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Review Article

Polypodiales a promising fern order as a source of anticancer agent: A comprehensive review

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Abstract

Ferns are vascular plants that have been extensively studied in recent decades for their phytochemical and anticancer activities. Polypodiales is an order of ferns consisting of 26 families with more than 9600 species (>80% of the total number of fern species). There have been many reports on the potential activity of plants and their phytochemicals that belong to the Polypodiales order in the search for anticancer agents. However, until now, there has been no comprehensive review of the anticancer activity of ferns, specifically in the order. This research is based on a thorough analysis of relevant literature in Scopus and PubMed databases from 1979 to 2022. The literature search used specific keywords, with criteria for this review appropriate for cell-based experiments and molecular mechanisms of anticancer activity. *In vivo* assay, chemopreventive or cytoprotective activity, and testing of combinations of plants or compounds were excluded. A total of 66 species were distributed in 11 families of the order Polypodiales, were summarized, constructed and discussed the traditional use, pharmacology, and phytochemicals associated with anticancer properties. The comprehensive research study showed that plants of the order Polypodiales and their phytochemicals exhibit anticancer effects against various cancers. Pteridaceae is a family that contains the most anticancer bioactive compounds. ent-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid (5F), terpenoid from Pteridaceae family exhibits promising against colorectal, gastric, hepatocellular, lung, laryngeal, nasopharyngeal, and breast cancer cell lines. The ability to induce apoptosis through several pathways that can activate the mitochondrial-mediated apoptosis pathway, such as inhibiting the NF-kB pathway and increasing ROS formation. Further research is needed to explore more ferns, reveal their active compounds activity and mechanism of action, and conduct *in vivo* assay to confirm their efficacy and safety for the development of cancer treatment.

Keywords: anticancer; cytotoxic; fern; *in vitro*; molecular mechanism; Polypodiales order

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Introduction

Cancer is a primary global health concern. According to recent data and trends, In the majority of countries, cancer is projected to overtake cardiovascular disease as the primary cause of early mortality in the current century (Bray *et al*., 2021). Estimates in 2020 of new cancer cases worldwide reached 19.3 million, with 10.0 million cancer deaths. By 2040, new cancer cases worldwide are projected to increase by 47% from those in 2020 to 28.4 million cases. The incidence and mortality rates for cancer are estimated using data from the GLOBOCAN 2020 cancer database, which consolidates information on 38 types of cancer from 185 countries (Ferlay *et al*., 2021; Sung *et al*., 2021).

The perfection of cancer treatment, both in terms of efficacy, safety, and economy, is still a problem in the world that has not yet found a solution; this is due to the variety of factors that cause cancer (Hoda, 2021; Tan *et al*., 2020). Currently used treatments, such as surgery, chemotherapy and radiation therapy, have many limitations. Cancer surgery is invasive and effective for removing early-stage cancers but not suitable for advanced cancers. Chemotherapy often causes side effects due to its non-selectivity against normal cells as well as severe resistance. Radiotherapy applications can be used to remove tumours to reduce tumour size, but have the limitation of damaging healthy tissue (Cui *et al*., 2018; Gyanani *et al*., 2021). Despite these limitations, ongoing research focuses on developing more precise, less invasive and effective treatments, including combinatorial strategies and innovative approaches such as stem cell therapy, ablation therapy and natural anticancer agents. Historically, natural products are essential in drug discovery, especially in the treatment of cancer and infectious disorders (Atanasov *et al*., 2015). As of 2019, out of the 259 drug molecules approved as antitumor and anticancer drugs in Western medicine, 100 are bioactive compounds derived from natural products, while the remaining ones are semisynthetic derivatives of those bioactive compounds and inspired by natural compound structures (Aldrich *et al*., 2022).

Research on medicinal plants is needed to unlock the potential of all plants, including "understudied" plants such as algae, lichens, fungi, mosses, and ferns. Today, it is estimated that 12,000 species of ferns exist globally (Nitta *et al*., 2022). The exact number of fern species is challenging since new species are still being identified and added yearly. Ferns are ubiquitous plants that grow in various locations worldwide, from tropical forests to the highlands. The ferns (Polypodiopsida) are among the most ancient vascular plant groups that exhibit many of the characteristics found in the earliest vascular plants on Earth (Pryer *et al*., 2001). Ferns have been used in traditional medicine across Europe, America, Asia, and Africa for over two millennia (Muhammad *et al*., 2020). Polypodiales is the order with the most significant number of fern species, consisting of 26 families and more than 80% of the total species (Nitta *et al*., 2022; PPG, 2016). Polypodiales is a fern order which is highly researched for its anticancer properties. Several secondary metabolites in this order possessed anticancer agents. However, numerous species within this order have yet to be examined for their anticancer activity or bioactive compounds. Accordingly, a comprehensive study is essential to understand the advancement of anticancer activity research within the Polypodiales order. To date, no report has extensively summarised the anticancer activity of ferns, particularly within the Polypodiales order. This review aims to present the currently available data on the use of ferns in the Polypodiales order for traditional cancer treatment, the activity of their extracts or fractions (exhibiting activity <1 mg mL^{-1}), and the secondary metabolites that may have anticancer properties (<100μM).

Materials and Methods

This review systematically searched two online databases, Scopus (*https://www.scopus.com/*) and PubMed (*https://pubmed.ncbi.nlm.nih.gov/*), for all articles on the activity and content of secondary metabolites from the Polypodiales order of ferns and their efficacy as anticancer agents. The reviewed research

data comprises articles published from 1979 to 2022. Specific keywords are used during the literature search process. We use the keywords "genus name" AND "cancer"; "genus name" AND "cytotoxic"; and "genus name" AND "tumor". Article titles and abstracts were screened thoroughly to exclude research that needed to be more relevant to the problem. The assessment covered all parts of ferns, including specific components like the rhizome (root), leaves, aerial parts (fronds), and whole parts. Relevant articles were screened to ensure they met the review's eligibility criteria. This study's inclusion criteria were open access journal only, English language, and suitability for in vitro assays of anticancer activity on cancer cell lines commonly used for screening and molecular mechanism studies. Exclusion criteria included studies published in non-English languages, articles not accessible in full text, review articles, irrelevant studies such as in vivo testing, chemopreventive or cytoprotective activity, irrelevant assay methods, and assays using combinations of plants or compounds. The PRISMA method presents the review process in a flowchart (Figure 1).

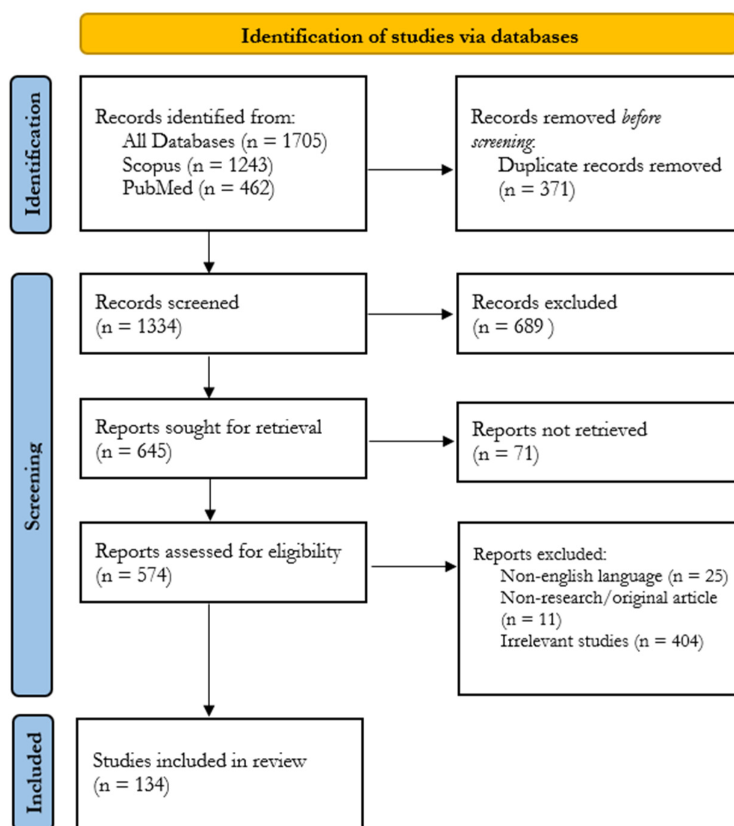

Figure 1. Flowchart of the articles selection process using the PRISMA method

Result and Discussion

Anticancer activities have been reported in the Polypodiales order, including in vitro screening and molecular mechanism investigations. This research dates back to 1979, with over 130 publications until 2022 (Figure 2a). The highest number of publications occurred during the decade spanning from 2011 to 2020. Starting in 2011, interest in research on ferns as anticancer agents grew rapidly. The focus of research during this period was on species that had never been studied, as well as further research in the search for cytotoxic compounds that have anticancer activity. According to this study, less than half of the 26 families have been reported, indicating very high opportunities for further exploration of these plants. Based on the search, less

than one per cent of the reported species from Polypodiales showed potential anticancer properties (Figure 2b). The active species are mostly dominated by families with many species, which may make them easy to find and collect, such as Pteridaceae, Thelypteridaceae, Dryopteridaceae and Polypodiaceae.

Ferns are known to produce a wide array of secondary metabolites, which include various phytochemicals with diverse bioactivities. This study revealed that 119 compounds from the order Polypodiales were reported to have promising cytotoxic or antiproliferative activity and molecular mechanism investigation. Terpenoids and flavonoids are the most prevalent active compounds from the order and are promising to be further developed as anticancer agents (Figure 2c). The terpenoid active compounds were reported to be produced in the species of Pteridaceae, Dennstaedtiaceae, Dryopteridaceae, Aspleniaceae, Polypodiaceae and Davalliaceae, while the Thelypteridaceae, Pteridaceae, Polypodiaceae, and Blechnaceae families were reported to have flavonoid active compounds. The Pteridaceae family is the largest source of active compounds among the compounds identified. Phytochemicals such as terpenoids, flavonoids, polyphenolics, chalcone, phloroglucinol, and alkaloids were found in the family, with terpenoids the major bioactive compound reported (Figure 2d).

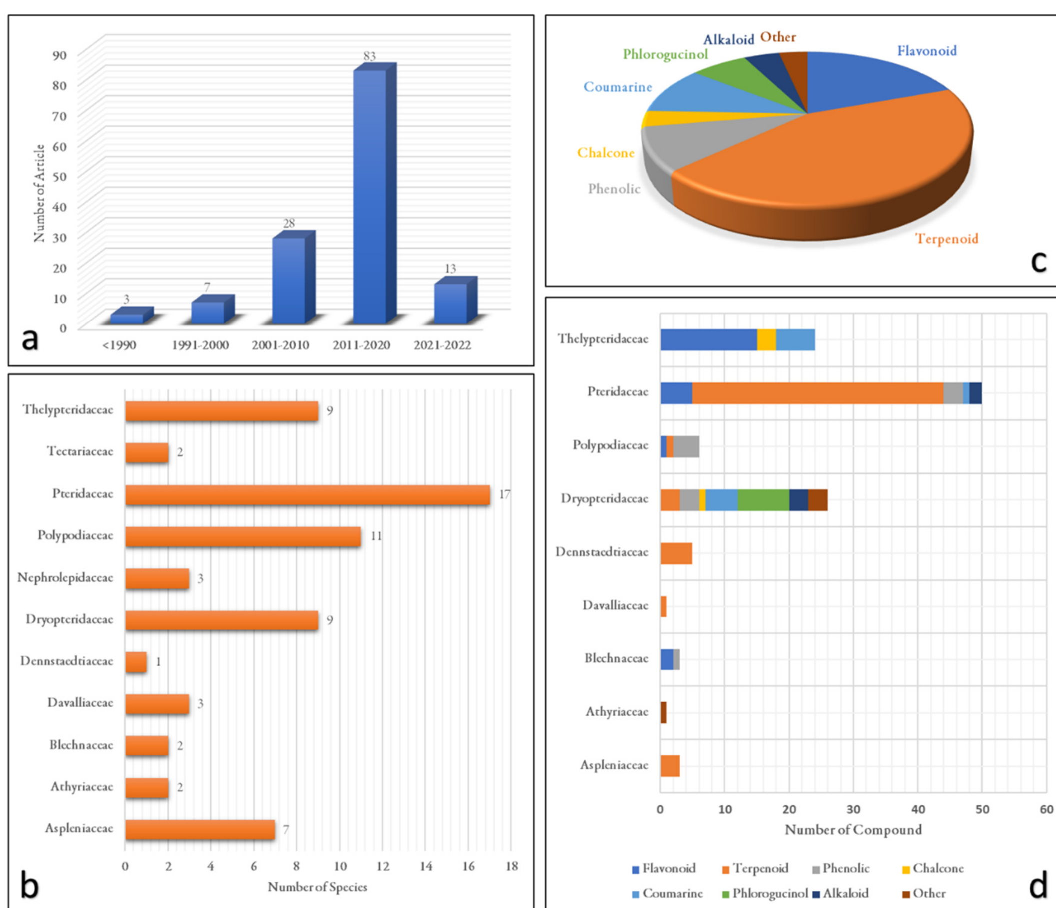

Figure 2. Analysis of order Polypodiales information from article selection a. Record the number of publications related to the order Polypodiales; b. Number of reported plant species per taxonomic family; c. Distribution of compound classes with potential anticancer activity; d. Distribution of anticancer active compounds per family of the order Polypodiales

Traditional uses of Polypodiales for cancer treatment

Polypodiales of ferns have been utilised in traditional medicine for over two millennia across various continents, including Africa, America, Asia, and Europe. The ethnomedicinal use of ferns for various diseases is extensive, but there are very few reports for cancer treatment. This could be due to the lack of traditional knowledge of cancer and its manifestations, whereas ethnomedicine research relies on traditional knowledge and anecdotal evidence, which may not be scientifically validated. This lack of rigorous testing and validation can make it difficult to confirm the efficacy of plant-based treatments for cancer (Kola *et al*., 2020). In the literature search, several uses of fern for cancer treatment were found. Traditional Chinese Medicine (TCM) features "*Gusuibu*", a traditional medicine consisting of six species of ferns: *Davallia divaricata* Blume, *Davallia mariesii* H.J.Veitch, *Davallia solida* (G.Forst.) Sw., *Drynaria roosii* Nakaike (syn. *Drynaria fortunei*), *Davallia griffithiana* Hook. (syn. *Humata griffithiana)*, and *Drynaria coronans* (Wall. ex Mett.) J.Sm. ex T.Moore (syn. *Pseudodrynaria coronans*). These ferns have been used in modern and traditional Chinese medicine practices, some for treating inflammation, cancer, ageing, circulatory diseases, and bone injuries (Chang *et al*., 2007). The medicinal plant *Macrothelypteris viridifrons* (Tagawa) Ching. is utilized by South Chinese communities to treat cancer and other ailments (Wei *et al*., 2011). Similarly, *D. mariesii* rhizome is used by South Koreans for the treatment of stomach cancer (Cui *et al*., 1990). In Indonesia, the use of ferns as an anticancer treatment within the North Sumatran community includes *Pteris ensiformis* Burm.f*., Bolbitis heteroclita* (C.Presl) Ching, *Lepisorus affinis* Ching. (syn. *Lepisorus longifolius*)*, Lepisorus buergerianus* (Miq.) C.F. Zhao, R. Wei & X.C. Zhang, and *Platycerium coronarium* (Konig) Desv. (Silalahi *et al*., 2015).

In Easter Island, Europe, *Lecanopteris pustulata* (G.Forst.) Perrie & Brownsey roots have been traditionally used to treat cancer (Holdsworth, 1992). The Inga tribe in the Americas uses *Adiantum macrophyllum* Sw. for the treatment of tumors and large cysts (Laferriere, 1994). Meanwhile, certain species of Polypodium, specifically *Serpocaulon maritimum* (Hieron.) A.R.Sm. (syn. *Polypodium maritimum*), are also used for cancer treatment in the Panama Islands (Gupta *et al*., 1979), and *Polypodium subpetiolatum* Hook. is used to treat skin tumors in Guatemala (Anderson *et al*., 1979; Gupta *et al*., 1979).

The ethnomedicinal use of ferns in African communities includes using *Hemionitis contracta* (Kunze) Christenh. (syn. *Cheilanthes contracta*) for cancer treatment (Charlson, 1980). Additionally, *Platycerium alcicorne* (P.Willemet) Desv. is used for treating all types of cancers in traditional medicine practices in Nigeria (Afolayan *et al*., 2020). A decoction made from the leaves and rhizomes of *Microgramma lycopodioides* (L.) Copel. is used in Uganda to treat leukemia, breast, liver, skin, and throat cancer (Schultz *et al*., 2020). Based on several reports on the use of ferns in ethnomedicine for cancer treatment, it is revealed that ferns are potential plants for drug discovery in cancer treatment.

Anticancer research of Polypodiales plants

Pharmacological investigations have indicated that extracts and fern-derived compounds exhibit diverse pharmacological effects, including their potential as anticancer agents. Several ferns have undergone screening to evaluate their potential as anticancer medicines (Table 1), including their molecular mechanisms. Polypodiales, the order with the most significant number of fern species, shows many species evaluated for anticancer activity compared to other fern orders. Polypodiaceae is the family with the most species reported anticancer activity out of 11 families belonging to the order Polypodiales, showing anticancer properties by testing extracts and fractions on cancer cells. Species from the *Drynaria, Lepisorus, Microsorum, Pyrrosia*, *Phlebodium* and *Polypodium* genera exhibit cytotoxic effects against numerous cancer cells. *Phlebodium aureum* (L.) J.Sm. (syn. *Polypodium leucotomos*) inhibits skin cancer cell proliferation by inhibiting MMPs and TGF-B while simultaneously stimulating TIMPs. *P. aureum* preferentially inhibits MMP-1, which suggests preventing interstitial collagen degradation and stimulates TIMP-2. Inhibition of the MMP-1 promoter through the Ap-

1 sequence suggests the involvement of the transcription factor AP-1. Inhibition of melanoma cell growth and modulation of extracellular matrix (ECM) remodeling mechanisms by *P. aureum* extract through regulation of apoptosis, heat-shock proteins (HSPs), MMP-1, or tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) inhibiting MMP-1. *P. aureum* inhibits the stimulation of MMP-1, TGF-β, and HSPs and promotes the expression of TIMP-1 (Philips *et al.*, 2009a; Philips *et al.*, 2009b). The administration of *P. aureum* extracts delayed skin tumor development by increasing glutathione S-transferase (GST) activity and decreasing glutathione disulfide (GSSG) content (Rodríguez-Yanes *et al.*, 2014). *Lepisorus fortuni* (T.Moore) C.M.Kuo exhibited significant antiproliferative activity against ER-negative breast cancer cells (BT20), osteosarcoma (U2OS), and lung cancer (A549). When tested for apoptosis on U2OS cells, *L. fortuni* induced apoptosis at 50 µg mL^{-1} concentration in the early stage (early apoptosis) and less than 25 µg mL^{-1} concentration in the late stage (late apoptosis) (Almosnid *et al.*, 2018).

Table 1. *In vitro* cytotoxicity activity from plant extracts/fraction of the Polypodiales order

Species (accepted name)	Part of plants	Assay (incub. time)	Cancer cell line	Anticancer activity (IC_{50}/EC_{50}/GI_{50}/% cell viability)	References
Aspleniaceae					
Asplenium ceterach L.	Aerial parts	MTT assay(24h)	HeLa	40.48 µg mL^{-1}	(Petkov *et al.*, 2021)
Asplenium dalhousiae Hook.	Aerial parts	MTT assay (24h)	MDA-MB-231	>60% (50 µg mL^{-1}) and >70% (300 µg mL^{-1})	(Al-Assar *et al.*, 2021)
Asplenium nidus L.	Whole plant	MTT assay (16-18h)	HepG2 and HeLa	23.85% and 33.09% (50 µg mL^{-1})	(Jarial *et al.*, 2018)
Asplenium scolopendrium L.	Aerial parts	MTT assay (24h)	HeLa	204.83 µg mL^{-1}	(Petkov *et al.*, 2021)
Asplenium trichomanes L.	Aerial parts	MTT assay (24h)	HeLa	120.68 µg mL^{-1}	(Petkov *et al.*, 2021)
Diplazium polypodioides Blume	Aerial parts	MTT assay (24h)	MDA-MB-231	>60% (50 µg mL^{-1}) and >90% (300 µg mL^{-1})	(Al-Assar *et al.*, 2021)
Athyriaceae					
Athyrium hohenackerianum (Kunze) T.Moore	Whole plants	MTT assay (48h)	A549, MCF-7, and HCT-116	179.74; 149.92 and 123.90 µg mL^{-1}	(Elasbali *et al.*, 2022)
Athyrium monomachii (Kom.) Kom.	Aerial parts	MTT assay	HepG2	220.32 (24h) and 113.51 µg mL^{-1} (48h)	(Qi *et al.*, 2017)
Blechnaceae					
Blechnum orientale L.	Leaves	MTT assay (72h)	HT-29	42.8 µg mL^{-1} (EtOAc fr.); 27.5 µg mL^{-1} (BuOH fr.); and 33.4 µg mL^{-1} (aq. fr.)	(Lai *et al.*, 2010)
Stenochlaena palustris (Burm.f.) Bedd.	Leaves	MTT assay (24h)	HeLa	5.83-19.40 µg mL^{-1}	(Arullappan *et al.*, 2017)
Davalliaceae					
Davallia bullata Wall. ex Hook.	Whole plants	CCK-8 assay (24h)	A549	72.16% (3.6 mg mL^{-1}/mL)	(Cao *et al.*, 2014)
Davallia formosana Hayata	rhizomes	MTT assay (48h)	LNCaP and C4-2	52.5 and 46.0 µg mL^{-1}	(Hsieh et al., 2020)
Dennstaedtiaceae					
Pteridium pubescens (Underw.) Christenh.	Aerial parts	MTT assay (48h)	NTERA2 and TCC	90 and 140 µg mL^{-1}	(Roudsari et al., 2012)
Dryopteridaceae					

Arachniodes carvifolia (Kunze) Ching	Roots	CCK-8 assay (24h)	HepG2	31.2 μg mL^{-1}	(Li *et al*., 2014)
Cyrtomium fortunei J.Sm.	Whole plant	MTT assay (24h)	HeLa, HepG2, SK-Hep2, LS174T	≥200 μg/mL all cell lines	(Herrmann *et al*., 2011)
	Leaves	MTT assay (72h)	MGC-803, Bcap-37, A549	150; 170; and 240 μg mL^{-1}	(Yang *et al*., 2015b)
Didymochlaena truncatula (Sw.) J.Sm.	roots	Resazurin assay (48h)	A2780	3.9 μg mL^{-1}	(Cao *et al*., 2006)
Dryopteris barbigera (Hook.) Kuntze	Leaves	MTT assay	MCF-7 and A549	71.7% and 66.8% (0.5 mg mL^{-1});	(Jan *et al*., 2022)
Dryopteris crassirhizoma Nakai	Rhizome	Resazurin assay (12h)	N-2A	232 μg mL^{-1}	(Mazzio & Soliman, 2009)
		MTT assay (24h)	HSC-3	90 μg mL^{-1}	(Lee *et al*., 2019)
Pleocnemia irregularis (C.Presl) Holttum	Aerial parts	MTT assay (72h)	K562	253.85 μg mL^{-1}	(Chai *et al*., 2015b)
Nephrolepidaceae					
Nephrolepis acutifolia (Desv.) Christ	Aerial parts	MTT assay (72h)	K562	190.82 μg mL^{-1}	(Chai *et al*., 2015b)
Nephrolepis cordifolia (L.) C.Presl	Aerial parts	MTT assay	A549 and MCF-7	46.2 and 47.9 μg mL^{-1}	(El-Tantawy *et al*., 2015)
Nephrolepis exatalta (L.) Schott	Aerial parts	MTT assay	A549 and MCF-7	43.5 and 44 μg mL^{-1}	(El-Tantawy *et al*., 2015)
Polypodiaceae					
Drynaria baronii Diels	Whole plants	MTT assay (24h)	HSC-2, HSC-3, HSC-4, Ca9-22, NA, T98G, HL-60	≥300 μg mL^{-1}	(Chu *et al*., 2009)
Drynaria roosii Nakaike	rhizomes	MTT assay (24h)	LNCaP and 22Rv1	>200 μg mL^{-1}	(Zhang *et al*., 2020b)
Drynaria rigidula (Sw.) Bedd.	leaves	Resazurin assay (48h)	MCF-7	18 μg mL^{-1} (fr. DCM)	(Nugraha *et al*., 2019)
Lepisorus fortuni (T.Moore) C.M.Kuo	Aerial parts	Resazurin assay (48h)	A549, BT20 and U2OS	20.8; 5.0; and 14.2 μg mL^{-1} (EtOAc fr.)	(Almosnid *et al*., 2018)
Microsorum punctatum (L.) Copel.	Aerial parts	MTT assay (24h)	K562	399.68 μg mL^{-1}	(Chai *et al*., 2015b)
Phlebodium aureum (L.) J.Sm.	Leaves	MTS/PMS chromogenic assay (24h)	SKBR3 and MDA-MB231	89% and 87% (1000 μg mL^{-1})	(Taylor *et al*., 2006)
Polypodium vulgare L.	fronds	MTT assay (24h)	HepG2, HeLa, MCF-7 and A549	44.2%; 49.0%; 72.5%; ~80% (2 mg mL^{-1})	(Farràs *et al*., 2021)
Pyrrosia petiolosa (Christ) Ching	Whole plants	MTT assay (24h)	A549	330 μg mL^{-1} (fr. n-buthanol)	(Cheng *et al*., 2014)
Pyrrosia piloselloides (L.) M.G.Price	Whole plants	MTT assay (72h)	HeLa	16.25 μg mL^{-1}	(Sul'ain *et al*., 2019)
		MTT assay (24h)	MCF-7	185.77 (fr.Hex); 39.54 (fr. DCM) and 107.89 μg mL^{-1} (residue)	(Wulandari *et al*., 2013)
Selliguea triloba (Houtt.) M.G.Price	Leaves and rhizomes	MTT assay	K562	58% and 61% (0.5 mg mL^{-1})	(Chai *et al*., 2013)
Pteridaceae					
Acrostichum aureum L.	Leaves	MTT assay (24h)	HeLa, T47D, WiDr	208.09; 487.12; and 89.19 μg mL^{-1}	(Arbiastutie *et al*., 2022)
Adiantum capillus-veneris L.	Leaves	MTT assay (24h)	MCF-7 and BT47	9 and 227 μg mL^{-1}	(Rautray *et al*., 2018)
Adiantum caudatum L.	Aerial parts	MTT assay (24h)	AGS, HT-29, and MDA-MB-435S	1.75; 1.48 and 1.23 mg mL^{-1}	(Uddin *et al*., 2011b)

Hemionitis farinosa (Forssk.) Christenh.	Whole plants	MTT assay (48h)	Hep3B	>40% (100 μg mL^{-1}); >55% (50 μg mL^{-1}); >65% (25 μg mL^{-1})	(Radhika *et al*., 2010)
Pityrogramma calomelanos (L.) Link	Aerial parts	Trypan Blue exclusion method (72h)	DLA, EA	16 and 18 μg mL^{-1}	(Sukumaran & Kuttan, 1991)
Pteris biaurita L.	Leaves	MTT assay (24h)	HepG2 and HeLa	65.77% and 53.44% (50 μg mL^{-1})	(Tiwary *et al*., 2015)
Pteris cretica L.	Whole plants	MTT assay (24h)	HeLa	34.26 μg mL^{-1} (aq.extr.) and 31.48 μg mL^{-1} ($CHCl_3$ extr)	(Kiran *et al*., 2018)
Pteris quadriureta Retz.	Leaves	MTT assay (24h)	MCF-7 and BT47	380 and 470 μg mL^{-1}	(Rautray *et al*., 2018)
Pteris vittata L.	Fronds	MTT assay (24h)	MCF-7	153.967 μg mL^{-1}	(Kaur *et al*., 2014)
	Aerial parts	MTT assay (24h)	A549, HepG2, PC-3, MCF-7	27.4%; 46.2%; 73.1%; and 55.2% (100 μg mL^{-1})	(Gaafar Alaa *et al*., 2018)
		MTT assay (72h)	K562	364.82 μg mL^{-1}	(Chai *et al*., 2015a)
Tectariaceae					
Tectaria coadunata (J.Sm.) C.Chr.	Whole plants	MTT assay (72h)	2008 and BxPC3	28.7 and 12.5 μg mL^{-1}	(Shrestha *et al*., 2019)
Tectaria cicutaria (L.) Copel.	Rhizomes	SRB assay (24h)	K562	11.9 μg mL^{-1}	(Karade & Jadhav, 2018)
Thelypteridaceae					
Thelypteris afra (Christ) C.F.Reed	Aerial parts	MTT assay (72h)	K562	194.5 μg mL^{-1}	(Chai *et al*., 2015b)
Thelypteris arida (D.Don) C.V.Morton	Aerial parts	MTT assay (72h)	K562	478.62 μg mL^{-1}	(Chai *et al*., 2015b)
Thelypteris glandulosolanosa (C.Chr.) R.M.Tryon	leaves	MTT assay (48h)	A549 and MCF-7	<30% and <60% (12.5 μg mL^{-1})	(Vera-Nuñez *et al*., 2022)
Thelypteris interrupta (Willd.) K.Iwats.	Aerial parts	MTT assay (72h)	K562	314.52 μg mL^{-1}	(Chai *et al*., 2015b)

The family of Pteridaceae has also shown anticancer effects on cancer cells, especially species in the *Pteris, Adiantum, Pityrogramma*, and *Hemionitis* genera. *Hemionitis farinosa* (Forssk.) Christenh. (syn. *Cheilanthes farinosa*) has been shown to have cytotoxic effects on human liver cancer cells (RAW264.7) without causing significant damage to normal cells. *H. farinosa* induces apoptosis in Hep3B cells, which display early-stage apoptosis as evidenced by DNA fragmentation analysis, DAPI staining of chromatin, comet assay, and Annexin V-FITC staining, thereby inhibiting cell growth (Radhika *et al*., 2010). *Adiantum capillus-veneris* L. and *Pteris quadriureta* Retz. inhibit the proliferation of MCF-7 and BT47 breast cancer cells and significantly decrease the expression of cyclin-D1, PCNA, and CDK4 proteins while increasing the expression level of p21. Each plant induces apoptosis by increasing the expression levels of Bax, caspase-3, and -9 and decreasing the expression level of Bcl-2, followed by the release of cytochrome c into the cytosol (Rautray *et al*., 2018).

Several genera in the Dryopteridaceae family have been reported to exhibit cytotoxic effects, including *Arachnoides, Didymochlaena, Dryopteris, Cyrtomium, Elaphoglossum*, and *Pleocnemia* genera. *Dryopteris crassirhizoma* rhizome (EEDC) exhibits potent cytotoxic activity against murine neuroblastoma cells. The inhibition of the fatty acid synthase enzyme, which is overexpressed in cancer cells, suppresses cancer growth by down-regulating the PI3K/Akt and JNK pathways, inducing cell cycle arrest in the S-phase and promoting programmed cell death (apoptosis) (Mazzio and Soliman, 2009). In human metastatic prostate cancer cells PC3 and PC3-MM2, EEDC exhibits significant anti-proliferative effects and triggers cell cycle arrest at the G0/G1 phase and apoptosis through activation of caspase-3, caspase-8, caspase-9, bid, and PARP (Chang *et al*.,

2010). EEDC inhibited the invasion and migration of oral SCC (HSC-3) cells. Furthermore, it inhibited the development of invadopodia, which disrupts the extracellular matrix (ECM) degradation responsible for cancer invasion and metastasis (Lee *et al*., 2019). *Arachniodes carvifolia* (Kunze) Ching (syn. *Arachniodes. Exilis*) effectively suppresses the proliferation of liver cancer cells by triggering apoptosis through the mitochondrial pathway. This was characterized by an increase in ROS levels and mitochondrial dysfunction in HepG2 cells; activation of caspase-3 and -9 resulting in increased release of cytochrome c; and an increase in the Bax/Bcl-2 ratio characterized by a decrease in Bcl-2 expression levels. Further analysis revealed that *A. carvifolia* stimulated mitogen-activated protein kinase (MAPK) through increased phosphorylation of p38 and total JNK. Additionally, *A. carvifolia* was found to inhibit the growth of hepatocellular carcinoma and increase the expression levels of Bax and caspase-3 while reducing the expression of Bcl-2, HIF-1α, and VEGF (Li *et al*., 2014, Li *et al*., 2017a).

Athyrium hohenackerianum (Kunze) T.Moore (Athyriaceae) exhibited cytotoxic potential against lung (A549), colon (HCT-116), and breast (MCF-7) cancer cells. Treating HCT-116 cells to this plant leads to the arrest of the cell cycle specifically in the S phase. *A. hohenackerianum* induces apoptosis in HCT-116 cells by increasing the production of p53, bax, and caspase-3, while decreasing the levels of Bcl-2 (Elasbali *et al*., 2022). In other species of the same genus, *Athyrium monomachii* (Kom.) Kom. shows promise as a cytotoxic agent that can trigger apoptosis in HepG2 cells through two distinct pathways: the extrinsic system mediated by death receptors and the intrinsic pathway mediated by mitochondria. In the intrinsic pathway, *A. monomachii* decreases the ratio of Bcl-2/Mito-Bax, leading to cytochrome c release from the mitochondria, which results in increased expression of cleaved caspase-3 and PARP cleavage, which causes apoptosis. In the extrinsic pathway, it occurs through the death ligand (Fas-L), resulting in procaspase-8 expression levels reduction and the expression of cleaved caspase-8 protein elevation. *A. monomachii* induces apoptosis through the PI3K/Akt and MAPK pathways and the NFkB signaling pathway. The cytotoxic activity of *A. monomachii* is associated with oxidative stress. It impacts the distribution of the cell cycle, leading to G2/M phase arrest and reduced levels of CDK1, CDK2, and cyclin D1 expression (Qi *et al*., 2017).

The Aspleniaceae, Dennstaedtiaceae, and Tectariaceae have been investigated for the potential of some species and even molecular mechanisms, but fewer than the previous families. *Asplenium ceterach* L., *Asplenium scolopendrium* L., and *Asplenium trichomanes* L. exhibited cytotoxic activity against cervical cancer (HeLa) cells, while *A. ceterach* demonstrated the highest potency by inducing programmed cell death. The treatment with these plants revealed a significant proapoptotic effect, characterised by a high percentage of cells undergoing late apoptosis. *A. ceterach* and *A. trichomanes* exhibited elevated levels of superoxide dismutase activity, which may cause cell death via the induction of oxidative stress and lead to cell death effects (Petkov *et al*., 2021). *Pteridium aquilinum* L. Kuhn commonly called Bracken fern, exhibits more significant cytotoxicity than normal cells. Three distinct cancer cell lines, TCC (urinary tract), NTERA2 (embryo), and MCF-7 (breast), were utilised in the assays. Bracken fern induced DNA damage, chromatin condensation, and apoptosis in TCC cells. In addition, it induces arrest at the G2/M phase, similar to vincristine (Roudsari *et al*., 2012). *Tectaria cicutaria* (L.) Copel. demonstrated a growth-inhibitory effect on K562 leukemia cancer cells. The induction of apoptosis by *T. cicutaria* occurred through a p53-dependent pathway and led to cell cycle arrest in the G0/G1 phase (Karade and Jadhav, 2018). Several species from Thelypteridaceae, Blechnaceae, Davalliaceae, and Nephrolepidaceae have been studied for their cytotoxic potential, but their molecular mechanisms have yet to be reported. The lack of species from both families that have been and have not been studied indicates a great opportunity for further exploration in the search for new anticancer drugs, considering that many of the described ferns have good potential. Based on all reported species, Polypodiaceae and Pteridaceae are the two dominant families reported to have anticancer activity; this is also supported by the molecular mechanisms associated with anticancer activity.

Cytotoxic phytochemical and their molecular mechanisms

Phytochemical investigations of Polypodiales have reported that they contain several compounds, including flavonoids, terpenoids, polyphenols, and alkaloids. The structure of the compounds may differ from those produced by higher plants, giving them the potential to serve as a significant source of chemical compound diversity. Many of these compounds have been found to possess anticancer activity and present the opportunity for further development (Annexe 1). Potential anticancer compounds from ferns of the order Polypodiales and their molecular mechanisms are listed below

Flavonoids compound

Flavonoids are secondary metabolites from natural compounds with a 15-carbon skeleton consisting of one heterocyclic ring and two phenyl rings. In plants, flavonoid compounds are basically biosynthesized through the shikimate acid pathway which produces a phenylpropanoid skeleton (C6-C3) (Corradini *et al.*, 2011; Liu *et al.*, 2021). This flavonoid is the second-largest group reported to have potential as an anticancer agent found in ferns (Figure 2c). These flavonoid compounds are found in almost all families, but those with anticancer potential are found in the Blechanceae, Polypodiaceae, Pteridaceae, and Thelypteridaceae. Protoapigenone (1) from *Macrothelypteris torresiana* (Gaudich.) Ching has strong anticancer activity compared to doxorubicin against various cells such as breast, liver, lung, leukemia, and cervical cancer (Huang *et al.*, 2010; Lin *et al.*, 2005). This compound can also suppress the growth of prostate cancer cells (LNCap), lung cancer cells (H1299), and ovarian cancer cells (SKOV3 and MDAH-2774). Treatment with protoapigenone caused prostate, lung, and ovarian cancer cells were found to arrest at the S and G2/M phases of the cell cycle. The suppression of the cell cycle is associated with alterations in the expression of cell cycle regulatory molecules, such as Cyclin B1, Cdk2, and Cdc25C. Protoapigenone decreased the protein levels of Bcl-xL and Bcl-2, activated caspase-3, and finally cleaved intact poly(ADP-ribose) polymerase (PARP). These findings suggest that protoapigenone exhibits selective toxicity and potent ovarian and prostate anticancer activity by inducing apoptosis (Chang *et al.*, 2008a; Chang *et al.*, 2008b).

Treatment with protoapigenone induces a significant DNA damage response activated by double-strand breaks (DSBs) through the ATM-NBS1 pathway in human lung cancer cells (Chiu *et al.*, 2009). Protoapigenone treatment of breast cancer cells (MDA-MB-231) can induce apoptosis through the mitochondrial pathway, as shown by the increase of cells in subG1 phase activation of caspase-3 and -9. Protoapigenone also induces apoptosis through MAPK pathways; this is shown by the phosphorylation of Bcl-2 and Bcl-xl induced by protoapigenone treatment. In the same cells, protoapigenone can act as anti-angiogenesis through the PI3K-Akt pathway (Chen *et al.*, 2011).

Protoapigenone analogs, DEHC (2), DEDC (3), and DICO (4) compounds have been reported as potentially active as anticancer. DEHC, extracted from *Macrothelypteris viridifrons* (Tagawa) Ching, showed significant cytotoxic effects against liver, prostate, lung, breast, leukemic, and colorectal cancer cells, with the most excellent sensitivity to colorectal cancer cells (HT-29). The DEHC compound inhibits the growth of HT-29 cells by inducing apoptosis through activation of the MAPK signaling pathway and caspase-3, -8, and -9. Furthermore, this is associated with reactive oxygen species-mitochondrial dysfunction (Wei *et al.*, 2011). The flavonoid compound DEDC extracted from *M. torresiana* can induce apoptosis in HepG2 cells. DEDC induces mitochondrial depolarization in the presence of reactive oxygen species (ROS). During apoptosis, the decreased expression of Bcl-2 and Bax are involved in regulating cytochrome c release from mitochondria. DEDC significantly stimulates caspase-3, -8, and -9, a hallmark of apoptosis. DEDC's apoptotic mechanism may involve p38 and JNK signaling (Liu *et al.*, 2011). DEDC causes neuroblastoma cell (SH-SY5Y) death by inducing apoptosis through increased ROS formation and cell cycle arrest at the G2/M phase. Apoptosis in these cells may also be due to increased activation of NF-kB. Apoptosis induction by DEDC was also closely associated with the blockade of STAT3 phosphorylation, decreased cyclin-B1 and Bcl2, and increased levels of p53 and p21 (Liu *et al.*, 2012). The DICO compound exhibits potential cytotoxic effects against liver (HepG2)

and colorectal (HT-29) carcinomas by arresting their cell cycles in the G2/M phase. In liver cancer cells, DICO causes apoptosis by inhibiting cyclin A, B1, and CDK1, promoting the expression of caspase-3, -9, and cleavage of PARP, reducing the expression of Bcl-2 while elevating the levels of ROS in the cells. In colon cancer cells, DICO induces apoptosis through negative regulation of STAT3 signal transduction, leading to increased Bax/Bcl-2 ratio and downregulated cyclin B1 leading to cell cycle arrest at the G2/M phase, which is responsible for apoptosis (Wei *et al.*, 2022; Zhou *et al.*, 2013).

Terpenoids compound

Terpenoids are natural compounds consisting of five isoprene carbons, derived from isopentenyl diphosphate (IPP) and its allylic isomer dimethylallyl diphosphate (DMAPP), and are the highest number of plant's secondary metabolites (Bergman et al., 2024). This compound is the most commonly isolated in ferns and has been reported to exhibit anticancer properties (Figure 2c). Active terpenoids have been identified in almost all families that have been reported, with the majority found in Pteridaceae (Figure 2d). The ent-kaurane diterpenoid, also known as ent-11α-hydroxy-15-oxo-kaur-16-en-19-oic acid (5F) (**5**), was isolated from *Pteris semipinnata* L. and *Pteris ensifromis* Burm.f. (Chen *et al.*, 2004; Shi *et al.*, 2017a). This compound has been shown to exhibit proliferative effects and induce apoptosis in various cancer cells, including colorectal, gastric, hepatocellular, lung, laryngeal, nasopharyngeal, and breast cancer. Compound 5F induces apoptosis in colorectal cancer cells (HT-29) by increasing the availability of p38 and iNOS. However, this effect can be alleviated by overexpression of Bcl-2 or Bcl-xL, which increases the activity of NF-κB and leads to apoptosis reversal (Chen *et al.*, 2004). Cell death induced by 5F compounds in anaplastic thyroid carcinoma cells (FRO cells) and nasopharyngeal carcinoma cells (CNE-2Z) is associated with the G2/M phase arrest of the cell cycle. Mitochondrial caspase-dependent and caspase-independent pathways are involved in cell death induction, activating JNK in MAPS cascades following an increase in ROS formation. The compound down-regulates Bcl-2, induces cytochrome c release, and activates the mitochondrial-mediated apoptosis pathway (Liu *et al.*, 2005a; Wu *et al.*, 2013).

Gastric carcinoma cell (MKN-45) death was induced via a p53-dependent pathway that involves a rapid ROS-generating mechanism in 5F treatment (Liu *et al.*, 2005b). This compound also showed the ability to induce apoptosis in hepatocellular carcinoma cells (HepG2) involving the activation of p53 and caspase-3 and to reduce the level of VEGF in the cytosol (Li *et al.*, 2010). In lung carcinoma cells (NCI-H460) and laryngeal cancer cells (UMSCC11A and UMSCC12), apoptosis induction is mediated by inhibiting the NF-kB pathway. Inhibition of the NF-kB pathway is through decreasing the levels of IκKβ and IκB and significantly reducing the expression of p50 and p65 mRNA, besides being able to significantly regulate the basal levels of Bax, EGFR, cyclin-D1, and COX-2 (Liu *et al.*, 2010; Vlantis *et al.*, 2010). In A549 lung cancer cells, treatment with compound 5F increased cell accumulation in the sub-G1 phase (apoptotic cells) and cell arrest in the G2/M phase. The expression of p21 and Bax was increased, and caspase-3 was activated, leading to the release of cytochrome c and apoptosis-inducing factor (Li *et al.*, 2012). The 5F compound inhibits the proliferation of three types of breast cancer cells (MDA-MB-231, MCF-7, and SK-BR-3). Apoptosis is induced through decreased Bcl-2 and increased expression of Bax, Bak, and caspase-3 (Wu *et al.*, 2017). Treatment with 5F on lung cancer cells (NCI-H23) revealed cell growth and proliferation inhibition and induced arrested cell cycle progression in the G0/G1 phase. Apoptosis by 5F is induced through downregulated expression of β-catenin, c-Myc, and cyclin D1 and upregulated GSK-3β (Li *et al.*, 2017c).

Pterisolic acid (**6**), isolated from *P. semipinnata*, has been found to inhibit the proliferation of colon cancer cells (HCT116) by suppressing the Dvl-2/GSK-3β/β-catenin pathway. This compound induces apoptosis by downregulating the expression of anti-apoptotic proteins (survivin, Bcl-2, and Bcl-XL) and anti-apoptotic factors (NF-kB p65 and p-p65). It also upregulates the expression of PARP cleavage, caspase-3, p53 (tumor suppressor), and pro-apoptotic proteins (Puma, Bax, and Bim). Moreover, it increases the permeability of the mitochondrial membrane and overexpresses intracellular ROS (Qiu *et al.*, 2017).

Pterosine compounds and their derivatives have been reported to exhibit significant anti-cancer activity on various cancer cells, such as colon, breast, gastric, cervical, lung, pancreatic, and others. These compounds are primarily isolated from species of *Pteris* genera, such as *P. cretica, P. dispar, P. ensiformis, P. multifida, P. semipinnata,* and *P. obtusiloba.* Furthermore, the pterosine compound has been confirmed to be found in other genera, *Acrostichum aureum* L.. (2R,3R)-Pterosin L 3-O-β-D-glucopyrannoside (**7**) derived from *P. Ensiformis* and *P. multifida* revealed selective activity against human leukemia cancer cells (HL-60) with IC_{50} value < 10 μg/mL and showed potent cytotoxic activity against oral squamous cell carcinoma (KB cell line), pancreatic cancer (PANC-1 cell line), and lung cancer (NCI-H446 cell line) (Chen *et al*., 2008; Harinantenaina *et al*., 2008; Ouyang *et al*., 2010). The compound (2S,3S)-pterosine C 3-O-β-D-(40-(E)-caffeoyl)-glucopyranoside (**8**) found in *P. multifida* has the potential to inhibit the proliferation of colon cancer cells (HCT116) and induce apoptosis by upregulating caspase-9 and procaspase-9 (Kim et al., 2017). The compound (2S,3S)-Sulfated Pterosin C (**9**) isolated from *A. Aureum* is a derivative of (2S,3S)-Pterosin C. The presence of a sulfate group at C-2 in (2S,3S)-Pterosin C can increase its cytotoxic effect. Based on the apoptosis assay in 24-hour treatment, it is known that the number of cells undergoing early apoptosis increases from 6.8% to 25.2% (Uddin *et al*., 2011a).

Another terpenoid compound, davallic acid (**10**), was recently isolated from *Davallia divaricata* Blume (Davalliaceae). This triterpenoid significantly induced apoptosis and inhibited the growth of lung cancer cells (A549) by increasing ROS levels and triggering the activation of caspase-3, caspase-8, and caspase-9. Furthermore, it increased Bax expression, caused mitochondrial membrane damage, inhibited Bcl-2 expression, and resulted in cytochrome c release (Cheng *et al*., 2012). Dryofraterpene A (**11**), isolated from the fern *Dryopteris Fragrans* (L.) Schott (Dryopteridaceae), significantly suppressed the growth and proliferation of five different types of cancer cells, including MCF-7, HepG2, HeLa, A549, and PC-3, without inducing necrosis at concentrations below 10μM (Zhong *et al*., 2017).

Polyphenolic derivatives compound

Polypodiaceae, Pteridaceae, Dryopteridaceae, and Blechnaceae exhibit a high content of phenolic compounds with anti-cancer activity. It has been reported that lignan compounds, liglaurates A, B, C, and D from *Drynaria roosii* of the Polypodiaceae family have revealed the highest cytotoxic effect on HeLa cervical cancer cells, with IC_{50} values below 0.2 μM. Liglaurates B (**12**) is a mixture of enantiomers, and after separating them, it was discovered that (+)-liglaurates B exhibited the best activity against the same cells with an IC_{50} of 0.02 μM (Wufuer *et al.*, 2022). Other phenolic compounds isolated from Pteridaceae and Dryopteridaceae are caffeic acid and its derivatives. Caffeic acid (**13**) has been isolated from *D. fragrans* and has cytotoxic activity against breast, lung, and cervical cancer cells (Liu *et al*., 2018). 4,5-dicaffeoyl quinic acid (**14**) and 4-caffeoyl quinic acid 3-O-methyl ether (**15**), caffeic acid derivatives, actively inhibited cervical cancer cell proliferation (KB) (Harinantenaina *et al.*, 2008).

Another class of phenolic compounds is the phloroglucinol derivatives reportedly isolated from the Dryopteridaceae family species, *D. fragrans, Didymochlaena truncatula* (Sw.) J.Sm., and *Elaphoglossum paleaceum* (Hook. & Grev.) Sledge. Dryofragin (**16**), isolated from *D. fragrans*, induced apoptosis in breast cancer cells (MCF-7) through the mitochondrial pathway, which correlates with the formation of intracellular ROS. Treatment with the compound on these cells affects the expression of apoptosis-related proteins, decreased Bcl-2, and increased Bax, which causes mitochondrial membrane potential (MMP) disruption followed by the release of cytochrome c, leading to activation of caspase-3 and -9 and cleavage of PARP (Zhang *et al*., 2012). Dryofragin inhibited cell migration and invasion in human osteosarcoma cells (U2OS) by increasing the levels of TIMP-1 and -2 through PI3K/AKT and p38 MAPK signaling pathways while decreasing the levels of MMP-2 and -9 (Su *et al*., 2016). Another phloroglucinol derivative, Aspidin PB (**17**), isolated from the same species, induces apoptosis in HepG2 hepatic cancer cells via a caspase-dependent

pathway that inhibits PI3K expression and Akt phosphorylation. Aspidin PB treatment also reduces GSK-3β expression and increases NAG-1 expression levels. During the apoptosis induced by Aspidin PB, the activation of caspase-3 and the cleavage of PARP were observed (Sun *et al.*, 2013b). Aspidin PB induces apoptosis in osteosarcoma in U2OS cells via the mitochondrial apoptotic pathway. This is indicated by the decrease of Bcl-2 and the increase of Bax and cytoplasmic cytochrome c levels, which subsequently raise caspase-3 and -9. Aspidin PB modulates the cell cycle by upregulating p21 and p53 while downregulating CDK2, causing cell cycle arrest in S-phase *(*Wan *et al.*, 2015). Aspidin BB (**18**) induced apoptosis in ovarian cancer cells (HO-8910) via the mitochondria-dependent pathway by increasing activated caspase-3 and cleavage of PARP. It also increased the Bax/Bcl-2 ratio, leading to the release of cytochrome c. Aspidin BB induces S-phase arrest in the cell cycle distribution, which involves pRb-E2F1-cyclin A/CDK2 and cyclin E/CDK2 (Sun *et al*., 2013a).

Chalcones are polyphenolic compounds found in many plants. They are intermediates of flavonoid compounds. Active chalcone compounds that have been successfully isolated from ferns of the family Polypodiales are distributed in the Dryopteridaceae, Pteridaceae, and mainly in the Thelypteridaceae family. Parasiticin C (19), chalcone-derived compounds with potential antiproliferative and cytotoxic activities have been isolated from the fern *Thelypteris parasitica* (L.) Tardieu (syn. *Cyclosorus parasiticus*). Parasiticin C (**19**) showed the most potent cytotoxic effect against various cancer cells, especially hepatocellular carcinoma (HepG2) cells. The compound exhibited the ability to cause cell death by inducing apoptosis in HepG2 cells (Wei *et al*., 2013). Another chalcone compound, interruptin A (**20**) and B (2**1**), isolated from *Thelypteris terminans* Panigrahi, had significantly stronger cytotoxic effects on breast and colon cancer cells, up to 7 times stronger than camptothecin, a drug still in use (Kaewsuwan *et al*., 2015).

Coumarin derivatives are among the polyphenol-derived secondary metabolites found in the families Dryopteridaceae and Pteridaceae. Some of these compounds isolated from ferns include pimpinellin (**22**) from *Cyrtomium Fortunei* J.Sm.; dryofracoumarin A (**23**), dryofracoumarin B (**24**), esculetin (**25**), isoscopoletin (**26**) from *D. fragrans*; and multifidarin A from *P. multifida*. Coumarin compounds isolated from *D. fragrans* showed potential cytotoxic effects against lung, breast, liver, stomach, and skin cancer cells (Ni *et al*., 2015; Yang *et al*., 2013b; Zhang *et al*., 2018; Zhao *et al*., 2014).

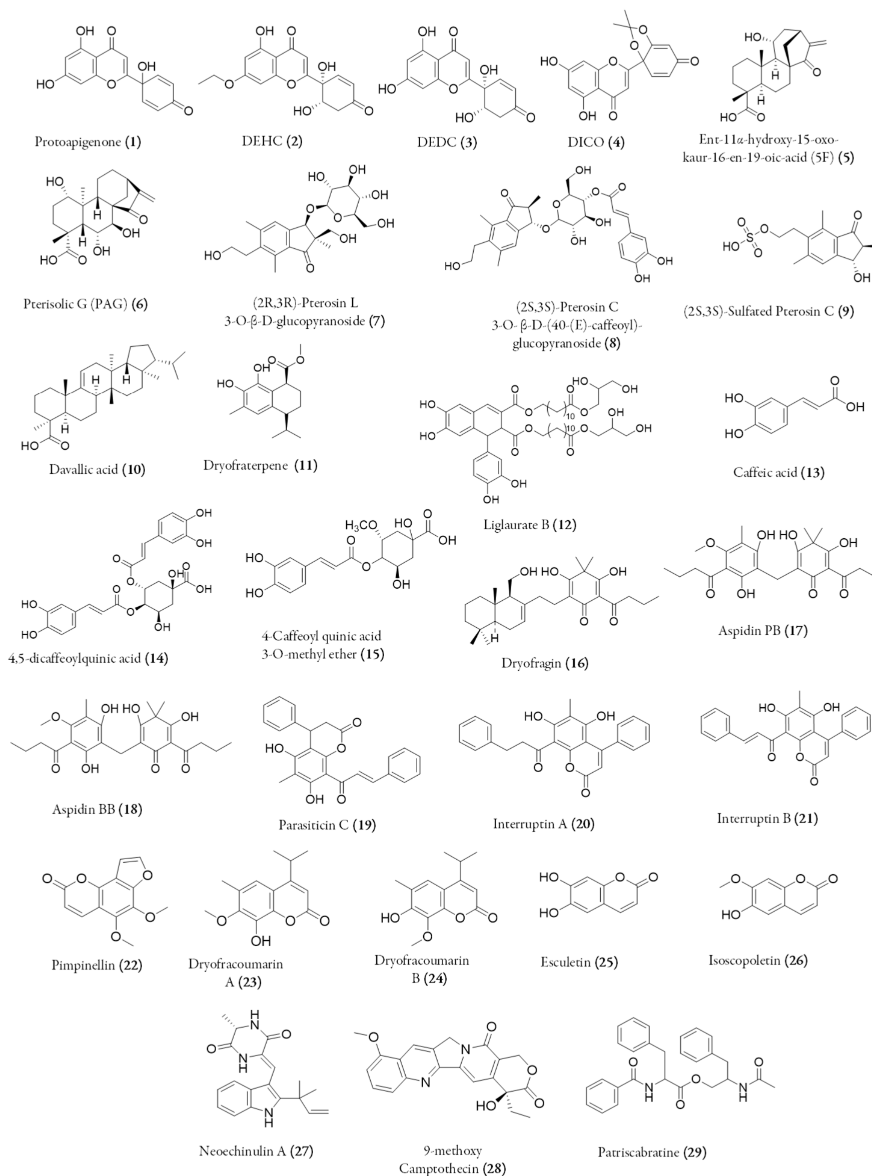

Figure 3. Significantly active secondary metabolites isolated from Polypodiales order as anticancer agent

<u>Alkaloids compound</u>

Alkaloid compounds are not commonly found in ferns but are present in some families of Dryopteridaceae and Pteridaceae. In the family Dryopteridaceae, alkaloids that have been reported to have anticancer activity are neoechinulin A (**27**) from *C. Fortunei* and 9-methoxycamptotechin (**28**) from *D. truncatula*. Neoechinulin A has potential activity against gastric (MGC-803), prostate (PC-3), and cervical (Bcap-37) cancer cells. In ovarian cancer cells (A2780), the cytotoxic effect of 9-methoxycamptotechin was three times greater than camptothecin, which was isolated from the same species (Cao *et al*., 2006; Yang *et al*., 2013a). In the Pteridaceae family, the active alkaloid that has been reported is patriscabratine (**29**), which was isolated from *A. aureum*. Patriscabratine exhibited significant cytotoxicity against gastric cancer cells (AGS) and breast cancer cells (MDA-MB-231 and MCF-7), but no cytotoxicity against fibroblast cells (NIH3T3) or

colon cancer cells (HT-29). Treatment with this compound can induce apoptosis at an early stage (early apoptosis) (Uddin *et al*., 2012).

Challenge and future insights

This review reveals that many plants and bioactive compounds from the order Polypodiales have the potential to be developed into new anticancer agents. Less than 50% of the families within this order have been explored for their plant potential and bioactive compounds. Based on literature studies, it is reported that many potential species come from families that have many members, such as Polypodiaceae, Dryopteridaceae, Pteridaceae, and Thelypteridaceae. Even within a single family, only a few species have been studied, indicating that there is still a significant opportunity for further exploration of Polypodiales species in the context of anticancer drug discovery. There are many different kinds of terpenoids, flavonoids, phenolic compounds, chalcone, phloroglucinol, and coumarin in Polypodiales species. Some of these compounds have not been found in other plants, while others have been identified in other plant species. These compounds have potential as anticancer agents. These compounds have the potential to be developed as anticancer agents. The review shows that compounds from the polypodiales order can provide anticancer effects by inhibiting several 'hallmarks of cancer,' including cell replication, cell death, invasion and metastasis, and angiogenesis. Inhibition of cell replication and stimulation of cell death are commonly observed mechanisms in cell cycle assays, apoptosis, and the expression of proapoptotic proteins. Polypodiales compounds have been shown to modulate the cell cycle by inducing arrest in the G2/M or S phases, leading to apoptosis. Compounds in the polypodiales order can trigger apoptosis of cancer cells through two pathways: the mitochondrial pathway (intrinsic) and the death-receptor pathway (extrinsic). The intrinsic mechanism is the most commonly reported. Polypodiales bioactive compounds increase reactive oxygen species (ROS) in the cell, affecting Bcl-2, Bax, and MMP expression levels. This, in turn, can increase the release of cytochrome c and activate caspase-3 and -9, which can increase PARP cleavage, ultimately leading to apoptosis (Figure 4).

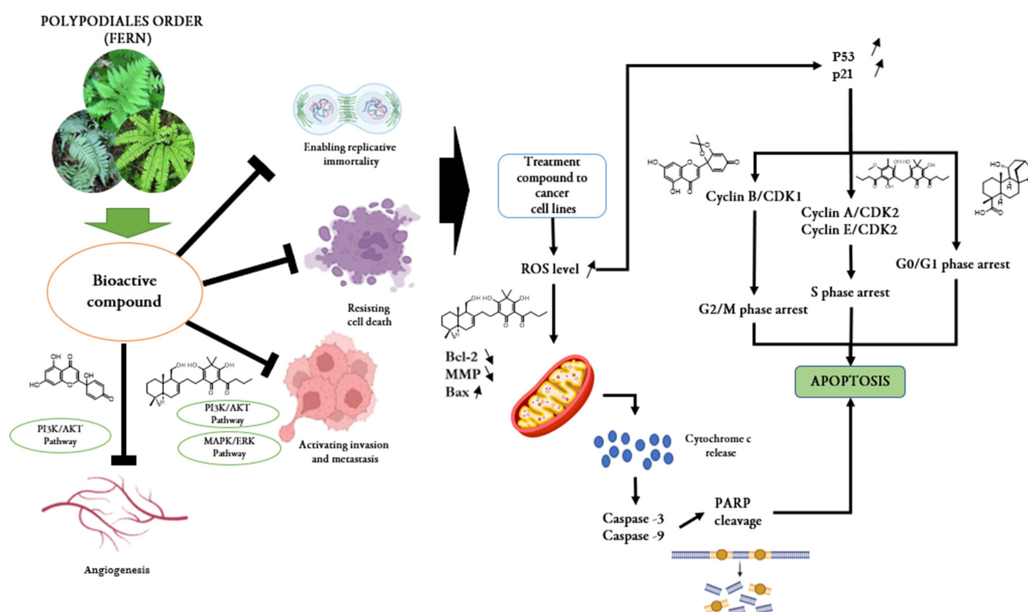

Figure 4. Proposed anticancer mechanism of Polypodiales order secondary metabolites

This literature review demonstrates the potential of polypodiales in the development of plant-based anticancer agents. Various assay methods and incubation times for in vitro testing can produce different results. Different assay methods will have different activity strength categories. Similarly, the length of incubation time for treatment with extract or compound samples will have different results when carried out at different incubation times. This causes limitations in comparing the potential between species and between secondary metabolite compounds from ferns.

Despite the high potential of fern as an anticancer, some limitations in the studies that have been conducted need to be addressed. The large number of species and families of Polypodiales that have not been explored is a challenge in the search for drugs from natural products. A significant number of ethnomedicine studies are based on traditional knowledge and anecdotal evidence, which may need more scientific validation. This lack of rigorous testing and validation can make it challenging to confirm the efficacy of plant-based treatments for cancer. Although fern exhibits promising anticancer properties, in vivo efficacy studies are imperative for further investigation. This is because it interacts with intricate biological systems, which are capable of mimicking the human body with greater fidelity than in vitro systems. This complexity is crucial for elucidating how drugs interact with diverse physiological processes and tissues, thereby facilitating a more accurate representation of how drugs interact with living organisms (Saad *et al*., 2024; Wang *et al*., 2016). In addition, there is a need for thorough toxicity and safety studies to ensure there are no adverse effects in humans. Through in vivo studies, it will help understand the mechanism of action of anticancer drugs. This knowledge is crucial for developing targeted therapies and overcoming resistance mechanisms.

Further research into more advanced molecular mechanisms for reported species or compounds and other species that have never been studied, *in vivo* efficacy and safety studies are of great importance and are a fundamental aspect of the research process. The data on extracts, fractions, and compounds in the order Polypodiales in relation to anticancer activity is continuously increasing and will be important for future studies. Propagating bioactive compounds in ferns is a challenging obstacle due to their wild nature. In the future, ferns will be studied for their pharmacological activities, particularly in anticancer research, due to the diversity of bioactive compounds and unexplored species.

Authors' Contributions

Conceptualization: DKP, PA, TH, ASN; acquisition of data, analysis, interpretation of data, writing - original draft: DKP, PA; Writing - review and editing: DKP, PA, TH, ASN. All authors read and approved the final manuscript.

Ethical approval (for researches involving animals or humans)

Not applicable.

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Conflict of Interests

The authors declare that there are no conflicts of interest related to this article.

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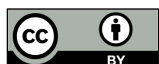

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Annexe 1

Annexe 1. Polypodiales secondary metabolites with potential anticancer properties

Family	Compound Name	Species	Part	Anticancer Potential Activity (IC_{50} / EC_{50} / GI_{50} /% cell death); (incub. time) *	References
Aspleniaceae	Aspleniumside A	*Asplenium ruprechtii*	whole parts	30.74 μM (HL-60) and 26.68 μM (HepG2); (24h)[3]	(Wang *et al.*, 2020)
	Aspleniumside B	*Asplenium ruprechtii*	whole parts	23.37 μM (HL-60) and 20.22 μM (HepG2); (24h)[3]	(Wang *et al.*, 2020)
	Aspleniumside C	*Asplenium ruprechtii*	whole parts	36.72 μM (HL-60) and 18.13 μM (HepG2); (24h)[3]	(Wang *et al.*, 2020)
Athyriaceae	Striatisporolide A	*Athyrium monomachii*	rhizomes	>20.0 μg mL^{-1} (HepG2, MCF-7, K562; 48h)[1]	(Liu *et al.*, 2016)
Blechnaceae	Proanthocyanidin (up to 12 epicatechin)	*Blechnum orientale*	leaves	7.0 μg mL^{-1} (HT29); 20.0 μg mL^{-1} (HCT116) and 16.0 μg mL^{-1} (HepG2); (72h)[1]	(Lai *et al.*, 2017)
	Kaempferol 3-O-(3‴-O-E-p-coumaroyl)-(6‴-O-E-feruloyl)-b-D-glucopyranoside	*Stenochlaena palustris*	fronds	35 μM (MCF-7); 70 μM (MDA-MB-231) and 72 μM (DU-145); (48h)[4]	(Chear *et al.*, 2019)
	Kaempferol 3-O-(3”,6” di-O-E-p-coumaroyl)-b-D-glucopyranoside	*Stenochlaena palustris*	fronds	<10 μM (MCF-7); 21 μM (MDA-MB-231) and 24 μM (DU-145); (48h)[4]	(Chear *et al.*, 2019)
Davalliaceae	Davallic acid	*Davallia divaricata*	rhizomes	43% (A549; 20 μM;24h)[1]	(Cheng *et al.*, 2012)
Dennstaedtiaceae	3β-O-α-L-rhamnopyranosyl- 7α-O-β-D-fucopyranosyl-ent-iospimara-8(14),15-diene	*Microlepia firma*	fronds	10.1 μM (A549); 9.8 μM (BGC-823); 9.5 μM (HCT15); 10.5 μM (HeLa); 11.1 μM (HepG2); 10.2 μM (MCF-7); and 10.6 μM (SK-Mel-2); (48h)[1]	(Hu *et al.*, 2015)
	3α-O-[2-O-acetyl-α-L-rhamnopyranosyl]-7α-O-β-D-fucopyranosyl-ent-iospimara- 8(14),15-diene	*Microlepia firma*	fronds	10.4 μM (A549); 10.6 μM (BGC-823); 9.8 μM (HCT15); 11.1 μM (HeLa); 11.9 μM (HepG2); 9.5 μM (MCF-7); and 9.9 μM (SK-Mel-2); (48h)[1]	(Hu *et al.*, 2015)
	3β-O-[β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranosyl]-7α-O-β-D-fucopyranosyl-ent-iospimara-8(14),15-diene	*Microlepia firma*	fronds	5.8 μM (A549); 6.0 μM (BGC-823); 6.4 μM (HCT15); 6.2 μM (HeLa); 6.6 μM (HepG2); 5.6 μM (MCF-7); and 6.1 μM (SK-Mel-2); (48h)[1]	(Hu *et al.*, 2015)
	3β-O-[β-D-fucopyranosyl-(1→2)-α-L-rhamnopyranosyl]-7α-O-β-D-fucopyranosyl-ent-iospimara- 8(14),15-diene	*Microlepia firma*	fronds	4.6 μM (A549); 4.9 μM (BGC-823); 5.3 μM (HCT15); 5.0 μM (HeLa); 5.7 μM (HepG2); 4.7 μM (MCF-7); and 5.3 μM (SK-Mel-2); (48h)[1]	(Hu *et al.*, 2015)
	3α,7β-dihydroxy-ent-iospimara-8(14),15-diene	*Microlepia firma*	fronds	9.8 μM (BGC-823) and 11.1 μM (HepG2); (48h)[1]	(Hu *et al.*, 2015)
Dryopteridaceae	Neoechinulin A	*Cyrtomium fortunei*	rhizomes	15.2 μM (MGC-803); 19.8 μM (PC3) and 24.2 μM (Bcap-37); (72h)[1]	(Yang *et al.*, 2013a)
	Pimpinellin	*Cyrtomium fortunei*	rhizomes	14.4 μM (MGC-803); 20.4 μM (PC3) and 29.2 μM (A375); (72h)[1]	(Yang *et al.*, 2013b)
	(10E,15E)-9,12,13-trihydroxyoctadeca-10,15-dienoic acid	*Cyrtomium fortunei*	rhizomes	18.3 μM (MGC-803); 21.3 μM (PC3) and 27.4 μM (Bcap-37); (72h)[1]	(Yang *et al.*, 2013a)
	(E)-3-methoxy-5-hydroxystilbene	*Didymochlaena truncatula*	roots	10 μg mL^{-1} (A2780; 48h)[6]	(Cao *et al.*, 2006)
	Albicanol	*Dryopteris fragrans*	whole plants	24.14 μM (MCF-7; 48h)[1]	(Zhao *et al.*, 2014)
			aerial parts	49.74 μM (A549; 48h)[3]	(Zhang *et al.*, 2018)
	Aspidin BB	*Dryopteris fragrans*	aerial parts	15.02 μM (HO-8910); 25.87 μM (MCF-7); 28.17 μM (PC-3); 31.93 μM (HCT-8); 29.11 μM (A549); 35.55μM (CEM); 33.89 μM (HepG2) and 26.31 μM (HeLa); (72h)[1]	(Sun *et al.*, 2013a)
	Aspidin PB			10.59 μM (HepG2;72h)[1]	(Sun *et al.*, 2013b)

Family	Compound Name	Species	Part	Anticancer Potential Activity (IC_{50} /EC_{50} /GI_{50}/% cell death); (incub. time) *	References
		Dryopteris fragrans	aerial parts	15.2 µM (Saos-2); 21.7 µM (U2OS); and 24.9 µM (HOS); (48h)[1]	(Wan *et al*., 2015)
	Aspidinol	*Dryopteris fragrans*	whole plants	12.59 µM (A549) and 10.58 µM (MCF-7); (48h)[1]	(Zhao *et al*., 2014)
			aerial parts	41.21 µM (U251); 17.76 µM (HeLa); 43.67 µM (HOS); 22.76 µM (MG63); 18.02 µM (HepG2); 39.61 µM (MB231)); 33.40 µM (SKBR-3) and 36.36 µM (U2OS); (48h)[3]	(Zhang *et al*., 2018)
	Caffeic acid	*Dryopteris fragrans*	whole plants	19.44 µM (MCF-7); 10.41 µM (A549) and 8.96 µM (SGC7901); (48h)[1]	(Liu *et al*., 2018)
	Camptothecin	*Didymochlaena truncatula*	roots	0.07 µg mL^{-1} (A2780; 48h)[6]	(Cao *et al*., 2006)
	9-methoxy Camptothecin	*Didymochlaena truncatula*	roots	0.02 µg mL^{-1} (A2780; 48h)[6]	(Cao *et al*., 2006)
	Dryofracoumarin A	*Dryopteris fragrans*	whole plants	6.56 µM (A549) and 10.14 µM (MCF-7); (48h)[1]	(Zhao *et al*., 2014)
			aerial parts	38.01 µM (A549); 48.39 µM (HepG2) and 25.59 µM (MB231); (48h)[3]	(Zhang *et al*., 2018)
	Dryofracoumarin B	*Dryopteris fragrans*	aerial parts	47.70 µM (A549); 15.12 µM (HeLa); 45.52 µM (HepG2) and 46.14 µM (U251); (48h)[3]	(Zhang *et al*., 2018)
	Dryofragin	*Dryopteris fragrans*	aerial parts	27.26 µM; 37.51 µM; and 76.10 µM (MCF-7;72h,48h and 24h)[1].	(Zhang *et al*., 2012)
	Dryofragone	*Dryopteris fragrans*	aerial parts	45.86 µM (A549); 25.37 µM (HeLa) and 46.13 µM (U251); (48h)[3]	(Zhang *et al*., 2018)
	Dryofraterpene A	*Dryopteris fragrans*	whole plants	1,58 µM (MCF-7), 3,53 µM (HepG), 1,65 µM (HeLa), 2,84 µM (A549) and 4,62 µM (PC-3); (48h)[3]	(Zhong *et al*., 2017)
	Esculetin	*Dryopteris fragrans*	whole plants	3.82 µM (A549); 2.73 µM (MCF-7); 10.15 µM (HepG2); (48h)[1]	(Zhao *et al*., 2014)
	Fragranoside B	*Dryopteris fragrans*	whole plants	2.65 µM (MCF-7;48h)[1]	(Liu *et al*., 2018)
	Isoscopoletin	*Dryopteris fragrans*	whole plants	5.25 µM (A549); 8.58 µM (MCF-7); 4.76 µM (HepG2); (48h)[1]	(Zhao *et al*., 2014)
	Norflavesone	*Dryopteris fragrans*	aerial parts	40.03 µM (A549; 48h)[3]	(Zhang *et al*., 2018)
	Vitamin E quinone	*Dryopteris fragrans*	aerial parts	37.41 µM (A549); 1.24 µM (HeLa); 38.13 µM (HepG2); 41.95 µM (MB231) and 41.95 µM (U2OS); (48h)[3]	(Zhang *et al*., 2018)
	trans-3-(3,4-dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl]cyclohex-1-ene	*Dryopteris fragrans*	whole plants	14.13 µM (A549); 17.81 µM (MCF-7); 17.90 µM (HepG2); (48h)[1]	(Zhao *et al*., 2014)
	cis-3-(3,4-dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl] cyclohex-1-ene	*Dryopteris fragrans*	whole plants	17.25 µM (A549); 16.45 µM (MCF-7); 23.75 µM (HepG2); (48h)[1]	(Zhao *et al*., 2014)
	2',4'-dihydroxy-6'-methoxy-3',5'-dimethylchalcone	*Dryopteris fragrans*	aerial parts	47.42 µM (A549); (48h)[3]	(Zhang *et al*., 2018)
	Paleacenin A	*Elaphoglossum paleaceum*	whole plants	>10 µM (MCF-7); 6.0 µM (SiHA); >10 µM (HF6) and 1.7 µM (PC3); (72h)[2]	(Arvizu-Espinosa *et al*., 2019)
	Paleacenin B	*Elaphoglossum paleaceum*	whole plants	>10 µM (MCF-7); 5.6 µM (SiHA); 6.4 µM (HF6) and 2.9 µM (PC3); (72h)[2]	(Arvizu-Espinosa *et al*., 2019)
Polypodiaceae	Chiratone	*Drynaria roosii*	rhizomes	2.92 µM (HeLa); 1.08 µM (PC3); and 2.45 µM (HepG2); (20h)[1]	(Liang *et al*., 2010)

Family	Compound Name	Species	Part	Anticancer Potential Activity (IC_{50} /EC_{50} /GI_{50}/% cell death); (incub. time) *	References
	Liglaurate A	*Drynaria roosii*	rhizomes	0.16 μM (HeLa); 9.20 μM (HCT-116); and >10 μM (MCF-7, HepG2 and MV4-11) (72h)[3]	(Wufuer *et al.*, 2022)
	Liglaurate B	*Drynaria roosii*	rhizomes	0.06 μM (HeLa); 8.81 μM (HCT-116); 4.04 μM (MCF-7); 4.61 μM (HepG2) and >10 μM (MV4-11); (72h)[3]	(Wufuer *et al.*, 2022)
	Liglaurate C	*Drynaria roosii*	rhizomes	0.34 μM (HeLa); 8.68 μM (HCT-116); and >10 μM (MCF-7, HepG2 and MV4-11); (72h)[3]	(Wufuer *et al.*, 2022)
	Liglaurate D	*Drynaria roosii*	rhizomes	0.17 μM (HeLa); 4.55 μM (HCT-116); 0.58 μM (MCF-7); 3.04 μM (HepG2) and >10 μM (MV4-11); (72h)[3]	(Wufuer *et al.*, 2022)
	Isoorientin	*Lepisorus thunbergianus*	whole plants	>50% (HepG2 and Huh-7;100 μmol;24h)[1]	(Yang *et al.*, 2015a)
Pteridaceae	Patriscabratine	*Acrostichum aureum*	aerial parts	197.3 μM (MCF-7); 69.8 μM (MDA-MB-231) and 133.6 μM (AGS); (24h)[1]	(Uddin *et al.*, 2012)
	(+)-Pinoresinol-4-O-sulfate	*Acrostichum aureum*	aerial parts	65.54 μM (LU-1); 73.78 μM (MCF-7); and 64.73 μM (HepG2); (72h)[2]	(Minh *et al.*, 2022)
	(2S,3S)-Sulfated Pterosin C	*Acrostichum aureum*	aerial parts	23.9 μM (AGS); 68.8 μM (HT-29); >100 μM (MDA-MB-231); and 64.4 μM (MCF-7); (24h)[1]	(Uddin *et al.*, 2011a)
	(17Z)-13,19-epoxycheilanth-1,17-diene-2-ol-3-one	*Hemionitis anceps*	whole plants	26.47 μM (A549); 12.63 μM (MCF-7); 21.53 μM (HL-7702)	(Jiang **et al.**, 2022)
	5-hydroxy-3,7,4'-trimethoxyflavon	*Hemionitis anceps*	whole plants	27.35 μM (A549); 24.21 μM (MCF-7); 54.58 μM (HL-7702)	(Jiang *et al.*, 2022)
	5-hydroxy-7,4'-dimethoxyflavone	*Hemionitis anceps*	whole plants	49.28 μM (A549); 18.24 μM (MCF-7); 63.63 μM (HL-7702)	(Jiang *et al.*, 2022)
	5,40-dihydroxy-3,7-dimethoxyflavon	*Hemionitis anceps*	whole plants	25.80 μM (A549); 14.54 μM (MCF-7); 85.97 μM (HL-7702)	(Jiang *et al.*, 2022)
	Hyperoside	*Hemionitis anceps*	whole plants	39.41 μM (A549); 19.38 μM (MCF-7); >100 μM (HL-7702)	(Jiang *et al.*, 2022)
	3,7,3',4'-tetramethyl-quercetin	*Hemionitis anceps*	whole plants	16.99 μM (A549); 10.07 μM (MCF-7); 60.56 μM (HL-7702)	(Jiang *et al.*, 2022)
	Aleuritopsis A	*Hemionitis michelii*	whole plants	13.8 μM (SKOV3) and 15.6 μM (MCF-7); (48h)[1]	(Li *et al.*, 2017b)
	Aleuritopsis B	*Hemionitis michelii*	whole plants	8.7 μM (SKOV3) and 11.3 μM (MCF-7); (48h)[1]	(Li *et al.*, 2017b)
	Alepterolic acid	*Hemionitis michelii*	whole plants	86.63 μM (A549) and 62.20 μM (MCF-7); (72h)[1]	(Zhang *et al.*, 2020a)
	Onychin	*Onychium japonicum*	aerial parts	2.58 μg mL^{-1} (P388)[1]	(Yunlong *et al.*, 1993)
	Japonicone A	*Onychium japonicum*	aerial parts	41.49% (HeLa); 45.87% (BEL-7402); and 25.10% (HL-60); (30 μg/mL; 72h)[1]	(Li *et al.*, 2007)
	Onychiol B	*Onychium japonicum*	aerial parts	5.62 μg mL^{-1} (P388)[1]	(Yunlong *et al.*, 1993)
	Creticolactone A	*Pteris cretica*	aerial parts	22.4 μM (HCT-116; 48h)[1]	(Lu *et al.*, 2019)
	13-hydroxyl-2(R),3(R)-pterosin L	*Pteris cretica*	aerial parts	15.8 μM (HCT-116; 48h)[1]	(Lu *et al.*, 2019)
	5,11β,12β-trihydroxy-15-oxo-ent-kuar-16-en-19-oic acid	*Pteris dispar*	whole plants	59.8 μM (KB)[1]	(Gou *et al.*, 2011)
	1α,3β-dihydroxyl norpterosin C	*Pteris dispar*	whole plants	36.5 μM (KB)[1]	(Gou *et al.*, 2011)
	ent-7α,9-dihydroxy-15-oxokaur-16-en-19,6β-olide	*Pteris ensiformis*	whole plants	5.3 μM (HCT116); 3.0 μM (HepG2) and 6.6 μM (BGC823); (48h)[1]	(Shi *et al.*, 2017a)
	(4R,4αS,6αR,9S,11R,11αS,11βR)-11-hydroxy-4,11β-dimethyl-8-methylene-7-oxotetradecahydro-6α,9-methanocyclohepta-[a]-	*Pteris ensiformis*	whole plants	3.0 μM (HCT116); 10.5 μM (HepG2) and 6.3 μM (BGC823); (48h)[1]	(Shi *et al.*, 2017b)

Family	Compound Name	Species	Part	Anticancer Potential Activity (IC_{50} /EC_{50} /GI_{50}/% cell death); (incub. time) *	References
	naphthalene-4-carboxylic acid				
	4-Caffeoyl quinic acid 3-O-methyl ether	*Pteris multifida*	aerial parts	12.3 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)
	4,5-dicaffeoylquinic acid	*Pteris multifida*	aerial parts	5.3 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)
	Dehydropterosin B	*Pteris multifida*	aerial parts	58.80 µM (A549); 37.64 µM (LoVo); 14.63 µM (PANC-1) and 5.19 µM (NCI-H446)[1]	(Ouyang *et al*., 2010)
	Ent-kaurane-2β,16α-diol	*Pteris multifida*	aerial parts	37 µM (Ehrlich ascites tumor cells; 72h)[1]	(Woerdenbag *et al*., 1996)
	Ent-kaur-16-ene-2β,15α-diol	*Pteris multifida*	aerial parts	37 µM (Ehrlich ascites tumor cells; 72h)[1]	(Woerdenbag *et al*., 1996)
	Multifidarin A	*Pteris multifida*	whole plants	>10 µM (NCI-H1650, HepG2, BGC 823, HCT-116 and A2780); (96h)[1]	(Ni *et al*., 2015)
	Multifidoside A	*Pteris multifida*	whole plants	10.63 (K562); 8.69 (HepG2); 14.16 µM (KB) and 11.28 µM (LoVo); (72h)[2,5]	(Ge *et al*., 2008)
	Multifidoside B	*Pteris multifida*	whole plants	9.57 (K562); 9.26 (HepG2) and 23.82 µM (KB); (72h)[2,5]	(Ge *et al*., 2008)
	Multifidoside B	*Pteris multifida*	whole plants	64.56 (K562) and 45.34 µM (KB); (72h)[2,5]	(Ge *et al*., 2008)
	Multikaurane A	*Pteris multifida*	whole plants	>10 µM (NCI-H1650, HepG2, BGC 823, HCT-116 and A2780); (96h)[1]	(Ni *et al*., 2015)
	Multikaurane B	*Pteris multifida*	whole plants	>10 µM (NCI-H1650, HepG2, BGC 823, HCT-116 and A2780); (96h)[1]	(Ni *et al*., 2015)
	Pterokaurane M_1	*Pteris multifida*	whole plants	26.5 µM (KB) and 20.34 µM (LoVo); (72h)[2]	(Ge *et al*., 2008)
	Pterokaurane M_2	*Pteris multifida*	whole plants	69.60 µM (KB) and 76.34 µM (LoVo); (72h)[2]	(Ge *et al*., 2008)
	Pterokaurane M_3	*Pteris multifida*	whole plants	81.86 (K562); 82.43 (HepG2); 53.66 µM (KB) and 91.66 µM (LoVo); (72h)[2,5]	(Ge *et al*., 2008)
	Pteroside A	*Pteris multifida*	aerial parts	18.8 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)
	Pteroside C	*Pteris multifida*	aerial parts	22.9 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)
	Pterosin B	*Pteris multifida*	aerial parts	50.1 µM (HCT-116)	(Kim *et al*., 2017)
		Pteris ensiformis	whole plants	3.7 µg mL^{-1} (HL-60, 72h)[1]	(Chen *et al*., 2008)
	(2S,3S)-Pterosin C 3-O-β-D-glucopyrannoside	*Pteris multifida*	aerial parts	2.3 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)
				47.98 µM (A549); 35.58 µM (LOVO); 5.45 µM (PANC-1) and 4.95 µM (NCI-H446)[1]	(Ouyang *et al*., 2010)
	(2S,3S)-Pterosin C 3-O-β-D-(40-(E)-caffeoyl)-glucopyra- noside	*Pteris multifida*	aerial parts	8.0 µM (HCT-116)	(Kim *et al*., 2017)
	(2S,3S)-Pterosin C 3-O-β-D-(60-(E)-p-coumaroyl)-glucopyranoside	*Pteris multifida*	aerial parts	17.2 µM (HCT-116)	(Kim *et al*., 2017)
	(2S,3S)-Pterosin C 3-O-β-D-glucopyranoside	*Pteris multifida*	aerial parts	32.9 µM (HCT-116)	(Kim *et al*., 2017)
	(2R,3R)-Pterosin L 3-O-β-D-glucopyranoside	*Pteris multifida*	aerial parts	24.7 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)
				37.61 µM (A549); 29.11 µM (LOVO); 12.07 µM (PANC-1) and 4.27 µM (NCI-H446)[1]	(Ouyang *et al*., 2010)
		Pteris ensiformis	whole plants	8.7 µg mL^{-1} (HL-60, 72h)[1]	(Chen *et al*., 2008)
	Wallichoside	*Pteris multifida*	aerial parts	28.3 µM (KB, 72h)[1]	(Harinantenaina *et al*., 2008)

Family	Compound Name	Species	Part	Anticancer Potential Activity (IC$_{50}$ /EC$_{50}$ /GI$_{50}$/% cell death); (incub. time) *	References
		Onychium japonicum	aerial parts	0.21 μg mL^{-1} (P388)[1]	(Yunlong *et al.*, 1993)
	Obtupterosin A	*Pteris obtusiloba*	aerial parts	27.5 μM (HCT116; 48h)[1]	(Peng *et al.*, 2020)
	Obtupterosin B	*Pteris obtusiloba*	aerial parts	30.6 μM (HCT116; 48h)[1]	(Peng *et al.*, 2020)
	Obtupterosin C	*Pteris obtusiloba*	aerial parts	12.8 μM (HCT116; 48h)[1]	(Peng *et al.*, 2020)
	Ent-11α-hydroxy-15-oxo-kaur-16-en-19-oic-acid (5F)	*Pteris semipinnata*	aerial parts	>90% (HT-29;100 μg mL^{-1};48h)[1]	(Chen *et al.*, 2004)
		Pteris ensiformis	whole plants	>75% (MKN-45;150 μg mL^{-1};24h)[1]	(Liu *et al.*, 2005b)
				4.52 μg mL^{-1} (NCI-H460; 48h)[1]	(Liu *et al.*, 2010)
				>70% (A549;80 μg mL^{-1};48h)[1]	(Li *et al.*, 2012)
				>60% (CNE-2Z ;80 μg mL^{-1};24h)[1]	(Wu *et al.*, 2013)
				17.6 μg mL^{-1} (CT26.WT); 42.6 μg mL^{-1} (HepG2) and 78.6 μg mL^{-1} (A549); (24h)[1]	(Qiu *et al.*, 2016)
				SK-BR-3 > 95%; MCF-7 ~50%; and MDA-MB-231>50% (40 μg mL^{-1};72h)[3]	(Wu *et al.*, 2017)
				3 μM (HCT116); 6.0 μM (HepG2) and 6.3 μM (BGC823); (48h)[1]	(Shi *et al.*, 2017a)
	Ent-7α,11α -dihydroxy-15-oxokaur-16-en-19,6β-olide	*Pteris semipinnata*	whole plants	13.8 μg mL^{-1} (CT26.WT); 15.6 μg mL^{-1} (HepG2) and 41.5 μg mL^{-1} (A549); (24h)[1]	(Qiu *et al.*, 2016)
	Pterisolic G (PAG)	*Pteris semipinnata*	aerial parts	16.15 μM and 4.07 μM (HCT-116; 48h&72h)[3]	(Qiu *et al.*, 2017)
Thelypteridaceae	Apigenin 4'-O-β-D-Glucoside	*Macrothelypteries torresiana*	whole plants	7.75 μg mL^{-1} (HepG2); 10.55 μg mL^{-1} (Hep3B); 8.64 μg mL^{-1} (MCF-7); and 1.30 μg mL^{-1} (MDA-MB-231)[1]	(Lin *et al.*, 2005)
	2-(cis-1,2-dihydroxy-4-oxo-cyclohex-5-enyl)-5,7-dihydroxy-Chromone (DEDC)	*Macrothelypteris torresiana*	aerial parts	>50% (HepG2; 5 μg mL^{-1}; 24h)[8]	(Liu *et al.*, 2011)
				11.5 μg mL^{-1} (A549); 6.2 μg mL^{-1} (PC-3); 5.2 μg mL^{-1} (SH-SY5Y); 8.4 μg mL^{-1} (MCF-7); (12h)[1]	(Liu *et al.*, 2012)
	2-(cis-1,2-dihydroxy-4-oxo-cyclohex-5-enyl)-5,7-dihydroxy-chromone	*Macrothelypteris torresiana*	aerial parts	10.0 μg mL^{-1} (HepG2); 8.4 μg mL^{-1} (MCF-7) and 13.3 μg mL^{-1} (K562); (48h)[1]	(Fang *et al.*, 2011)
	2-(trans-1,4-dihydroxy-cyclohexyl)-5,7-dihydroxy-chromone	*Macrothelypteris torresiana*	aerial parts	>20.0 μg mL^{-1} (HepG2, MCF-7, and K562; 48h)[1]	(Fang *et al.*, 2011)
	5',6'-dihydro-6'-methoxyprotoapigenone	*Macrothelypteris torresiana*	whole plants	5.88 μg mL^{-1} (HepG2); 1.74 μg mL^{-1} (Hep3B); 5.92 μg mL^{-1} (MCF-7); 13.30 μg mL^{-1} (A549); and 1.30 μg mL^{-1} (MDA-MB-231)[1]	(Lin *et al.*, 2005)
	Protoapigenin	*Macrothelypteris torresiana*	whole plants	1.60 μg mL^{-1} (HepG2); 20.00 μg mL^{-1} (Hep3B); 18.84 μg mL^{-1} (A549)[1]	(Lin *et al.*, 2005)
	Protoapigenone	*Macrothelypteris torresiana*	whole plants	1.60 μg mL^{-1} (HepG2); 0.23 μg mL^{-1} (Hep3B); 0.78 μg mL^{-1} (MCF-7); 3.88 μg mL^{-1} (A549); and 0.27 μg mL^{-1} (MDA-MB-231)[1]	(Lin *et al.*, 2005)
				0.69 μM (MDAH-2774); 0.78 μM (SKOV3); 3.66 μM (HeLa); 4.69 μM (C33A); 3.33 μM (468) and 5.13 μM (T47D); (48h)[7]	(Chang *et al.*, 2008a)
				3.7 μM (LN-Cap; 48h)[7]	(Chang *et al.*, 2008b)
				2.74 μM and 1.49 μM; (H1299; 24h& 48h)[1]	(Chiu *et al.*, 2009)
				2.3 μg mL^{-1} (HepG2); 0.6 μg mL^{-1} (Tca8113); 0.8 μg mL^{-1} (MCF-7); 0.3 μg mL^{-1} (M5); and 0.9 μg mL^{-1} (K562); (72h)[1]	(Huang *et al.*, 2010)
				1.6 μM (MDA-MB-231; 48h)[1]	(Chen *et al.*, 2011)
				5.03 μM (MDA-MB-231); 3.96 μM (BT474)[1]	(Liu *et al.*, 2019)

Family	Compound Name	Species	Part	Anticancer Potential Activity (IC_{50} /EC_{50} /GI_{50}/% cell death); (incub. time) *	References
	DICO	*Macrothelypteris torresiana*	rhizomes	4.75 µg mL^{-1}and 6.26 µg mL^{-1} (HepG2; 24&48h)[1]	(Zhou *et al*., 2013)
		Macrothelypteris viridifrons	rhizomes	6.28 µg mL^{-1}and 4.13 µg mL^{-1} (HT-29; 24h&48h)[1]	(Wei *et al*., 2022)
	2-(cis-1, 2-dihydroxy-4-oxo-cyclohex-5-enyl)-5-hydroxy-7-eth- oxy-chromone (DEHC)	*Macrothelypteris viridifrons*	roots	7.03 µg mL^{-1} (HepG2); 9.15 µg mL^{-1} (PC-3); 6.61 µg mL^{-1} (A549); 6.98 µg mL^{-1} (MCF-7); 8.43 µg mL^{-1} (MOLT-4); 5.25 µg mL^{-1} (HT-29); (24h)[1]	(Wei *et al*., 2011)
	Parasiticin A	*Thelypteris parasitica*	leaves	8.05 µM (SW1990); 11.63 µM (MDA-MB-231); 11.2 µM (MCF-7); 10.59 µM (HepG2); 16.2 µM (A549); and 10.8 µM (ALL-SIL)[2]	(Wei *et al*., 2013)
	Parasiticin B	*Thelypteris parasitica*	leaves	8.52 µM (SW1990); 10.62 µM (MDA-MB-231); 9.44 µM (MCF-7); 12.7 µM (HepG2); 7.13 µM (A549); and 12.1 µM (ALL-SIL)[2]	(Wei et al., 2013)
	Parasiticin C	*Thelypteris parasitica*	leaves	2.33 µM (SW1990); 4.88 µM (MDA-MB-231); 4.16 µM (MCF-7); 1.6 µM (HepG2); 5.5 µM (A549); and 6.06 µM (ALL-SIL)[2]	(Wei *et al*., 2013)
	5,7-dihydroxy-4-phenyl-8-(3-phenyl-trans-acryloyl)-3,4-dihydro-1-benzopyran-2- one	*Thelypteris parasitica*	leaves	9.32 µM (SW1990); >20 µM (MDA-MB-231); 17.52 µM (MCF-7); 9.74 µM (HepG2); >20 µM (A549); and 16.2 µM (ALL-SIL)[2]	(Wei *et al*., 2013)
	20-hydroxy-40,60-dimethoxychalcone	*Thelypteris parasitica*	leaves	17.3 µM (SW1990); >20 µM (MDA-MB-231); 9.41 µM (MCF-7); 17.98 µM (HepG2); >20 µM (A549); and >20 µM (ALL-SIL)[2]	(Wei *et al*., 2013)
	20,40-dihydroxy-60-methoxy-30,50-dimethyl-chalcone	*Thelypteris parasitica*	leaves	6.64 µM (SW1990); 9.67 µM (MDA-MB-231); 8.49 µM (MCF-7); 2.82 µM (HepG2); 7.89 µM (A549); and 9.5 µM (ALL-SIL)[2]	(Wei *et al*., 2013)
	20,40-dihydroxy-60-methoxy-30-methylchalcone	*Thelypteris parasitica*	leaves	6.97 µM (SW1990); 9.19 µM (MDA-MB-231); 7.24 µM (MCF-7); 15.81 µM (HepG2); 8.42 µM (A549); and 12.54 µM (ALL-SIL)[2]	(Wei *et al*., 2013)
	Interruptin A	*Thelypteris terminans*	aerial parts	0.35 ng mL^{-1} (MCF-7) and 0.15 ng mL^{-1} (HT-29; 72h)[2]	(Kaewsuwan *et al*., 2015)
	Interruptin B	*Thelypteris terminans*	aerial parts	0.16 ng mL^{-1} (MCF-7) and 0.13 ng mL^{-1} (HT-29; 72h)[2]	(Kaewsuwan *et al*., 2015)
	Abacopterin A	*Thelypteris penangiana*	rhizomes	3.5 µg mL^{-1} (HepG2); 54.13 µM (MCF-7); 28.29 µM (HepG2); 15.50 µM (HCT-116); and 20.77 µM (BGC-823); (48h)[1]	(Shen *et al*., 2020; Zhao *et al*., 2006)
	Abacopterin B	*Thelypteris penangiana*	rhizomes	4.1 µg mL^{-1} (HepG2; 72h)[1]	(Zhao *et al*., 2006)
	Abacopterin C	*Thelypteris penangiana*	rhizomes	4.0 µg mL^{-1} (HepG2)[1]; 38.74 µM (MCF-7); 20.02 µM (HepG2); 15.77 µM (HCT-116); and 18.43 µM (BGC-823); (48h)[1]	(Shen *et al*., 2020; Zhao *et al*., 2006)
	Abacopterin D	*Thelypteris penangiana*	rhizomes	3.1 µg mL^{-1} (HepG2; 72h)[1]	(Zhao *et al*., 2006)
	Eruberin B	*Thelypteris penangiana*	rhizomes	21.93 µM (HepG2); 19.61 µM (HCT-116); and 24.13 µM (BGC-823); (48h)[1]	(Shen *et al*., 2020)
	Triphyllin A	***Thelypteris penangiana***	**rhizomes**	**31.77 µM (HepG2); 25.17 µM (HCT-116); and 21.66 µM (BGC-823); (48h)[1]**	**(Shen *et al*., 2020)**