properties of the fern extract (Gomes et al. 2001). In keeping with this proposal and the fact that vitiligo is a chronic inflammatory skin disorder (Taïeb 2012), improved repigmentation in vitiligo patients following a combined NB-UVB and oral antioxidant (vitamin E) supplementation therapy has been reported (Elgoweini and Din 2009). In UV-irradiated mice, the fern extract reduced acute inflammation by inhibiting cyclooxygenase-2 (Zattra et al. 2009). Oral administration of a *P. leucotomos* extract, in combination with PUVA therapy, suppressed the proliferation of peripheral blood mononuclear cells in vitiligo patients (Reyes et al. 2006). In vitro, the fern extract also decreased the levels of pro-inflammatory cytokines (IL-2, IFN-, and TNF-α) and induced the production of the anti-inflammatory cytokine IL-10

in human peripheral blood mononuclear cells (Gonzalez et al. 2000).

Antidiabetic activity

The antidiabetic potential of *P. hastata* and *P. triloba* has been studied using cell-based and biochemical assays. (−)-Epiafzelechin 3,5-di-*O*-β-D-apiofuranoside isolated from *P. hastata* improved glucose consumption by insulin-resistant HepG2 cells as well as the translocation of glucose transporter 4 (GLUT4) to the surface of skeletal muscle cells (Ma et al. 2013a, b). On the other hand, leaf and rhizome aqueous extracts of *P. triloba* have demonstrated in vitro glucosidase inhibitory activity (Chai et al. 2013a). Notably, despite the crude nature of the *P. triloba* leaf extract, its EC_{50} value was on the same order of magnitude as that of quercetin, indicating that they have similar potencies (56 vs. 22 g/mL). These results, although still preliminary, suggest that the genus *Phymatopteris* produces bioactive compounds that can affect different therapeutic targets relevant to type 2 diabetes.

The potential of *Phymatopteris* phytochemicals as antidiabetic agents may be enhanced by their antioxidant activity. Selected flavonol glycosides, phenolic acids and phenolic acid derivatives isolated from *P. hastata* have shown radical scavenging activity (Duan et al. 2012a), and the antioxidant activity of organic solvent fractions of *P. hastata* has been correlated with their phenolic contents (Su et al. 2011). A crude aqueous extract of *P. triloba* leaves exhibited both antiglucosidase activity and stronger superoxide scavenging activity than ascorbic acid (Chai et al. 2013b). The extract also exhibited nitric oxide scavenging and ferric reducing activities (Chai et al. 2013a, b). Phenolics detected in *P. triloba* leaf extracts, myricetin and sinapic acid (Chai et al. 2013b), are known to have antiglucosidase/anti-hyperglycemic (Cherng et al. 2013; Tadera et al. 2006) and antioxidant activities (Cos et al. 1998; Jalaludeen and Pari 2011). Oxidative stress is a key factor in the pathogenesis of diabetic complications associated with postprandial hyperglycemia (Aryangat and Gerich 2010). Therefore, dual-function anti-hyperglycemic agents with antioxidant activity may provide additional benefits compared to single-function anti-hyperglycemic agents. Taken together, these findings on the bioactivities and chemical constituents of *P. hastata* and *P. triloba* justify deeper investigations into the antidiabetic potential of species from the *Phymatopteris* genus.

Davalliaceae

A flavonoid-rich (0.258 mg/mL) extract of *D. cylindrica* exhibited a free radical (O_2-, DPPH. and ABTS.) scavenging potential slightly greater than that of rutin (0.25 mg/mL), along with cytotoxic effects on A549 cells and dose-dependent inhibition of acetylcholinesterase (Cao et al. 2014).

Athyriaceae

Athyrium multidentatum (Doll) Ching is one of the most common ferns in the north-east of China and exhibits several pharmacologically relevant effects such as tranquilization, blood pressure reduction, and diuresis. Polysaccharide-rich fractions from this fern were found to exhibit strong antioxidant activity (Sheng et al. 2011; Liu et al. 2011a, b, c, 2013a, b; Sheng 2014; Sheng and Sun 2014), and a polysaccharide extract from *A. multidentatum* (Doll.) Ching showed remarkable anti-aging activity (Liu et al. 2015). Striatisporolide A isolated from rhizomes of *A. multidentatum* exhibited significant cytoproliferative and minor cytoprotective effects on HUVECs arising from interference with ROS generation and apoptosis (Liu et al. 2016).

Perspectives

Fern species are essential constituents of ecosystems and produce a wide array of bioactive components with diverse activities. Many of them are used in traditional medicines and could potentially be used to treat various diseases. However, wild fern plants around the world are subject to many severe threats due to environmental change, and significant losses of fern species and habitats have occurred, leading to a profound loss of biodiversity. At present, there is comparatively little data in the literature relating to the phytochemistry of ferns and their bioactivities, despite their potential as sources of novel bioactive compounds. Further analysis and testing of wild ferns to determine their biological properties and identify their active constituents could thus enable important

improvements in human healthcare and help to valorize natural biodiversity. To this end, a survey will be performed to identify rare, traditional and wild fern species used in foods and medicines. High value products, pharmaceuticals and bioactive food ingredients from ferns will be harvested sustainably for analysis, and their nutritional and phytochemical profiles will be investigated to determine the bioactivity and toxicity of their extracts and components. In addition, the antioxidant and anti-inflammatory activity of selected fractions/purified compounds and ingredients will be examined in selected in vitro and cellular models. The ability of a diet enriched with fern foods and ingredients selected based on in vitro and ex vivo experiments to modulate clinically relevant parameters, oxidative and inflammatory stress, and cardiovascular function in overweight subjects will be assessed.

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