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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 cough[4] 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 *Athirium* 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 antiparasitic 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 Maharastra (India), fronds and rhizome of *A. hohenackerianum* 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]

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

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 compounds[47] including polyphenols, flavonoids, terpenoids, carotenoids, sterols, peptides and polysaccharides etc., showing many biological properties[38,48–53] such as antioxidant[54] 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

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′-azinobis-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 *Staphyllococcus 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, $^{\bullet}$OH scavenging activity and ferric reducing power with EC_{50} 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 Sun[25] 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 IC_{50} 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 IC_{50} 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 (NFκB) 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]

Striatisporolide 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 IC_{50} 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 H_2O_2-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 H_2O_2 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; IC_{50} 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 E_2 (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 ethnophamacological, 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.

References

1. Valizadeh H, Sonboli A, Kordi FM, Dehghan H, Bahadori MG. Cytotoxicity, antioxidant activity and phenolic content of eight fern species from North of Iran. *Pharmaceut Sci*. 2015;21(1):18–24.
2. Wei R, Zhang XC. *Athyrium sessilipinnum*: a new lady fern (Athyriaceae) from southern China. *Brittonia*. 2016;68(4):440–447.
3. Wood KR, Wagner WL. *Athyrium haleakalae* (Athyriaceae), a new rheophytic fern species from East Maui, Hawaiian Islands: with notes on its distribution, ecology, and conservation status. *PhytoKeys*. 2017;76:115–124.
4. Di Novella R, Di Novella N, De Martino L, Mancini E, De Feo V. Traditional plant use in the National Park of Cilento and Vallo di Diano, Campania, Southern, Italy. *J Ethnopharmacol*. 2013;145(1):328–342.
5. Powell JM. *Ethnobotany*. vol. 106. New Guinea: New Guinea Vegetation; 1976.
6. Sathiyaraj G, Muthukumar T, Ravindran KC. Ethnomedicinal importance of fern and fern allies traditionally used by tribal people of Palani Hills (Kodaikanal), Western Ghats, South India. *J Med Herbs Ethnomed*. 2015;1(1):4–9.
7. Bahadori MB, Kordi FM, Ahmadi AA, Bahadori S, Valizadeh H. Antibacterial evaluation and preliminary phytochemical screening of selected ferns from Iran. *Res J Pharmacogn*. 2015;2(2):53–59.
8. Eskandari M, Riazi B, Shirzadian S, Mazooji A. Investigation of fern species in Guilan province. *Rostaniha*. 2012;13:1–9.
9. Mozaffarian VA. *Identification of Iranian Medicinal and Aromatic Plants*. first ed. Tehran: Farhange Moaser Press; 2012.
10. Shaikh SD, Masal VP, Shaikh AS. Ethnomedicinal uses of some pteridophytes from Konkan region of Maharashtra, India. *Int J Pharmaceut Chem Sci*. 2014;3(1):62–65.
11. Singh BP, Upadhyay R. Medicinal pteridophytes of Madhya Pradesh. *J Med Plants Stud*. 2014;2(4):65–68.
12. Chai T-T, Elamparuthi S, Yong A-L, Quah Y, Ong H-C, Wong F-C. Antibacterial, anti-glucosidase, and antioxidant activities of selected highland ferns of Malaysia. *Bot Stud*. 2013;54(1):55.
13. Parihar P, Parihar L. Some pteridophytes of medical importance from Rajasthan. *Nat Product Radiance*. 2006;5(4):297–301.
14. Sarker SK, Hossain ABME. Pteridophytes of greater Mymensingh district of Bangladesh used as vegetables and medicines. *Bangladesh J Plant Taxon*. Jun 2009;16(1):47–56.
15. Vyas MS, Sharma BD. *Ethnobotanical Importance of the Ferns of Rajasthan. Indigenous Medicinal Plants Including Microbes and Fungi*. New Delhi: Today and tomorrow's printers and publishers; 1988.
16. Liu Y, Wujisguleng W, Long C. Food uses of ferns in China: a review. *Acta Soc Bot Pol*. 2012;81(4):263–270.
17. Qi G, Yang L, Xiao C, Shi J, Mi Y, Liu X. Nutrient values and bioactivities of the extracts from three fern species in China: a comparative assessment. *Food Funct*. 2015;6(9):2918–2929.
18. Sheng JW, Liu DM, Li ZJ, Qi L, Zhang WF. Bioactivity-guided fractionation for antioxidant property of *Athyrium multidentatum* (Doll) Ching. rhizome. *J Med Plants Res*. 2011;5(32):7000–7005.
19. Liu D, Sheng J, Li Z, et al. Antioxidant activity of polysaccharide fractions extracted from *Athyrium multidentatum* (Doll.) Ching. *Int J Biol Macromol*. 2013;56:1–5.
20. Qi G, Liu Z, Fan R, et al. *Athyrium multidentatum* (Doll.) Ching extract induce apoptosis via mitochondrial dysfunction and oxidative stress in HepG2 cells. *Sci Rep*. 2017;7(1):2275, 2017/05/23.
21. Corrigan D. Medicinal plants in folk Tradition–an ethnobotany of Britain and

Ireland by David E. Allen and Gabrielle Hatfield (natural history museum, London, and the royal botanic gardens, Kew). Timber press, Portland, OR. J Nat Prod. 2004/12/01 2004;67(12):2154-2154.
22. Mimhina Y, Watanabe I, Ohru K, et al. Studies on inhibitors of mammalian DNA polymerase α and β sulfolipids prom a pteridcphyte, *Athymum niponeum*. *Biochem Pharmacol*. 1998;55:537–541.
23. Han XZ, Ma R, Chen Q, et al. Anti-inflammatory action of *Athyrium multidentatum* extract suppresses the LPS-induced TLR4 signaling pathway. *J Ethnopharmacol*. 2018;217:220–227.
24. Sheng JW. Preparation and antioxidant activity of *Athyrium multidentatum* (Doll.) Ching polysaccharide derivatives. *J Chem Pharmaceut Res*. 2014;6(6): 1129–1135.
25. Sheng J, Sun Y. Antioxidant properties of different molecular weight polysaccharides from *Athyrium multidentatum* (Doll.) Ching. *Carbohydr Polym*. 2014;108:41–45.
26. Soare LC, Ferdes M, Stefanov S, et al. Antioxidant activity, polyphenols content and antimicrobial activity of several native pteridophytes of Romania. *Not Bot Horti Agrobot*. 2012;40(1):53–57.
27. Liu DM, Sheng JW, Mu J, Li WZ, Li ZJ, Sun YL. Antioxidant activities of an active fraction from *Athyrium multidentatum* (Doll.) Ching. *J Chem Pharmaceut Res*. 2016;8(6):458–462.
28. Liu DM, Sheng JW, Wang SH, Zhang WF, Zhang W, Zhang DJ. Cytoprotective effects of striatisporolide a isolated from rhizomes of *Athyrium multidentatum* (Doell.) ching on human umbilical vein endothelial cells. *Molecules (Basel, Switzerland)*. 2016;21(10).
29. Pal SK. Study of solvent extracts of some selected ferns for antimicrobial activity. *Indian J Biol Sci*. 2012;18:33–37.
30. Kumarpal S. Study of activity of some medicinal ferns of darjeeling. *Int J Sci Res Publ*. 2013;3(8).
31. Parihar P, Parihar L, Bohra A. Antibacterial activity of *Athyrium pectinatum* (Wall.) Presl. *Nat Prod Radance*. 2006;5(4):262–265.
32. Parihar P, Parihar L, Bohra A. *In vitro* antibacterial activity of fronds (leaves) of some important pteridophytes. *J Microbiol Antimicrob*. 2010;2(2):19–22.
33. Hintz T, Matthews KK, Di R. The use of plant antimicrobial compounds for food preservation. *BioMed Res Int*. 2015;2015:246264.
34. Raeisi S, Ojagh SM, Sharifi-Rad M, Sharifi-Rad J, Quek SY. Evaluation of *Allium paradoxum* (M.B.) G. Don. and *Eryngium caucasicum* trauve. Extracts on the shelf-life and quality of silver carp (*Hypophthalmichthys molitrix*) fillets during refrigerated storage. *J Food Saf*. 2017;37(3), e12321.
35. Raeisi S, Sharifi-Rad M, Quek SY, Shabanpour B, Sharifi-Rad J. Evaluation of antioxidant and antimicrobial effects of shallot (*Allium ascalonicum* L.) fruit and ajwain (*Trachyspermum ammi* (L.) Sprague) seed extracts in semi-fried coated rainbow trout (*Oncorhynchus mykiss*) fillets for shelf-life extension. *Lwt-Food Sci Technol*. 2016;65:112–121.
36. Mohanka R, Priyanka. Plant extract as natural food preservative against spoilage fungi from processed food. *Int J Curr Microbiol Appl Sci*. 2014;3(8): 91–98.
37. Sharifi-Rad M, Nazaruk J, Polito L, et al. *Matricaria* genus as a source of antimicrobial agents: from farm to pharmacy and food applications. *Microbiol Res*. 2018:76–88.
38. Prakash B, Kujur A, Singh P, Kumar A, Yadav A. Plants-derived bioactive compounds as functional food ingredients and food preservative. *J Nutr Food Sci*. 2017;1:1–7.
39. Tiwari BK, Valdramidis VP, O'Donnell CP, Muthukumarappan K, Bourke P, Cullen PJ. Application of natural antimicrobials for food preservation. *J Agric Food Chem*. 2009;57(14):5987–6000.
40. Sharifi-Rad M, Roberts TH, Matthews KR, et al. Ethnobotany of the genus *Taraxacum*—phytochemicals and antimicrobial activity. *Phytother Res*. 2018. https://doi.org/10.1002/ptr.6157.
41. Mishra AP, Sharifi-Rad M, Shariati MA, et al. Bioactive compounds and health benefits of edible *Rumex* species-A review. *Cell Mol Biol*. 2018;64(8):27–34.
42. Mishra AP, Saklani S, Salehi B, et al. *Satyrium nepalense*, a high altitude medicinal orchid of Indian Himalayan region: chemical profile and biological activities of tuber extracts. *Cell Mol Biol*. 2018;64(8):35–43.
43. Mishra AP, Saklani S, Sharifi-Rad M, et al. Antibacterial potential of *Saussurea obvallata* petroleum ether extract: a spiritually revered medicinal plant. *Cell Mol Biol*. 2018;64(8):65–70.
44. Salehi B, Ayatollahi SA, Segura-Carretero A, et al. Bioactive chemical compounds in *Eremurus persicus* (Joub. & Spach) Boiss. essential oil and their health implications. *Cell Mol Biol*. 2017;63(9):1–7.
45. Sharifi-Rad J, Ayatollahi SA, Varoni EM, et al. Chemical composition and functional properties of essential oils from nepeta schiraziana boiss. *Farmacia*. Sep-Oct 2017;65(5):802–812.
46. Abdolshahi A, Naybandi-Atashi S, Heydari-Majd M, et al. Antibacterial activity of some Lamiaceae species against *Staphylococcus aureus* in yoghurt-based drink (Doogh). *Cell Mol Biol*. 2018;64(8):71–77.
47. Sharifi-Rad M, Iriti M, Sharifi-Rad M, Gibbons S, Sharifi-Rad J. Anti-methicillin-resistant *Staphylococcus aureus* (MRSA) activity of Rubiaceae, Fabaceae and Poaceae plants: a search for new sources of useful alternative antibacterials against MRSA infections. *Cell Mol Biol*. 2016;62(9):39–45.
48. Sharifi-Rad J, Salehi B, Schnitzler P, et al. Susceptibility of herpes simplex virus type 1 to monoterpenes thymol, carvacrol, p-cymene and essential oils of *Sinapis arvensis* L., *Lallemantia royleana* Benth. and *Pulicaria vulgaris* Gaertn. *Cell Mol Biol*. 2017;63(8):42–47.
49. Sharifi-Rad J, Salehi B, Varoni EM, et al. Plants of the *Melaleuca* genus as antimicrobial agents: from farm to pharmacy. *Phytother Res*. 2017;31(10): 1475–1494.
50. Sharifi-Rad M, Varoni EM, Salehi B, et al. Plants of the genus *Zingiber* as a source of bioactive phytochemicals: from tradition to pharmacy. *Molecules (Basel, Switzerland)*. 2017;22(12).
51. Salehi B, Mishra AP, Shukla I, et al. Thymol, thyme, and other plant sources: health and potential uses. *Phytother Res*. 2018;32(9):1688–1706.
52. Sharifi-Rad M, Varoni EM, Iriti M, et al. Carvacrol and human health: a comprehensive review. *Phytother Res*. 2018;32(9):1675–1687.
53. Salehi B, Zucca P, Sharifi-Rad M, et al. Phytotherapeutics in cancer invasion and metastasis. *Phytother Res*. 2018;32(8):1425–1449.
54. Wang J, Hu S, Nie S, Yu Q, Xie M. Reviews on mechanisms of in vitro antioxidant activity of polysaccharides. *Oxid Med Cell Longev*. 2016;2016, 5692852.
55. Lu Y, Wang D, Hu Y, Huang X, Wang J. Sulfated modification of epimedium polysaccharide and effects of the modifiers on cellular infectivity of IBDV. Carbohydr Polym. 2008/01/24/2008;71(2):180-186.
56. Wu Q, Zheng C, Ning Z-X, Yang B. Modification of low molecular weight polysaccharides from tremella fuciformis and their antioxidant activity in vitro. *Int J Mol Sci*. 2007;8(7):670–679.
57. Spencer JP, Jenner A, Aruoma OI, et al. Intense oxidative DNA damage promoted by L-dopa and its metabolites. Implications for neurodegenerative disease. *FEBS Lett*. 1994;353(3):246–250.
58. Sharifi-Rad J, Sharifi-Rad M, Salehi B, et al. In vitro and in vivo assessment of free radical scavenging and antioxidant activities of *Veronica persica* Poir. *Cell Mol Biol*. 2018;64(8):57–64.
59. Yuan H, Zhang W, Li X, et al. Preparation and in vitro antioxidant activity of kappa-carrageenan oligosaccharides and their oversulfated, acetylated, and phosphorylated derivatives. *Carbohydr Res*. 2005;340(4):685–692.
60. Behera BC, Verma N, Sonone A, Makhija U. Evaluation of antioxidant potential of the cultured mycobiont of a lichen Usnea ghattensis. *Phytother Res*. 2005;19(1):58–64.
61. Chen Y, Xie MY, Nie SP, Li C, Wang YX. Purification, composition analysis and antioxidant activity of a polysaccharide from the fruiting bodies of *Ganoderma atrum*. *Food Chem*. 2008;107:231–241.
62. Yamauchi R, Tatsumi Y, Asano M, Kato K, Ueno Y. Effect of metal salts and fructose on the autoxidation of methyl linoleate in emulsions. *Agric Biol Chem*. 1988;52(3):849–850.
63. Ellouali M, Boisson-Vidal C, Durand P, Jozefonvicz J. Antitumor activity of low molecular weight fucans extracted from brown seaweed *Ascophyllum nodosum*. *Anticancer Res*. 1993;13(6a):2011–2019.
64. Qi H, Huang L, Liu X, Liu D, Zhang Q, Liu S. Antihyperlipidemic activity of high sulfate content derivative of polysaccharide extracted from *Ulva pertusa* (Chlorophyta). *Carbohydr Polym*. 2012;87(2):1637–1640.
65. Levine RL, Stadtman ER. Oxidative modification of proteins during aging. *Exp Gerontol*. 2001;36(9):1495–1502.
66. Wang J, Zhang Q, Zhang Z, Zhang J, Li P. Synthesized phosphorylated and aminated derivatives of fucoidan and their potential antioxidant activity in vitro. *Int J Biol Macromol*. 2009;44(2):170–174.
67. Liu DS, Huang YL, Ma LY, Lu CJ, Liu WZ. Chemical constituents and their cytotoxic activities of the secondary metabolites of *Penicillium janthinellum*. *Chin Tradit Patent Med*. 2016;38:830–834.
68. Stewart M, Capon RJ, Lacey E, Tennant S, Gill JH. Calbistrin E and two other new metabolites from an Australian isolate of *Penicillium striatisporum*. *J Nat Prod*. 2005;68(4):581–584.