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Fern flavonoids: Phytochemical diversity, environmental determinants and biological properties

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ABSTRACT

Ferns belong to the oldest evolutionary lineages of vascular plants, yet they remain a relatively poorly understood group in terms of phytochemistry and biological activity. In recent years, the flavonoids found in ferns have attracted increasing interest due to their important physiological role in plants and their potential health benefits. The aim of this article is to present the current state of knowledge regarding flavonoids present in ferns, with particular emphasis on their phytochemical diversity, environmental factors, and biological properties. Available data indicate that ferns are characterized by high qualitative and quantitative variability in flavonoid compounds. In various taxa, both simple flavones and flavonols, as well as their glycosides, proanthocyanidins, biflavonoids, and other phenolic derivatives have been identified. The accumulation of flavonoids in fern tissues depends on many environmental factors, such as light conditions, soil moisture, altitude, salinity, and UV radiation. Among the biological properties, the antioxidant activity of flavonoid-rich extracts and fractions is the best documented, while data on anticancer and antimicrobial activity, although promising, still require further research. The main limitations of the current state of knowledge include the heterogeneity of research methods, insufficient structural characterization of the active compounds, and a lack of *in vivo* studies and toxicological analyses.

Keywords: ferns; flavonoids; secondary metabolites; antioxidant activity; cytotoxicity; antimicrobial activity; environmental factors.

INTRODUCTION

Ferns are among the oldest extant vascular plants and are considered an important model group in research on the evolution of land plants (Fernández, 2018; Marchant et al., 2022; Moussa et al., 2024). Their evolutionary history, spanning hundreds of millions of years, is reflected both in their morphological diversity and in the wealth of their physiological and biochemical adaptations. It is estimated that this group comprises over 10,500–12,000 species, making ferns one of the most species-rich groups of vascular plants after angiosperms (Fernández, 2018; Marchant et al., 2022; Moussa et al., 2024).

However, the significance of ferns is not limited solely to their evolutionary and ecological value. In many regions of the world, they have long been used by humans as ornamental, utilitarian, edible, and medicinal plants (Kreshchenok et al., 2021; Ojha & Devkota, 2021; Kumari et al., 2026). Edible ferns are particularly important in Southeast Asia, China, Nepal, India, Russia, and the Pacific Islands, where they serve as both local vegetables and ethnomedical raw materials (Oyeyemi et al., 2019; Roy & Chaudhuri, 2020). Despite their evolutionary, ecological, and ethnobotanical importance, ferns remain less well understood in terms of phytochemistry and pharmacology than many spermatophytes (Cao et al., 2017; Moussa et al., 2024). Available reports indicate ongoing research gaps regarding the composition of secondary metabolites, ecological functions of these compounds, and potential applications (Sulasmi et al., 2019; Bandyopadhyay & Dey, 2022). From an ethnobotanical perspective, incomplete documentation of edible and medicinal uses also remains relevant (Ojha & Devkota, 2021). At the same time, ferns represent a valuable but still underutilized source of genetic, physiological, and biochemical diversity that can provide new insights for both basic biology and applied research. Ferns constitute an evolutionarily distinct group of vascular plants and remain a less well-understood source of secondary metabolites than angiosperms. Among the bioactive compounds found in ferns, flavonoids are of particular importance, as they participate in both the plants' adaptive processes and may determine their potential biological properties (Soneji, Szumny, & Wróblewska, 2026). Metabolomic studies also indicate that ferns may allocate a larger proportion of assimilated carbon to secondary metabolism than angiosperms, which may partially explain their high phytochemical diversity (Soneji et al., 2026).

From a phytochemical perspective, the secondary metabolites of ferns, including flavonoids and other phenolic compounds, are particularly important (Cao et al., 2017; Moussa et al., 2024). These compounds help protect plants against environmental stress, UV radiation, and biotic factors (Wang, Ding, et al., 2020; Mitoi et al., 2024). They are also being studied as potential bioactive compounds with health-promoting properties, including antioxidant, anticancer, and antimicrobial effects (Bandyopadhyay & Dey, 2022; Singha et al., 2024).

The aim of this article is to present the current state of knowledge regarding flavonoids found in ferns, with particular emphasis on their qualitative and quantitative variation, the influence of environmental factors on their accumulation, and the biological properties of flavonoid-rich extracts and fractions. Particular attention is paid to antioxidant, anticancer, and antimicrobial activity, as well as to the ecological significance and application potential of this group of plants.

FLAVONOIDS IN FERNS

Chemical structure and structural classes of fern flavonoids

Flavonoids are polyphenolic secondary metabolites with a characteristic C_6–C_3–C_6 carbon skeleton, consisting of two aromatic rings, designated A and B, connected by a three-carbon bridge, which in most species forms a heterocyclic ring C. The structural diversity of flavonoids stems primarily from the degree of oxidation and saturation of ring C, the position of ring B relative to the benzo-γ-pyrone system, and the presence of hydroxyl, methoxyl, sugar, prenyl, or geranyl substituents. Based on this, the following groups are distinguished, among others: flavones, flavonols, flavanones, flavan-3-ols, isoflavones, chalcones, anthocyanins, and dimeric biflavonoids (Chen et al., 2023).

Several structural classes of flavonoids have been described in ferns. Among the flavonols, the presence of quercetin and kaempferol has been reported, while rutin, hyperoside, and quercitrin have been identified as glycosidic derivatives of flavonols. Among the flavones and their derivatives, luteolin, apigenin, and vitexin (a C-glycoside of apigenin) were identified. The literature on ferns has also noted the presence of flavan-3-ols and proanthocyanidins, such as catechin, procyanidins, and prodelphinidins, as well as chalcones and isoflavones, including isookanin and tectoridin, detected in a cell culture of *Cyathea smithii*. A particularly interesting group consists of ugonins from *Helminthostachys zeylanica*, i.e., prenylated or geranylated flavonoids of chemotaxonomic significance and biological potential. The presence of such diverse classes of compounds indicates that fern flavonoids include both metabolites common to vascular plants and compounds more specific to selected taxa (Cao et al., 2017; Rybczyński et al., 2025; Shah et al., 2026).

CHARACTERISTICS OF FLAVONOIDS IN FERNS

Flavonoids are among the most important classes of secondary metabolites in ferns and constitute a significant component of their biochemical diversity (Cao et al., 2017; Bandyopadhyay & Dey, 2022; Moussa et al., 2024). Ferns contain a wide range of phytochemicals, including alkaloids, polyphenols, terpenoids, steroids, and other groups of metabolites. Some of the compounds found in ferns are typical of vascular plants, while others may be of chemotaxonomic significance or indicate the metabolic specificity of this group (Cao et al., 2017; Moussa et al., 2024). Phytochemical data indicate that ferns contain both common plant flavonoids, such as quercetin, kaempferol, luteolin, rutin, taxifolin, and vitexin, as well as more specific flavonoid metabolites. The presence of flavonoids and phenolic acids has been confirmed in European fern species, confirming that this group can be a source of diverse polyphenolic compounds. Among the analyzed species, *Athyrium distentifolium*, *Blechnum spicant*, *Dryopteris borreri*, and *D. cambrensis* stood out in particular, differing in their flavonoid profiles and the content of individual compounds (Langhansova et al., 2026). The diversity of flavonoids in ferns is also confirmed at the taxonomic family level. In the *Marattiaceae family*, apigenin, luteolin, violanthin, and isoviolanthin were identified, while in the *Pteridaceae, Adiantaceae*, *Aspleniaceae*, and *Davalliaceae* families, rutin and catechin were detected (Soneji et al., 2026). These data indicate that the flavonoid profile of ferns may be both widespread, encompassing compounds typical of many vascular plants, and more taxonomically specific. Quantitative studies of ferns have shown significant variation in total flavonoid content among species. In a group of six selected edible and medicinal ferns (*Christella arida*, *C. dentata, Nephrolepis acutifolia*, *Microsorum punctatum*, *Pleocnemia irregularis, Pteris vittata*), the highest flavonoid content was found in *P. irregularis*, and the lowest in *M. punctatum* (Chai et al., 2015a). In turn, among five other edible and medicinal fern species (*Davallia denticulata*, *Blechnum orientale*, *Diplazium esculentum*, *P. vittata*, *Stenochlaena palustris*), *D. denticulata* stood out for its particularly high flavonoid content (Chai et al., 2015b). Ferns do not constitute a phytochemically homogeneous group, and flavonoid content is clearly species-specific (Wang et al., 2017; Xia et al., 2014; Pekgöz & Çinbilgel, 2019).

The flavonoid content of selected fern species is summarized in Table 1. The major flavonoids and other phenolic compounds identified in selected ferns are presented in Table 2.

Available reports indicate that fern flora contains both classic flavonoids and more complex phenols, flavonoid glycosides, procyanidins, biflavonoids, and other phenolic derivatives (Cao et al., 2017; Moussa et al., 2024).

Overall, these data indicate that ferns constitute a phytochemically highly diverse group of plants, and flavonoids are one of their key components (Gyeltshen et al., 2022; Imperato, 2006; Wang et al., 2017).

Table 1. Flavonoid content in selected fern species

Species	Test	Value	Unit	Reference
Pleocnemia irregularis	TF	367,88	mg QE/g of extract	(Chai et al., 2015a)
Christella arida	TF	324,24	mg QE/g of extract	(Chai et al., 2015a)
Nephrolepis acutifolia	TF	246,67	mg QE/g of extract	(Chai et al., 2015a)
Microsorum punctatum	TF	15,73	mg QE/g of extract	(Chai et al., 2015a)
Davallia denticulata	TF	639,09 ± 1,39	mg QE/g of extract	(Chai et al., 2015b)
Blechnum orientale	TF	470,91 ± 7,87	mg QE/g of extract	(Chai et al., 2015b)
Diplazium esculentum	TF	329,39 ± 2,98	mg QE/g of extract	(Chai et al., 2015b)
Pteris vittata	TF	155,76 ± 1,84	mg QE/g of extract	(Chai et al., 2015b)
Nephrolepis cordifolia	TF	5,63 ± 0,13	mg QE/g of extract	(Oyeyemi et al., 2019)
Isoetes sinensis	TF	10,74 ± 0,25	mg/g of extract	(Wang et al., 2020)
Asplenium ceterach	Highest total flavonoid content	232,67	µg CE/mL	(Pekgöz & Çinbilgel, 2019)
Matteuccia struthiopteris	Highest flavonoid content during drought stress	9,40	mg/g FW	(Wang et al., 2019)
Athyrium multidentatum	Highest flavonoid content after rehydration	12,23	mg/g FW	(Wang et al., 2019)

Notes: TF – total flavonoid content; QE – quercetin equivalent; CE – catechin equivalent; FW – fresh weight. The values for *M. struthiopteris* and *A. multidentatum* correspond to the maximum flavonoid levels obtained, respectively, during drought stress and after plant rehydration. For *A. ceterah*, the highest total flavonoid content determined in the plant extract is presented.

Table 2. Major flavonoids and other phenolic compounds identified in selected ferns

Species / group	Identified compounds	Method	Conclusion	Reference
Asplenium ceterach	catechin, quercetin, chlorogenic acid, caffeic acid	HPLC	complex phenolic profile; presence of flavonoids and phenolic acids	(Pekgöz & Çinbilgel, 2019)
Isoetes sinensis	apigenin, apigenin-7-glucuronide, acacetin-7-O-glucopyranoside, homoplantagenin, isoetin, kaempferol-3-O-glucoside, quercetin derivatives, limocitrin-neo, prodelphinidin, nothofagin	HPLC-ESI-QTOF-MS	presence of flavones, flavonols, prodelphinidin and dihydrochalcone indicates a complex flavonoid profile	(Wang, et al., 2020)
Pseudocyclosorus ochthodes, *Phymatodes scolopendria*, *Stenochlaena palustris*	rutin, hyperoside, quercitrin, quercetin	TLC	qualitative variation in flavonoid profiles between species	(Sulasmi et al., 2019)
Pseudocyclosorus ochthodes	rutin, hyperoside, quercitrin, quercetin	TLC	all four investigated flavonoids were present	(Sulasmi et al., 2019)
Phymatodes scolopendria	rutin, hyperoside, quercitrin, quercetin	TLC	all four investigated flavonoids were present	(Sulasmi et al., 2019)
Stenochlaena palustris	rutin, hyperoside, quercitrin, quercetin	TLC	all four investigated flavonoids were present	(Sulasmi et al., 2019)
Dryopteris hirtipes	hyperoside, quercitrin, quercetin	TLC	rutin was absent; three of the four investigated compounds were present	(Sulasmi et al., 2019)
Pteris vittata	rutin, hyperoside, quercitrin and quercetin were not detected	TLC	none of the four analyzed flavonoids was detected	(Sulasmi et al., 2019)
Marattiaceae	apigenin, luteolin, violanthin, isoviolanthin	metabolomic analysis / review data	presence of flavones and flavone C-glycosides confirms the diversity of fern flavonoid profiles	(Soneji et al., 2026)
Pteridaceae, Adiantaceae, Aspleniaceae, Davalliaceae	rutin, catechin	metabolomic analysis / review data	presence of typical flavonoids and flavan-3-ols in different fern families	(Soneji et al., 2026)
selected ferns, mainly Pteridaceae	matteuorienates A-C, matteflavoside G, matteucin, methoxymatteucin, cyrtominetin, hydroxymatteucinol	phytochemical / review data	fern-characteristic compounds, potentially relevant chemotaxonomically and biologically	(Soneji et al., 2026)
Pityrogramma trifoliata	trifoliatol, complex flavonoids, chalcones, dihydrochalcones, flavanones	isolation and compound identification	presence of complex flavonoid structures confirms high structural diversity and potential chemotaxonomic significance	(Rodriguez et al., 2022)

Notes: HPLC – high-performance liquid chromatography; HPLC-ESI-QTOF-MS – high-performance liquid chromatography coupled with electrospray ionization and quadrupole time-of-flight mass spectrometry; TLC – thin-layer chromatography.

The genus *Diplazium* includes ferns of both nutritional and medicinal value (Kumari et al., 2026). It has been shown that species of this genus may be a source of macronutrients, minerals, vitamin C, and flavonoids. The presence of various groups of secondary metabolites, such as phenols, flavonoids, alkaloids, saponins, steroids, tannins, terpenoids, phytosterols, and glycosides, has been confirmed in D. esculentum. The literature on this species also notes the presence of the flavanone glycoside eriodictyol 5-O-methyl ether 7-O-β-D-xylosyl galactoside, indicating that edible ferns may contain not only general phenolic fractions but also specific flavonoid compounds (Kumari et al., 2026).

A particularly interesting group of fern flavonoids are the ugonins, described in *Helminthostachys zeylanica*. These compounds are considered chemotaxonomically characteristic metabolites of this species. Ugonins have a flavonoid skeleton, often modified by the presence of prenyl or geranyl groups, which may influence their biological activity. To date, ugonins A–Y have been described, and their activities include, among others, anti-inflammatory, antioxidant, antidiabetic, neuroprotective, anti-osteoporotic, immunomodulatory, and anticancer effects. For this reason, *H. zeylanica* represents one of the most important examples of ferns containing specialized flavonoids with therapeutic potential (Shah et al., 2026).

In addition to ugonins, compounds of particular interest from the perspective of fern chemotaxonomy include matteuorienates A–C, matteflavoside G, matteucin, methoxymatteucin, cyrtominetin, and hydroxymatteucinol (Soneji et al., 2026). The presence of such metabolites underscores that ferns are not merely a source of commonly occurring flavonoids, such as quercetin, kaempferol, or luteolin, but can also synthesize more specialized phenolic compounds of potential biological significance. A particularly interesting group of secondary metabolites in ferns consists of so-called complex flavonoids, which are found mainly in members of the Pteridaceae family. A new complex flavonoid named trifoliatol was isolated from the species *Pityrogramma trifoliata*, along with a number of previously described complex flavonoids, chalcones, dihydrochalcones, and flavanones (Rodriguez et al., 2022). These results confirm the high structural diversity of flavonoid compounds found in ferns and highlight their potential chemotaxonomic significance. Unlike many angiosperms, in which simple flavonoids and their glycosides predominate, some ferns contain complex flavonoid structures with additional ring systems and stereogenic centers. These compounds may serve as valuable chemotaxonomic markers and a potential source of new biologically active substances (Rodriguez et al., 2022).

THE EFFECT OF ENVIRONMENTAL FACTORS ON FLAVONOID CONTENT IN FERNS

The biosynthesis of flavonoids in ferns is strongly dependent on environmental conditions. Light intensity, temperature, salinity, drought, and mineral nutrition can influence the accumulation of flavonoids and other phenolic compounds in fern tissues (Soneji et al., 2026). Abiotic stress is of particular importance, as it can increase the content of flavonoids, polyphenols, and phenolic acids in members of many fern families, indicating the role of these metabolites in protective and adaptive mechanisms (Soneji et al., 2026). Environmental factors can influence the biosynthesis and accumulation of flavonoids in ferns, which is why research is being conducted on how ferns respond to various stressors (Pietrak et al. 2024) demonstrated that mild stress (~525 μmol m^{-2} s^{-1} PPFD) applied to *Polystichum setiferum* fern cultures resulted in a significant reduction in total flavonoid synthesis, while having no effect on *P. setiferum* 'Proliferum'. The authors demonstrated that the total flavonoid content in the leaves of *P. setiferum* and *P. setiferum* 'Proliferum' was positively correlated with the content of reducing sugars (R = 0.86), antioxidant activity (R = 0.79), and negatively correlated with free amino acid content (R = -0.79). In the case of the ornamental fern *Dryopteris erythrosora*, stress induced by excess light (551.9–890.1 μmol m^{-2} s^{-1} PPFD) significantly increased the total flavonoid content in the leaves (Pietrak et al. 2022). Similarly, when *D. erythrosora* plants were grown in saline soil supplemented with NaCl (100 mmol dm^{-3}), a significant increase in total flavonoid content was observed. When comparing the effect of different types of stress on flavonoid content in *D. erythrosora* leaves, it was shown that light stress stimulated the production of these metabolites more strongly than salinity stress. Similarly, in the ferns *Matteuccia struthiopteris*, *Athyrium multidentatum*, and *Osmunda cinnamomea var. asiatica*, an increased total flavonoid content in the leaves was observed when the plants were exposed to high light levels (Wang et al. 2020). In other studies (Pietrak et al. 2025), the effects of drought stress and salinity stress ($CaCl_2$) on growth and biochemical changes in the Japanese fern *Athyrium nipponicum cv. Metallicum* were evaluated. It was demonstrated that stresses caused by water deficiency and excessive salinity led to a reduction in total flavonoid content in the leaves. In contrast, the flavonoid content in the rhizomes of *A. nipponicum cv. Metallicum* exposed to salinity stress was increased compared to the control, by an average of 15% (Pietrak et al. 2025). Under drought stress, increased flavonoid biosynthesis was observed in the edible

Table 3. Flavonoid content in selected fern species

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Pleocnemia irregularis	TF	367.88	mg QE/g of extract	(Chai et al., 2015a)
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Blechnum orientale	TF	470.91 ± 7.87	mg QE/g of extract	(Chai et al., 2015b)
Diplazium esculentum	TF	329.39 ± 2.98	mg QE/g of extract	(Chai et al., 2015b)
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Isoetes sinensis	TF	10.74 ± 0.25	mg/g of extract	(Wang et al., 2020)
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ferns *Athyrium multidentatum* and *Matteuccia struthiopteris* (Wang et al. 2019). Environmental pollution can also lead to changes in the levels of secondary metabolites. Pietrak et al. (Pietrak et al. 2024) demonstrated that the evergreen ferns *P. setiferum* and *P. setiferum* 'Proliferum' growing under stress conditions caused by the presence of lead (1000 mg dm^{-3}) in the substrate exhibited increased levels of total polyphenols and flavonoids. The results suggest that lead acted as an elicitor, stimulating the production of metabolites in both fern taxa (Pietrak et al. 2024). Table 3 summarizes the effects of selected environmental factors on flavonoids in ferns.

In summary, the available data indicate that the flavonoid content in ferns should be considered a plastic trait, dependent on the interaction of numerous environmental factors. Drought, salinity, light intensity, heavy metal contamination, elevation above sea level, and soil composition can influence flavonoid biosynthesis, but the direction and magnitude of these changes are most often species-specific (Pekgöz & Çinbilgel, 2019; Pietrak et al., 2025; Sulasmi et al., 2019).

BIOLOGICAL PROPERTIES OF FERN FLAVONOIDS

The biological properties of fern extracts represent one of the most rapidly developing areas of research. Findings to date indicate that flavonoid-rich fractions may exhibit antioxidant, cytotoxic, and antimicrobial activity; however, the strength of these effects depends on the species, the type of extract, the analytical method used, and the biological model (Chai et al., 2015a, 2015b; Langhansova et al., 2026).

Antioxidant activity

The antioxidant activity of fern extracts is one of the most frequently described biological activities of this group of plants (Cao et al., 2017; Roy & Chaudhuri, 2020; Dvorakova et al., 2021). Polyphenols and flavonoids in ferns play a significant role in scavenging free radicals and mitigating the effects of oxidative stress. In the case of *Diplazium*, this activity was primarily assessed using DPPH, ABTS, and H_2O_2 assays, as well as other methods related to reactive oxygen species found a negative correlation between the total content of phenols and flavonoids and the IC_{50} value in the DPPH assay, indicating that extracts with a higher phenolic content exhibited stronger antioxidant activity (Kumari et al. 2026).

The importance of flavonoids in the antioxidant activity of ferns stems not only from their ability to neutralize free radicals, but also from their physiological function within the plant. Flavonoids help protect cells from oxidative stress and support the fern's adaptation to adverse environmental conditions (Soneji et al., 2026). For this reason, the antioxidant activity of fern extracts should be interpreted both in the context of their potential health-promoting effects and the role of these compounds in the plant's response to stress.

However, the relationship between phytochemical composition and antioxidant activity should not be interpreted solely in quantitative terms. The biological effect is determined not only by the total flavonoid content but also by their qualitative profile, the presence of other polyphenols, and the method of extract preparation. One of the best-documented examples is *Isoetes sinensis*, which has been shown to possess significant antioxidant activity as assessed by the DPPH, ABTS, superoxide anion scavenging, reducing power, and FRAP assays (Wang, Ding, et al., 2020). Furthermore, chemical analysis revealed the presence of flavones, flavonols, prodelphinidin, and nothofagin, suggesting a link between the complex flavonoid profile and the observed bioactivity (Wang, Ding, et al., 2020). In the case of *Asplenium ceterach*, however, significant differences were observed between populations in terms of DPPH radical scavenging activity (Pekgöz & Çinbilgel, 2019).

An analysis of *D. esculentum* also provided very important data. A study on this species concluded that it exhibits high total antioxidant activity as assessed by the ABTS, FTC, TBA, and FRAP methods (Roy & Chaudhuri, 2020). Importantly, in an in vivo model using rats, the hydroalcoholic extract of *D. esculentum* reduced lipid peroxidation levels, further underscoring the importance of this species as a source of antioxidant compounds (Roy & Chaudhuri, 2020; Dvorakova et al., 2021).

A good example of this complexity is the research on *Onoclea sensibilis*, *Polypodium vulgare*, and *Polystichum polyblepharum*, in which the addition of *Camelina sativa* seed cake had different effects on flavonoid content and antioxidant activity depending on the species. The most consistent response was observed in *P. polyblepharum*, where an increase in flavonoid content was accompanied by an increase in antioxidant activity as measured by the DPPH and FRAP methods. In the other species, this relationship was less clear-cut, suggesting that the antioxidant potential of fern extracts results from the combined action of various groups of metabolites (Pietrak et al., 2022).

Anticancer activity

The anticancer potential of ferns is most often evaluated at the level of total extracts; therefore, the contribution of individual flavonoids requires careful interpretation. In a study on *Leucostegia immersa*, a hydroalcoholic leaf extract exhibited antiproliferative activity against A549 lung cancer cells, with no significant cytotoxicity toward the normal HEK293 cell line. LC-MS analysis revealed the presence of 36 phytochemicals, and further network analysis and molecular docking indicated the potential significance of selected compounds in interacting with proteins associated with NSCLC. Although flavonoid compounds were detected in the extract, conclusions regarding anticancer activity should be drawn with caution, as the most important candidates identified by the authors were primarily irinotecan, cancentrine, and grossamide (Bhattacharyya et al., 2026).

Langhansova et al. demonstrated the cytotoxic activity of selected European fern extracts against cancer cell lines. Particularly significant results were obtained for *Dryopteris aemula* and *Dryopteris borreri* against SW480 cells, while *Athyrium distentifolium* exhibited activity against HeLa cells. At the same time, the authors assessed the effect of the extracts on non-cancerous cells, which allowed for a more cautious interpretation of their therapeutic potential. The presence of flavonoids such as luteolin, quercetin, kaempferol, rutin, taxifolin, and vitexin may contribute to the observed biological activity; however, the effects of the extracts should be considered as a result of the entire phytochemical profile, which also includes phenolic acids and phloroglucinols (Langhansova et al., 2026).

The anticancer potential represents another important area of research into the bioactivity of ferns. It is emphasized that the compounds found in ferns may exhibit cytotoxicity, chemopreventive effects, and the ability to inhibit the proliferation of selected cell lines (Cao et al., 2017; Bandyopadhyay & Dey, 2022; Shah et al., 2026). The anticancer activity of ferns may be associated with the presence of various classes of secondary metabolites, including flavonoids and other phenolic compounds. Many fern metabolites exhibit cytotoxic activity against cancer cells, and some of them may act by activating apoptotic pathways (Soneji et al., 2026). It should be emphasized, however, that most studies have evaluated the effects of whole extracts or fractions; therefore, attributing anticancer activity to individual flavonoids requires further mechanistic research.

A study of six edible and medicinal ferns (*P. irregularis*, *C. arida*, *N. acutifolia*, *M. punctatum*, *C. dentata*, *P. vittata*). In this study, all extracts exhibited cytotoxicity against the K562 leukemia cell line, and some of them demonstrated activity comparable to that of 5-fluorouracil (Chai et al., 2015a). Roy and Chaudhuri noted that *D. esculentum* exhibits cytotoxic potential, although the effect depends on the type of extract and the model used (Roy & Chaudhuri, 2020). At this stage of the research, it can therefore be concluded that extracts and compounds derived from ferns show real anticancer potential, but this requires further validation in more advanced biological models (Moussa et al., 2024; Langhansova et al., 2026; Shah et al., 2026).

Antimicrobial activity

In response to the growing antibiotic resistance among microorganisms and the increasing importance of biofilms as a mechanism that enhances their survival and tolerance to antimicrobial agents, the search for effective plant-derived antimicrobial compounds is one of the most actively explored areas of research on natural bioactive compounds (Gerschler et al., 2025; Ma et al., 2026, Asokan et al., 2026). It should be noted, however, that antimicrobial activity of ferns was typically assessed for total extracts. Therefore, the direct contribution of flavonoids to the antimicrobial effect requires further confirmation. The data on the antimicrobial activity of ferns are less consistent than those on their antioxidant activity; however, the available literature suggests that this group may represent a promising source of compounds active against bacteria, fungi, and parasites (Cao et al., 2017; Bandyopadhyay & Dey, 2022; Roy & Chaudhuri, 2020). Some of the most comprehensive experimental data among the sources analyzed pertain to *D. esculentum*, whose extracts exhibited activity against many Gram-positive and Gram-negative bacteria (Roy & Chaudhuri, 2020).

Extracts from the *Diplazium* genus have been reported to exhibit antimicrobial, anti-inflammatory, antispasmodic, antioxidant, laxative, and immunostimulatory effects. highlighted that data on the antimicrobial activity of this species remain limited, but available studies indicate that extracts from the leaves, roots, and rhizomes of *D. esculentum* exhibit activity against selected bacteria, including *Escherichia coli, Salmonella typhi, S. arizonae*, and *Staphylococcus aureus* (Kumari et al. 2026). In some studies, antimicrobial activity is reported without independent experimental validation (Chai et al., 2015a; Kreshchenok et al., 2021; Huang et al., 2025;). Nevertheless, the available data as a whole suggest that ferns represent an interesting group of plants for the search for new anti-infective compounds, although further research using standardized microbiological methods and better-characterized active fractions is necessary (Roy & Chaudhuri, 2020; Bandyopadhyay & Dey, 2022; Moussa et al., 2024).

One of the best-documented examples of the antifungal activity of fern flavonoids is provided by compounds isolated from *Pityrogramma trifoliata*. In *in vitro* studies, both leaf surface exudates and selected flavonoids exhibited activity against the dermatophytes *Trichophyton rubrum* and *T. mentagrophytes*. The most active compounds had MIC values ranging from 7.8 to 31.2 μg/mL (Rodriguez et al., 2022).

Minor modifications to the chemical structure of flavonoids can significantly affect their biological activity. Methoxylation of ring B led to a marked reduction in the antifungal activity of the tested flavanones, highlighting the importance of structure–activity relationships in assessing the antimicrobial potential of fern flavonoids (Rodriguez et al., 2022).

An interesting addition to the data on the antimicrobial activity of ferns are reports of antiviral activity. Matteucin and methoxymatteucin from *Pentarhizidium orientale* and *Matteuccia intermedia* as well as matteflavoside G from *Matteuccia struthiopteris* exhibit antiviral activity by inhibiting the neuraminidase of the H1N1 virus (Soneji et al., 2026). Selected biological properties of flavonoids, phenolic fractions, and fern extracts are summarized in Table 4. The data collected show that antioxidant activity is the best documented, while cytotoxic and antimicrobial activity, although promising, still require further validation and standardization of research methods.

Anti-inflammatory activity

Studies on European ferns have shown that their methanol extracts can inhibit enzymes of the arachidonic acid pathway, including COX-1, COX-2, and 5-LOX. Langhansova et al.

Table 4. Selected biological properties of flavonoids, phenolic fractions, and fern extracts

Species	Type of activity	Main result (unit)	Research model	Conclusion	Type of data	Reference
Isoetes sinensis	antioxidant	ABTS IC50 = 3.2 mg/μL; DPPH IC50 = 4.8 mg/μL	ABTS, DPPH, FRAP, reducing power, O2− assays	very strong antioxidant activity	flavonoids + extract	(Wang, Ding, et al., 2020)
Asplenium ceterach	antioxidant	best DPPH result: IC50 = 47.91 μg/mL, site 22	DPPH assay	antioxidant activity varied between sites	phenolics + extract	(Pekgöz & Çinbilgel, 2019)
Diplazium esculentum	antioxidant	high activity in ABTS, FTC, TBA, FRAP and phosphomolybdenum assays	review data in vitro and in vivo	strong radical-scavenging and reducing potential	extract	(Roy & Chaudhuri, 2020)
Christella dentata	cytotoxic	EC50 = 194.50 μg/mL	K562 leukemia cells	activity comparable to 5-fluorouracil	crude extract	(Chai et al., 2015a)
Nephrolepis acutifolia	cytotoxic	EC50 = 190.82 μg/mL	K562 leukemia cells	activity comparable to 5-fluorouracil	crude extract	(Chai et al., 2015a)
Pleocnemia irregularis	cytotoxic	EC50 = 253.85 μg/mL	K562 leukemia cells	promising source of cytotoxic compounds	crude extract	(Chai et al., 2015a)
Pteris vittata	cytotoxic	EC50 = 364.82 ± 15.94 μg/mL	K562 leukemia cells	highest activity among the five species analyzed in the study	crude extract	(Chai et al., 2015b)
Diplazium esculentum	α-glucosidase inhibition	EC50 = 6.85 ± 0.08 μg/mL	enzyme assay	very strong antidiabetic potential	crude extract	(Chai et al., 2015b)
Diplazium esculentum	antibacterial	activity against, among others, S. aureus, E. coli, V. cholerae and S. typhimurium	review data	strong antimicrobial potential depending on extract type	extract	(Roy & Chaudhuri, 2020)
Matteuccia struthiopteris	antioxidant response to drought	increase in FC, TPC and PCC during drought	drought stress experiment	flavonoids participate in non-enzymatic antioxidant protection	FC/TPC/PCC	(Wang et al., 2019)
Athyrium multidentatum	antioxidant response to drought	higher FC, TPC, PCC and greater drought resistance than in M. struthiopteris	drought stress experiment	species more resistant to water deficit	FC/TPC/PCC	(Wang et al., 2019)
Pityrogramma trifoliata	antifungal	MIC = 7.8-31.2 μg/mL for the most active compounds	*Trichophyton rubrum*, *Trichophyton mentagrophytes*	surface flavonoids show strong activity against dermatophytes	isolated flavonoids + leaf exudates	(Rodriguez et al., 2022)
Pityrogramma trifoliata	structure-activity relationship	methoxylation of ring B decreased antifungal activity	dermatophytes	minor structural modifications significantly influence biological activity	isolated flavonoids	(Rodriguez et al., 2022)
selected fern flavonoids	antiviral	inhibition of H1N1 virus neuraminidase	enzyme assay / viral model	matteucin, methoxymatteucin and matteflavoside G show antiviral potential	isolated flavonoids	(Soneji et al., 2026)

Notes: ABTS, DPPH, FRAP, FTC and TBA – antioxidant activity assays; IC50 – concentration inhibiting 50% of activity; EC50 – half-maximal effective concentration; MIC – minimum inhibitory concentration; FC – flavonoid content; TPC – total polyphenol content; PCC – proanthocyanidin content.

demonstrated that at a concentration of 10 μg/mL, most of the tested extracts effectively inhibited COX-1, with *Dryopteris cambrensis* and *Athyrium distentifolium* exhibiting particularly strong activity comparable to that of ibuprofen. Moderate inhibition of 5-LOX was also observed in many species. The authors attributed the anti-inflammatory activity partly to the presence of flavonoids containing a 3,4-catechol group, such as luteolin, quercetin, rutin, and taxifolin (Langhansova et al., 2026).

ECOLOGICAL SIGNIFICANCE AND APPLICATION POTENTIAL

Flavonoids in ferns may have both ecological and practical significance. As phenolic compounds, they help protect cells from oxidative stress and may also account for some of the biological activity of the extracts. Species in which the presence of both typical flavonoids, such as quercetin, kaempferol, luteolin, and rutin, as well as more characteristic metabolites, e.g., ugonins in *Helminthostachys zeylanica*, has been demonstrated are of particular practical importance. These data indicate that ferns may be a valuable source of compounds relevant to pharmacology, nutraceuticals, and plant biotechnology (Langhansova et al., 2026; Shah et al., 2026).

The high flavonoid content may increase ferns' tolerance to environmental stress, as these compounds help protect against oxidative stress, UV radiation, and other abiotic factors (Soneji et al., 2026). At the same time, the presence of diverse flavonoids and specialized phenolic metabolites forms the basis for the potential applications of ferns in pharmaceuticals, nutraceuticals, and plant biotechnology. For this reason, ferns can be viewed not only as a group of evolutionary and ecological significance but also as a promising source of bioactive natural compounds (Soneji et al., 2026).

The flavonoids present in ferns not only perform functions related to biological activity but also play an important ecological role. In species of the genus *Pityrogramma*, these compounds may accumulate primarily in glandular trichomes located on the underside of the leaves, where they form characteristic secretions known as farina (Rodriguez et al., 2022). This type of metabolite localization suggests their possible involvement in protecting the leaf surface from environmental and biotic factors, while also highlighting the importance of ferns as a source of specialized metabolites with potential applications.

The significance of ferns extends beyond phytochemistry alone and encompasses a wide range of nutritional, medicinal, environmental, and economic applications. In many regions of the world, edible ferns are an important source of wild food, and some of them are also used as medicinal raw materials (Roy & Chaudhuri, 2020; Dvorakova et al., 2021; Kumari et al., 2026). A study of Nepali ferns has shown that many species are used there as food, traditional medicine, or both (Kreshchenok et al., 2021; Ojha & Devkota, 2021).

The nutritional value of edible ferns is also significant. *Nephrolepis cordifolia* has been described as a valuable edible fern with high levels of fiber, protein, carbohydrates, vitamin C, and minerals, while containing low levels of certain anti-nutritional factors (Oyeyemi et al., 2019). In turn, *D. esculentum* exhibited high protein levels and a broad amino acid profile, and the authors highlighted its potential not only for human consumption but also for animal feed and pharmaceutical applications (Roy & Chaudhuri, 2020; Kumari et al., 2026).

The potential applications of ferns also include their use as sources of nutraceuticals and pharmacologically active compounds. Studies on the biological activity of extracts have highlighted, among other things, the antidiabetic potential of *D. esculentum* and several other edible ferns (Chai et al., 2015a, 2015b). Reviews also highlight the potential for using ferns as sources of compounds for functional foods, dietary supplements, cosmetics, and new drugs (Bandyopadhyay & Dey, 2022; Moussa et al., 2024; Shah et al., 2026).

From the perspective of application potential, it is also important to note that the phytochemical composition of ferns can be influenced by growing conditions. The addition of organic components to the growing medium, such as *Camelina sativa* oilseed cake, can increase the flavonoid content and antioxidant activity of selected species, particularly *Polystichum polyblepharum*. This approach combines the valorization of by-products from the oil industry with the possibility of controlled increases in the content of secondary metabolites in plant material, although it requires an assessment of the species, the dosage of the additive, and the safety of the raw material on a case-by-case basis (Pietrak et al., 2022).

The ecological aspect is also important. The reports indicate that ferns can play a significant role in phytoremediation and environmental purification, and certain species are of interest from the perspective of environmental biotechnology and research on tolerance to metals and other stressors (Bandyopadhyay & Dey, 2022; Cao et al., 2017). In the case of edible ferns, the issue of sustainable use of natural resources also remains very important (Dvorakova et al., 2021; Kreshchenok et al., 2021).

In vitro cell cultures also represent an interesting area of application. conducted a metabolomic analysis of a suspension culture of the tree fern *Cyathea smithii* using LC/MS and GC/MS techniques. The study identified 160 primary and secondary metabolites and nearly 2,000 compounds of unknown identity. Of particular significance was the detection of three flavonoids previously unreported in *C. smithii* cell cultures: the chalcone isookanin, the methoxy derivative of the flavone gardenin B, and the isoflavone tectoridin (Rybczyński et al. 2025). These results indicate that fern suspension cultures can serve as a model for studying flavonoid biosynthesis and as a potential platform for the biotechnological production of secondary metabolites.

LIMITATIONS AND PERSPECTIVES

When interpreting data on the flavonoid content and biological activity of ferns, the effect of the extraction solvent used must be taken into account. Studies on *Diplazium* have shown that extracts prepared using different solvents, including methanol, ethanol, chloroform, and water, may differ in their metabolite content and antioxidant activity. This means that comparing results across publications requires caution, as differences in extract activity may result not only from the biological characteristics of the species but also from different extraction procedures (Kumari et al., 2026).

An increase in flavonoid content induced by heavy metals should not automatically be interpreted as a beneficial trait of the plant material. Demonstrated that in *Polystichum setiferum* and *P. setiferum* 'Proliferum', lead could stimulate the accumulation of polyphenols and flavonoids; however, at the same time, the plants accumulated Pb, mainly in their underground parts (Pietrak et al. 2024). For this reason, ferns growing in sites contaminated with heavy metals may be of interest in the context of phytoremediation, but their use as a source of bioactive compounds requires a separate toxicological assessment. The mere increase in flavonoid content under metal stress does not imply that the raw material is safe for nutritional, pharmaceutical, or cosmetic applications.

Although the number of studies devoted to ferns is steadily increasing, the current state of knowledge is still hampered by a number of methodological limitations. Many studies have used summary measurements of total flavonoid content without parallel comprehensive identification of the dominant compounds in the extracts (Mitoi et al., 2024; Roy & Chaudhuri, 2020). This makes it difficult to unambiguously link the observed biological activity to specific metabolites, particularly when older chemotaxonomic or screening data are compared with modern metabolomic studies (Richardson, 1989; Rybczyński et al., 2025). Similar caution applies to studies focused mainly on nutritional or preliminary phytochemical evaluation (Oyeyemi et al., 2019).

An additional problem is the lack of uniformity in extraction procedures, analytical standards, and test models (Mitoi et al., 2024; Sulasmi et al., 2019). This limits the ability to directly compare numerical values across reports and to draw general conclusions about the relationship between flavonoid levels and the strength of the biological effect (Langhansova et al., 2026; Shah et al., 2026).

With regard to biological activity, most of the available data come from in vitro tests or screening studies (Chai et al., 2015a, 2015b). There are far fewer studies involving in vivo models, bioavailability assessments, safety evaluations, and dose-response analyses (Roy & Chaudhuri, 2020; Shah et al., 2026). This is particularly true for anticancer and antimicrobial activity, which, although promising, still require more rigorous experimental validation (Langhansova et al., 2026).

In the future, there is a particular need for research utilizing modern chromatographic and spectrometric techniques to fully identify active compounds (Langhansova et al., 2026; Rybczyński et al., 2025). Comparative studies conducted according to standardized protocols are also needed to clarify the relationship between chemical composition and biological activity (Wang et al., 2017; Mitoi et al., 2024). From the perspective of agricultural, horticultural, and biotechnological sciences, controlled regulation of flavonoid accumulation through light, substrate composition, salinity, or other environmental factors remains a promising direction (Xia et al., 2014).

CONCLUSIONS

Ferns constitute a chemically and biologically diverse group of plants in which flavonoids play an important physiological and practical role. In many species, significant qualitative and quantitative variability in flavonoid compounds has been demonstrated, including classic flavones and flavonols, flavonoid glycosides, procyanidins, biflavonoids, and more specialized metabolites such as ugonins.

A particularly well-documented biological property of fern flavonoid extracts and fractions is their antioxidant activity. There is also a growing body of data on the cytotoxicity and anticancer potential of certain species, although the relationship between high total flavonoid content and the potency of the biological effect is not always clear. Regarding antimicrobial activity, the available results are more scattered, but they also point to the promising potential of some fern extracts. Environmental studies show that flavonoid biosynthesis in ferns is a plastic trait and can be modulated by drought, salinity, light, temperature, elevation, soil composition, and heavy metal contamination. However, this answer is complex and highly dependent on the species and ecological context, and therefore requires careful interpretation.

Ferns are a group of plants that remain poorly understood but are highly promising from the perspective of phytochemistry, bioactivity, and practical applications. Despite growing interest in the biological potential of ferns, the precise identification of active compounds, their relationship with chemical composition and biological activity, safety profile, and practical applicability of selected species remain insufficiently established.

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