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Natural products isolation studies of native Australian fern species

Thinley Gyeltshen[A], Jason A. Smith[A,*] and Alex C. Bissember[A,*]

For full list of author affiliations and declarations see end of paper

*Correspondence to:
Jason A. Smith
School of Natural Sciences – Chemistry, University of Tasmania, Hobart, Tas., 7001, Australia
Email: jason.smith@utas.edu.au

Alex C. Bissember
School of Natural Sciences – Chemistry, University of Tasmania, Hobart, Tas., 7001, Australia
Email: alex.bissember@utas.edu.au

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ABSTRACT

Natural products isolation studies of 16 native Australian fern species have been undertaken, facilitated by pressurised hot water extraction (PHWE). Fourteen of these fern species have not been the subject of natural products isolation research previously. In total, 14 different compounds were isolated from 12 of these 16 different fern species. This included γ- and δ-lactones; flavonoid glycosides, a dihydrobenzofuran neolignan, in addition to hydroxycinnamate/caffeic acid esters. More specifically, the lactones 5,6-dihydro-5-hydroxy-6-methyl-2*H*-pyran-2-one, 5-(1-hydroxyethyl)-2(5*H*)-furanone and osmundalin were obtained from *Todea barbara*, while a dihydrobenzofuran neolignan, (−)-*trans*-blechnic acid were found in *Austroblechnum penna-marina* subsp. *alpina*, and the shikimate ester 5-*O*-caffeoylshikimic acid was isolated from *Parablechnum wattsii*. In addition, flavonoids and their glycoside derivatives, kaempferol 3-*O*-glucopyranoside, 4*β*-carboxymethyl-(−)-epicatechin, (2*R*)-eriodictyol-7-*O*-*β*-D-glucopyranoside, naringin, quercitrin, quercetin 3-*O*-(6″-acetyl)-*β*-D-glucopyranoside, rutin, and tiliroside were isolated from seven other fern species.

Keywords: ferns, flavonoid, glycoside, natural products, natural products isolation, neolignan, *Polystichum*, *Todea*.

Introduction

Ferns are a group of vascular plants bearing complex leaves called megaphylls. These plants do not produce flowers or seeds and reproduce via spores. There are more than 12 000 species of ferns that are widely distributed across the globe, with the greatest diversity typically found in the tropics.[1] Ferns represent the phylogenetic bridge between the lower and higher plants in the plant kingdom. For centuries, ferns have been used in many different contexts: as food, medicines, and ornaments. The fiddleheads (or croziers) of many fern species often feature in Asian cuisine. Indeed, it is reported that 52 species feature in Chinese food and it is estimated that the actual number of edible ferns may extend to 144 species.[2] In Japan, ostrich (*Matteuccia struthiopteris* (L.) Tod.), bracken (*Pteridium aquilinum* (L.) Kuhn), and royal ferns (*Osmunda japonica* Thunb.) are the most popular edible ferns that are harvested.[3] In Australia, the sporocarps of the small freshwater fern, nardoo (*Marselia drummondii* A. Braun) are consumed as baked cakes by first nations people following proper and extensive preparation.[4] In addition to their use in cuisine, many fern species feature in traditional pharmacopoeias and are used to treat an array of ailments.[5–8] In this context, relative to other species of vascular plants, ferns and lycophytes are poorly represented.[9]

Ferns and lycophytes, like angiosperms, are a rich source of phytochemicals with interesting biological properties. Natural products isolation studies reveal that they contain flavonoids, terpenoids (including steroids), and polyphenols (Fig. 1).[5,10] They also contain more distinctive alkaloid secondary metabolites. For example, lycopodium alkaloids such as lycopodine (**1**), lycodine (**2**), fawcettimine (**3**), and phlegmarine (**4**) skeletons have been isolated from Lycopodiaceae and Huperziaceae.[10–12] Flavonoids are commonly isolated from numerous fern species. For example, species of

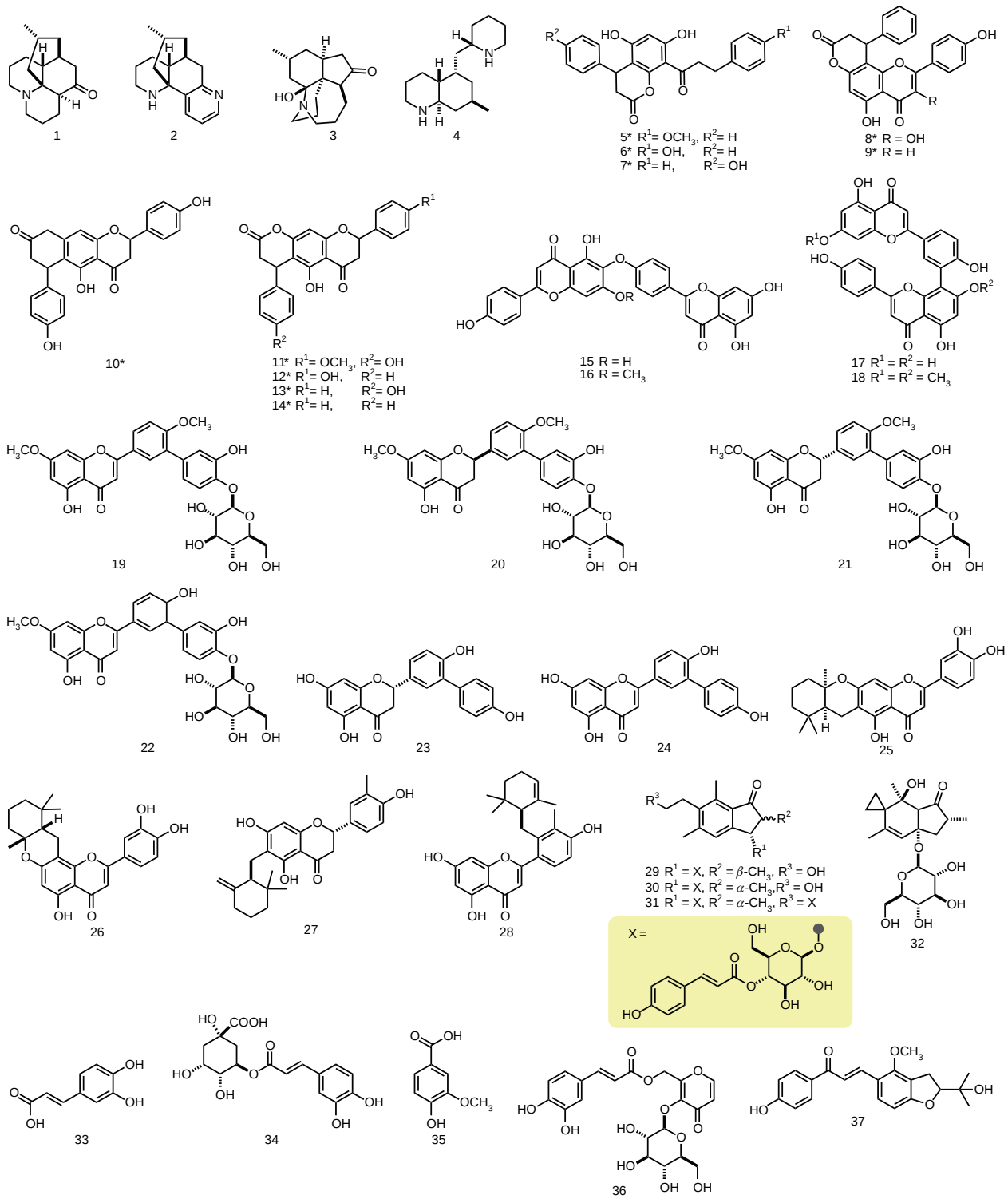


Fig. 1. Examples of secondary metabolites isolated from ferns and lycophytes: alkaloids (**1**–**4**), complex flavonoids (**5**–**28**), sesquiterpenoids (**29**–**32**) and miscellaneous natural products (**33**–**37**); *stereogenic centres were not assigned in these molecules

the genus *Pteris* are rich in flavonoids with mainly *α*- and *β*-glucosides, galactosides, rhamnosides or arabinosides present.[13,14] Distinctive flavonoids that have been isolated include neoflavonoids, calomelanols A–J (**5**–**14**) from farinose of *Pityrogramma calomelanos* (L.) Link,[15,16] bioflavonoids such as hinokiflavone (**15**), 7″-*O*-methylhinokiflavone (**16**) amentoflavone (**17**) and 7,7″-di-*O*-methylamentoflavone (**18**) from *Selaginella tamariscina*

(P.Beauv.) Spring,[17] involvenflavones A–F (**19–24**) from *S. involven* (Sw.) Spring[18] and prenylated flavonoids (**25–28**) from *Helminthostachys zeylanica* (L.) Hook.[19] Many sesquiterpenoid compounds with indane or cadinene skeletons are found in ferns.[10] Sesquiterpenyl indanones, known as pterosins, and their glycosides (pterosides) have been isolated from bracken fern species and polypodiaceous ferns.[20] For example, multifidosides A–C (**29–31**) have been isolated from *Pteris multifida* Poir.[14] and the carcinogenic pteroside, ptaquiloside (**32**) has been isolated from *Pteridium aquilinium* (L.) Kuhn.[21] The terpenoids obtained from ferns are typically *ent*-kaurane-, *ent*-atisane- and *ent*-primarane-type diterpenoids, which are present in *Pteris* species.[22] Labdane- and clerodane-type diterpenoids, diterpenoid glycosides and triterpenoids are major constituents in the Gleicheniaceae family,[23–26] and ecdysteroids have been isolated from species of genera *Microsorum* and *Diplopterygium* in the family Polypodiaceae.[27–31] Phenolic compounds are another class of secondary metabolites widely distributed in ferns. Commonly isolated molecules of this type include caffeic (**33**), chlorogenic (**34**) and vanillic (**35**) acids.[10,32,33] The glycosylated phenolic acid, 7-*O*-caffeoylhydroxymaltol-3-β-D-glucopyranoside (**36**) was isolated from *Pteris ensiformis* Burm.,[33–35] in addition to a chalcone derivative, licoagrochalcone D (**37**) from *Pteris multifida* Poir.[36]

Natural products research concerning ferns native to Australia are mainly restricted to toxicity studies. For example, the sporocarps of the freshwater fern nardoo, *Marsilea drummondii* A. Braun, which are used for food by Australian Aborigines,[4] are reportedly toxic to humans, cattle, and sheep.[37] Studies on this waterfern has revealed that its toxicity derives from high levels of the enzyme thiaminase which breaks down thiamine (vitamin B1).[38] Similarly, bracken ferns *Pteridium aquillinum* (L.) Kuhn and *P. esculentum* (G.Forst.) Nakai have been the subject of many phytochemical and pharmacological studies in order to elucidate the mechanism of toxicity involving the carcinogenic norsesquiterpene glucoside, ptaquiloside (**32**).[39–42] Consequently, many sesquiterpenoid compounds have been isolated from *P. aquillinum* (L.) Kuhn.[20,43–45] The presence of ptaquiloside has been reported in fern species from the genera *Pteris*, *Microlepia*, *Hypolepis* and *Chelianthes*.[43,44,46] Beyond their toxicity, very limited information regarding the phytochemistry of ferns found in Australia exists. Nevertheless, due to their wide geographic distribution, many native Australian ferns are also found in Asia and South America and natural products isolation studies of species found in these locations have been undertaken. For example, *Helminthostachys zeylanica* (L.) Hook which is found widely distributed in tropical parts of Asia, the Pacific region, and Australia,[1] contains prenylated flavonoids, ugonins,[47,48] cyclised geranyl stilbenes, and ugonstiblenes.[49] Similarly, *Salvinia* species have a global distribution and the species, *S. auriculata* Aubl. and a hybrid, *S.xmolesta* D.S.Mitch. are found in Australia.[1] Bioactivity-guided phytochemical investigation of these two Australian species allowed for the isolation of more than sixty different secondary metabolites that include diterpenes, polyphenols, fatty acids, triterpene, apocarotenoids, acyclic sesquiterpenoids, monoterpenes, jasmonates, steroids and coumarins.[50–52] However, a large number of native Australian ferns, particularly endemic species, have not been the subject of natural products isolation studies.

In this report, a total of 16 Australian native fern species formed the basis of natural products isolation studies. Specifically, our research concerned *Todea barbara* (L.) T. Moore, *Alsophila australis* (R.Br.) Domin, *Dicksonia antarctica* Labill., *Calochlaena dubia* (R.Br.) M. D. Turner & R. A. White, *Polystichum proliferum* (R.Br.) C. Presl, *P. vestitum* (G. Forst.) C. Presl, *Pellaea falcata* (R.Br.) Fée, *Lecanopteris pustulata* subsp. *pustulata* (G. Forst.) Testo & A. R. Field, *Oceaniopteris cartilaginea* (Sw.) Gasper & Salino, *Lomaria nuda* (Labill.) Willd., *Doodia australis* (Parris) Parris, *Austroblechnum penna-marina* (Poir.) Gasper & V. A. O. Dittrich subsp. *alpina* (R.Br.) S. Jess. & L. Lehm., *Parablechnum wattsii* (Tindale) Gasper & Salino, *Gleichenia alpina* R.Br., *Histiopteris incisa* (Thunb.) J.Sm. and *Pteridium esculentum* (G. Forst.) Nakai subsp. *esculentum*. Two of these species, *Polystichum vestitum* (G. Forst.) C. Presl and *Gleichenia alpina* R.Br., were previously thought to be endemic to Tasmania,[53] however, these species were recently found in New Zealand.[1] We isolated a total of 14 different compounds (**38–51**) from 12 native Australian fern species, including γ- and δ-lactones; flavonoid glycosides, a dihydrobenzofuran neolignan, in addition to hydroxycinnamate/caffeic acid esters (Fig. 2).

Results and discussion

For each of the 16 native Australian fern species that we investigated, PHWE of leaf material, followed by liquid–liquid extraction of the aqueous PHWE extract with ethyl acetate provided a crude organic extract after concentration under reduced pressure. In each case, the remaining aqueous phase was concentrated under reduced pressure to afford a crude aqueous extract. The combined yield (% w/w) of the respective crude extracts thus obtained is shown in Table 1. With the exception of *P. vestitum* (0.38% w/w), yields of crude extracts were >0.5% w/w in all cases. The crude extracts were then subjected to various standard flash column chromatography and preparative thin layer chromatography procedures.

Dicksonia antarctica and *Pteridium esculentum* are the only 2 of these 16 fern species that have been the subject of previous natural products isolation studies. Previously, the phenolic compounds (5*S*,6*S*,9*S*,10*S*)-15-hydroxycadina-3,11-dien-2-one and *p*-hydroxystyrene β-vicianoside, in addition to *p*-hydroxystyrene β-D-glucoside, kaempferol 3-*O*-β-D-glucoside, kaempferol 3-*O*-(2-*O*-β-D-xylosyl)-β-D-glucoside, kaempferol

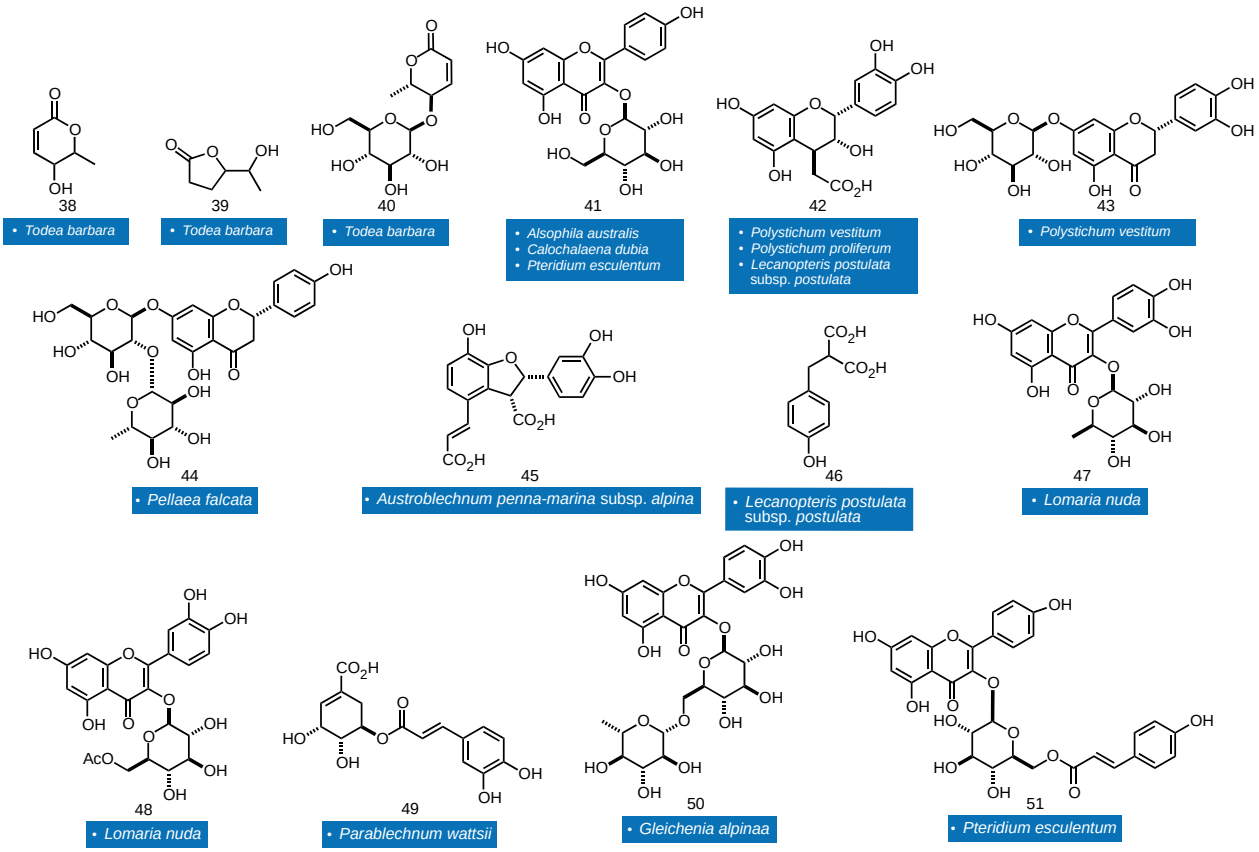


Fig. 2. Secondary metabolites **38**–**51** isolated from 12 of the 16 native Australian fern species investigated in this study.

Table 1. Yields (% w/w) of the respective crude extracts obtained following PHWE of 16 native Australian fern species in this study.

Entry	Fern species	Leaf material (g)	Crude extract (mg)	Yield (% w/w)
1	*Todea barbara*	29	646	2.23
2	*Alsophila australis*	30	268	0.89
3	*Calochalaena dubia*	30	575	1.92
4	*Polystichum vestitum*	30	114	0.38
5	*Polystichum proliferum*	30	240	0.80
6	*Pellaea falcata*	30	1000	3.33
7	*Austroblechnum penna-marina* subsp. *alpina*	29	409	1.41
8	*Lecanopteris pustulata* subsp. *pustulata*	30	154	0.51
9	*Lomaria nuda*	30	254	0.85
10	*Parablechnum wattsii*	30	523	1.74
11	*Gleichenia alpina*	29	793	2.73
12	*Dicksonia antarctica*	30.5	298	0.98
13	*Doodia australis*	31	617	1.99
14	*Oceaniopteris cartilaginea*	33	1500	4.55
15	*Histiopteris incisa*	35	877	2.51
16	*Pteridium esculentum*	150	2700	1.80

3-*O*-(6-*p*-coumaroyl)-*β*-D-glucoside and chlorogenic acid have been isolated from *P. esculentum* fronds (1.2 kg of dry plant material).[54] 4-*O*-Caffeoylshikimic acid and 4-*O*-(*p*-coumaroyl) shikimic acid were isolated from croziers of *D. antarctica* (2.4 kg of fresh plant material) in 1997.[55,56] In this present study, secondary metabolites were not isolated from *D. antarctica*, *Doodia australis*, *Oceaniopteris cartilaginea* and *Histiopteris* species. However, 14 different compounds were isolated from the remaining 12 fern species we investigated. A combination of standard ^{1}H, ^{13}C and 2D (COSY, HMBC and HSQC) NMR spectroscopic techniques were employed to elucidate the structures of these compounds. In each case, these data were consistent with equivalent data reported in the literature. Specifically, we obtained 5,6-dihydro-5-hydroxy-6-methyl-*2H*-pyran-2-one (**38**), 5-(1-hydroxyethyl)-2(*5H*)-furanone (**39**), osmundalin (**40**), astragalin (**41**), 4*β*-carboxymethyl-(−)-epicatechin (**42**), (*2R*)-eriodictyol-7-*O*-*β*-D-glucopyranoside (**43**), naringin (**44**), (−)-*trans*-blechnic acid (**45**), (*p*-hydroxybenzyl)malonic acid (**46**), quercitrin (**47**), quercetin 3-*O*-(6″-acetyl-*β*-D-glucopyranoside) (**48**), 5-*O*-caffeoylshikimic acid (**49**), rutin (**50**), and tiliroside (**51**) (Fig. 2).

5,6-Dihydro-5-hydroxy-6-methyl-*2H*-pyran-2-one (**38**) and 5-(1-hydroxyethyl)-2(*5H*)-furanone (**39**) were obtained as a mixture from *Todea barbara* in a ~2:1 ratio, as judged by NMR spectroscopic and GC-MS analysis (see Supplementary Material). Osmundalin (**40**) was also isolated from *T. barbara*. Lactones **38**–**40** have been isolated from *Osmunda japonica*, a common Japanese fern species, and are reported to exhibit antifeedant properties against the larvae of yellow butterfly, *Eurema hecabe mandarina*.[57,58] In addition, all three natural products have also been isolated from *Angiopteris caudatiformis*, a fern species used in Chinese folk medicine for the treatment of a broad range of ailments.[59] Natural products **38** and **39** have been isolated from the fern species *A. esculenta*[60] and angiopteroside, an epimer of osmundalin (**40**), was isolated from *Angiopteris evecta*.[61]

4*β*-Carboxymethyl-(−)-epicatechin (**42**),[62] was isolated from *Polystichum vestitum*. This secondary metabolite has been isolated from *Davallia divaricata*,[62] *D. solida*[63] and *Dryopteris crassirhizoma*.[64] We also obtained molecule **42** from *Polystichum proliferum* and *Lecanopteris pustulata subsp. pustulata*. All of these fern species are members in the order Polypodiales. Dihydrobenzofuran neolignane, (−)-*trans*-blechnic acid (**45**) was isolated from *Austroblechnum pennamarina* subsp. *alpina*; a species formerly classified within the genus *Blechnum*. (−)-*trans*-Blechnic acid (**45**) and its epimer, epiblechnic acid, represent characteristic constituents of the family Blechnaceae.[65] Blechnic acid has been isolated from various fern species, including *Blechnopsis orientalis*, *Spicantopsis amabilis*, *S. niponica*, *Woodwardia orientalis*, *W. prolifera*, *Brainea insignis*[65] and *Struthiopteris spicant*.[66] We isolated 5-*O*-caffeoylshikimic acid (**49**) (0.5% w/w yield) from *Parablechnum wattsii* (also formerly in the genus *Blechnum*). Compound **49** is a major secondary metabolite present in this fern and a known enzymatic browning agent present in dates, *Phoenix dactylifera*.[55,67] It is a major phytochemical and an anti-thiamine factor isolated from *Pteridium aquillinum* var. *latiusculum* and reportedly causes depression of leucocytes and thrombocytes in calves.[68] 5-*O*-Caffeoylshikimic acid is found widely distributed in Equisetaceae family and in ferns from the families Adiantaceae, Dryopteridaceae, Athyriaceae, Dennstaedtiaceae, Osmundaceae and Thelypteridaceae.[69] Interestingly, we isolated *p*-hydroxybenzylmalonic acid (**46**) and 4*β*-carboxymethyl-(–)-epicatechin (**42**) from *Lecanopteris pustulata* subsp. *pustulata*. Natural product **46** has been isolated from liquorice previously.[70] Liquorice primarily derives from three species, *Glycyrrhiza glabra*, *Glycyrrhiza uralensis* and *Glycyrrhiza inflata* and the presence of *p*-hydroxybenzylmalonic acid (**46**) has been reported from all three.[71]

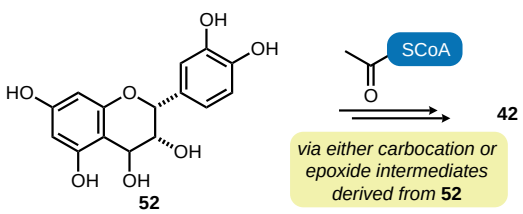
Flavonoid glycosides **41**, **43**, **44**, **47**, **48**, **50**, and **51** were also isolated in our study. Specifically, we obtained the common flavonoid glucoside astragalin (**41**) from *Alsophila australis*, *Calochalaena dubia* and *Pteridium esculentum*. It has been isolated from many plant species including from the bracken fern *P. aquilinum*.[72–76] We isolated (*2R*)-eriodictyol-7-*O*-*β*-D-glucopyranoside (**43**) from *P. vestitum*. This natural product has been isolated from a wide range of flowering plants.[77–85] In ferns, its presence has been identified in species of *Pyrrosia*.[86] Molecule **43** is a reported Nrf2 activator and confers protection against cisplatin-induced toxicity and cerebral ischemic injury.[84,87] Naringin (**44**) and rutin (**50**) were isolated from *Pellaea falcata* and *Gleichenia alpina*, respectively. Both are commonly reported flavonoid glycosides found in citrus, and exhibit a broad range of pharmacological activity.[88–95] Compounds **44** and **50** have also been found in fern species.[96–99] Trace amounts of quercitrin (**47**) and quercetin 3-*O*-(6″-acetyl)-glucoside (**48**) were isolated from *Lomaria nuda*. Both molecules are present in an array of plant species and possess wide ranging biological properties. Tiliroside (**51**), a kaempferol flavonoid glucoside with a coumaroyl moiety, was isolated from *Pteridium esculentum*. Its presence has been identified in various plant species, including *P. aquilinum*; and compound **51** is a reported carcinogen found in bracken fern.[100–103] However, tiliroside also exhibits profound anti-hyperglycemic, anti-hyperlipidemic and antioxidant effects, and has potential therapeutic applications for the treatment of diabetes.[100,104–106]

Among the 14 secondary metabolites isolated in this study, osmundalin (**40**), 4*β*-carboxymethyl-(−)-epicatechin (**42**) and *trans*-blechnic acid (**45**) have only been isolated from fern sources to date (Table 2). This reveals that various Australian fern species investigated in our study contain secondary metabolites that are consistent with other members in the genera, families or orders that are found distributed beyond Australia. For example, *Todea barbara* is exclusively a southern hemisphere species and both *Osmunda japonica* and *Angiopteris caudatiformis* are species found in eastern Asia

Table 2. Distribution of isolated secondary metabolites **38**–**51** in ferns species.

Natural product	Ferns	Exclusive to fern species
38: osmundalactone	*Todea barbara; Osmunda japonica*	–
	Angiopteris caudatiformis	
39: 5-(1-hydroxyethyl)-2(5*H*)-furanone	*Todea barbara; Osmunda japonica*	–
	Angiopteris caudatiformis	
40: osmundalin	*Todea barbara; Osmunda japonica*	Yes
	Angiopteris caudatiformis	
41: astragalin	*Alsophila australis; Calochalaena dubia*	–
	Pteridium esculentum; Pteridium aquilinum	
42: 4*β*-carboxymethyl-(–)-epicatechin	*Davallia divaricate; Davallia solida*	Yes
	Dryopteris crassirhizoma	
	Polystichum vestitum; Polystichum proliferum	
	Lecanopteris pustulata subsp. *pustulata*	
43: (2*R*)-eriodictyol-7-*O*-*β*-D-glucopyranoside	*Polystichum vestitum; Pyrrosia (genus)*	–
44: naringin	*Pellaea falcata; Elaphoglossum spathulatum*	–
	Ceterach officinarum; Drynaria fortune	
45: *trans*-blechnic acid	*Austroblechnum penna-marina* subsp. *alpina*	Yes
	Blechnopsis orientalis; Spicantopsis amabilis	
	Spicantopsis niponica; Struthiopteris spicant	
	Woodwardia orientalis	
	Woodwardia prolifera; Brainea insignis	
46: *p*-hydroxybenzylmalonic acid	*Lecanopteris pustulata* subsp. *pustulata Diplazium esculentum*	–
47: quecertin-3-*O*-(6′-*O*-acetyl)glucoside	*Lomaria nuda*	–
48: quercitrin	*Lomaria nuda*	–
49: 5-*O*-caffeoylshikimic acid	*Parablechnum wattsii; Phoenix dactylifera*	–
	Dicksonia antarctica	
	Pteridium aquilinum var. *latiusculum*	
50: rutin	*Gleichenia alpina*	–
	Sphaerostephanos arbusculus	
51: tiliroside	*Pteridium esculentum; Pteridium aquilinum*	–

regions. *trans*-Blechnic acid (**45**) has only been obtained from fern species of the family Blechnaceae. The remaining natural products are regularly isolated from angiosperms, including various fern species. 4*β*-Carboxymethyl-(−)-epicatechin (**42**) is a particularly rare natural product and its isolation solely from ferns suggests that its formation might derive from a biosynthetic pathway unique to certain fern species (Scheme 1).



Scheme 1. Overview of possible biosynthetic pathway leading to 4*β*-carboxymethyl-(−)-epicatechin (42).

Conclusions

Our natural products isolation studies provide further evidence that fern species represent a source of structurally diverse phytochemicals with interesting biological properties. Phytochemical screening of 16 native Australian ferns enabled the isolation of 14 previously reported compounds.

The structures of these compounds were primarily elucidated via 1D (^{1}H and ^{13}C) and 2D (COSY, HSQC and HMBC) NMR spectroscopy. In each case, the characterisation data were consistent with equivalent data reported in the literature. These isolated compounds included flavonoid glycosides, caffeic acid esters, lactones, and a dihydrobenzofuran neolignan. Lactone molecules, 5,6-dihydro-5-hydroxy-6-methyl-*2H*-pyran-2-one, 5-(1-hydroxyethyl)-2(*5H*)-furanone and osmundalin were isolated from *Todea barbara*. 4*β*-Carboxymethyl-(−)-epicatechin was isolated from both species of *Polystichum* investigated in this study. Our isolation of (−)-*trans*-blechnic acid from *Austroblechnum penna-marina* subsp. *alpina* is consistent with this natural product representing a characteristic compound in the family Blechnaceae.

Experimental

Plant material

Leaf material from 13 ferns *Todea barbara*, *Alsophila australis*, *Dicksonia antarctica*, *Calochlaena dubia*, *Polystichum proliferum*, *P. vestitum*, *Pellaea falcata*, *Lecanopteris pustulata* subsp. *pustulata*, *Oceaniopteris cartilaginea*, *Lomaria nuda*, *Doodia australis*, *Austroblechnum penna-marina* subp. *alpina* and *Parablechnum wattsii* were collected from the Royal Botanical Gardens of Tasmania in Hobart during February 2020. Aerial parts of *Gleichenia alpina* was collected from Wombat Moor at Mt Field National Park (42.6829°S, 146.6174°E; 1073 m above sea level) in February 2021. *Histiopteris incisa* was collected from Mt Field National Park (42.7806°S, 146.5844°E; 461 m above sea level) in February 2021. Aerial parts of *Pteridium esculentum* were collected from five healthy plants growing at Marion Bay (42.8218°S, 147.8671°E) in October 2021. Voucher specimens have been provided to the Tasmanian Herbarium, Tasmanian Museum and Art Gallery (no. HO607603–HO607618). With the exception of *Pteridium esculentum*, all plant material was air-dried for 2 weeks and stored prior to extraction. *P. esculentum* plant material was dried in an oven at 45°C for 3 days prior to extraction.

General

Solvents used in all experiments were of analytical grade or purified by standard laboratory procedures. Plant material was ground using a Sunbeam spice grinder. Pressurised hot water extraction (PHWE) was performed using Breville Expresso Machine Model 800ES. This PHWE method is a well-established natural products extraction technique.[107–109] The extracted organic solvents were dried using anhydrous $MgSO_4$ and Na_2SO_4. Solvents were removed under reduced pressure on a rotary evaporator. Flash column chromatography was performed using flash grade silica gel (Kieselgel 60). Automated flash chromatography was performed using a Grave Reveleris X2 flash column chromatography system or a Büchi Flash Pure system with 40 μm silica gel cartridges. TLC analysis was performed using Merck silica gel 60-F_{254} plates. NMR spectroscopy was performed on a Bruker Avance III NMR spectrometer operating at 400 MHz (^{1}H) and 100 MHz (^{13}C) or Bruker Ascend^{TM} 600 NMR spectrometer operating at 600 MHz for (^{1}H) and 150 MHz (^{13}C). The deuterated solvents used were D_2O, $CDCl_3$, acetone-d_6, CD_3OD and DMSO-d_6. Spectra were calibrated by assignment of the residual solvent peak to δ_H 7.26 and δ_C 77.16 for $CDCl_3$; δ_H 2.50 and δ_C 39.52 for DMSO-d_6; δ_H 3.31 and δ_C 49.00 for CD_3OD; δ_H 4.79 for D_2O; and δ_H 2.05 and δ_C 29.84 for acetone-d_6.[110] Infrared spectroscopy was performed using a Shimadzu FTIR 8400s spectrometer, with samples prepared as thin films on NaCl plates. Gas chromatography mass spectrometry (GC-MS) experiments were performed on Agilent 6850 GC and Agilent 5975C mass spectrometers. HRESIMS analyses were conducted on a Thermo LTQ Orbitrap XL mass spectrometer (Thermo Fisher Scientific).

Extraction and isolation

PHWE of *Todea barbara*

T. barbara dried leaflets (29 g) were finely ground using a spice grinder, mixed with sand (~4 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (646 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (10 g). *Extract A*: Extract A (646 mg) was redissolved in EtOAc, adsorbed onto silica/Celite® (1:1 mixture by mass), and subjected to flash column chromatography {silica; hexanes (50 mL), 10% acetone/hexanes (50 mL), 20% acetone/hexanes (100 mL), 30% acetone/hexanes (150 mL), 40% acetone/hexanes (100 mL), 50% acetone/hexanes (50 mL), 60% acetone/hexanes (50 mL) and acetone (150 mL)} to provide a mixture of compounds **38** and **39** (23 mg, 0.8% w/w yield in a ~2:1 ratio) as colourless crystalline solids. This mixture was analysed by GC-MS. *Extract B*: Extract B (10 g) was soaked in MeOH (~200 mL) for 1 h, repeated five times, combined, and concentrated to provide extract B.1 (4 g). Extract B.1 was then soaked in acetone (~200 mL) for 1 h, repeated 5 times, combined, and concentrated to provide extract B.2 (~2 g). Extract B.2 (~1 g) was redissolved in acetone, absorbed onto silica/Celite® (1:1 mixture by mass), and subjected to flash column chromatography {silica; hexanes (50 mL), 10% acetone/hexanes (100 mL), 50% acetone/hexanes (50 mL), acetone (50 mL) and 50% MeOH/acetone (50 mL)}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined to afford six fractions,

F.1–6. Fraction F.5 (709 mg) was again adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; hexanes (50 mL), 10% acetone/hexanes (50 mL), 30% acetone/hexanes (200 mL), 50% acetone/hexanes (200 mL), and acetone (30 mL)}, which provided compound **40** (570 mg, 2.0% w/w yield) as an off-white solid. Extract B.1 (1.5 g) was absorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (75 mL), 13% MeOH/CH_2Cl_2 (150 mL), 27% MeOH/CH_2Cl_2 (75 mL), 53% MeOH/CH_2Cl_2 (150 mL) and MeOH (100 mL)}. Following TLC and ^{1}H NMR spectroscopic analysis the resulting fractions were combined to afford four fractions, F.1–4. Fraction F.3 (641 mg) was redissolved in MeOH, absorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (50 mL), 25% MeOH/CH_2Cl_2 (100 mL), 66% MeOH/CH_2Cl_2 (75 mL) and MeOH (50 mL)}, which provided compound **40** (30 mg, 2.0% w/w yield) as an off-white solid.

*Osmundalactone (**38**)*.[57] Colourless crystalline solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (1H, dd, J = 9.9 and 2.3 Hz; H-4), 5.92 (1H, dd, J = 9.9 and 1.9 Hz; H-3), 4.31 (1H, m; H-6), 4.18 (1H, d, J = 8.7 Hz; H-5), 1.42 (3H, d, J = 6.4 Hz; 7-CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.2 (C-2), 148.5 (C-4), 120.7 (C-3), 79.0 (C-6), 67.7 (C-5), 18.2 (7-CH_3) ppm.

*5-(1-Hydroxyethyl)-2(5H)-furanone (**39**)*.[57,58] Colourless crystalline solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.35 (1H, m; H-5), 4.08 (1H, m; H-6), 2.53 (1H, m; H-3a), 2.48 (1H, m; H-3b), 2.19 (1H, m; H-4a), 2.12 (1H, m; H-4b), 1.13 (3H, d, J = 6.5 Hz; 7-CH_3) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.5 (C-2), 83.5 (C-5), 67.4 (C-6), 28.6 (C-3), 20.9 (C-4), 17.7 (7-CH_3) ppm.

*Osmundalin (**40**)* (CAS# 54835-71-1).[57] Off-white solid. [α] –65.1° (*c* 0.075, MeOH), lit. [α] –107° (*c* 1.0, MeOH).[58] ^{1}H NMR 600 MHz, CD_3OD) δ 7.04 (1H, dd, J = 9.9 and 2.9 Hz; H-3), 5.98 (1H, dd, J = 9.9 and 1.5 Hz; H-2), 4.48 (1H, quintet, J = 7.4 Hz; H-5), 4.45 (1H, d, J = 7.8 Hz; H-1′), 4.43 (1H, ddd, J = 7.6, 2.8 and 1.5 Hz; H-4), 3.85 (1H, dd, J = 11.8 and 5.6 Hz; H-6′b), 3.79 (1H, dd, J = 11.8 and 1.9 Hz; H-6′a), 3.33 (1H, t, J = 8.9 Hz; H-3′), 3.26 (2H, m; H-4′,5′), 3.16 (1H, t, J = 9.1 Hz; H-2′), 1.42 (3H, d, J = 6.5 Hz; 6-CH_3) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 165.14 (C-1), 147.71 (C-3), 121.55 (C-2), 102.81 (C-1′), 79.29 (C-5), 78.16 (C-5′), 77.95 (C-3′), 74.82 (C-2′), 73.36 (C-4), 71.49 (C-4′), 62.72 (C-6′), 18.57 (C-6) ppm.

PHWE of *Alsophila australis*

A. australis dried leaflets (30 g) were finely ground using a spice grinder, mixed with sand (~6 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (2 × 200 mL and 150 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (268 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (7 g). *Extract A*: Extract A (268 mg) was redissolved in EtOAc and MeOH, absorbed onto silica/Celite® (1:1 mixture by mass), and subjected to flash column chromatography {silica; hexanes (100 mL), 50% EtOAc/hexanes (100 mL), EtOAc (100 mL), 10% MeOH/EtOAc (100 mL) and 20% MeOH/EtOAc (100 mL)}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined to afford five fractions, F.1–5. Fraction F.3 (146 mg) was redissolved in EtOAc and MeOH, adsorbed onto absorbed onto silica/Celite® (1:1 mixture by mass), and subjected to flash column chromatography {silica; CH_2Cl_2 (150 mL), 20% EtOAc/CH_2Cl_2 (100 mL), 40% EtOAc/CH_2Cl_2 (100 mL), 60% EtOAc/CH_2Cl_2 (100 mL), 80% EtOAc/CH_2Cl_2 (100 mL), EtOAc (100 mL) and 20% MeOH/EtOAc (100 mL)}, which afforded compound **41** (12 mg, 0.04% w/w) as a pale-yellow solid.

*Astragalin (**41**)* (CAS# 480-10-4).[73,75] Pale-yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 8.06 (2H, d, J = 8.9 Hz; H-2′,6′), 6.90 (2H, d, J = 8.9 and 1.9 Hz; H-3′, 5′), 6.41 (1H, d, J = 2.1 Hz; H-8), 6.21 (1H, d, J = 2.1 Hz; H-6), 5.26 (1H, d, J = 7.4 Hz; H-1″), 3.69 (1H, dd, J = 11.9 and 2.3 Hz; H-6a″), 3.53 (1H, dd, J = 11.9 and 5.6 Hz; H-6b″), 3.40–3.46 (2H, m; H-2″,3″), 3.32 (1H, m; H-4″), 3.21 (1H, m; H-5″) ppm; ^{13}C NMR (150 MHz, CD_3OD) δ 179.54 (C-4), 165.98 (C-7), 163.10 (C-5), 161.58 (C-4′), 159.09 (C-2), 158.52 (C-9), 135.45 (C-3), 132.28 (C-2′,6′), 122.80 (C-1′), 116.07 (C-3′,5′), 105.75 (C-10), 104.04 (C-1″), 99.87 (C-6), 94.73 (C-8), 78.43 (C-5″), 78.04 (C-3″), 75.73 (C-2″), 71.36 (C-4″), 62.62 (C-6″) ppm.

PHWE of *Calochlaena dubia*

C. dubia leaflets (30 g) were finely ground using a spice grinder, mixed with sand (~6 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (3 × 200 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide dark green extract A (575 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (10 g). *Extract A*: Extract A (315 mg) was redissolved in MeOH and EtOAc, absorbed onto silica/Celite® (1:1 mixture by mass), and subjected to automated flash chromatography {silica cartridge (24 g); 0–100% EtOAc/hexanes and 0–50% MeOH/EtOAc, for 12 min with flow rate of 28 mL/min}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined to give nine fractions, F.1–9. Fraction F.8 (41 mg) was subjected to flash column chromatography

{silica; CH_2Cl_2 (50 mL), 10% MeOH/CH_2Cl_2 (200 mL) and 50% MeOH/CH_2Cl_2 (20 mL)}, which provided compound **41** (4 mg, 0.014% w/w).

PHWE of *Polystichum vestitum*

P. vestitum dried leaflets (30 g) were finely ground using a spice grinder, mixed with sand (~6 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide extract A (114 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (7 g). *Extract A*: Extract A (114 mg) was redissolved in EtOAc and MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass), and subjected to automated flash column chromatography {silica cartridge (4 g); 0–100% EtOAc/hexanes and 0–50% MeOH/EtOAc, for 26 min with flow rate 12 mL/min)} and afforded compound **42** (30 mg, 0.1% w/w) as a light brown solid. Following TLC and ^{1}H NMR spectroscopic analysis, the fractions were combined to give six fractions, F.1–6. Fractions F.3–5 (27 mg) were combined and subjected to flash column chromatography {silica; CH_2Cl_2 (50 mL), 5% MeOH/CH_2Cl_2 (50 mL), 15% MeOH/CH_2Cl_2 (50 mL) and 40% MeOH/CH_2Cl_2 (30 mL)} to provide compound **43** (4 mg) as a yellow solid. *Extract B*: Extract B (4 g) was redissolved in MeOH and water, adsorbed onto silica/Celite® (1:1 mixture by mass), and fractionated through a silica plug (150 mL of EtOAc, 10% MeOH/EtOAc, 20% MeOH/EtOAc, 30% MeOH/EtOAc, 40% MeOH/EtOAc and 50% MeOH/EtOAc) which afforded six fractions, F.1–6. Following ^{1}H NMR spectroscopic analysis, fractions F.1 and 2 (145 mg) were recombined, absorbed onto silica and subjected to flash column chromatography {silica; CH_2Cl_2 (100 mL), 2.5% MeOH/CH_2Cl_2 (100 mL), 5% MeOH/CH_2Cl_2 (100 mL), 10% MeOH/CH_2Cl_2 (100 mL), 15% MeOH/CH_2Cl_2 (100 mL), 20% MeOH/CH_2Cl_2 (100 mL) and 35% MeOH/CH_2Cl_2 (100 mL)} to provide compound **42** (10 mg, 0.035% w/w).

4β-Carboxymethyl-(–)-epicatechin ***(42)*** (CAS# 146805-53-0).[62] Light-brown solid. ^{1}H NMR (600 MHz, acetone-d_6) δ 7.08 (1H, d, J = 1.7 Hz; H-2′), 6.87 (1H, dd, J = 8.2 and 1.8 Hz; H-6′), 6.81(1H, d, J = 2.2 Hz; H-5′), 6.04 (1H, d, J = 2.2 Hz; H-8), 5.94 (1H, d, J = 2.2 Hz; H-6), 4.93 (1H, s; H-2), 4.01 (1H, s; H-3), 3.46 (1H, d, J = 6.2 Hz; H-4), 3.05 (1H, dd, J = 16.4 and 3.5 Hz; H-1b″), 2.45 (1H, dd, J = 16.4 and 11.2 Hz; H-1a″) ppm. ^{13}C NMR (150 MHz, acetone-d_6) δ 173.9 (2″-COOH), 157.9 (C-7,9), 156.3 (C-5), 145.5 (C-4′), 145.3 (C-3′), 132.2 (C-1′), 119.3 (C-6′), 115.6 (C-5′), 115.3 (C-2′), 102.7 (C-10), 96.6 (C-8), 95.8 (C-6), 75.4 (C-2), 70.2 (C-3), 39.1 (C-1″), 36.0 (C-4) ppm.

*(2R)-Eriodictyol-7-O-β-*D*-glucopyranoside* ***(43)*** (CAS# 38965-51-4).[80] Yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 6.82 (1H, s, H-2′), 6.69 (2H, t, J = 10.9 Hz, H-5′,6′), 6.11 (1H, s, H-6), 6.09 (1H, s, H-8), 5.23 (1H, d, J = 12.5 Hz, H-2), 4.87 (1H, t, J = 6.6 Hz, H-1″), 3.88 (1H, d, J = 12.1 Hz, H-6a″), 3.69 (1H, m, H-6b″), 3.42–3.47 (3H, m, H-2″,3″,5″), 3.39 (1H, m, H-4″), 3.13 (1H, dd, J = 17.5 Hz, H-3a), 2.75 (1H, d, J = 17.0 Hz, H-3b) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 198.5 (C-4), 167.0 (C-7), 164.9 (C-9), 164.6 (C-5), 146.9 (C-3′), 146.5 (C-4′), 131.5 (C-1′), 119.3 (C-6′), 116.3 (C-5′), 114.8 (C-2′), 104.9 (C-10), 101.2 (C-1″), 97.9 (C-8), 96.9 (C-6), 80.7 (C-2), 78.3 (C-3″), 77.8 (C-5″), 74.7 (C-2″), 71.2 (C-4″), 62.3 (C-6″), 44.1 (C-3) ppm.

PHWE of *Polystichum proliferum*

P. proliferum leaves (30 g) were finely ground using a spice grinder, mixed with sand (7 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide extract A (240 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to afford a dark brown extract B (4 g). *Extract A*: Extract A (240 mg) was redissolved in CH_2Cl_2 and MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass), and subjected to flash column chromatography {silica; CH_2Cl_2 (200 mL), 10% MeOH/CH_2Cl_2 (100 mL), 20% MeOH/CH_2Cl_2 (100 mL) and 40% MeOH/CH_2Cl_2 (200 mL)} which provided compound **42** (16 mg, 0.06% w/w).

PHWE of *Pellaea falcata*

P. falcata dried leaflets (30 g) were finely ground using a spice grinder, mixed with sand (~8 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 3 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (1.0 g). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (8 g). *Extract A*: Extract A (1.0 g) was redissolved in EtOAc and MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to automated flash chromatography {silica cartridge (12 g); (0–100% EtOAc/hexanes and 0–50% MeOH/EtOAc for 21 min with a flow rate of 28 mL/min)}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined to afford seven larger fractions, F.1–7.

Fraction F.5 was redissolved in MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) subjected to flash column chromatography {silica; CH_2Cl_2 (50 mL), 10% MeOH/CH_2Cl_2 (100 mL), 20% MeOH/CH_2Cl_2 (50 mL) and 40% MeOH/CH_2Cl_2 (50 mL)} which provided compound **44** (21 mg, 0.7% w/w) as a yellow solid.

Naringin ***(44)*** (CAS# 10236-47-2).[111,112] Yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.32 (2H, d, J = 8.5 Hz; H-2′,6′), 6.82 (2H, d, J = 8.5 Hz; H-3′,5′), 6.18 (1H, d, J = 2.0 Hz; H-8), 6.16 (1H, d, J = 2.1 Hz; H-6), 5.37 (1H, dd, J = 12.9 and 2.7 Hz; H-2), 5.25 (1H, s; H-1″), 5.09 (1H, d, J = 7.6 Hz; H-1‴), 3.93 (1H, s; H-2″), 3.85–3.90 (2H, m; H-6a″,5‴), 3.62–3.69 (2H, m; H-3‴,6b″), 3.57-3.60 (2H, m; H-2″,5″), 3.43–3.46 (1H, m; H-3″), 3.39 (2H, t, J = 9.5 Hz; H-4″,4‴), 3.16 (1H, dd, J = 17.2 and 12.9 Hz; H-3a), 2.75 (1H, dd, J = 17.2 and 2.8 Hz; H-3b), 1.28 (3H, d, J = 6.2 Hz; 6‴-CH_3) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 198.5 (C-4), 166.6 (C-7), 164.9 (C-5), 164.6 (C-9), 159.1 (C-4′), 130.8 (C-1′), 129.1 (C-2′,6′), 116.3 (C-3′,5′), 104.9 (C-10), 102.5 (C-1‴), 99.4 (C-1″), 97.8 (C-6), 96.7 (C-8), 80.7 (C-2), 79.0 (C-2″), 78.9 (C-3″), 78.1 (C-5″), 73.9 (C-4‴), 72.2 (C-3‴), 71.2 (C-2‴), 71.2 (C-4″), 69.9 (C-5‴), 62.3 (C-6″), 44.1 (C-3), 18.2 (6‴-CH_3) ppm.

PHWE of *Austroblechnum penna-marina* subsp. *alpina*

A. penna-marina subsp. *alpina* dried leaflets (29 g) were finely ground using a spice grinder, mixed with sand (~7.5 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further three times to provide a combined extract (800 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (409 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (6 g). *Extract A*. Extract A (400 mg) was redissolved in MeOH and EtOAc, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; hexanes (100 mL), 20% EtOAc/hexanes (200 mL), 40% EtOAc/hexanes (100 mL), 60% EtOAc/hexanes (100 mL), 80% EtOAc/hexanes (100 mL), EtOAc (50 mL), 10% MeOH/EtOAc (100 mL) and MeOH/EtOAc (100 mL)} that provided compound **45** (8.9 mg, 0.3% w/w) as a pale-green solid.

Blechnic acid ***(45)*** (CAS# 146805-53-0).[113] Pale-green solid. [α] –23.2° (*c* 0.0345, MeOH), lit. [α] –28° (*c* = 1.0, MeOH).[65] ^{1}H NMR (600 MHz, CD_3OD) δ 7.47 (d, J = 15.9 Hz; H-7′), 7.03 (d, J = 8.5 Hz; H-6′), 6.86 (d, J = 2.0 Hz; H-2), 6.74 (dd, J = 8.2, 1.9 Hz; H-6), 6.71 (d, J = 8.4 Hz; H-5), 6.65 (d, J = 8.2 Hz; H-5′), 6.16 (d, J = 15.9 Hz; H-8′), 5.83 (d, J = 9.3 Hz; H-7), 4.50 (d, J = 9.3 Hz; H-8) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 173.6 (C-9), 170.6 (C-9′), 149.6 (C-3′), 146.5 (C-4), 146.0 (C-3), 145.1 (C-4′), 143.3 (C-7′), 129.3 (C-1), 129.1 (C-2′), 124.5 (C-1′), 122.6 (C-6′), 119.7 (C-6), 118.0 (C-5′), 117.8 (C-8′), 115.9 (C-5), 115.1 (C-2), 88.4 (C-7), 55.3 (C-8) ppm. HRESIMS *m/z* calcd for $C_{18}H_{14}O_8Na$ $[M + Na]^+$ 381.0586; found 381.0581.

PHWE *Lecanopteris pustulata* subsp. *pustulata*

L. pustulata subsp. *pustulata* dried leaflets (30 g) were finely ground using a spice grinder, mixed with sand (~7 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL) and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (154 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (5.6 g). *Extract A*. Extract A (118 mg) was redissolved in MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; hexanes (30 mL), 30% EtOAc/hexanes (50 mL), 60% EtOAc/hexanes (100 mL), 80% EtOAc/hexanes (50 mL), EtOAc (50 mL), 20% MeOH/EtOAc (50 mL) and 50% MeOH/EtOAc (25 mL)}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined to afford six larger fractions, F.1–6. Fractions F.2 (19.5 mg) was redissolved in CH_2Cl_2 and MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (25 mL), 5% MeOH/CH_2Cl_2 (25 mL) and 20% MeOH/CH_2Cl_2 (25 mL)}. Following TLC analysis, the resulting fractions were combined to afford three fractions F.1–3; and F.2 provided compound **42** (12 mg, 0.04% w/w). *Extract B*. Extract B (5.6 g) was redissolved in MeOH and water, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash chromatography {silica; EtOAc (200 mL), 10% MeOH/EtOAc (200 mL), 20% MeOH/EtOAc (200 mL) and 30% MeOH/EtOAc (200 mL)} that provided five fractions, F.1–5. Fraction F.1 (127 mg) was redissolved in MeOH and CH_2Cl_2, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (50 mL), 5% MeOH/CH_2Cl_2 (100 mL), 10% MeOH/CH_2Cl_2 (50 mL), 30% MeOH/CH_2Cl_2 (100 mL) and MeOH (30 mL)} that provided compound **46** (4.8 mg, 0.016% w/w) as an off-white solid.

(p-Hydroxybenzyl)malonic acid ***(46)***.[70] Off-white solid. ^{1}H NMR (600 MHz, acetone-d_6) δ 7.05 (2H, d, J = 8.3 Hz; H-2′,6′), 6.68 (2H, d, J = 8.3 Hz; H-3′,5′), 3.53 (1H, t, J = 7.6 Hz; H-2), 3.06 (2H, d, J = 7.6 Hz; H-3); ^{1}H NMR (600 MHz, DMSO-d_6) δ 6.99 (2H, d, J = 8.4 Hz; H-2′,6′), 6.63 (2H, d, J = 8.4 Hz; H-3′,5′), 3.39 (1H, m, H-2), 2.92 (2H, d, J = 7.5 Hz; H-3) ppm. ^{13}C NMR (150 MHz, acetone-d_6) δ 172.9 (C-1), 157.1 (C-4′), 130.9 (C-2′,6′), 130.9 (C-1′), 116.2 (C-3′,5′), 55.4 (C-2), 35.2 (C-3); ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.7 (C-1), 155.7 (C-4′), 129.6 (C-2′,6′),

128.7(C-1′), 114.9 (C-3′,5′), 53.5 (C-2), 33.5 (C-3) ppm. HRESIMS *m/z* calcd for $C_{10}H_{10}O_5Na$ $[M + Na]^+$ 233.0426; found 233.0423.

PHWE of *Lomaria nuda*

L. nuda fronds (30 g) were finely ground using a spice grinder, mixed with sand (~6 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (254 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark brown extract B (5 g). *Extract A*. Extract A (254 mg) was redissolved in MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to automated flash chromatography {silica cartridge (4 g); 0–40% MeOH/EtOAc for 17 min}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined into seven large fractions, F.1–7. Fraction F.3 (14.5 mg) was redissolved in MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (50 mL), 5% MeOH/CH_2Cl_2 (50 mL), 10% MeOH/CH_2Cl_2 (50 mL), 20% MeOH/CH_2Cl_2 (50 mL) and MeOH (20 mL)} which provided compound **47** (2.5 mg, 0.01% w/w) as a yellow solid and compound **48** (5 mg, 0.016% w/w) as a yellow solid.

*Quercetin-3-O-(6′-O-acetyl)glucoside (**47**)* (CAS# 54542-51-7).[114] Yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.81 (1H, d, J = 2.2 Hz; H-6′), 7.63 (1H, dd, J = 8.5 and 2.2 Hz; H-5′), 6.88 (1H, d, J = 8.5 Hz; H-2′), 6.44 (1H, d, J = 2.0 Hz; H-8), 6.23 (1H, d, J = 2.0 Hz; H-6), 5.08 (1H, d, J = 7.9 Hz; H-1″), 4.18 (1H, dd, J = 11.4 and 7.8 Hz; H-6a″), 4.07 (1H, dd, J = 11.4 and 4.5 Hz; H-6b″), 3.83 (1H, dd, J = 9.6 and 7.4 Hz; H-2″), 3.80 (1H, d, J = 3.3 Hz; H-3″), 3.70 (1H, dd, J = 7.7 and 4.6 Hz; H-5″), 3.58 (1H, dd, J = 9.4 and 3.1 Hz; H-4″), 1.83 (3H, s; 2‴-$COCH_3$) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 179.4 (C-4), 172.5 (1‴-CO), 167.3 (C-7), 162.9 (C-5), 158.6 (C-9), 157.8 (C-2), 150.0 (C-4′), 145.8 (C-3′), 135.7 (C-3), 123.1 (C-6′), 122.8 (C-1′), 117.6 (C-5′), 116.0 (C-2′), 105.8 (C-1″), 105.1 (C-10), 100.4 (C-6), 95.1 (C-8), 74.9 (C-3″), 74.5 (C-5″), 72.9 (C-2″), 70.2 (C-4″), 64.5 (C-6″), 20.4 (2‴-$COCH_3$) ppm.

*Quercitrin (**48**)* (CAS# 522-12-3).[115] Yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.33 (1H, d, J = 2.1 Hz; H-2′), 7.30 (1H, dd, J = 8.3 and 2.1 Hz; H-6′), 6.91 (1H, d, J = 8.3 Hz; H-5′), 6.34 (1H, d, J = 2.1 Hz; H-6), 6.18 (1H, d, J = 2.1 Hz; H-8), 5.35 (1H, s; H-1″), 4.22 (1H, m; H-2″), 3.75 (1H, m; H-3″), 3.42 (1H, m; H-5″), 3.35 (1H, m; H-4″), 0.95 (3H, d, J = 6.2 Hz; 6″-CH_3) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 179.5 (C-4), 167.3 (C-7), 163.1 (C-5), 159.1 (C-2), 158.6 (C-9), 149.9 (C-4′), 146.5 (C-3′), 136.1 (C-3), 122.9 (C-6′), 122.8 (C-1′), 116.9 (C-5′), 116.4 (C-2′), 105.5 (C-10), 103.5 (C-1″), 100.3 (C-6), 95.0 (C-8), 73.3 (C-4″), 72.1 (C-3″), 72.0 (C-5″), 71.9 (C-2′), 17.6 (6′-CH_3) ppm.

PHWE of *Parablechnum wattsii*

P. wattsii dried leaf material (30 g) was finely ground using a spice grinder, mixed with sand (~6 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 120 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (523 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark-brown extract B (7 g). *Extract A*. Extract A (523 mg) was redissolved in MeOH, adsorbed onto silica and subjected to automated flash chromatography {silica cartridge (12 g); 0–100% EtOAc/hexanes and 0–40% MeOH/CH_2Cl_2 for 13 min at a flow rate of 25 mL/min} which provided compound **49** (143 mg, 0.5% w/w) as a dark-brown solid. Approximately 60 mg of compound **49** was absorbed onto silica and further purified by flash column chromatography {silica, 20% MeOH/CH_2Cl_2 (150 mL) then 40% MeOH/CH_2Cl_2 (100 mL)} which provided compound **49** as a pale-yellow/-green solid (20 mg).

*5-O-Caffeoylshikimic acid (**49**)* (CAS# 73263-62-4).[55] Pale-yellow/-green solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.56 (1H, d, J = 15.9 Hz; H-7′), 7.04 (1H, d, J = 1.7 Hz; H-2′), 6.95 (1H, dd, J = 8.2 and 1.6 Hz; H-6′), 6.83 (br s; H-2), 6.78 (1H, d, J = 8.2 Hz; H-5′), 6.28 (1H, dd, J = 15.9 Hz; H-8′), 5.25 (1H, dd, J = 13.2 and 5.6 Hz; H-5), 4.40 (1H, s; H-3), 3.90 (1H, dd, J = 7.9 and 4.1 Hz; H-4), 2.87 (1H, dd, J = 18.8 and 4.9 Hz; H-6a), 2.32 (1H, dd, J = 18.4 and 5.1 Hz; H-6b) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 170.3 (C-7), 168.6 (C-9′), 149.6 (C-4′), 147.2 (C-7′), 146.8 (C-3′), 138.2 (C-2), 131.1 (C-1), 127.7 (C-1′), 123.0 (C-6′), 116.5 (C-5′), 115.2 (C-2′), 115.1 (C-8′), 71.4 (C-5), 70.1 (C-4), 67.4 (C-3), 29.4 (C-6) ppm. HRESIMS *m/z* calcd for $C_{16}H_{16}O_8Na$ $[M + Na]^+$ 359.0845; found 359.0738.

PHWE of *Gleichenia alpina*

G. alpina dried aerial parts (29 g) were finely ground using a spice grinder, mixed with sand (~4 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated further two times to provide a combined extract (600 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (200 mL and 2 × 150 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (646 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark-brown extract B (10 g). *Extract A*.

Extract A (793 mg) was adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; EtOAc (300 mL), 10% MeOH/EtOAc (150 mL), 20% MeOH/EtOAc (150 mL), 30% MeOH/EtOAc (150 mL), 40% MeOH/EtOAc (150 mL) and MeOH (100 mL)}, to afford six fractions, F.1–6. Fraction F.3 (202 mg) was and adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (50 mL), 10% MeOH/CH_2Cl_2 (50 mL), 20% MeOH/CH_2Cl_2 (100 mL), 20% MeOH/CH_2Cl_2 (150 mL) and MeOH (50 mL)} which provided compound **50** (6.9 mg, 0.02% w/w) as a yellow solid that contained minor impurities.

*Rutin (**50**)* (CAS# 153-18-4).[116] Yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.67 (1H, d, J = 2.2 Hz; H-2′), 7.63 (1H, dd, J = 8.4 and 2.2 Hz; H-6′), 6.88 (1H, d, J = 8.4 Hz; H-5′), 6.41 (1H, d, J = 2.1 Hz; H-8), 6.21 (1H, d, J = 2.1 Hz; H-6), 5.11 (1H, d, J = 7.7 Hz; H-1″), 4.52 (1H, d, J = 1.4 Hz; H-1‴), 3.80 (1H, dd, J = 11.2 and 1.5 Hz; H-6a″), 3.63 (1H, dd, J = 3.3 and 1.6 Hz; H-2‴), 3.54 (1H, dd, J = 9.5 and 3.5 Hz; H-3‴), 3.38–3.49 (4H, m; H-2″,3″,5‴,6b″), 3.25–3.34 (3H, m; H-4″,5″,4‴), 1.12 (3H, d, J = 6.2 Hz; 6‴-CH_3) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 179.4 (C-4), 166.1 (C-7), 162.9 (C-5), 159.3 (C-2), 158.5 (9), 149.8 (C-4′), 145.8 (3′), 135.6 (C-3), 123.5 (C-6′), 123.1 (C-1′), 117.7 (C-2′), 116.1 (C-5′), 105.6 (C-10), 104.7 (C-1″), 102.4 (C-1‴), 99.9 (C-6), 94.9 (C-8), 78.2 (C-3″), 77.2 (C-5″), 75.7 (C-2″), 73.9 (C-4‴), 72.2 (C-3‴), 72.1 (C-2‴), 71.4 (C-4″), 69.7 (C-5‴), 68.5 (C-6″), 17.9 (C-6‴) ppm.

PHWE of *Dicksonia antarctica*

D. antarctica dried leaflets (30.5 g) were finely ground using a spice grinder, mixed with sand (~7 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further three times to provide a combined extract (800 mL). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (150 mL and 2 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (298 g). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark-brown extract B (5 g). No compounds could be isolated by flash column chromatography.

PHWE of *Doodia australis*

D. australis dried leaflets (31 g) were finely ground using a spice grinder, mixed with sand (~7 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL). The aqueous extract was extracted with EtOAc (150 and 2 × 100 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (617 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark-brown extract B (3.5 g). No compounds could be isolated by flash column chromatography.

PHWE of *Oceaniopteris cartilaginea*

O. cartilaginea dried leaflets (33 g) were finely ground using a spice grinder, mixed with sand (~8 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further two times to provide a combined extract (600 mL) and extracted with EtOAc (400 mL and 2 × 200 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (1.5 g). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark-brown extract B (~2 g). No compounds could be isolated by flash column chromatography.

PHWE of *Histiopteris incisa*

H. incisa dried leaflets (35 g) were finely ground using a spice grinder, mixed with sand (~16 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further three times to provide a combined extract (800 mL) and extracted with EtOAc (3 × 250 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (877 mg). The remaining aqueous phase was concentrated under reduced pressure (50°C) to yield a dark-brown extract B (3 g). No compounds could be isolated by flash column chromatography.

PHWE of *Pteridium esculentum*

Aerial parts of *P. esculentum* (150 g) were finely ground using a spice grinder, mixed with sand (~75 g), and extracted via PHWE (35% EtOH/H_2O). This provided a hot extract (200 mL) that was cooled immediately in an ice bath. This process was repeated a further nine times to provide a combined extract (2 L). The extract was concentrated under reduced pressure (35°C) to remove EtOH and extracted with EtOAc (3 × 500 mL). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide extract A (2.7 g). The remaining aqueous phase was concentrated under reduced pressure (50°C) to afford brown extract B (32 g). *Extract A*. Extract A (1.5 g) was redissolved in MeOH, adsorbed onto silica/Celite® (1:1 mixture by mass) and subjected to flash column chromatography {silica; CH_2Cl_2 (250 mL), 10% MeOH/CH_2Cl_2 (250 mL), 20% MeOH/CH_2Cl_2 (250 mL), 30% MeOH/CH_2Cl_2 (250 mL), 40% MeOH/CH_2Cl_2 (250 mL) and MeOH (200 mL)}. Following TLC and ^{1}H NMR spectroscopic analysis, the resulting fractions were combined to provide seven fractions, F.1–7. Fraction F.4 (150 mg) was redissolved in 20% MeCN/H_2O solution and subjected to automated flash chromatography (12 g C18 cartridge; 0–100% MeCN/H_2O for 17 min with a flow rate of 28 mL/min). Following TLC and ^{1}H NMR spectroscopic analysis, the

resulting fractions were combined to afford four fractions, F.1–4. Fraction F.2 (19 mg) was redissolved in $MeOH/CH_2Cl_2$ solution and subjected to flash column chromatography {silica; 10% $MeOH/CH_2Cl_2$ (10 mL)} to provide compound **41** (12 mg, 0.006% w/w) as a pale-yellow solid. The fraction F.4 (42 mg) was subjected to preparative TLC which provided compound **51** (25 mg, 0.02% w/w) as a yellow solid.

*Tiliroside (**51**)* (CAS# 20316-62-5).[117,118] Yellow solid. ^{1}H NMR (600 MHz, CD_3OD) δ 7.98 (2H, d, J = 8.8 Hz; H-2′,6′), 7.40 (1H, d, J = 15.9 Hz; H-7‴), 7.30 (2H, d, J = 8.5 Hz; H-2‴,6‴), 6.82 (2H, d, J = 8.8 Hz; H-3′,5′), 6.79 (2H, d, J = 8.6 Hz; H-3‴,5‴), 6.30 (1H, d, J = 1.9 Hz; H-8), 6.13 (1H, d, J = 2.0 Hz; H-6), 6.07 (1H, d, J = 15.9 Hz; H-8‴), 5.23 (1H, d, J = 7.3 Hz; H-1″), 4.31 (1H, dd, J = 11.8 and 1.9 Hz; H-6a″), 4.20 (1H, m; H-6b″), 3.41–3.50 (3H, m; H-2″,3″,5″), 3.31 (1H, m; H-4″) ppm. ^{13}C NMR (150 MHz, CD_3OD) δ 179.4 (C-4), 168.6 (9‴-CO), 166.3 (C-7), 162.9 (C-5), 161.5 (C-4′), 161.2 (C-4‴), 159.3 (C-2), 158.5 (C-9), 146.6 (C-7‴), 135.2 (C-3), 132.2 (C-2′,6′), 131.2 (C-2‴,6‴), 127.1 (C-1‴), 122.7 (C-1′), 116.8 (C-3‴,5‴), 116.1 (C-3′,5′), 114.7 (C-8‴), 105.5 (C-10), 104.1 (C-1″), 100.1 (C-6), 94.9 (C-8), 78.0 (C-3″), 75.7 (C-2″,5″), 71.7 (C-4″), 64.3 (C-6″) ppm.

Supplementary material

Supplementary material is available online.

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Author affiliation
[A]School of Natural Sciences – Chemistry, University of Tasmania, Hobart, Tas., 7001, Australia.