The Genus *Cetraria* s. str.

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The genus *Cetraria* s. str. (Parmeliaceae family, Cetrarioid clade) consists of 15 species of mostly erect brown or greenish yellow fruticose or subfoliose thallus. These *Cetraria* species have a cosmopolitan distribution, being primarily located in the Northern Hemisphere, in North America and in the Eurasia area.

Cetraria traditional uses Pseudomonas aeruginosa

1. Traditional Uses

Among the species of the genus *Cetraria*, *C. islandica* (L.) Ach. has been the most widely used in traditional medicine. Its folk uses have been reported in a variety of documents, including handbooks, pharmacopoeias, compendia and pharmacognostical texts [1]. The main uses for *C. islandica*, commonly known as Iceland moss, are for the treatment of digestive and respiratory diseases. Herbal preparation varies from decoctions, tinctures and aqueous extracts to infusions. Hence, in Iceland, *C. islandica* has been used to the relief of both gastric and duodenal ulcers [2]. Moreover, decoctions of *C. islandica* were used to treat colds in Finland [3]. Furthermore, for centuries, *C. islandica* was famous as a laxative and antitussive in Central Europe. In addition to uses to treat respiratory and digestive conditions, *C. islandica* has been used in other countries for other medical purposes. This is the case in Sweden, where it has been used to treat nephritis and diabetes [4], and in Turkey, where it has been employed as a hemostatic and antihemorrhoidal agent [5][6]. Moreover, *C. islandica* has been used for tuberculosis in several countries including Spain, France, and Turkey [3][6][7]. These medicinal properties have been attributed mainly to its lichen acids, such as fumaroprotocetraric acid (2.6–11.5%), protocetraric acid (0.2–0.3%), protolichesterinic acid (0.1–1.5%) and usnic acid (0.04%) [8][9].

Based on the therapeutic benefits of *C. islandica*, comminuted herbal substances and soft extracts of this lichen in the form of syrup, oral gum, and lozenges have been marketed to relieve dry and irritating coughs and hoarseness. Moreover, combined commercial drug products have been developed that contain *C. islandica* together with other medicinal plants (*Thymus vulgaris* L., *Hyssopus officinalis* L., *Saponaria officinalis* L. and *Marrubium vulgare* L., among others) for the inflammatory processes of the upper airway, for the management of bronchial secretions and for the alleviation of coughs [1].

Other ethnobotanical studies have revealed traditional uses for other *Cetraria* species. Hence, in the Catalan Pyrenees (Spain), *Cetraria cucullata* (Bellardi) Ach. has been employed for asthma [7].

Many of the traditional uses of *Cetraria* spp. have been validated, such as antidiabetic and anti-inflammatory, and other new pharmacological activities are being investigated, such as cytotoxic and genotoxic/antigenotoxic, which researchers will discuss later in the section of pharmacological activities.

In addition to the medicinal uses of *C. islandica*, its nutritional value is noteworthy. It is mainly consumed as tea. Moreover, in Italy, it is a food supplementation product valued for its digestive-facilitating properties [1]. In Northern Europe, during times of famine, it was used for bread, sometimes mixed with rice or flour [10][11]. Furthermore, *C. islandica* is approved as a flavoring for alcoholic beverages in United States [12]. In Iceland, *C. islandica* is used in a variety of recipes including soups, porridges and sausages, and is added to "skyr" (curd) [9], and it is also marketed as a bitter alcoholic beverage (38% alcohol content) called "*Cetraria islandica* schnapps" [11]. On the other hand, in Russia, during the years 1942–1943, *C. islandica* was used to industrially extract glucose because of the beet sugar scarcity [11]. Moreover, the lichen species *Cetraria ericetorum* Opiz was chopped up and added to soups for flavoring [13]. In addition to food uses in humans, the species *C. islandica* has been used as food for pigs and cows, especially during World War II [13]. Finally, it is also worth mentioning its uses in cosmetics. *C. islandica* is part of the composition of diversity cosmetic products, including shampoos and conditioners, deodorants, toothpastes, exfoliating and anti-cellulite creams, manicure and pedicure products, and aftershave lotions. Moreover, the lichen *Cetraria nivalis* (L.) Ach. is used in rejuvenating cream formulations [14].

2. Therapeutic Potential

2.1. Antibacterial, Antifungal and Antitrypanosomal Activities

The antibacterial and antifungal activities of species of the genus *Cetraria* have been investigated for *Cetraria pinastri*, *Cetraria aculeata* and *Cetraria islandica*. These lichen species have shown antibacterial activity against a broad group of both Gram-positive and Gram-negative bacteria. Hence, the Gram-positive microorganisms sensitive to the methanol extract of *Cetraria pinastri* were *Enterococcus fecalis* (Minimum Inhibitory Concentration (MIC) 0.23 mg/mL), *Micrococcus lysodeikticus* (MIC 0.46 mg/mL) and *Staphylococcus aereus* (MIC 0.94 mg/mL). The only Gram-negative bacteria that was sensitive to the methanol extract of *Cetraria pinastri* was *Escherichia coli*, with an MIC value of 1.87 mg/mL [15]. In another study, the antimicrobial activity of the ethanol, acetone and diethylether extracts of *Cetraria acuelata* against 12 different Gram-positive (*Bacillus cereus*, *Bacillus subtilis*, *Listeria monocytogenes*, *Staphylococcus aureus and Streptococcus faecalis*) and Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Pseudomonas syringae*, *Proteus vulgaris*, *Aeromonas hydrophila* and *Yersinia enterocolitica*) bacteria was investigated. The three extracts tested showed antimicrobial activity against all bacteria species, except for the Gram-negative bacteria *Pseudomonas syringae*, *Klebsiella pneumoniae* and *Yersinia enterocolitica*. The most potent of the three tested *Cetraria aculeata* extracts was the diethylether extract, being especially active against the Gram-positive bacteria *Bacillus cereus*, *Bacillus subtilis*, *Listeria monocytogenes* and *Streptococcus faecalis*, and against the Gram-negative bacteria *Pseudomonas aeruginosa* and *Proteus vulgaris*, with MIC values of 8460 µg/mL [16].

Regarding the antimicrobial activity of *Cetraria islandica*, the extracts of methanol, acetone, water, and light petrolatum were assayed against *Helicobacter pylori* by using the Kirby and Bauery disk diffusion test. The light petrolatum extract of *Cetraria islandica* was the one that showed the greatest inhibitory capacity, followed by the acetone extract. However, the methanol and water extracts showed no activity. In addition, it was demonstrated that the compound responsible for the antimicrobial activity in the light petrolatum extract was the protolichesterinic acid [17]. In another study, the antimicrobial activity of the methanol extract of *Cetraria islandica* against Gram-positive species such as *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus cereus*, and against Gram-negative species such as *Escherichia coli* and *Proteus mirabilis*, was evaluated. The results show that the methanol extract of *Cetraria islandica* was more active against *Escherichia coli* with an MIC value of 2.5 mg/mL, followed by *Staphylococcus aureus* (MIC 1.25 mg/mL), *Proteus mirabilis* (MIC 1.25 mg/mL), *Bacillus subtilis* (MIC 0.625 mg/mL) and *Bacillus cereus* (MIC 0.312 mg/mL) [18].

In addition to studies evaluating the antibacterial activity of the lichen extracts from *Cetraria* species, the antimicrobial action of the compound protolichesterinic acid, isolated from *Cetraria*, *Cetraria aculeata* and *Cetraria islandica*, was investigated against different types of Gram-positive and Gram-negative bacteria. Hence, in one study, the protolichesterinic acid was active against *Escherichia coli* (MIC 7341 µg/mL), *Bacillus subtilis* (MIC 7341 µg/mL), *Pseudomonas aeruginosa* (MIC 7341 µg/mL) and *Listeria monocytogenes* (MIC 3670 µg/mL) [16]. In another study, the inhibitory capacity of the protolichesterinic acid was evaluated against a total of 35 *Helicobacter pylori* strains randomly selected from human biopsy samples, obtaining MIC values ranging from 16 to 64 µg/mL [17].

Apart from their antibacterial activity, *Cetraria* species, specifically *Cetraria aculeata*, *Cetraria pinastri* and *Cetraria islandica*, have been found to be active against pathogenic fungi. Hence, the methanol extract of *Cetraria pinastri* showed antifungal activity against *Acremonium chrysogenum* (MIC 3.75 mg/mL), *Alternaria alternata* (MIC 1.87 mg/mL), *Aspergillus flavus* (MIC 7.5 mg/mL), *Aspergillus niger* (MIC3.75 mg/mL), *Candida albicans* (MIC 1.87 mg/mL), *Cladosporium cladosporioides* (MIC 0.94 mg/mL), *Fusarium oxysporum* (MIC 7.5 mg/mL), *Mucor mucedo* (MIC 7.5 mg/mL), *Paecilomyces variotii* (MIC 15 mg/mL), *Penicillium verrucosum* (MIC 15 mg/mL) and *Trichoderma harsianum* (MIC 3.75 mg/mL). In another study, the ethanol, acetone, and diethyl ether extracts of *Cetraria aculeata* were assayed against the fungal species *Penicillum* sp., *Cladosporium* sp., *Fusarium oxysporum*, *Fusarium culmorum*, *Rhizopus* sp., *Fusarium moniliforme*, *Fusarium solani* and *Aspergillus* sp. The results show that none of the extracts of *Cetraria aculeata* had antifungal activity [15][16]. Finally, the methanol extract of *Cetraria islandica* was investigated on *Aspergillus flavus*, *Candida albicans*, *Fusarium oxysporum*, *Penicillium purpurescens* and *Trichoderma harsianum* species. *Cetraria islandica* showed a high antifungal activity against *Aspergillus flavus* and *Penicillium purpurescens*, with MIC values of 5 mg/mL, followed by its activity against Fusarium *oxysporum* and *Trichoderma harsianum*, with MIC values of 2.5 mg/mL. The lowest antifungal activity of the methanol extract of *Cetraria islandica* was against *Candida albicans* (MIC 1.25 mg/mL) [18].

In addition to the antifungal and antibacterial activity studies, the antitrypanosomal activity against *Trypanosoma brucei brucei* of bioactive compounds isolated from *Cetraria islandica* species was also evaluated. Protolichesterinic acid, fumarprotocetraric acid, lichesterinic acid and protocetraric acid were isolated. It was

observed that only protolichesterinic acid (MIC 12.5 µM) and lichesterinic acid (MIC 6.30 µM) showed antitrypanosomal activity, with protolichesterinic acid being more effective [19].

2.2. Antioxidant Activity

Oxidative stress is characterized by an imbalance between the production of reactive species (ROS) and the antioxidant defense activity. This pathological state has been associated with many chronic and/or degenerative diseases, such as diabetes, Alzheimer's disease, and cardiovascular disease. The use of exogenous antioxidants that act as scavengers or that modulate the endogenous antioxidant system is one of the most promising therapies used to deal with oxidative stress. In this context, phenolic compounds have turned out to be powerful antioxidants. The efficacy is directly related to the number of hydroxyl groups in the phenolic structure [20]. Lichens produce unique phenolic compounds as secondary metabolites that have aroused great research interest due to their antioxidant capacity [21].

Ranković B et al. evaluated the antioxidant activity of the methanol extract of *Cetraria pinastri* species by measuring the oxidation products of linoleic acid. The results have revealed that this lichen species was able to inhibit linoleic acid oxidation by 48.8%. This activity is related to its high polyphenol content of 32.9 mg/g in the dry extract [15].

Likewise, antioxidant activity studies have been carried out with the methanol extract and the ethyl acetate extract of *Cetraria aculeata*. In general, the antioxidant capacity of the methanol extract was higher than that of the ethyl acetate extract. Hence, the methanol extract showed an IC_{50} value of 51.65 µg/mL in the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, a value of 45.55 µg/mL for lipid peroxidation inhibition capacity, a value of 50.43 µg/mL for ferrous ion chelating capacity and a value of 90.1 µg/mL for hydroxyl radical scavenging activity. Regarding antioxidant enzymes, the methanol extract of *C. aculeata* increased superoxide dismutase (SOD) and glutathione peroxidase (GPx) enzymes' activities. On the contrary, a slight increase in malondialdehyde (MDA) levels and a decrease in reduced glutathione (GSH) levels were also observed at low doses [22].

On the other hand, the lichen in which the antioxidant activity has been the most studied is *Cetraria islandica*. Hence, the methanol extract of *Cetraria islandica* exhibited a high reduction capability and powerful free radical scavenging, as shown in the DPPH assay (IC_{50} 678.38 µg/mL), superoxide anion assay (IC_{50} 792.48 µg/mL) and reducing power assay (from 0.0512 µg/mL to 0.4562 µg/mL) [18]. In another study, Kotan E. et al. investigated the antioxidant ability of the methanol extract of *Cetraria islandica* (5 and 10 µg/mL) in an aflatoxin B1 induced oxidative stress model in blood lymphocytes from healthy non-smoking volunteers. The methanol extracts of this lichen species increased SOD and glutathione peroxidase (GPx) enzyme activities, and decreased MDA levels. The most protective concentration of *Cetraria islandica* was 5 µg/mL [23]. In addition to the methanol extract, the aqueous extract of *Cetraria islandica* has shown antioxidant activity using the thiocyanate method and the reducing antioxidant power, superoxide anion radical and DPPH assays. Different concentrations of the aqueous extract of *Cetraria islandica* (50, 100 and 250 µg) inhibited the peroxidation of linoleic acid by 96 to 100%. Moreover, this extract reduced iron from its ferric state to its ferrous state in a significant and concentration-dependent manner,

this activity being higher than in the reference compound BHT. Moreover, the aqueous extract of *Cetraria islandica* at a concentration of 100 µg showed a higher superoxide radical scavenging activity than the reference compounds hydroxybutylanisole (BHA), butylated hydroxytoluene (BHT), and quercetin [24]. Furthermore, the ethanol extracts of *Cetraria islandica* (96%, 70% and 40%) showed antioxidant activity. The DPPH assay showed that the ethanol extract 70% and ethanol extract 40% had IC_{50} values of 2.40 mg/mL and 2.45 mg/mL; the Ferric Reducing Antioxidant Power (FRAP) assay revealed that the ethanol extract 96% had the highest value of 486 µmol/L, and the 2, 2′-Azinobis-3-ethyl-benzo-thiazoline-6-sulphonic acid (ABTS) assay demonstrated that the ethanol extract 40% of this lichen was the most active [25]. In another study, Kosanic M. et al. compared the antioxidant activities of different extracts (methanol, water, and acetone) of *Cetraria islandica* by using the DPPH assay, reducing antioxidant power method and superoxide anion radical assay. This study revealed that the methanol extract had the highest activity in all these methods, followed by the acetone extract and aqueous extract [26]. Recently, it has been observed that melanin extracted from *Cetraria islandica* also possesses free radical scavenging and reducing capacity in the DPPH assay, with an IC_{50} of 405 µg/mL [27].

Finally, based on the antioxidant properties and considering the implications of oxidative processes in diabetes and neurodegenerative diseases, there are several studies focused on the protective effect of *Cetraria islandica*. Hence, the aqueous extract of this lichen species increased the activity of the antioxidant enzymes SOD, catalase (CAT), and GPx, and reduced the levels of the lipid peroxidation biomarker MDA in human erythrocytes with type 1 diabetes mellitus [28]. Moreover, the aqueous extract of *Cetraria islandica* decreased the total oxidative stress (TOS) and increased the total antioxidant capacity (TAC) in streptozotocin-induced Diabetes Mellitus type 1 Sprague-Dawley rats [29]. Using the same model, the aqueous extract of *Cetraria islandica* (250–500 mg/kg/day) increased the levels of SOD, CAT and GSH, and reduced the levels of MDA [30][31][32]. Regarding neuroprotection studies, the protective role of *Cetraria islandica* and its isolated secondary metabolite fumarprotocetraric acid has been demonstrated in a hydrogen peroxide-induced oxidative stress model on human U373MG astrocytoma cells and human SH-SY5Y neuroblastoma cells. The methanol extract of *Cetraria islandica* at 10 µg/mL concentration increased cell viability, reduced intracellular ROS production and MDA levels, and increased the ratio of reduced/oxidized glutathione (GSH/GSSG). The depsidone fumarprotocetraric acid at 1 µg/mL in the neurons model and 25 µg/mL in the astrocytes decreased lipid peroxidation levels and intracellular ROS production and increased the ratio GSH/GSSG. Moreover, this compound ameliorated the H_2O_2-induced mitochondrial dysfunction and alterations in calcium homeostasis and inhibited apoptotic cell death. Its neuroprotective activity is related, at least in part, to its ability to activate the Nrf2 pathway that regulates antioxidant enzymes. Furthermore, both the lichen extract and fumarprotocetraric acid showed scavenging activities in the oxygen radical absorbance capacity (ORAC) assay (value of 3.06 µmol TE/mg and 5. 07 µmol TE/mg, respectively) and in the DPPH assay (IC_{50} value of 1183.55 µg/mL and 1393.83 µg/mL, respectively) [33][34].

2.3. Immunomodulatory and Anti-Inflammatory Activities

The immunomodulatory activity has been investigated on *Cetraria islandica* aqueous extracts and the isolated compounds fumarprotocetraric acid and protolichesterinic acid, and the polysaccharides lichenan and isolichenan on the maturation of dendritic cells. This study showed that the aqueous extract and the polysaccharide lichenan

reduced the IL-12p40/IL-10 ratio and CD209 expression and increased CD86 expression. Moreover, this lichen extract showed anti-inflammatory properties at a dose of 2.5 mg/kg on a BSA-induced arthritis rat model, as evidenced in the reduction in the diameter between the right and left knees [35].

It is also noteworthy that the study on the polysaccharide α-1,3/1,4-D-Glucan (Ci3) isolated from *Cetraria islandica* (100 ug/mL) showed an increase in granulocytic phagocytosis and a decrease in complement-induced hemolysis [36].

2.4. Cytotoxic, Genotoxic and Antigenotoxic Activities

The cytotoxic activities of the lichen species *Cetraria acuelata* and *Cetraria islandica* and their isolated bioactive compounds have been evaluated on different types of malignant cells. Hence, the methanol extract of *Cetraria islandica* reduced the cell viability of the human breast cancer cells (MCF-7) (IC_{50} value of 19.51 µg/mL), the human liver cancer cells (HepG2) (IC_{50} value of 181.05 µg/mL), human melanoma cells (FemX) (IC_{50} value of 22.68 µg/mL) and human colon carcinoma cells (LS174) (IC_{50} value of 33.74 µg/mL) [18][33]. On the other hand, the ethanol extract of *Cetraria islandica* was able to reduce cell viability in MCF-7 cells (IC_{50} 9.2047×10^{-5} g/mL), also showing an increase in protein levels of AMP-activated kinases-α1 (AMPK-α1) and ERK1/2 [37]. The compound protolichesterinic acid, isolated from *Cetraria islandica*, decreased cell viability and caused morphological changes at a concentration of 20 µg/mL on breast carcinomas T-47D and ZR-75-1 and erythro-leukaemia K-562 cells. Moreover, this secondary metabolite inhibited DNA synthesis at the concentrations of 1.1 µg/mL on ZR-75-1 cells, 3.8 µg/mL on T-47D cells and 11.2 µg/mL on K-562 cells. This activity is related to the ability of protolichesterinic acid to inhibit 5-lipoxygenase [38]. Thorsteinsdottir et al. conducted a study in which it was observed that protolichesterinic acid, in addition to reducing human lung cancer cells' (A549) viability, also induced a decrease in Leucine Rich Repeat Containing 8 VRAC Subunit A (LRRC8A) protein expression, as well as volume-sensitive taurine release under hypotonic conditions [39]. On the other hand, the fumarprotocetraric acid, isolated from *Cetraria islandica*, did not inhibit the cell growth of the human cells T-47D (breast) and Panc-1 (pancreas) [40]. Moreover, the lichenan from *Cetraria islandica* was also not active against the human myeloid leukemia U937 cells [41].

In addition to *Cetraria islandica*, the cytotoxic activity of *Cetraria aculeata* has been studied. The acetone extract of this lichen species was active against HeLa (human uterus carcinoma) (IC_{50} value of 200 µg/mL), A549 (human small lung carcinoma) (IC_{50} value of 500 µg/mL) and 5RP7 (c-H-ras transformed-rat embryonic fibroblasts) (IC_{50} value of 280 µg/mL) [42].

Regarding the studies performed to evaluate the genotoxic/antigenotoxic activities of *Cetraria* species, it has been highlighted that the species *Cetraria aculeata* showed a significant antigenotoxic effect on TA98 and TA100 strains of *Salmonella typhimurium but* had no effect in human lymphocytes [42]. On the other hand, the methanol extract showed antigenotoxic activity against *Salmonella typhimurium* strains TA1535 and TA1537, and a slight decrease in sister chromatid exchange (SCE) formation [43]. In another work, it has been shown that the methanol extract of *Cetraria islandica* (from 50 to 200 µg/mL) had genotoxic potential in cultured peripheral venous blood from

healthy donors by increasing both the number of BN cells containing micronuclei (MNi) and the number of MNi in BN cells [18].

2.5. Cell Differentiation and Depigmentation Activities

The effect of β-1,3/1,4-Glucan (Lichenan), isolated from *Cetraria islandica*, on cell differentiation has recently been evaluated in primary normal human epidermal keratinocytes (NHEK) and HaCaT keratinocytes using immunofluorescence. A decrease in cell proliferation and an increase in protein expression of specific differentiation-related markers such as cytokeratin 10 (CK10) and involucrin were observed in NHEK cells. In addition, the gene expressions of CK, involucrin, transglutaminase, loricrin and filaggrin genes, which are involved in cell differentiation, were also increased [44].

The depigmenting activity was evaluated in chloroform, chloroform–methanol, methanol, and water extracts of *Cetraria islandica* species. The chloroform–methanol extract showed the highest inhibition capacity on tyrosinase (IC_{50} 86 µg/mL). A cell viability assay was performed on human melanoma cells (MeWo) with IC_{50} values of 264 µg/mL. Melanin assays demonstrated a significant reduction in melanin levels. On the other hand, zebrafish embryo models were used to determine the melanogenesis effects of the extract showing an inhibition of melanogenesis, and therefore a reduction in pigmentation [45].

Table 1. Pharmacological activities of *Cetraria* spp.

Lichen Species	Extracts/Active Compounds	Experimental Model	Activities	Results	References
Cetraria aculeata (Schreb.) Fr.	Diethyl ether extract Ethanol extract Acetone extract	Gram-positive: *Bacillus cereus*, *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus*, *Listeria monocytogenes* Gram-negative: *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pseudomonas syringae*, *Aeromonas hydrophila*, *Yersinia enterocolitica*, *Klebsiella pneumoniae*	Antibacterial	Antimicrobial activity against *B. cereus*, *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *Streptococcus*, *B. subtilis*, *A. hydrophila*, *L. monocytogenes*	[16]
	Diethyl ether extract Ethanol extract Acetone extract	*Penicillum* sp., *Cladosporium* sp., *Fusarium oxysporum*, *F. culmorum*, *F. moniliforme*, *F. solani*, *Rhizopus* sp, *Aspergillus* sp.	Antifungal	No antifungal activity detected	[16]
	Acetone extract	TA98 and TA100 strains of *S. typhimurium*	Antigenotoxicity	↑ Inhibition of frameshift mutations in TA98 than in TA100	[42]
	Methanol extract	*Salmonella typhimurium* TA1535 and TA1537 *E. coli* WP2uvrA Human lymphocyte cells	Antigenotoxicity	Antimutagenic activity against *Salmonella typhimurium* No activity against *E. coli* ↓ formation of SCE	[43]
	Methanol extract Ethyl acetate	Radical scavenging activity	Antioxidant	Methanol extract >>> ethyl acetate extract	[22]

Lichen Species	Extracts/Active Compounds	Experimental Model	Activities	Results	References
	extract			Methanol extract: DPPH (IC_{50} 51.6 µg/mL); lipid peroxidation inhibition capacity (IC_{50} 45.5 µg/mL); ferrous ion chelating capacity (IC_{50} 50.4 µg/mL; hydroxyl radical scavenging activity (IC_{50} 90.1 µg/mL)	
	Methanol extract	Human lymphocytes cells	Antioxidant	↑ SOD, GPX, MDA levels ↓ GSH	[43]
	Acetone extract	HeLa cells, A549 cells and 5RP7 cells	Cytotoxic	↓ Cell viability	[42]
	Methanol extract	*Salmonella typhimurium* TA1535 *E. coli* WP2uvrA	Genotoxicity	No activity	[43]
Cetraria islandica (L.) Ach	Methanol extract Acetone extract Light petrolatum extract Aqueous extract	*Helicobacter pylori*	Antibacterial	Light petrolatum extract > Acetone extract	[17]
	Methanol extract	Gram-positive: *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus* Gram negative: *Escherichia coli*, *Proteus mirabilis*	Antibacterial	Antimicrobial activity against all bacteria	[18]
	Methanol extract	*Aspergillus flavus*, *Candida albicans*, *Fusarium oxysporum*, *Penicillium purpurescen*, *Trichoderma harsianum*	Antifungal	Antifungical activity against all fungi	[18]
	Aqueous extract	Streptozotocin-induced Diabetes Mellitus type 1 Sprague-Dawley rats	Antidiabetic	Slight insulin increase No inhibition of glucose levels ↓ infiltration of immune cells, vacuolization, and intensity of fibrosis in the kidney ↑ SOD and GSH, ↓ MDA	[30]
	Aqueous extract	Streptozotocin-induced Diabetes Mellitus type 1 Sprague-Dawley rats	Antidiabetic	No body weight change ↓ glucose ↑ insulin levels ↑ SOD, CAT and GSH levels ↑ glycogen of hepatocytes ↓ intensity of fibrosis	[31]
	Aqueous Extract	Streptozotocin-induced Diabetes Mellitus type 1 Sprague-Dawley rats	Antidiabetic	↓ TOS ↑ TAC ↑ regeneration and erythropoiesis ↑ MCV, MCH, MCHC	[29]

Lichen Species	Extracts/Active Compounds	Experimental Model	Activities	Results	References
Cetraria islandica (L.) Ach	Aqueous extract	BSA-induced arthritis in rats	Anti-inflammatory	↓ reduction in the diameter between the right and left knee	[35]
	Aqueous extract	Streptozotocin-induced Diabetes Mellitus type 1 Sprague-Dawley rats	Antioxidant	↑ SOD and CAT ↓ MDA level Light prevention of pancreatic cells destruction	[32]
	Aqueous extract	Streptozotocin-induced Diabetes Mellitus type 1 Sprague-Dawley rats	Antioxidant	↑ SOD, GSH ↓ MDA levels Prevention of renal cell destruction.	[30]
	Aqueous extract	Human erythrocytes with type 1 diabetes mellitus	Antioxidant	↑ SOD, CAT and GPx ↓ MDA levels	[28]
	Methanol extract	Blood lymphocytes from human nonsmoking healthy volunteers	Antioxidant	↑ SOD and GPx ↓ MDA	[23]
	Aqueous extract	Radical scavenging activity	Antioxidant	96–100% inhibition upon lipid peroxidation of linoleic acid system ↑ Superoxide radical scavenging activity	[24]
	Ethanol extract	Radical scavenging activity	Antioxidant	DPPH, FRAP and ABTS	[25]
	Methanol extract	Radical scavenging activity	Antioxidant	DPPH (IC_{50} 678.3 µg/mL) Superoxide anion scavenging activity (IC_{50} 792.4 µg/mL) Reducing power range 0.0512 to 0.4562 µg/mL	[18]
	Melanin	Radical scavenging activity	Antioxidant	DPPH (IC_{50} 405 µg/mL)	[27]
	Protolichesterinic acid, Lichesterinic acid, Protocetraric acid, Fumarprotocetraric acid	*Trypanosoma brucei brucei*	Antitrypanosomal	Protolichesterinic acid MIC value 12.5 µM Lichesterinic acid MIC value 6.30 µM Protocetraric acid and Fumarprotocetraric acid no antitrypanosomal activity detected	[19]
	β-1,3/1,4-Glucan lichenan	Keratinocytes (NHEK) cells HaCaT keratinocytes cells	Cellular differentiation	↓ Proliferation ↑ CytoKeratin 10 (CK) in the cytoplasm ↑ Involucrin expression Dose-dependent CK gene	[44]

References

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Lichen Species	Extracts/Active Compounds	Experimental Model	Activities	Results	References
				expression regulation ↑ Involucrin transcription levels ↑ Transglutaminase gene expression Gene expression regulation of loricrin and filaggrin ↑ Gene group related to cellular differentiation	
	Protolichesterinic acid	A549 cells	Cytotoxic	No change in 5-lipoxygenase activity ↓ LRRC8A expression ↓ cell viability	[39]
	Protolichesterinic acid	T-47D cells, K-562 cells and ZR-75-1 cells	Cytotoxic	Morphological changes in T-47D and K-562 ↓ Cell viability ↓ DNA synthesis Inhibition of 5-lipoxygenase	[38]
	Ethanol extract	MCF7 cells	Cytotoxic	↓ Cell viability (IC_{50} 9.2047 × 10^{-5} g/mL) ↓ PPAR-g levels ↑ AMPK-α1 and ERK1/2 levels ↑ Apoptotic cell percentage after 24 h ↓ P53, Caspase 3 and Bcl-2 dose dependent	[37]
	Methanol extract	FemX and LS174 cells	Cytotoxic	FemX (IC_{50} 22.6 µg/mL) LS174 (IC_{50} 33.7 µg/mL)	[18]
Cetraria islandica (L.) Ach	Lichenan	U937 cells	Cytotoxic	No active	[41]
	Methanol extract	MCF-7 and HepG2 cells	Cytotoxic	MCF-7 (IC_{50} 181.0 µg/mL) HepG2 (IC_{50} 19.5 µg/mL)	[33]
	Fumarprotocetraric acid	T-47D and Panc-1	Cytotoxic	No antiproliferative effect	[40]
	Chloroform–methanol, extract	Developing zebrafish embryos	Depigmenting	↓ Pigmentation (IC_{50} 44 µg/mL)	[45]
	Chloroform–methanol extract	Radical scavenging activity MeWo	Depigmenting	Tyrosinase inhibition (IC_{50} 86 µg/mL) Cell viability assay (IC_{50} 264 µg/mL) ↓ Melanin levels	[45]

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Lichen Species	Extracts/Active Compounds	Experimental Model	Activities	Results	References
	Aqueous extract	Human erythrocytes with type 1 diabetes mellitus	Genotoxicity	↑ Proliferation index ↓ DNA damage ↓ SCE	[28]
	Methanol extract	Peripheral venous blood	Genotoxicity	↑ Number of BN cells containing MNi and number of MNi in BN cells	[18]
	Aqueous extract Fumarprotocetraric acid, Protolichesterinic acid, Lichenan and isolichenan	Human monocytes differentiated into mature dendritic cells.	Immunomodulating	Aqueous extract and lichenan were active ↑ CD86 and ↓ CD209 and IL-12p40/IL-10	[35]
	(1 --> 3) -(1 --> 4)-α-D-Glucan polysaccharide Ci-3	Whole blood	Immunomodulating	↑ Granulocytic phagocytosis ↓ Complementarily induced hemolysis	[36]
	Fumarprotocetraric acid	Radical scavenging activity SH-SY5Y and U373-MG cells	Neuroprotective	ORAC (5.07 µmol TE/mg), DPPH (IC_{50} 1393.83 µg/mL) ↑ cell survival, GSH/GSSG ↓ lipid peroxidation, ROS caspase-3 activation Avoid mitochondrial dysfunction and alterations in calcium homeostasis ↓ Pro-apoptotic signals Nrf2 pathway	[34]
Cetraria islandica (L.) Ach	Methanol extract	U373 MG cells	Neuroprotective	ORAC (3.06 µmol TE/mg), DPPH (IC_{50} 1183.55 µg/mL) ↑ Cell viability and GSH/GSSG ratio ↓ ROS generation and lipid peroxidation	[33]
Cetraria pinastri (Scop.) Gray.	Methanol extract	Gram-positive: *Enterococcus fecalis*, *Staphylococcus aureus*. Gram-negative: *Escherichia coli*, *Klebsiella pneumoniae Micrococcus lysodeikticus*, *Pseudomonas aeruginosa*	Antibacterial	Antimicrobial activity against all bacterial strains	[15]
Cetraria pinastri (Scop.) Gray.	Methanol extract	*Alternaria alternate*, *Aspergillus flavus*, *A. niger*, *Candida albicans*, *Cladosporium cladosporioides*, *Paecilomyces variotii*, *Acremonium chrysogenum*, *Fusarium oxysporum*, *Penicillium verrucosum Trichoderma harsianum*	Antifungal	Antifungal activity against all fungal species tested	[15]
Cetraria pinastri (Scop.)	Methanol extract	Thiocyanate method	Antioxidant	48.79% inhibition of the oxidation of linoleic acid	[46]

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Lichen Species	Extracts/Active Compounds	Experimental Model	Activities	Results	References
Gray.					

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