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Athyrium plants - Review on phytopharmacy properties

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ABSTRACT

Athyrium plants consist of more than 230 species that are largely distributed in the Sino-Himalayan region and the Western Pacific islands. *Athyrium* species are being used in traditional medicine worldwide to treat various ailments such as cough, rheumatic pain, scorpion stings, sores, burns and scalds, intestinal fever, pain, specifically breast pain during child birth, to increase milk flow, as an antiparasitic, anthelmintic, and carminative. A deep look in the literature has revealed that *Athyrium* species have been poorly investigated for their food preservative applications and *in vivo* and *in vitro* biological and phytochemical studies. However, some *Athyrium* species have demonstrated antimicrobial, anti-inflammatory, antioxidant, antiproliferative and anti-HIV potential. *Athyrium multidentatum* (Doll.) Ching is the most investigated species and the biological activities of their extracts, such as they antioxidant properties, seem to be related to the sulfate contents of their polysaccharides. This review provides an update on the ethnopharmacology, phytochemistry and biological properties of *Athyrium* plants that might be useful for further research. Of course, well-designed clinical trials will be required for some species to be used as therapy.

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1. Introduction

Athyrium or ferns, in the family Athyriaceae Alston, is a genus composed of ca. 230–300 species of terrestrial or epilithic plants with mostly erect or occasionally creeping or ascending rhizomes. *Athyrium* are mainly distributed in the Sino-Himalayan region including Southwest China, Sichuan Basin, Tibet-Yunnan Plateau and Nepal and secondarily in the Western Pacific islands such as Japanese Archipelago, the Ryukyu Islands, Taiwan, and the Philippines.^{1–3} *Athyrium* species are being used in traditional medicine throughout their range to treat various ailments such as cough⁴ and sores,^{5,6} and as antiparasitic,^{7–9} anthelmintic^{6–15} and diuretic agents.^{6,16–18}

Their phytochemical and biological properties have been poorly explored and scientific knowledge of their chemical constituents is limited.¹⁸ The great medicinal potency of *Athyrium* plants has been associated with the presence of several classes of natural compounds such as flavonoids, phenols, alkaloids, steroids, triterpenes and polysaccharides.^{17,18} In addition, *Athyrium* plants have been shown to contain nutrients, such as protein, carbohydrates, fats, antioxidants and vitamins, which benefit health in many ways.¹⁷

Several extracts from ferns exhibited remarkable antioxidant capacity, comparable to vitamin C, making them good food preservatives. They have also exhibited a promising effect on the inhibition of cell proliferation and stimulated apoptosis in the human liver cancer cell line (HepG2).¹⁹ The strong superoxide radical-scavenging and reducing power of *Athyrium* genus have been attributed to its polysaccharides.^{19,20}

A. multidentatum (Döll) Ching (AMC) is the most investigated species. It is a well-known nutritious potherb and traditional Chinese medicine native to northeast China, especially in the Changbai Mountain area. Moreover, Liu et al.,¹⁹ reported that polysaccharides extracted from AMC possess high antioxidant activity as mentioned above. Also, it possesses high antiproliferative activity.^{19,20} The present review provides an overview of the ethnopharmacy, phytochemistry and biological properties of *Athyrium* plants.

2. Traditional medicine uses of *Athyrium* plants

Athyrium species have been used in traditional medicine systems in different parts of the world (Table 1). For instance, *A. felix-femina* (L.) Roth has been used along with honey to cure cough in Diano valley (Province of Salerno, Campania region, Italy),⁴ while a

decoction of *A. felix-femina* has been used in decoction as an anti-parasitic and anthelmintic agent.^{8,9} In Iran, the rhizome is used also used as an antiparasitic and anthelmintic.⁷ The Rajasthan Bheels (a tribe from India) used the rhizome of *A. pectinatum* (Wall. ex Mett.) T. Moore as a strong anthelmintic.^{13,15} The people of Mymensing district of Bangladesh used fresh leave juice of *A. asperum* (Blume) Milde in children as an anthelmintic and carminative.¹⁴ In Maharashtra (India), fronds and rhizome of *A. hohenerianum* T. Moore are used as decoction against rheumatic pain as well as an anthelmintic.¹⁰ In addition, the rhizome paste has been used against scorpion sting.¹⁰ *A. falcatum* Bedd. has been used by the people of Madhya Pradesh (India) as an anthelmintic.¹¹ The people of Palani Hills (Western Ghats of South India) used its fronds and roots in their traditional medicine practices. For instance, the young fronds were consumed to treat internal ailments such as cancer and the roots consumed as an anthelmintic.⁶ *A. lanceum* T. Moore roots are used to overcome pain, specifically breast pain during child birth. It also increases milk flow and the dried powder when applied to sores is found to be useful.⁶ Moreover, it has been used as a remedy for burns and scalds, against intestinal fever,²¹ and anti-inflammatory herb for the treatment of ascariasis in Malaysia.¹² In New Guinea, *Athyrium* is used to treat sores.⁵ AMC has also been used in traditional Chinese medicine for its tranquilizer, antihypertensive and diuretic properties.^{16–18}

3. Food preservative applications of *Athyrium* plants

Microbial food safety is a global problem with significant effect on human health.^{33–35} In fact, food-borne pathogens are important causes of illness and death.^{36,37} According to the World Health Organization, unsafe food results in illnesses of at least 2 billion people worldwide annually and can be deadly.^{33,38} In addition, oxidative deterioration of food may also cause lipid peroxidation, nutritional loss, off-flavor and color impairment. Both microbial and oxidative deterioration decrease functional and nutritional value of food and consumers' acceptance.³⁸

To ensure food safety and prevent spoilage of food, a number of physical and chemical preservation techniques have been developed. Thermal processing destroys vegetative microorganisms but this technique may lead to undesirable organoleptic and nutritional effects.^{33,39} Several synthetic food preservatives (benzoic acid, sorbic acid, propionic acid, salts, BHA, BHT etc.) are commonly used to reduce the microbial growth rate or viability and extend the shelf life. Because of increasing regulatory restrictions, consumer awareness and microbial resistance, alternative natural sources of new antimicrobial compounds including plants, must be investigated.^{33,38–43}

Since ancient time, plants and their derived essential oils and extracts have been used for many purposes, especially in medicine and food industry as flavoring agents and food preservatives.^{33,36,44–46} Plants contain a diversity of bioactive compounds⁴⁷ including polyphenols, flavonoids, terpenoids, carotenoids, sterols, peptides and polysaccharides etc., showing many biological properties^{38,48–53} such as antioxidant⁵⁴ and antimicrobial activity.^{34,39,47}

The use of *Athyrium* plants and their derivatives for food preservation and safety as alternative sources of natural antimicrobial and antioxidant agents have been poorly investigated. However, polysaccharides and their derivatives found in *Athyrium* plants have been explored for their multipharmacological activities and applications in food and pharmaceutical industries especially as antioxidants.⁵⁴ Of note, the antioxidant activities of polysaccharides depend on type of sugar, glycosidic branching, flexibility and configuration of the chains.⁵⁵ Liu et al.¹⁹ prepared the polysaccharide extract from AMC and found it to be a neutral

Table 1
Traditional uses and Biological activities of *Athyrium* spp.

Traditional use	Reference
Antihypertensive	16–18
Antiparasitic and anthelmintic	6–11,13–15
Burns and scalds	21
Cancer	6
Carminative	14
Cough	4
Diuretic	6,16–18
Increases milk flow	6
Intestinal fever	21
Scorpion bite	10
Rheumatic pain	10
Sores	5,6
Tranquilizer	16–18
Biological activity	
Anti-HIV	22
Anti-inflammatory	23
Antioxidant	1,17–19,24–27
Antiproliferative	17,20,28
Antimicrobial	7,26,29–32

heteropolysaccharide, mainly made of glucose, galactose, rhamnose, mannose, and arabinose. The polysaccharide extract showed strong reducing power and scavenging activities on hydroxyl and superoxide radicals, and chelating abilities and the authors suggested a significant correlation between antioxidant activities with molecular weight and sulfate content.¹⁹ Notably, high molecular weight polysaccharides are less active than low molecular weight ones due to their poor penetration capability on cell-membranes.⁵⁶ In addition, another study demonstrated the strong antioxidant and reducing power of the acetylated, sulfated and phosphorylated derivatives of polysaccharides from the same plant.²⁴ Low molecular weight polysaccharide derivatives from AMC rhizome also showed strong scavenging ability on 1,1-diphenyl-2-picrylhydrazyl (DPPH), superoxide and hydroxyl radicals.²⁵ Superoxide anion and hydroxyl radicals are reactive oxygen species (ROS) that can cause oxidative damage to biomolecules including DNA, lipids and proteins, and induce severe tissue damage or cell death.^{57,58}

Soare et al.²⁶ reported a good antioxidant activity of the methanolic extract of *A. filix-femina* leaves that positively correlated with the total phenolic compounds. In another study, *A. filix-femina* exhibited strong 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical-scavenging activity.¹

The antimicrobial and antioxidant potencies of *Athyrium* suggest it could be used as alternative natural preservatives to ensure food safety and meet the consumer demands related to natural food additives.

4. Biological activities of *Athyrium* plants

Only a few *Athyrium* plants have been investigated for their biological activities, mostly focused on antibacterial and antioxidant properties (Table 1).

4.1. *In vitro* activity

4.1.1. Antimicrobial assays

A. filix-femina (L.) Roth had good antimicrobial activity in acetone extract for both Gram-negative and Gram-positive bacteria with zones of inhibition of 7–20 mm diameter against *Escherichia coli* and *Bacillus megaterium*.²⁹ *A. filix-femina* extract showed low antimicrobial activity with inhibition zone of 7–8 mm extract against *Staphylococcus aureus* and *Enterococcus faecalis* and a minimum inhibitory concentration (MIC) value of 600 µg/mL against *Bacillus cereus* and *Saccharomyces cerevisiae*.²⁶ However, the methanol extracts obtained from rhizome and leaves of *A. filix-femina* were found to have strong antibacterial potential against *E. coli*, *S. aureus*, and *B. megaterium* with MIC value ranging from 8 to 32 µg/mL.^{7,30}

Parihar et al.^{31,32} showed that the leaf extract of *A. pectinatum* inhibited the growth of *Salmonella arizonae*, but did not inhibit the growth of *E. coli* or *Salmonella typhi*. Aqueous and alcoholic extracts of *A. pectinatum* were found effective against *E. coli*, *S. arizonae*, *S. typhi* and *S. aureus*.^{31,32}

4.1.2. Antioxidant activity

Liu et al.¹⁹ reported that the antioxidant activity of AMC is related to the amount of peptides, present in the form of polysaccharide–peptide complexes. This study suggested that the molecular weight and sulfate content of AMC polysaccharides played very important roles on antioxidant activity.¹⁹ Moreover, Yuan et al.⁵⁹ found that the presence of sulfate, acetyl or phosphate could enhance the antioxidant activity of polysaccharide *in vitro*. Similarly, Behera et al.⁶⁰ found that polysaccharides having small polysaccharide/peptide ratios showed higher scavenging activities. Chen et al.⁶¹ also suggested that the mechanism of antioxidant

action of polysaccharides might be linked to the supply of hydrogen from the polysaccharide–peptide complexes, or the combination of the complexes with the radical ions, where the reaction was then terminated.

Ferrous ions are considered the most important pro-oxidants in food systems,⁶² so the chelating effect on ferrous ions is widely used to evaluate antioxidant activity. Liu et al.¹⁹ reported high chelating effect on ferrous ions of the AMC polysaccharides.

As Liu et al.¹⁹ noticed, the chelating power could be related to the sulfate contents of the AMC polysaccharides. Sulfated polysaccharides are often involved in many biological activities in animal cells, such as cell recognition, cell adhesion or regulation of receptor functions, which are of interest in medicine.⁶³ Qi et al.⁶⁴ also observed that the higher the sulfate content of a polysaccharide, the stronger the antioxidant activity and anti-hyperlipidemic activity. The hydroethanolic extract of the dried aerial parts of AMC, defatted with petroleum ether and purified using an AB-8 macroporous resin, showed significant DPPH, ABTS, •OH scavenging activity and ferric reducing power with EC₅₀ of 15.0, 4.6, 48.0 and 13.2 µg/mL, respectively.¹⁷ The extract also protected protein oxidation in a dose-dependent manner at concentration of 5–100 µg/mL.¹⁷ Besides protein fragmentation, the oxidation of arginine, threonine, lysine and proline may also generate carbonyl derivatives considered to be a marker of ROS-mediated protein oxidation.⁶⁵ Similarly, AMC purified extract in the range of 5–100 µg/mL efficiently inhibited 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH) -induced oxidation of albumin from bovine serum (BSA) carbonyl in a dose-dependent manner. In addition, AMC also inhibited lipid peroxidation in a dose-dependent manner and had the greatest cellular antioxidant activity, with cellular antioxidant activity values of 88.1 µM quercetin equivalents per g extract. AMC had powerful protective effects on biological macromolecules including proteins and lipids, indicating their potential use in the chemoprevention of diseases related to ROS.

Sheng et al.¹⁸ also reported that the *n*-butanol fraction of the methanol extract of AMC exhibited strong superoxide anion-scavenging capacity and strong reducing power. In another study, Sheng and Sun²⁵ degraded AMC rhizomes by using hydrogen peroxide and ascorbic acid mixtures to obtain four low molecular polysaccharides derivatives. Their results showed that high molecular weight polysaccharides showed prominent reducing power and DPPH activity, whereas low molecular weight polysaccharides exhibited relatively stronger free-radical scavenging activity.²⁵ Total sugar and sulfate content could affect the scavenging capability of the samples against superoxide radicals.²⁵ Wang et al.⁶⁶ found over-sulfated fucoidan, a sulfated polysaccharide found mainly in various species of brown algae and brown seaweed, had much greater antioxidant activity than fucoidan itself.

The oxidative stress theory of aging is based on the hypothesis that age-associated functional losses are due to the accumulation of ROS-induced damages. Anti-aging effects of AMC have been reported and linked to its polysaccharide content and could thus be used as a promising adjuvant agent for aging prevention.²⁷

4.1.3. Antiproliferative activity

AMC significantly inhibited the tumor growth of hepatocellular carcinoma,^{20,28} suggesting that it could be a promising agent for treatment of cancer. The purified AMC extract showed antiproliferative potency on HepG2 cells with IC₅₀ values of 220 µg/mL after 24 h and 114 µg/mL after 48 h.²⁰ A non-significant toxic effect was observed on human liver cell line, HL-7702, with IC₅₀ values of 332 µg/mL after 24 h and 304 µg/mL after 48 h. On the other hand, AMC extract showed strong inhibition of cell growth and induced apoptosis and cell cycle arrest in HepG2 cells by significantly

upregulating the protein expressions of Fas and its ligand Fas-L, which initiated the extrinsic pathway of apoptosis. In addition, AMC extract also suppressed the expression level of anti-apoptotic protein (Bcl-2) and triggered the translocation of Bax from cytoplasm to mitochondria, and the Bcl-2/Mito-Bax ratio gradually decreased in a concentration-dependent manner. Moreover, the expression levels of cleaved caspase-3 and the cleavage of PARP were increased in a dose-dependent manner after treatment with AMC for 24 h. This means that AMC induces apoptosis in HepG2 cells through both intrinsic and extrinsic pathways. AMC evoked apoptosis *via* modulation of the phosphatidylinositol-3-kinase and protein kinase B (PI3K/Akt), mitogen-activated protein kinase (MAPK), nuclear factor kappa B (NFkB) and nuclear factor erythroid 2-related factor 2 (Nrf2) pathways and their downstream transcriptional cascades.²⁰ AMC treatment also resulted in an increase in the percentage of cells in the G2/M phase in a concentration-dependent manner. Protein expressions of cyclin-dependent kinases (CDKs) CDK1, CDK2 and cyclin D1 were both markedly decreased on exposure of the cells to AMC, which suggested that AMC could induce cell cycle arrest in G2/M phase associated with decreases of CDK1, CDK2 and cyclin D1.^{17,20}

Striatosporolide A (SA) has been isolated from the rhizomes of *A. multidentatum*. This is a simple butenolide derivative with a fragrant odor.^{67,68} It was reported to possess cytotoxic activity on the human lung carcinoma cell line (A549) with an IC₅₀ value of 36.5 μM (7.75 μg/mL).²⁸

SA at 100 μM increased cell viability rate in human umbilical vein endothelial cells (HUVECs) to 128%. Meanwhile, in H₂O₂-treated HUVECs, SA pre-incubated at 50 μM enhanced cell viability by 56.9%. In both cases, the cell apoptosis rates were reduced to 2.2% and 3.1%, respectively. SA prevented the overproduction of ROS in HUVECs induced by H₂O₂ and the fluorescent intensity was abated after pre-incubation with 100 μM SA.²⁸

4.1.4. Anti-HIV activity

Mimhina et al.²² isolated three sulfolipids from the pteridophyte *A. niponicum* (Mett.) Hance that were evaluated on human immunodeficiency virus (HIV). The sulfolipids at 6 pg/mL were found to significantly inhibit the activities of both calf DNA polymerase α (pol. α) and rat DNA polymerase β (pol. β). Calf thymus terminal deoxynucleotidyl transferase was inhibited moderately by the sulfolipids. The sulfolipids appear to be selective inhibitors of the mammalian DNA polymerases *in vitro*. Sulfolipids also inhibited the mammalian pol. α, pol. β, and HIV-RT in a concentration-dependent manner; IC₅₀ for inhibition of pol. α and pol. β was 1.5 and 3 μg/mL, respectively, and almost complete inhibition (more than 90–95%) was achieved at 6 and 8 μg/mL, respectively. The sulfolipids were slightly more effective on pol. α than pol. β.²²

4.2. In vivo studies

The *in vivo* anti-inflammatory activity of the 95% ethanol extract of AMC dried aerial parts has been reported in a lipopolysaccharide (LPS)-induced inflammatory model in mice.²³ AMC extract inhibited NO and prostaglandin E₂ (PGE₂) production by suppressing their inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX-2) gene expression in LPS-induced peritoneal macrophages. The secretion of interleukins (IL-6 and IL-1β), and tumor necrosis factor (TNF-α) were also decreased through the down-regulation of mRNA levels. The AMC anti-inflammatory effects seem to be mediated *via* suppression of the toll-like receptor 4 (TLR4) signaling. In *in-vivo* experiments, the cell count and cytokines (TNF-α, IL-1β and IL-6) levels in bronchoalveolar lavage fluid (BALF) decreased significantly in a dose-dependent manner in the AMC extract groups. In particular, the effect of 10 mg/kg AMC extract was

similar to that of the positive control dexamethasone.²³

Qi et al.^{17,20} also studied the *in-vivo* antitumor activity of AMC purified extract in a xenograft tumor model in which HepG2 cells were injected subcutaneously into nude mice. Mice were treated with AMC (25 or 100 mg/kg) daily for 31 days. It was noticed that AMC had a significant inhibitory effect on tumor size compared to the control group. Caspase-3 and Ki-67 staining confirmed an increase in apoptosis and a reduction in proliferative cells in AMC-treated tumor animals in comparison to the untreated control.^{17,20}

5. Conclusions and future perspectives

Overall, this review summarized the ethnopharmacological, pharmacological, and phytochemical aspect of *Athyrium* plants. Only three *Athyrium* species have been investigated for their phytochemical constitution and biological activities. The demonstrated antimicrobial, anti-inflammatory, antioxidant, and anti-HIV *in vitro* and *in vivo* potencies warrant further clinical investigations in order to be used as therapy. However, other species from the *Athyrium* genus require a thorough investigation to reveal their real clinical value.

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