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Systematic Review: Antioxidant and Neuroprotective Capacity of Species of the Genus *Asplenium* (Monilophyta: Aspleniaceae) †

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Abstract: The genus *Asplenium* L. comprises about 700 species of terrestrial, epiphytic, and saxicolous habits distributed in temperate and tropical regions around the world, exhibiting a high chemical richness with variable biological activity. In this review, compounds with antioxidant activity that constitute a pharmacological potential in diseases of the central nervous system are detailed. *Asplenium nidus* L. species presents a high concentration of phenols and flavonoids evidenced by antioxidant activity assays, such as DPPH, FRAP, total phenols, total flavonoids, and ORAC, and represent compounds with bioactive potential, including neuroprotection. The species *Asplenium adiantum-nigrum* L. presents a high antioxidant potential of its rhizome extracts exhibited in DPPH and ABTS assays, attributed to the high concentration of mangiferin. the xanthone mangiferin is a compound also present in other species of genera, such as *Asplenium ceterach* L. and *Asplenium montanum* Willd., in significant amounts. This xanthone has studies on its neuroprotective effect through different targets, some of them being the acetylcholinesterase enzymes, the 5-lipooxygenase enzyme, and the antioxidant activity itself. All these mechanisms of action of mangiferin constitute an object of study for its effect on memory loss, which can be relayed in Alzheimer's disease.

Keywords: *Asplenium*; bioactive compounds; antioxidant capacity; neuroprotection

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1. Introduction

Ancestral ferns have been widely used in many cultures as phytotherapeutic agents, covering the treatment of diverse and varied conditions from infections of pathogens, to combat kidney stones, asthma, stomach pains, and also as anti-inflammatory agents [1]. This in turn has prompted the emergence of multiple studies around the world to identify the components responsible for the biological activity of these plants.

Asplenium L. is a genus that has about 700 species of terrestrial, epiphytic, and saxicolous habitats distributed in temperate and tropical regions in the world [1]. All this diversity in species also translates into a great diversity of compounds, such as flavonoids, which are a group of bioactive compounds being among the most common that can be found in this genus. All this has aroused interest in the scientific research due to the phytotherapeutic potential of these compounds, such as the effect of antioxidant activity and neuroprotective effect [2].

Among the variety of compounds identified in the genus, *Asplenium* L. one can contain the natural C-glucoside, mangiferin (2-C-β-D-gluco-pyranosyl-1,3,6, 7-tetrahydroxyxanthone; $C_{19}H_{18}O$), a type of xanthone that has been detected in the species *Asplenium balearicum* Shivas, *Asplenium bradleyi* D.C. Eaton, *Asplenium pinnatifidum* Nutt., *Asplenium* × *stotleri* Wherry (pro. sp.), *Asplenium serra* Langsd. and Fisch, *Asplenium ceterach* L., and *Asplenium montanum* Willd [1]. The importance of this compound lies in its potential for the treatment of neurodegenerative diseases in cellular and animal models, together with its high antioxidant

activity and the ability to scavenge hydroxyl radicals. In addition, it reports an important effect on β-amyloid peptide activity and the ability to inhibit acetylcholinesterase (AChE) and lipooxygenase (LOX) enzymes [3].

2. Methods

A literature search was performed dating until March 2021 in the databases WoS, Scopus, ScienceDirect, and PubMed, using the keywords: "Asplenium", "antioxidant", "neurodegenerative diseases", "neuroprotection". References from relevant review articles were also identified, as well as others registered in the section of similar articles in PubMed.

3. Results and Discussion

Methanolic extracts of *Asplenium adiantum-nigrum* L. and *Asplenium ruta-muraria* L., evaluated by UHPLC/DAD/-HESI-MS/MS, have shown different phenolic compounds, among which are phenolic acids and derivatives, flavonoids and derivatives, and xanthones. Table 1 shows the concentrations of the most relevant compounds present in three plant organs sampled for each species (rhizome, fronds, roots), expressed in milligrams per gram of fresh weight (FW) [1].

Table 1. Compounds present in the vegetative organs of *A. adiantum-nigrum* and *A. ruta-muraria*.

Compounds		Concentration (mg/g FW)	
		A. adiantum-nigrum	***A. ruta-muraria***
Phenolic acids and derivatives	Gallic acid	0.69 ± 0.01 (Rhizome)	-
	Protocatechuic acid	1.61 ± 0.06 (Rhizome)	1.29 ± 0.01 (Rhizome, Roots), 1.29 ± 0.04 (Fronds)
	Gentisic acid	0.13 ± 0.08 (Fronds)	0.11 ± 0.01 (Rhizome, Roots), 0.11 ± 0.06 (Fronds)
	p-Hydroxybenzoic acid	0.63 ± 0.05 (Fronds)	0.44 ± 0.11 (Fronds)
	Aesculin	0.39 ± 0.05 (Fronds)	0.51 ± 0.03 (Fronds)
	Chlorogenic acid	0.62 ± 0.03 (Rhizome)	2.05 ± 1.05 (Roots)
	Caffeic acid	0.59 ± 0.06 (Rhizome)	0.21 ± 0.02 (Fronds)
	p-Coumaric acid	2.82 ± 0.74 (Rhizome)	1.00 ± 0.08 (Fronds)
	Ferulic acid	0.23 ± 0.01 (Rhizome)	-
	Rosmarinic acid	1.69 ± 0.01 (Roots)	0.03 ± 0.01 (Fronds)
Flavonoids and derivatives	Epigallocatechin	3.71 ± 1.33 (Rhizome)	9.12 ± 1.56 (Rhizome)
	Epicatechin	-	1.26 ± 0.01 (Rhizome)
	Gallocatechin gallate	-	10.29 ± 0.67 (Fronds)
	Epigallocatechin gallate	1.15 ± 0.09 (Fronds)	1.74 ± 0.18 (Fronds)
	Rutin	0.27 ± 0.01 (Roots)	0.24 ± 0.01 (Roots)
Xanthones	Mangiferin glucoside	507.69 ± 19.58 (Rhizome)	0.51 ± 0.01 (Rhizome)
	Mangiferin	598.29 ± 20.82 (Rhizome)	0.70 ± 0.12 (Rhizome)

It should be noted that xanthones represent the most abundant compounds, especially in *A. adiantum-nigrum*, with concentrations greater than 500 (mg/g FW) [1].

Mangiferin, a compound present in a large number of species of the genus *Asplenium* [1] (Figure 1), possesses qualities that make it a potential candidate for use in phytotherapy. Its performance in AChE and LOX enzyme inhibition tests, antioxidant activity by the DPPH method, and its action on the activity of β-amyloid peptides in neurons, in vitro, are presented below.

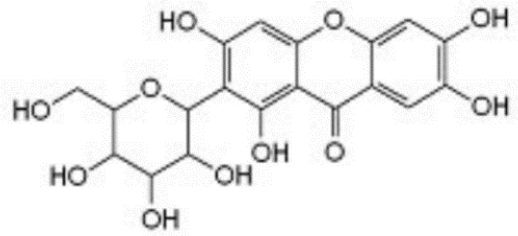

Figure 1. Chemical structure of mangiferin ($C_{19}H_{18}O_{11}$).

The inhibition of the AChE enzyme by the compound mangiferin is quite significant, obtaining a value for IC50 of 55.42 ± 1.52 μg/mL in comparison to galantamine, a compound used as a standard in AChE assays (IC50: 5.543 ± 0.213 μg/mL). Therefore, its action is considered potential to prevent the loss of the neurotransmitter acetylcholine in the progression of Alzheimer's disease [3].

Regarding the LOX enzyme, mangiferin has presented inhibition results for IC50 of 42.28 ± 0.63 μg/mL, which is significant, compared to the routine standard (IC50: 7.46 ± 0.18 μg/mL). It should be noted that LOX is a key enzyme in inflammatory processes responsible for the production of leukotrienes and other inflammatory mediators [3].

As an antioxidant agent, mangiferin has shown an IC50 value in the DPPH method of 18.50 ± 0.18 μg/mL [3]. This activity corroborates the neuroprotective action of this compound through the pathway of reducing H_2O_2-induced oxidative damage [4].

Mangiferin has demonstrated a concentration-dependent activity in the reductive effect on β-amyloid peptide deposits, with significant results at concentrations of 10 μg/mL and maximal at 20 μg/mL, in in vitro tests [3]. The β-amyloid peptide is responsible for toxic effects to neurons in the course of Alzheimer's disease, in addition to its action in ROS production that increases neurotoxicity [5].

In general, the flavonoid profiles present in the species of the Aspleniaceae family are complex to characterize and differentiate. Regarding flavonols, kaempferol derivatives mainly encompass 3,7-glycosides, as well as 3,4′-diglycosides and 3,7,4′-triglycosides. In *Asplenium sulcatum* Lam., the presence of O-methylated kaempferol glycosides has been reported. On the other hand, C-glycoside flavones are represented by luteolin and apigenin, and C-sugars may occasionally occur as O-glycosides. O-glycoside flavones have been found in three *Asplenium* species, including scutellarein 6-O-glucoside in *Asplenium belangeri* Bory [6,7].

4. Conclusions

Species of the genus *Asplenium* present bioactive compounds of the polyphenolic type that stand out for their significant antioxidant activity and potential to reduce causes of neurotoxicity in Alzheimer's disease, such as amyloid plaques and oxidative stress. In addition, their metabolomic profiles contribute to the taxonomic separation with other groups of ferns, with which they share morphological similarities.

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