Progress in Nutrition 2021; Vol. 23, N. 3: e2021153 DOI: 10.23751/pn.v23i3.9833

Review

Lichen: A comprehensive review on Lichens as a natural sources exploring nutritional and biopharmaceutical benefits

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Abstract. Lichens are used as traditional medicines, rich in nutritional values, and have been described as potent medicines in various pharmacopoeias world-wide. Lichens are environmental biological indicators for human operations to change the ecosystem and also generate a range of unique secondary metabolites with varying biological potential. In addition to their prospective biological role as photoprotection, anticancer, anti-hepatotoxic, antidiabetic, allelopathic, and immunomodulatory, etc. Over the past few decades, the interest in lichens as a source of novel bioactive molecules has been renewed and increasing. Research on lichens secondary metabolites and nutritional value even at the international level has been scanty. This review summarizes the present status of characterization, nutritional values, and pharmaceutical properties of lichens and their applications. This study provides a baseline for future studies, particularly those dealing with nutritional and medicinal aspects of lichens.

Keywords: Lichen, Fungi, photobiont, symbiosis, anticancer, antimicrobial

Introduction

In creating vegetation on bare rocky fields, lichens are called to be the pioneers. They are the first members of the barren rocky region to colonize and lead in rock disintegration during development by forming enzymes like oxalic acid, carbonic acid, etc. The term symbiosis was the first time used in 1877 to describe the symbiotic relationship between fungi and algae. The word symbiosis was originally used to define two organisms living together, bringing advantages to each- other. It is a significant element of long-living fungi (mycobiont), while algae or cyanobacteria (photobiont) are associated with a tiny part. The fungal partner accounts for about 98% of Ascomycota, while Basidiomycota continues and anamorphic fungi (1). Whereas the number of photobionts reported about 156 species in literature from 56 genera (2).

Lichens produce a broad variety of unique secondary metabolites that belong to aliphatic and aromatic chemical substances of low molecular weight. Most of the compounds accumulate in the exterior cortex, such as usnic, atranorin, fungal melanins, parietin and some of them in the medullary layer (3, 4). Lichens produce a host of chemicals that are likely to diminish predator attacks. Only a few insects, including some moths and beetles, feed on lichens. Lichen's pharmacological potential is only feasible because of the existence of secondary metabolites as a taxon-specific distribution (5-7). Secondary metabolite allocation patterns can correlate with individual morphology and geography (8, 9).

Lichen produces many rare secondary products which are not present in other plants. The uniqueness of many of the aromatic products had early developed a chemical interest in lichen substances. Lichens are an underutilized source of industrially important biological activities and their potential has yet to be fully explored and utilized. Bioactive compounds extracted from lichen hold great promise for biopharmaceutical applications and in the production of new formulations or innovations to support human life. This review is intended to summarize the past and current research and development trends in the nutritional value, use of lichens and their bioactive compounds in traditional medicine and other biopharmaceutical applications of commercial interest.

1.1 Distribution of lichens

Lichen's habitats are varied, they can survive in a distinct setting and their development can be influenced by abiotic factors such as accessibility of light, wind velocity, moisture and temperature (10, 11). Lichen-associated microbes are an important component of lichen thalli, which can provide distinct symbiosis roles. Studies showed that bar-coded pyrosequencing bases were used to examine related bacteria subjected to lichen-borne alphaproteobacteria. The bacteria examined were discovered to be strongly linked to the lichen-associated lineage of Rhizobiales known as nitrogen fixers (12).

Lichens are resistant species that can survive in deserts that scorch and freeze tundra. Two main characteristics are suggested to have significant roles in their achievement: (1) their drying survival capability and (2) their complicated chemistry. When moisture is inaccessible, lichens can dry entirely and can sustain a full loss of body water without dying. Lichen thalli are poikilohydrous, meaning that their water status follows reflexively the atmospheric humidity to activate the lichen metabolism quickly (13-15). It requires only minutes to recover the photosynthetic device in Antarctic lichens after the dark winter (16, 17). The algal portion in lichens can activate their photosynthesis with water vapor, lichens require liquid water for cyanobacteria (17).

Parasyri et al. (2018) showed that lichen, as a micro-ecosystem, is tolerant to three extreme circumstances, total dehydration, exceptionally low temperature (-196°C) and hypoxia, while particular pathways are enabled to allow lichen to deal with these stress conditions through ecological stability (18). Dehydrated thallus can handle temperatures reaching -196°C/77K effectively. Not only that, but it can also generate molecular hydrogen in light and darkness under anoxic conditions. The molecular hydrogen could then be used as a fuel to satisfy elevated effectiveness and pollution-free energy requirements in space (18).

Antarctica has a very harsh climate and little vegetation. Lichens are the most abundant about 350 species reported from Antarctica (14, 19). The lichen fruticose thalli belong to the *Usnea* genus and *Umbilicaria*, which is dominated in the Antarctic region, can reach a height of up to 20 cm and is regarded to be the biggest primary producer. Crustose lichen thalli also vary widely over the sandstone in form and size (20). They can readily and rapidly desiccate up to 97 percent of water to become an anabiotic disease (21).

Park et al. (2018) recently reported *Psoroma antarcticum* from Antarctica's South Maritime Shetland and the South Orkney Islands. The new species is strongly linked to the lichen *Psoroma hypnorum* but it is quite different in cup-shaped apothecia, smaller ascospores, and thalli with gray-to-black melanin in particular. The entire research is based on its inner variability and association with other species based on genetic analysis (22).

Some lichen may survive in the water-deficient environment for a long time and may resume physiological exercise under the appropriate condition, known as poikilohydric lichen (23-25). Lichen has a gene of drought resistance and its function can be understood by transferring the gene to another organism that can fight water-deficient issues anywhere in the globe (26-28). The different research showed that the antioxidant capacity of lichens in drought resistance was found to be dominant (29, 30). In research, the exposure of heat stress to three lichens with the capacity to resist drought sedates the redox status of reduced glutathione and oxidized glutathione during drying and rehydration (31). For instance, lichen in particular *Endocarpon pusillum* discovered that the up-regulation of the antioxidant enzyme, glutathione and thioredoxin gene was linked to the antioxidant capacity under 20 percent of PEG-induced dehydration stress (30). The *Endocarpon pusillum* mycobiont region was used to characterize single Trx protein that has the activity in transgenic yeasts through heterologous expression as disulfide reductase and chaperone activities. Therefore, mycobiont is more resistant than phycobiont to drought (32).

Lichen metabolites

Lichens generate a wide range of secondary metabolites, most of which are distinctive. On the exterior surfaces of the hyphae, these chemically varied lichen substances accumulate.

1.1 Bioactive metabolites from mycobionts

Ingolfsdottir (2002) has assessed the medicinal potential of the prevalent lichen metabolites, Usnic acid (33). Since Usnic acid effectively stimulates the metabolism of cellular energy, it has been integrated into products for weight loss. The compound Methyl-β-orcinol carboxylate obtained from lichen and patented for use with methicillin-resistant *Staphylococcus aureus* and possesses potential with pathogenic human fungi resistant to polyene and azole antibiotics (34). Lichens are wealthy in pigments that may vary with the quantity of irradiance during the season (4, 35). The pigments can screen ultraviolet B for melanins and parietin (35); Collema cyanobacterial lichen patent that provides 80% UVB irradiation protection (36). Some lichens such as *Heterodermia obscurata* and *Nephroma laevigatum* can be used in dyes due to the presence of anthraquinones and in the paper industry as catalysts in the manufacturing of wood pulp (37, 38).

2.2 Metabolites from photobionts

Cyanobacteria from marine and freshwater generate a wide variety of peptides and a rich source of blended peptide polyketides (39). Microcystins are the most frequently isolated bioactive compounds produced by lichen-associated *Nostoc* sp. strain IO-102I (40). Another compound carotenoids are commercially significant natural pigments commonly found in algal lichen symbiont and free-living green algae *Trentepohlia* (13). Lichen-originated green algae and cyanobacteria are likely to be a source of useful properties as therapeutics. The current understanding of photobiont's diversity and phylogeny reveals significant knowledge gaps in this field (41).

Nutritional aspects of lichen

Lichens are readily available in boreal forests and are high in non-structural carbohydrates and low in fiber that can be easily digested and provide enough energy and are thus eaten by small mammals in the wild at a very high rate. Part of the lichen status is eaten by reindeer, caribou, and deer in winter. Libyan sheep graze in the desert at Aspiliciaesculenta, some mollusks and insects occasionally eat lichens (42).

Most lichen contains nutritional components such as *Cladonia stellaris* contains 2.0% as water-soluble carbohydrates, 3.1% as crude protein (43), and 78.4% as hemicellulose but only 1.7% as cellulose. *Bryoria fremontii* is North America's medicinal and regularly used edible lichen-a source of starvation for many groups (44). Lichens contain polysaccharides and have been found to generate three key types of structures: α-glucans, β-glucans, and galactomannans (45, 46). The β-glucan and galactomannan-type lichen polysaccharides has been suggested to be of chemotaxonomic consequence. The mycobiont was found to produce the polysaccharides alike to those of the parent lichen whereas the phycobiont produced different polysaccharides (47).

Nitrogen may be restrictive for lichen growth and distribution, we lack knowledge of available N sources and N acquisition levels for lichens in their natural environment. In addition, the issue of how different lichens vary in their ability to absorb different N compounds has been dealt with poorly (48, 49). The amount of carotenoids found in a range from 23.25 to 123.5 g/g of dry weight found in lichen, along with chlorophylls and phycobilins known to serve as light-energy receptors and prevent degradation of chlorophyll by molecular oxygen (50).

Lichen products can protect lichens from nutrient deficiencies such as dibenzofuran Usnic acid, a extensive secondary cortical metabolite produced by lichen-forming fungi that promotes intracellular absorption of Cu^{2+} in epiphytic lichens. In this respect, lichen generates divaric acid depside and usnic acid, indicating that this depside facilitates the absorption of Cu^{2+} to survive in their low nutrient habitats (51).

Ethnopharmacological aspects of Lichen

Traditional knowledge (TK) relates to local and indigenous groups around the world's knowledge, procedures, and technologies. TK inherited by indigenous communities, transmitted through orally from generation to generation. TK has evolved from knowledge acquired over the decades and is primarily practical in areas such as health, agriculture, fisheries, horticulture, and forestry (52). Plants are prominent sources of medicine, well described in traditional systems of medicines like Indian Ayurveda, Traditional Chinese Medicine (TCM), Western Medical Herbalism, and Tibetan medicine (53). Traditional Chinese Medicine includes 11,146 species of medicinal plants (54). Around 10,000 plant species used for medicinal purposes and about 1200 to 1500 have been officially incorporated into ayurvedic pharmacopeia in the Indian subcontinent (55).

Several works of literature have recognized the ethnical uses of plants from different regions of the world, but ethnic uses of lichens are not well documented. Most ethnobotanists have ignored cryptogams, both historically and currently. However, in some temperate countries of Asia, Africa, Europe, and USA lichens have been extensively studied. In Asian countries, ethnic studied of lichens are well documented from India, China, Nepal, and Tibet (56-60).

Crawford (2019) reported 60 genera of lichens used as traditional medicine. The most common genera of lichens used as medicine are *Cetraria islandica, C. nivafis* (Parmeliaceae), *Cladonia coccifera*, *C. pyxidata* (Cladoniaceae), *Usnea plicata,* (Usneaceae), *Peltigera canina, P. Venosa, P. horizontalis*, *P. polydactyla* (Peltigeraceae), *Lobaria pulmonaria* (Stictaceae), *Xanthoria parietina* and *Evernia prunastri* (Usneaceae) ~~(57)~~. In traditional medicine, lichens are usually used for treating wounds, skin disorders, respiratory, gynecological and obstetric concerns (60-62). Most of the lichens are non-poisonous, but some examples of poisonous lichens exist like *Bryoria fremontii, B. tortuosa, Cetraria pinastri, and Letharia vulpina* are well known poisonous lichens due to the presence of some secondary metabolites present in them like vulpinic acid or pinastrinic acid (59).

Lichens are consumed as traditional foods, medicines and in holy sacrificial fires known as 'HAVAN' or 'HOMA,' since millennia and play crucial roles in ecosystem function as well as human welfare. During the middle-ages lichens prominently used by medicinal practitioners (59). *Evernia furfuracea* has been used as a drug in an Egyptian vase belongs to the 18th Dynasty (1700-1600 BC). In Europe, lichens were primarily used for food because of their easy availability and nutritive value (63). Shipal is the first record of the use of lichen as medicine in Atharveda (1500 B.C.) (57). Charrila a crude drug isolated from *Parmelia* is broadly sold in Indian markets for curing several ailments (64). Gathered interesting ethnobotanical information between different areas of the Indian continent during field research (57, 65, 66).

In the context of India, there are several reports available on lichens used by various ethnic groups. Saklani and Upreti (1992) reported that folk of Sikkim uses *Peltigera canina* as a remedy for liver ailments, *Heterodermia diademata* (Physciaceae) used for cuts and injuries, *Parmelia cirrhata* (Parmeliaceae) used as a vegetable, *Peltigera polydactyla* (Peltigeraceae) used for stopping the bleeding, *Stereocaulon himalayense* (Stereocaulaceae) used for urinary trouble and blisters of the tongue (61). Pathak et al. (2016) reported *Hypotrachyna cirrhata* and *Flavoparmelia caperata*are used against wound infections, burn and bite, by the folks of Sikkim and Tamil Nadu, India (67).

Shah (2014, 1998) recorded the exportation and use of 3 species of lichen *Parmotrema nilgherrense, Everniastrum nepalense* and *Everniastrum cirrhatum* for indigenous pharmaceutical applications (62, 68). Lai and Upreti (1995) recorded 3 lichens *Buellia cf subsoriroides* used as a replacement for ' henna ' in the Garhwal area (India), Parmeli asancti-angeli is used by Central India's Gond and Oraon tribes to treat white patches around the throat that cause ringworm-like skin disease (69). *Usnea longissima* used as stuffing for pillows and cushions by the Bhotia tribe and other Garhwal Himalayan residents. Lal (1988) noted that the Baiga tribe of Madhya Pradesh used *Usnea longissima* to treat a bone fracture (66). Upreti and Chatterjee (2007) evaluated the global distribution of ethnomedicinal data on over 50 lichen taxa (70). Upreti et al. (2005) mentioned 15 species of lichen used as food, medicine or aesthetics by different ethnic groups in India and Nepal in their daily lives (57). Upreti and Negi (1996) reported in Schaerer ethnobotanical use of *Thamnolia vermicularis* and discovered that this is primarily used by Bhotias tribes to kill worms in milk (71). The medicinal value of *Parmelia sulcata* as mentioned in the ancient Indian medicinal scheme was defined by Kaushal and Upreti (2001) (72). Rai et al. (2014) reported the use of *Heterodermia diademata* on wounds as infection and water protection (73). Vinayaka and Krishnamurthy (2012) recorded ethnobotanical uses of 6 species of lichen from separate tribal communities in southern India, 6 species of *Parmotrema reticulatum, P. tinctorum, Ramalina pacifica* used for food, *Heterdermia diademata* and *P. cristiferum* used for medicinal purposes, and *Usnea galbinifera* used for pillow and decorative purposes (74). Kala (2002) revealed that the Bhotiya tribal community of high altitude Garhwal Himalaya, Uttaranchal, India produced natural dye from lichens (75).

Devkota et al. (2017) recorded 7 species of lichen used by nine distinct Nepalese populations, including *Everniastrum cirrhatum*, *Parmotrema cetratum* and *E. nepalense* used for food, *Heterodermia diademata* and *Ramalina* species used for therapeutic purposes, *Usnea longissima* as ritual, esthetic and bedding products, and *Thamnolia vermicularis* as spiritual and esthetic (59). Limbu and Rai (2013) reported that the Limbu community of eastern Nepal used *Heterodermia diademata* along with *Eupatorium odoratum* for the dealing of cuts and wounds (76). Kunwar et al. (2010) reported an extract of lichens and decoction was applied for the treatment of moles in Nepal (58).

Ahmadjian and Nilsson (1963) reported that *Cetraria islandica* is widely marketed in apothecary shops in Sweden and is claimed to be useful in treating lung disease, diabetes, and catarrh (77). Londono-Castaneda et al. (2017) (78) recorded 3 lichens species were used by Pankararu indigenous community in Brazil as medicine, *Parmelinella salacinifera*, *Heterodermia galactophylla,* and *Parmotrema wrightii* are used to treat problem related with digestive system such as vomiting and diarrhoea. An aqueous extract of these three species used for the therapy of epilepsy and cultural diseases through the smoker.

Wang et al. (2001) reported ethnic peoples of Yunnan Province China use 5 species of lichens as foods source, *L. kurokawae, Lobaria isidiophora, Ramalina conduplicans, L. yoshimurae, and R. sinensis*, and 5 others species as medicinal teas, *Lethariella cashmeriana, L. semanderi, L. sinensis, Thamnolia vermicularis, and T. subulifor* (56). Song and Gang (2013) reported numerous lichen species used by indigenous communities of China. *Cladonia amaurocraea* used for headaches and dizziness. *Cladonia cervicornis* used for scalds, cuts, and coughing up blood. *Cladonia fenestralis* used as a medicinal tea. *Cladonia fruticulosa* extract used to treat bacterial infections on the skin. *Rhizoplaca chrysoleuca* used for tuberculosis, intestinal obstruction, burns and scalds, skin infections, and pain relief. *Bryoria asiatica* used for dizziness, kidney deficiency, heart palpitation, difficulty urinating. *Usnea ceratina* used for coughs, headache, infection, pulmonary tuberculosis, inflamed lymph channels. *Usnea pectinata* used for stopping bleeding, releasing pain, and bloody feces. *Cetraria islandica* decoction drunk to improve digestion and strengthen the stomach. *Parmotrema tinctorum* used for blurred vision, bleeding from the uterus, bleeding from external injuries, sores, and swelling. *Punctelia borreri* used for blurred vision, bleeding from the uterus and external injuries (79). Afolayan et al. (2002) reported that *Usnea barbata* used by African folks for the treatment of mammary infections in cattle (80).

In European countries, several reports were documented on the ethnobotanical uses of lichens by the indigenous peoples for food, fodder, medicine, and aesthetics. Important lichen species used by indigenous peoples of Europian countries are *Cladonia pyxidata, Cladonia cornuta, Cladonia coccifera, Cetraria islandica, Evernia prunastri, Hypogymnia physodes, Lobaria pulmonaria, Peltigera canina, Peltigera aphthosa, Usnea plicata, Usnea hirta, Usnea florida, Usnea barbata*, and *Xanthoria parietina* (60,63).

Lichen's pharmaceutical properties

Lichens originated in most adverse habitats of earth and many medical applications can be helpful to researchers. Secondary metabolites are usually referred to as lichen acids generated by mycobiont and spread in the form of amorphous or crystals on the surface of lichens. Lichen acids contain a variety of biological potential including antioxidant, anticancer (81), enzyme inhibitory (82), antiviral (83), antifungal (84), antidiabetic (85), allelopathy (86), antipyretic, crop growth inhibitory, cytotoxic, anti-hepatotoxic (87) and antiproliferative properties. Recently revealed the pharmacological and therapeutic potential of lichens are shown in Table 1 and Fig. 1.

Antifungal property

Padhi et al. (2019) reported a new secondary metabolite aspergyllone, isolated from an endolichenic fungus *Aspergillus niger* Tiegh discovered in the lichen *Parmotrema ravum* Serus, collected in India. The compound has powerful anti-fungal activity against *Candida parapsilosis* and also tests against pathogens from plants, humans, and food (88). The antimicrobial activity is frequently discovered in lichens, and this research shows that the Himalayan lichen *Bulbothrix setschwanensis* has both antibacterials against *S. aureous* and anti-fungal (*Cryptococcus neoformans*) capacity (89). The ethanol extract of four lichens *Parmotrema-reticulatum, Everniastrum cf. vexans, Peltigera laciniate*

Table 1. Lichen's pharmacological potential and its active ingredients have biological potential against different organisms/cell lines.

S.N.	Lichens	Biological potential	Active ingredients	Name of the organism/cell lines	References
1	*Parmotrema ravum*	Antifungal	Aspergyllone	*Candida parapsilosis*	88
2	*Evernia mesomorpha*	Antibacterial	Divaricatic acid	*Staphylococcus aureus* and *Enterococcus faecium*	84
3	*Evernia mesomorpha*	Antifungal	Vancomycin	*Candida albicans*	84
4	*Everniastrum cf. vexans, Parmotrema blanquetianun, Parmotrema reticulatum, Peltigera laciniata*	Antibacterial	Ethanolic extract	*Staphylococcus aureus, Listeria monocytogenes, Proteus vulgaris, Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia*	90
5	*Everniastrum cf. vexans, Parmotrema blanquetianun, Parmotrema reticulatum, Peltigera laciniata*	Antifungal	Ethanolic extract	*Candida albicans, C. glabrata, C. krusey, C. parapsilopsis, C. tropicalis,* and *Cryptococcus neoformans*	90
6	*Usnea longissima*	Antibacterial	Silver nanoparticles	*Staphylococcus aureus, Streptococcus mutans, Streptococcus pyrogenes, Streptococcusviridans, Corynebacterium xerosis, Corynebacterium diphtheriae, Klebsiella pneuomoniae*	93
7	Niebla sp.	Anticancer	Tumidulin	Cancer stem cells (CSC221), DLD1, and HT29 cells	81
8	*Parmotrema hababianum*	Antihyperglycemic	Ethanol extract	Streptozotocin-induced diabetic rat	85
9	*Usnea hirta* (L.), *Parmotrema robustum, Parmotrema tinctorum, Pleurosticta acetabulum, Flavoparmelia baltimorensis, Usnea florida*	Allelopathy	Acetone extract	*Physcomitrella patens* (Moss)	86
10	*Rangiferinus against*	Anti-hepatotoxic	Ethanol extract	Male Wistar rats	87
11	*Bulbothrixsetschwanensis*	Antifungal	Acetone extract	*Cryptococcus neoformans*	89
12	*Usnea longissima*	Antifungal	Usnic acid derivatives, Usone, Isousone	*Trichophyton rubrum* spp.	92

Table 1. Lichen's pharmacological potential and its active ingredients have biological potential against different organisms/cell lines.

S.N.	Lichens	Biological potential	Active ingredients	Name of the organism/cell lines	References
13	*Parmelia reticulata*	Allelopathic	Hexane, Ethyl Acetate and Methanol extracts	*Phalaris minor* retz (weed)	101
14	*Cladonia humilis*	Antidiabetic	Methanol Extract	Hyperglycemic mice	116
15	*Ramalina sinensis, Heterodermialeucomelos, Herpothallon* sp., *Parmatorema reticulatum*	α-amylase inhibitory activity	Hexane, Ethyl acetate, Methanol and Ethanol extracts	*Aspirgillus oryzae*	117
16	*Evernia prunastri* (L.), *Ramalina fastigiate, Cladonia rangiformis*	Antibacterial	Various extracts	*Escherichia coli*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Proteus mirabilis* and *Pseudomonas aeruginosa*	121
17	*Umbilicaria tornata*	Antioxidant and antitumor	Crude extract	HeLa, HepG2, A375, MCF-7, SGC7901 and Caco2 cancer cells	122
18	*Pseudevernia furfuracea, Platismatia glauca*	Proapoptotic, Antimigratory	Various extracts	Colorectal cancer (HCT-116 and SW-480) cell	123
19	*Usnea sps.*, *Parmotrema sps.*	Antifungal	Acetone, Ethanol Extract	*Aspergillus niger, Aspergillus flavus*, *Candida sps., Trycophyton sps.*	124
20	*Usnea longissima*	Anti-urease and anti-elastase	Ethanol extract	--	125
21	*Dirinariaconsimilis*	Anti-inflammatory	Acetone extract	Male albino rats	126
22	*Pseudevernia furfuracea* (L.)	Antioxidant	acetone extract	--	**127**
23	*Leptogium trichophorum*	Anti-inflammatory	Actinofuranones	RAW 264.7 macrophage cells.	128
24	*Parmotremaaustrosinense*	UV Protectant	(3R)-5-Hydroxymellein	HaCaT cells	129
25	*Evernia prunastri*, *Ramalina fastigiata*	Antifungal and anti-biofilm	Acetone extract	Candida albicans	130
26	*Everniastrum vexans*	Anti-migratory	Atranorin	Human lung cancer cells	131
27	*Vulpicida pinastri*	Photo protective	Vulpinic acid, Pinastric acid and Usnic acid	Keratinocyte cell lines	132
28	*Xanthoria parietina*	Antiproliferative	Parietin	Human breast cancer cells	133
29	*Stereocaulonevolutum*	Antiviral activity	Atranorin	Hepatitis C virus	134
30	*Parmotrema* tinctorum	Allelopathic	Lecanoric acid	*Lactuca sativa* cv. *Grand Rapids* and *Allium cepa* cv. *Baia Periforme*	135

and *Parmotrema blanquetianun* has antifungal activity against six fungi viz *Listeria monocytogenes*, *Staphylococcus aureus, Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli,* and *Klebsiella pneumonia* (90). The active lichen compounds xanthone derivatives have antifungal activity against *T. rubrum*, *E. floccosum* and *M. canis* clinical strains (91). Yu et al. (2016) showed that the usnic acid derivatives usone and isousone have a dose-dependent fungal inhibition activity against *Trichophyton rubrum* spp (92).

Anti-bacterial property

Plaza et al. (2018) reported four ethanolic extracts of lichens that have antibacterial activity against *Pseudomonas aeruginosa, Staphylococcus aureus, Proteus vulgaris, Escherichia coli, Klebsiella pneumonia* and *Listeria monocytogenes* (90). The lichen active compounds xanthones derivatives have antibacterial activity against multi-drug resistant pathogenic microbes such as *Enterococcus faecalis* and *Staphylococcus aureus* (91). Recent research has shown that the synthesis of eco-friendly

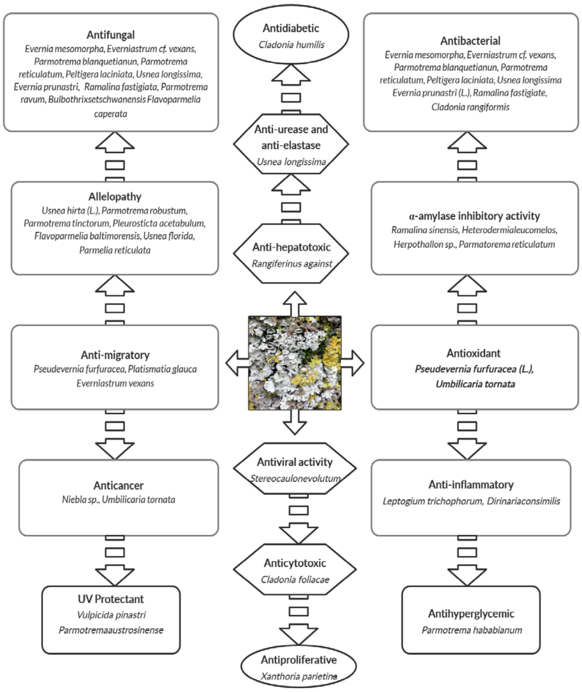

Figure 1. Biological and medicinal properties of lichens.

biogenic manufacturing of silver nanoparticles from lichen *Usnea longissimi*, synthetic nanoparticles, is cost-effective and can avoid pollution from the atmosphere. The size of synthetic nanoparticles between the 9.40-11.23 nm range by involving the function of usnic acids, amines, phenols, aldehydes and ketones in reducing silver into a silver nanoparticle. The active nanoparticles have gram-positive antimicrobial activity (*Streptococcus pyrogenes, Streptococcus mutans, Corynebacterium diphtheriae* and *Corynebacterium xerosis*) and gram-negative antimicrobial activity against strains (*Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneuomoniae*) (93).

Anti-drug resistance bacteria

Bate et al., (2020) investigated the antibacterial activity of six lichens methanol extracts against nine multidrug-resistant clinical bacteria isolates, out of which *Usnea articulata* and *Usnea florida* possesses the highest activity with minimum inhibitory concentrations of 4–10 mg/mL (94). The secondary divaricate metabolite separated and purified from *Evernia mesomorpha* in the latest research and recognized by LC-MS, 1H-, 13C- and DEPT-NMR. The divaricate compound has antimicrobial ability against Methicillin-resistant *Staphylococcus aureus* (3A048; an MRSA) and can be used to treat drug-resistant bacteria or infection with MRSA (84). Tozatti et al., (2016) demonstrated that the synergistic effects of usnic acid isolated from *Usnea steineri* against four resistant bacterial strains of *Staphylococcus epidermidis* (MIC 3.12 μg/mL), *Staphylococcus aureus* and *Staphylococcus haemolyticus* (MIC 12.5 μg/mL). However, usnic acid did not show any synergistic antimicrobial effects in combination with penicillin and tetracycline (95).

Tyrosinase-Inhibitory action

Tyrosinase is a key enzyme in mammalian cells to avoid excessive melanin pigment production. Melanin has the property of absorbing ultraviolet radiation to safeguard the skin and also removing reactive oxygen species (ROS) in the skin of mammals. It is therefore used in the cosmetics and medicine sectors (82). The inhibition of surplus tyrosinase enzyme manufacturing is therefore required (96). Some lichens have the property to prevent the activity of tyrosinase. Behera et al. (2006) proved that in lichens such as *Graphis assamensis, Graphina multistriata, Graphis Phaeographopsisindica,* and *Graphis nakanishiana*, tyrosinase inhibitory activity occurred considerably (97). Some edible and medicinal lichens disclosed in tyrosinase inhibition property (*Usnea longissima* and *Umbilicaria esculenta*) (98).

Allelopathic

Allelopathy is a natural phenomenon in an organism that generates secondary metabolites known as allelochemicals that can have beneficial or negative impacts on another organism (99, 100). The lichen extract shows negative allelopathic effects on bryophytes (moss Physcomitrella) by inhibiting protonemic and gametophore development owing to the existence of secondary usnic acid metabolites (86). Goel et al. (2014) have shown that Himalayan lichen's allelopathic potential, *Parmelia reticulate*, can inhibit weed development, especially *Phalaris minor*, which grows with wheat and barley plants (101). Another research showed that the impacts on the setting of saxicolous lichen secondary metabolites usnic acid, parietin and norstic acid as biocides to prevent ecotoxicity against microcolonial bacteria *Coniosporium perforans, Coniosporium apollinis*, green algae *Scenedesmus ecornis* and coccoid cyanobacteria *Chroocococcus minutus* (102).

Photoprotective

Exposure of Ultra-violet radiation (UV-A and UV-B) contributes to skin cancer, suppression of the immune system, and premature aging, which is now a worldwide issue. Sunscreens are available on the market as one of the options to protect against radiation, various types of sunscreen such as skincare, eye care, lip care and hair care (103, 104). Some higher plants, mosses, and most lichens can tolerate desiccation, the lichen's photobiont component prevents fluorescence emission by reducing load segregation in Photosystem II (PSII) reaction centers. For instance, some lichens are capable of stopping UV radiation, particularly *Parmelia sulcate*, *Peltigera neckeri* and *Lobaria pulmonaria* (105).

Lichen's therapeutic potential

Anti-hepatotoxic

Liver cirrhosis is the main human health problem caused by excessive alcohol consumption (106). Alcohol intakes lead to a rise in NADH/NADP in hepatocytes that interrupt β-oxidation of fatty acids in mitochondria and also boost lipid transport from the tiny intestine to the liver, resulting in fat deposition in the body that does not function correctly (107). For the therapy of fever, liver diseases, arthritis, seizures, tuberculosis and constipation, reindeer lichen (*Cladonia rangiferina*) has already been reported. The reindeer lichen extract can be used to decrease liver damage and tissue toxicity associated with alcohol (87).

Anticancer potentialSecondary lichen metabolites are now of huge significance in the pharmaceutical industry; the therapy of cervical cancer after pre-treatment with usnic acid and zinc sulfate is feasible (108). Some types of lichen from the Himalayas and Nepal, such as *Alectoria ochroleuca* and *Nephroma expallidum*, were chemopreventive for cancer (109). In contrast to *Salmonella typhimurium*, the extract of *Cetraria aculeata* was antigenotoxic (110). Some lichens, *Collema flaccidum* in particular, belong to the Collemataceae family, which includes active ingredients Bianthraquinone, colleflaccinosides and glycosides acquire antitumor activity (111). In the past research, *Usnea barbata* (usnic acid) lichen's acetone extract has powerful anti-cancer activity against human melanoma and human colon carcinoma cell lines at 12.72 and 15.66 µg/mL IC50 values (112). The active ingredient usnic acid and it's derivative (usenamines) separated from the lichen *Usnea longissimi* can cause apoptosis of HepG2 cells in another research (92).

Another study revealed that the ethyl acetate and acetone extract of lichen *Pseudevernia furfuracea* and *Platismatia glauca* possesses highest cytotoxicity against HCT-116 (IC50=21.2±1.3) µg/mL and SW-480 (IC50=51.3±0.8 µg/mL) cell lines respectively (113). Hong et al. (2018) showed that the lichen *Stereocaulon alpnum* gathered from the Antarctic region exercising anticancer activity against human cervix adenocarcinoma (HeLa cells) and human colon carcinoma (HCT116 cells) cell lines owing to the existence of lobaric acid and secondary metabolites of lobarstin (114). These secondary metabolites improve the arrest of the cell cycle causing important dose- and time-dependent reduction in the development of cancer cells.

Antidiabetic potential

Diabetes is well recognized and continues to spread disease worldwide, creating health-related complications, and there are no drugs on the market to fight diabetes. Diabetes mellitus is the dominant diabetes type (90%) characterized by chronic enzymatic hyperglycemia (115). Some crops are recorded, while others are being investigated to overcome the illnesses. Lichens are the untouchable field of diabetes treatment. Ganesan et al. (2016) reported having anti-diabetic agents in the lichen *Parmotremaha babianum* that significantly reduce blood glucose levels (85). Zhang et al. (2012) proved that the *Cladonia humilis* extract orally fed to the alloxan-induced hyperglycemic mice and found significant reduction in blood glucose levels.

In spite of this, *in vitro* treatment improves the amount of insulin secretion and glycogen synthesis (116).

Ramalina sinensis contains natural compounds against multiple enzymes for inhibitory operations. The breakdown of starch by α-amylase enzyme leads to the hyperglycemia cause increase in the blood glucose level, and this lichen has the potential to inhibit the activity of α-amylase enzyme results decrease in blood glucose level and prevent it from noninsulin-dependent diabetes-type-2 (117). Starch breakdown by α-amylase enzyme outcomes in increased blood glucose levels caused by hyperglycemia and this lichen can inhibit α-amylase enzyme activity resulting in decreased blood glucose levels and prevent non-insulin-dependent type-2 diabetes.

Immunomodulatory effect

Change in the body's immune system with the help of biological agents that activate or suppress immunity. *Cetraria islandica* has been used as traditional medicine during inflammatory situations. Two compounds protolichesterinic and fumarprotocetraric acids purified from lichen and tested against maturation of the dendritic cells assessed by secretion of IL-10 and IL-12p40. The upregulating secretion leads to the anti-inflammatory activity, also observed the less arthritis with aqueous lichen extract (118).

Antiviral

The extract *Teloschistes chrysophthalmus* used by chromatographic techniques to purify secondary metabolites usnic acid and parietin. Usnic acid and parietin purified products used for antiviral activity and virucidal impact (against Junin and Tacaribe arenaviruses) respectively. The experiment was conducted directly on the nuclei of the virus (virucidal assay) to verify the activity against the characteristics that inactivate the virus. The arenavirus JUNV (Junin virus) has to cause hemorrhagic Argentine fever in humans (119) and has been used as a model system as a prospective bioterrorism agent (120). The reduction in JUNV production from infected Vero cells possible by the use of usnic acid in a dose (9.9 μm and 20.6 μm respectively) dependent manner. It is feasible to reduce the output of JUNV from infected Vero cells by using usnic acid in a dose-dependent way (9.9 μm and 20.6 μm respectively) (83).

Conclusion and future perspective

As a reservoir of biologically active compounds, lichen metabolites have shown promising outcomes. Even from a restricted amount of research, it can be concluded that lichen-derived bioactive compounds are highly promising for biopharmaceutical applications as reported for antidiabetic, anti-urease and anti-elastase, anti-hepatotoxic, anti-viral, anti-cytotoxic and antiproliferative activity, and need to be investigated in the collection of scarce and scattered biological activity information and ethnomedicine uses.

Lichens are an important part of nature, and are beneficial to humans after a thorough preparation a few organisms were used as food. Globally, lichens play a key role in nutrient preservation and distribution, such as carbon, nitrogen, trace elements, soil composition, and rock weathering. Lichens possess variety of chemical compounds and can easily digestible varied from species to genera. Some lichens species such as *Cetraria nivalis, Cetraria islandica,* and *Cladonia arbuscula* posses' high *in vitro* digestibility (69-77% dry matter).

It is apparent from careful examination of lichens bioprospecting studies that selected lichen species based on prior knowledge systems that they had better prospecting for drugs. The existence of low lichen biomass may be the primary reason for research to discontinue further screening even though some leads have been obtained about drug prospecting. In additions, cultured photobiont and mycobiont may enhance after manipulating the culture media to obtain greater biomass production for medicinally important secondary metabolites.

With a multitude of biological activities, lichens are an authoritative source of unique secondary metabolites. So many applications for new lichen metabolites have been revealed and will remain under investigation in the future. Recent inventions involving lichen metabolites include the latest antibiotics against bacteria and fungi, antidiabetics, farming pesticides, particular enzyme oxidation enzymes, and UVB protection compounds. So far, no patent has been approved for green algae from lichens. A new lichenology age will have to begin with the lichen fungus and photobiont genome sequencing. Despite their wide spectrum of biological activities, mycologists and agro-chemists have long ignored lichens, primarily because of their slow development in nature and their artificial cultivation problems. As a result, the phase of lichen metabolites' large-scale industrial manufacturing has not yet been reached. In order to develop, optimize and scale up promising lichen-based technologies of elevated industrial and domestic significance, more research and development is needed.

There is still a potential in lichens for various pharmacological activities such as antidiabetic, anti-inflammatory, antiviral, immunomodulatory, analgesic, anticancer, jaundice, renal issues, digestive disorders and mental illnesses. It could be a good opportunity for researchers to apply the lichen and its extracts in animal models to reveal the toxicity profile as well as discuss the abortion mechanism for different disorders. Lichens possess great potential that needs to be completely established explored and used for human well-being and for the good of our community.

Funding's: This work was supported by the Yeungnam University Research Fund (2020).

Conflicts of interest: There is no conflict of interest among the authors.

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