Pharmaceutical Biology

ISSN: 1388-0209 (Print) 1744-5116 (Online) Journal homepage: informahealthcare.com/journals/iphb20

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To cite this article: Vasudeo P. Zambare & Lew P. Christopher (2012) Biopharmaceutical potential of lichens, Pharmaceutical Biology, 50:6, 778-798, DOI: 10.3109/13880209.2011.633089

To link to this article: https://doi.org/10.3109/13880209.2011.633089

Pharmaceutical Biology, 2012; 50(6): 778–798

ISSN 1388-0209 print/ISSN 1744-5116 online
DOI: 10.3109/13880209.2011.633089

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REVIEW ARTICLE

Biopharmaceutical potential of lichens

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Abstract

Context: Lichens are composite organisms consisting of a symbiotic association of a fungus (the mycobiont) with a photosynthetic partner (the phytobiont), usually either a green alga or cyanobacterium. The morphology, physiology and biochemistry of lichens are very different from those of the isolated fungus and alga in culture. Lichens occur in some of the most extreme environments on the Earth and may be useful to scientists in many commercial applications.

Objective: Over the past 2 decades, there has been a renewed and growing interest in lichens as a source of novel, pharmacologically active biomolecules. This review summarizes the past and current research and development trends in the characterization and use of lichens and their bioactive compounds in traditional medicine and other biopharmaceutical applications of commercial interest.

Methods: The present review contains 10 illustrations and 188 references compiled from major databases including Science Direct, Chemical Abstracts, PubMed and Directory of Open Access Journals.

Results: Lichen morphology, symbiosis, diversity and bioactivities including enzyme inhibitory, antimicrobial, antifungal, antiviral, anticancer, anti-insecticidal and antioxidant actions were reviewed and summarized. Recent progress in lichens and lichen-forming fungi was discussed with emphasis on their potential to accelerate commercialization of lichen-based products.

Conclusions: Lichens are an untapped source of biological activities of industrial importance and their potential is yet to be fully explored and utilized. Lichen-derived bioactive compounds hold great promise for biopharmaceutical applications as antimicrobial, antioxidant and cytotoxic agents and in the development of new formulations or technologies for the benefit of human life.

Keywords: Lichens, biopharmaceutical potential, morphology, symbiosis, diversity, bioactivities, lichen-forming fungi

Introduction

Lichens are symbiotic plant-like organisms, usually composed of a fungal partner, mycobiont, and one or more photosynthetic partners, phytobiont, most often either a green alga or cyanobacterium (Sre-Indrasutdhi, 2005). Although the dual nature of these lichens is now widely recognized and lichen products have been used in traditional medicine for centuries, they are less studied and understood than the single microorganisms (Nash, 1996). Lichen species comprise more than 20% of the global fungal biodiversity and as unique symbiotic organisms that occur in some of the most extreme environments on Earth—arctic tundra, hot deserts, rocky coasts, toxic slag heaps, etc. The substances that lichens produce to survive in these extreme environments are also unique but little understood. As our understanding of the bioregulatory role of different endogenous biomolecules and their mechanism of action develops, more attention is drawn to lichens as a promising source for drug discovery (Karthikaidevi et al., 2009). Although bioactive phenolic compounds with new chemical structures of pharmaceutical interest have been recently reported (Boustie & Grube, 2005), most research effort has been focused on the discovery of new lichen species and lichen

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(Received 19 August 2011; revised 28 September 2011; accepted 14 October 2011)

taxonomy, and despite recent progress, only usnic acid has been used for pharmaceutical and cosmetic product development to date (Cansaran et al., 2006). This review is intended to summarize the past and current research and development trends in the characterization and use of lichens and their bioactive compounds in traditional medicine and other biopharmaceutical applications of commercial interest.

Lichen morphology

The morphology of the lichenized thallus is strongly influenced by the phytobiont and its direct contact with the mycobiont (Figure 1). Lichen thalli have been grouped as: (1) crustose (phytobiont in a distinct layer below an upper mycrobiont cortical layer with no lower cortex); (2) leprose (groups of phycobiont surrounded by mycobiont); (3) foliose (leafy; phycobiont in a layer below an upper cortex with a discrete cortex below, separate from the substratum on which it grows; (4) filamentose (filamentous; phycobiont surrounded by a sheath of mycobiont); and (5) fruticose (shrubby; erect, vertical or trailing; radial in structure, often attached at the base, with the phycobiont in a layer inside the outer cortex).

As the potential relationships of mycobionts and phytobionts may in fact be quite complex, a rigorous classification of the types of relationships between them was developed by Rambold and Triebel (1992). Since lichens cannot be regarded as individuals from a genetic and evolutionary perspective, this has major implications in many areas of lichen investigation such as developmental and reproductive studies (Nash, 1996). In culture, the unlichenized mycobionts remain relatively amorphous and initiate thallus development when they first come in contact with their phytobiont (Ahmadjian, 1993). There is a variation in the degree to which the symbiosis is obligatory for the partners involved. The green alga *Trebouxia*, which occurs in approximately 20% of all lichens, has rarely been found as a free-living organism. In contrast, other phytobiont genera such as *Gleocapsa, Nostoc, Scytonema* and *Trentepohlia* commonly occur in both lichenized and free-living state (Lücking et al., 2009). In some cases, the free-living populations (*Nostoc* and *Scytonema*) and their lichenized counterparts (*Collema* and *Peltula*) occur in the same habitat such as desert soils. The ability of the same phytobiont species to occur in a free-living and lichenized state at the same time is not well described (Beck, 2002) because relatively few lichen algae have been identified as species, and generally, the systematics at the species level of many cyanobacteria and unicellular green algae are not well resolved. Nevertheless, it appears that most lichens are highly specific in their choice of phytobiont (Beck et al., 1998; Rambold et al., 1998). The mycobionts growth is normally fairly slow and they are unlikely to survive well in a free-living state due to competition with other fungi and/or nutrient consumption by other organisms (Nash, 1996). Multiple phytobiont species (e.g., Trebouxia) have also been isolated from different lichen thalli belonging to the same lichen species (Friedl, 1989; Ihda et al., 1993). Thus, most mycobionts are assumed to have an obligate relationship to lichenization, although the specificity of the mycobiont for a particular phytobiont may not be as great as one might assume.

Lichen symbiosis

The lichen symbiosis is a very successful one as lichens are found in almost all terrestrial habitats from the tropics to the polar-regions. As a result of the symbiosis, the lichen's phytobiont and mycobiont have expanded into many habitats where separately they would be rare or non-existent. For example, most free-living algae and cyanobacteria normally occur in aquatic or very moist terrestrial habitats, but as lichens they also occur abundantly in habitats that are frequently dry. Lichenization is one mechanism where mycobiont enhances the water uptake and reduce the light intensity to which the phytobiont is exposed (Ertl, 1951). Thus, there may well be benefits to lichenization from the perspective of the phytobiont. In lichens, fungi share the photosynthetically derived carbon source from algae and in return provide water and nutrients to algae.

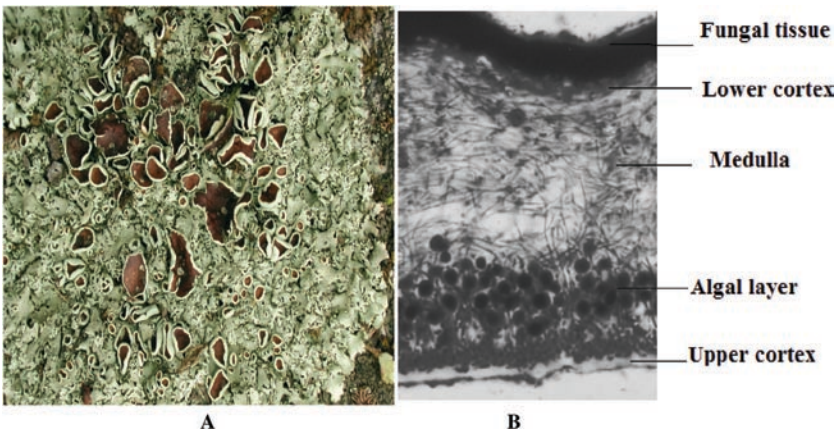

Figure 1. (A) Lichen thallus, (B) Vertical section of a foliose lichen thallus, showing (bottom to top) the upper cortex of compact fungal tissue (mycobiont), the algal layer (phycobiont), medulla of loosely interwoven hyphae, and the lower cortex of compacted dark brown fungal tissue (mycobiont).

Overall, it may be less important to evaluate lichenization from a strict cost/benefit perspective than to recognize it as a prominent example of a successful symbiosis. As a result of this symbiosis, lichens produce characteristic secondary metabolites and bioactive compounds, which seldom occur in other organisms. Additional studies will undoubtedly help elucidate further our understanding of the lichen symbiosis.

Lichen diversity

Among the terrestrial autotrophs of the world, lichens exhibit intriguing morphological variation in miniature. In color they exhibit a fantastic array of orange, yellow, red, green, gray, brown, and black (Wirth, 1995; Brodo et al., 2001). Lichens vary in size from less than 1 mm to long, pendulous forms that hang over 2 m from tree branches. Almost all lichens are perennials, although a few ephemerals (e.g. *Vezdaea*) are known. At the other extreme, some lichens are estimated to survive well over 1000 years and may be useful in dating rock surfaces (Beschel, 1961). Linear growth varies from imperceptible to many millimeters in a year.

Lichens occur commonly as epiphytes on trees and other plants, and in some ecosystems, epiphytic lichen biomass may exceed several hundred kg/ha (Coxson & Nadkarni, 1995). In addition, they frequently colonize bare soil, where they are an important component of cryptogamic soil crusts in arid and semi-arid landscapes (Evans & Johansen, 1999; Belnap & Lange, 2003). Furthermore, lichens occur almost ubiquitously on rocks with the most obvious ones occurring as epiliths, either growing over the surface or embedded within the upper few millimeters. A few lichens even occur endolithically within the upper few millimeters of the rock in Antarctica (Friedmann, 1982). In the tropics and subtropics, some rapidly growing lichens even colonize the surface of leaves as epiphylls (Lücking & Bernecker-Lücking, 2002). Although most lichens are terrestrial, a few occur in freshwater streams (e.g. *Peltigera hydrothyria*) and others—in the marine intertidal zone (e.g. *Lichina* spp. and the *Verrucaria* maura group). Lichens occur in most terrestrial ecosystems of the world, but their biomass contribution varies from insignificant to being a major component of the whole ecosystem (Kershaw, 1985). In many polar and subpolar ecosystems, lichens are the dominant autotrophs (Longton, 1988). Ladd (2009) studied a total of 161 taxa of lichens and related fungi from the Gulf Coastal Plain in south-central Arkansas. Recently, a new lichen species of *Caloplaca obamae* was discovered in the Channel Island National Park of Santa Rosa Island, California (Knudsen, 2009). It produced a thin thallus with orange granules (30–50 μm diameter) and discontinuous algal layer (50–100 μm thick). In comparison to the reported associated species *C. ludificans, C. obamae* did not produce ascospores and apothecia.

The formation of lichen associations represents one of the most successful lifestyles among fungi. Representing 20.6% of the 64,200 described fungi, the mycobionts belong to different subdivisions such as ascomycotina, basidiomycotina, deutromycotina, mastigomycotina, and myxomycotina. Out of the 13,250 lichen-forming fungal species described to date, nearly 13,000 are ascomycetes, approximately 50 are basidiomycetes and 200 are deutromycyces. Lichen-forming fungi represent 46.3% (Figure 2) of all described ascomycetes and are the focal point to understanding the ascomycete relationships (Hawksworth, 1988; DePriest, 2004). Very few lichen species belong to basidiomycotina, deutromycotina, mastigomycotina, myxomycotina but not a single species belongs to the zygomycotina subdivision. Furthermore, within the ascomycetes, all lichen fungi belong to any of the three classes: the Sordariomycetes, the Lecanoromycetes, or the Eurotiomycetes (Figure 3). Of these classes, the Lecanoromycetes is nearly exclusively lichenized and contains an overwhelming majority of all lichen-forming species. Before the advent of molecular studies, ascomycetes were classified on the basis of their reproductive structures. This system divided fungi into traditional classes such as apothecial Discomycetes, cleiostothecial Plectomycetes, and perithecial Pyrenomycetes, with asexual forms classified as anamorphic Deuteromycetes. Classification using molecular phylogenies has allowed researchers to modify these classes to monophyletic groups (Gargas & Taylor, 1995; Spatafora, 1995; Lumbsch, 2000) and subsequently a new phylogenetic system has been proposed by Eriksson and Winka (1997). Recently, a report co-authored by 103 researchers from various institutions worldwide on the discovery of 100 new species of lichenized fungi representing a wide taxonomic and geographic range was published in Phytotaxa (Lumbsch et al., 2011). The newly described species were: *Acarospora flavisparsa, A. janae, Aderkomyces thailandicus, Amandinea maritima, Ampliotrema cocosense, Anomomorpha lecanorina, A. tuberculata, Aspicilia mansourii, Bacidina sorediata, Badimia multiseptata, B. vezdana, Biatora epirotica, Buellia sulphurica, Bunodophoron pinnatum, Byssoloma spinulosum, Calopadia cinereopruinosa, C. editae,*

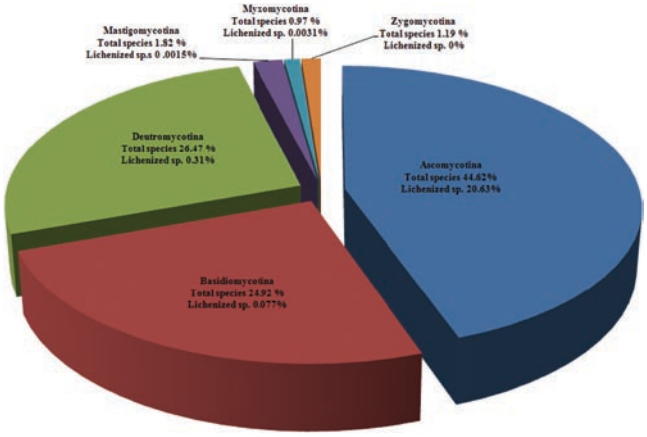

Figure 2. Distribution of lichen species in various subdivisions of fungi (Source: Hawksworth, 1988).

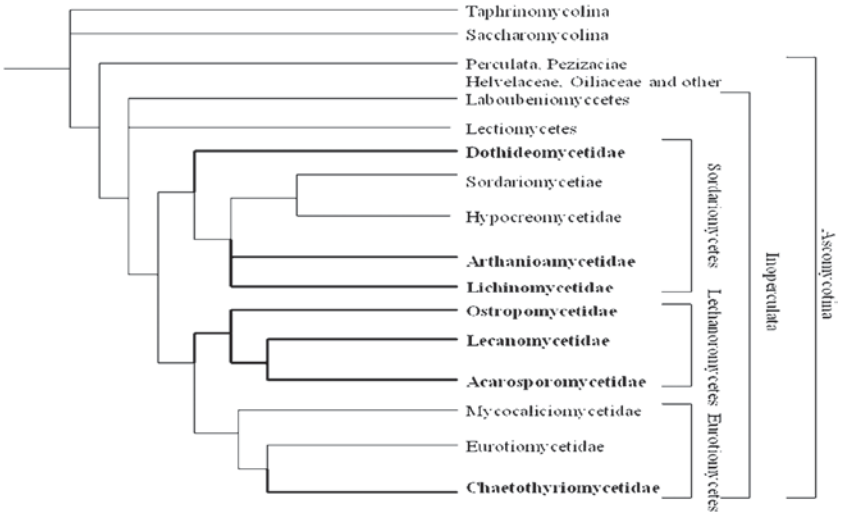

Figure 3. Phylogenetic relationship in phylum Ascomyceta (Source: Tehler & Wedin, 2008). Lichenized texa are marked with thick lines and with names in bold.

Caloplaca brownlieae, C. decipioides, C. digitaurea, C. magnussoniana, C. mereschkowskiana, C. yorkensis, Calvitimela uniseptata, Chapsa microspora, C. psoromica, C. rubropulveracea, C. thallotrema, Chiodecton pustuliferum, Cladonia mongkolsukii, Clypeopyrenis porinoides, Coccocarpia delicatula, Coenogonium flammeum, Cresponea ancistrosporelloides, Crocynia microphyllina, Dictyonema hernandezii, D. hirsutum, Diorygma microsporum, D. sticticum, Echinoplaca pernambucensis, E. schizidiifera, Eremithallus marusae, Everniastrum constictovexans, Fellhanera borbonica, Fibrillithecis sprucei, Fissurina astroisidiata, F. nigrolabiata, F. subcomparimuralis, Graphis caribica, G. cerradensis, G. itatiaiensis, G. marusa, Gyalideopsis chicaque, Gyrotrema papillatum, Harpidium gavilaniae, Hypogymnia amplexa, Hypotrachyna guatemalensis, H. indica, H. lueckingii, H. paracitrella, H. paraphyscioides, H. parasinuosa, Icmadophila eucalypti, Krogia microphylla, Lecanora mugambii, L. printzenii, L. xanthoplumosella, Lecidea lygommella, Lecidella greenii, Lempholemma corticola, Lepraria sekikaica, Lobariella sipmanii, Megalospora austropacifica, M. galapagoensis, Menegazzia endocrocea, Myriotrema endoflavescens, Ocellularia albobullata, O. vizcayensis, Ochrolechia insularis, Opegrapha viridipruinosa, Pannaria phyllidiata, Parmelia asiatica, Pertusaria conspersa, Phlyctis psoromica, Placopsis imshaugii, Platismatia wheeleri, Porina huainamdungensis, Ramalina hyrcana, R. stoffersii, Relicina colombiana, Rhizocarpon diploschistidina, Sticta venosa, Sagenidiopsis isidiata, Tapellaria albomarginata, Thelotrema fijiense, Tricharia nigriuncinata, Usnea galapagona, U. pallidocarpa, Verrucaria rhizicola, and *Xanthomendoza rosmarieae* (Lumbsch et al., 2011).

Lichen compounds and traditional biomedical uses

Many lichens are known to produce unique secondary metabolites and have considerable biological activities (Vartia, 1973; Richardson, 1988; Lawrey, 1989; Elix, 1996). Many lichens are edible; however, some lichens contain toxic substances. According to Asahina and Shibata (1971) and Dayan & Romagni (2001), the lichen compounds may be classified into the following groups: (1) aliphatic lichen substances (including acids, zeorin compounds, polyhydric alcohols); (2) aromatic lichen substances (including pulvic acid derivatives, depsides, depsidones, quinones, xanthone derivatives, diphenyleneoxide derivatives, nitrogen containing compounds, triterpenes, tetronic acids); and (3) carbohydrates (polysaccharides). To date, the chemistry of about a third of all lichen species has been studied and about 350 secondary metabolites have been identified. The chemical structures of approximately 200 of them have been established. Lichen's secondary metabolites are usually insoluble in water and can be extracted into organic solvents. They amount to between 0.1 and 10% of the dry weight of the thallus, sometimes up to 30% (Varita, 1973). The chemical structures of some common lichen compounds are presented in Figure 4. These substances have been mostly identified as lactones (e.g., protolichessterinic acid), phenolic compounds (e.g., atranol and resorcinol), depsides (e.g., diffractic acid), pulvinic acid derivative (e.g., vulpinic acid), dibenzofurans and usnic acids (e.g., usnic acid). In addition, other lichen substances like atranorin, stictic acid, lecanoric acids and pannarin have been frequently studied (Khanuja et al., 2007; Ranković & Mišić, 2008; Gomes et al., 2002).

Although lichens have been used for medical purposes since ancient times, information on the edible and medicinal uses of lichens is scattered (Chevallier, 1996). The medicinal use of lichens can be traced back to the 18th dynasty (1700–1800 BC) when *Evernia furfuracea* (L.) Mann or (Parmeliaceae) was first used as a drug (Launert, 1981). Some lichens were claimed to be good for coughs, jaundice, rabies and restoring lost hair (Pereira, 1853). Herbal medicine texts made account of several species of lichens including *Cladonia, Evernia, Lobaria, Parmelia, Peltigera, Pertusaria, Physica, Rocella, Usnea* and *Xanthoria* (Perez-Llano, 1944a). During the middle

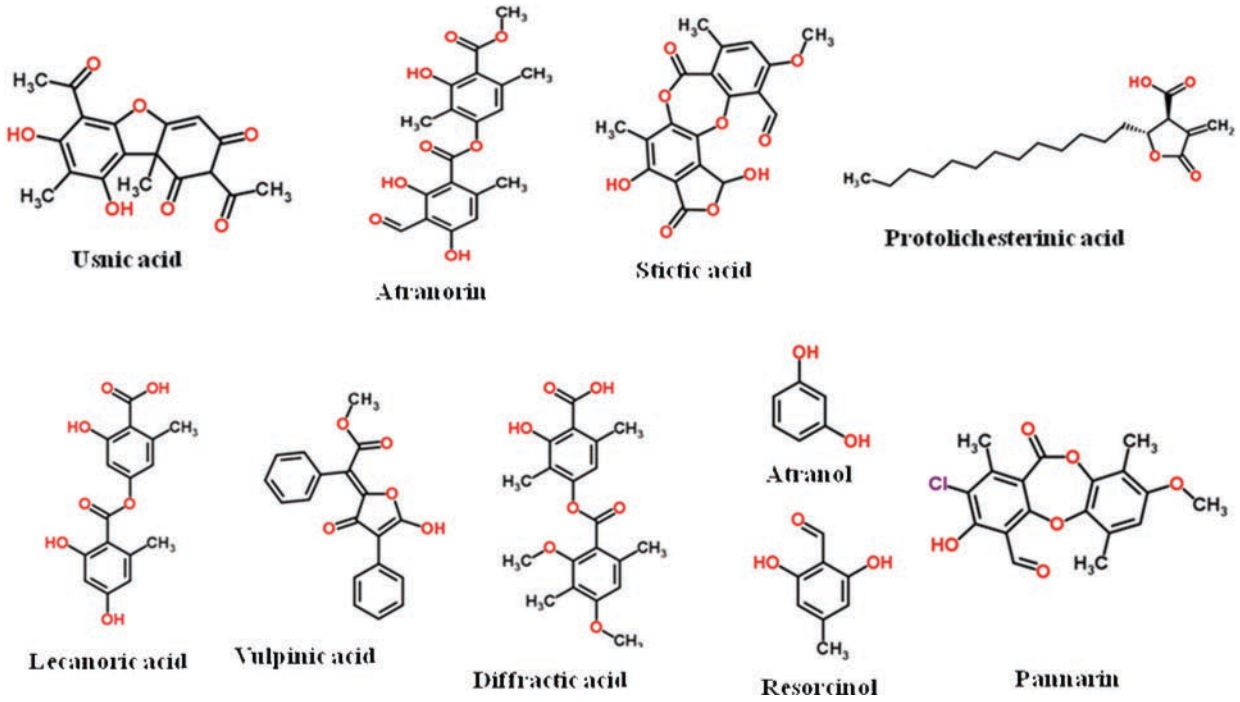

Figure 4. Some common lichen compounds.

age, lichens figured prominently in the herbals used by practitioners. However, lichens have been essentially overlooked to a great extent by the modern pharmaceutical industry, despite all the evidence of biological activity in lichen extracts provided in literature (Khanuja et al., 2007). The people of Northern California used *Letharia vulpina* (L.) Hue. (Parmeliaceae) in stomach diseases (Malhotra et al., 2008). A novel species of *Dictyonema* was used by the Waorani as hallucinogen (Davis & Yost, 1983). In the Arabian medicine, *Alectoria usneoides* was used in the treatment of splenomegaly (enlarged spleen). *Usnea* sp. was used in the Traditional Chinese Medicine (TCM), homeopathic system of medicine and traditional medicine in the Pacific Islands and New Zealand. *Usnea* sp. is valued for its demulcent properties and finds use in treatments of mild inflammation of the oral and pharyngeal mucosa. *Usnea filipendula* Stirt was used in the former Soviet Union for cuts and wounds (Chevallier, 1996). The Spanish folk medicine has documented the use of lichens in various medical aliments (Malhotra et al., 2008). Decoction of *Pseudoevernia furfuracea* (L.) Zopf. (Parmeliaceae) is used in Alfacar and Viznar in respiratory ailments. *Ramalina bourgeana* Mont. ex Nyl. (Ramalinaceae) is consumed for diuretic and stone-dissolving (lithontriptic) properties (González-Tejero, 1995). The lichen *Xanthoparmelia scabrosa* (Taylor) Hale (Parmeliaceae) is an ingredient in various aphrodisiac formulations sold on the international market. Traditionally, *Cetraria islandica* (L.) was used to treat mild inflammation of the oral and pharyngeal mucosa, dyspepsia, and loss of appetite. In the European folk medicine, *Cetraria islandica* (L.) was used in cancer treatment (Chevallier, 1996). Reindeer lichens such as *Cladonia rangiferina* (L.) F. H. Wigg. syn. *Cladina rangiferina* (L.) Nyl. (Cladoniaceae) were commonly used to treat colds, arthritis, fever (Perez-Llano, 1944b) as well as jaundice constipation, convulsions, coughs, and tuberculosis (Brown, 2001). Three *Parmelia* sp. are contained in the Indian drug chharila used as aphrodisiac (Lal & Upreti, 1995; Kumar & Upreti, 2001). In India, *Parmelia chinense* finds applications as diuretic and as liniment for headache and powder to heal wounds, whereas the Tinea (ringworm) like disease is treated with *Parmelia sanctiangeli*. *Parmelia peforatum* is medically recognized in Afghanistan (Chandra & Singh, 1971). *Parmelia nepalense* (Talyor) Hale ex Sipman is used in Nepal for treatment of toothache and sore throat (Kumar et al., 1996). In the Western Himalayas, *Thamnolia vermicularis* (Schwartz) Ach. (Icmadophilaceae) is used as antiseptic (Negi & Kareem, 1996). In Sikkim (India), *Heterodermia diademata* (Talyor) D.D. Awas., (Physciaceae) was used for cuts and wounds (Saklani & Upreti, 1992). Several reviews have discussed the pharmaceutical potential and biological activities of lichen substances (Huneck, 1999; Muller, 2001; Yamamoto, 2000; Boustie & Grube, 2005).

Many countries have developed commercial pharmacological products based on lichen substances. For instance, usnic acid (Ingolfsdottir, 2002) was used in anticeptic products in Germany (Camillen 60 Fudes spray and nail oil) and Italy (Gessato™ shaving). However, at high doses, usnic acid has been shown to exhibit toxic effects (acute oral toxicity, LD_{50} of 0.84 g/kg) and fatal hepatotoxicity (~500 mg/day of usnic acid) in mice (Durazo et al., 2004; Neff et al., 2004). Icelandic lichens were marketed in cold remedies formulation by the trade names of Isla-Moos® (Engelhard Arzneimittel GmbH & Co. KG, Germany) and Broncholind®

(MCM Klosterfrau Vertriebsgesellschaft mbH, Germany). In Japan, lichen extracts or substances were used in cosmetics, pharmaceuticals and neutraceutical products. The riminophenazine antibiotics, exemplified by clofazimine (Lamprene®), were developed as antimycobacterial drugs (Reddy et al., 1999). The antituberculous activity of these drugs was due to the active compounds diploicin and depsidone extracted from the Irish lichen *Buellia canescens* (Barry, 1946; Barry & Twomey, 1950; Nolan et al., 1948).

Biological activities of lichens

Lichens produce a wide array of biologically active primary (intracellular) and secondary (extracellular) metabolites (Lauterwein et al., 1995). Primary metabolites include amino acids, polyols, carotenoids, polysacharids and vitamins. Some, like the polysaccharide cell wall compounds lichenan and isolichenan, have taxonomic significance. Carotenoid compounds have also been intensely studied for dues to evolutionary relationships. Lichen's secondary metabolites, often called lichen acids, are produced primarily by the mycobiont, secreted onto the surface of lichen's hyphae either in amorphous forms or as crystals. Past and current studies show that lichen's secondary metabolites exert a wide variety of biological activities that include antibiotic, antimycobacterial, antiviral, anti-inflammatory, analgesic, antipyretic, plant growth inhibitory, antiherbivore, enzyme inhibitory, antiproliferative and cytotoxic effects (Shawuti & Abbas, 2007).

Antibacterial activities of lichens

It is well known that pathogenic microbes pose serious threats to human health and are increasing in prevalence in institutional health care settings (James et al., 1997) due to the growing resistance that infectious agents have developed against antibiotics (Babita et al., 2008). Therefore, new alternatives for combating the spread of infection through antibiotic-resistant microbes are necessary for keeping pace with the evolution of 'super' pathogens. Natural products are proposed as a therapeutic alternative to conventional antimicrobial treatment (Ali et al., 1999; Nimri et al., 1999). Among them, lichen-derived products and their antibiotic properties are of special interest to scientists (Lawrey, 1986) as up to 50 % of all lichens have been reported to possess antibiotic activities (Sharnoff, 1997).

Historically, Burkholder (1944) has first pioneered research on lichens as antibacterial agents. One of the most frequently reported lichen-derived products with a strong antimicrobial activity is usnic acid (Ingolfsdottir, 2002). Usnic acid, evernic acid and vulpinic acid inhibited the growth of the Gram-positive bacteria *Staphylococcus aureus, Bacillus subtilis* and *Bacillus megaterium*, but had no affect on the gram negative bacteria *Escherichia coli* or *Pseudomonas aeruginosa* (Lawrey, 1986). Acetone, chloroform, diethyl ether, methanol and petroleum ether extracts of *Parmelia sulcata* containing salazinic acid demonstrated antibacterial activity against *Aeromonas hydrophila, Bacillus cereus, Bacillus subtilis, Listeria monocytogenes, Proteus vulgaris, Yersinia enterocolitica, Staphylococcus aureus, Streptococcus faecalis, Candida albicans* and *Candida glabrata* (Candan et al., 2007). Diethyl ether, acetone and ethanol extracts of *Cetraria aculeate* contained protolichesterinic acid with promising antibacterial activity against nine bacteria belonging to Gram-positive and Gram-negative groups (Türka et al., 2003). Most of the antibacterial activities were tested on *Bacillus, Pseudomonas, E. coli, Staphylococcus aureus, Kleibsiella, Candida, Salmonella*, *Yersinia* and *Proteus* sp. (Inglfsdottir et al., 1985; Yilmaz et al., 2004; Ranković & Mišić, 2008; Karthikaidevi et al., 2009; Karagöz et al., 2009; Taya et al., 2004; Martins et al., 2010; Manojlovic et al., 2010; Ranković et al., 2010; Santiago et al., 2010; Swathi et al., 2010; Zambare et al., 2010).

Any bioactive compound, which is studied for antimicrobial activity, must have a specific concentration for an effective killing performance that varies with the compound's chemical structure, the test microorganism and its resistance to the bioactive compound. Minimal inhibitory concentrations (MICs) are used to characterize the biological activity of various lichen solvent extracts. Solvents include acetone, methanol, ethanol, diethyl ether, chloroform and petroleum ether. Among these, methanol is the most commonly used solvent for extraction of bioactive compound from lichens (Tables 1 and 2). The antimicrobial pattern of lichen extracts varies with the microbes and their cell membrane composition which is different in Gram-positive and Gram-negative microbes. In Gram-positive bacteria, *Bacillus* and *Staphylococcus* are the most dominantly genera studied on lichen extracts, followed by *Mycobacterium, Streptococcus, Listeria* and *Micrococcus* (Table 1). Among the *Bacillus* species, *B. sublitis* was the most sensitive microorganism to lichen substances such as atranorin, protolichsterinic acid, salazinic acid, usnic acid, norstictic acid, protoacetraric acid, fumaroprotoacetraric acid, atranol, lecanoric acid, stictic acid, divericatic acids and zeorin. In addition to the above active components (except atranol), *Staphylococcus* sp. was also sensitive to alectosarmentin and barbatic acid (Table 1). Likewise, lichen active compounds, present in lichen extracts, were found active against various against Gram-negative microbes (Table 2). Next to *E. coli* as the most studied Gram-negative microorganism, pathogens like *Aeromonas, Anterobacter, Helicobacter, Kleibsiella, Pseudomonas* and *Proteus* sp. have also been proved sensitive to lichen active compounds (Table 2).

Antifungal activities of lichens

The acetone and methanol extracts of *Lasallia pustulata* (L.) Méret. (Umbilicariaceae), *Parmelia sulcata* Taylor and *Umbilicaria crustulosa* (Ach.) Frey (Umbilicariaceae) manifested a very selective antifungal activity (Ranković et al., 2007). Usnic acid together with isodivaricatic acid, 5-propylresorcinol, divaricatinic acid were identified as antifungal agents (Schmeda-Hirschmann et al., 2008). Acetone, chloroform, diethyl ether, methanol and

Table 1. Antibacterial activity of lichen species against Gram-positive bacteria.

Lichen	Active compound	MIC values	Test microbes	References
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	2960*,3025§, 8460‡	*Bacillus cereus*	Türk et al., 2003
		0.6¶		Swathi et al., 2010
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	3.9*, 15.6§, 31.2‡, 1.9ǁ,46.8 □		Yılmaz et al., 2004
Usnea ghattensis	Usnic acid	0.005-0.01¶	*B. licheniformis,*	Behera et al. 2005
		0.005-0.01¶	*B. megaterium*	
Lasallia pustulata	NS#	0.78*	*B. mycoides*	Ranković et al., 2007
Cladonia furcata	Fumarprotocetraric acid	0.062¶		Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.062¶		
Parmelia caperata	Protocetraric acid	0.062¶		
Parmelia conspresa	Stictic acid	0.5¶		
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	0.78*,¶		Ranković et al., 2010
Lecanora frustulosa	Divaricatic acid, Zeorin	1.56*, 0.78¶		Ranković et al., 2010
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	1480*, 6050§, 8460‡	*B. subtilis*	Türk et al., 2003
Usnea barbata	NS	0.1*,¶		Madamombe & Afolayam, 2003
Ramalina farinacea	Usnic acid, Norstictic acid Protocetraric acid	0.026*		Tay et al., 2004
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	3.9*,§, 7.8‡, 0.48ǁ, 2.9 □		Yılmaz et al., 2004
Usnea ghattensis	Usnic acid	0.005-0.01¶		Behera et al. 2005
Stereocaulon vesuvianum	Atranol	NS		Khanuja et al., 2007
Cladonia furcata	Fumarprotocetraric acid	0.062¶		Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.062¶		
Parmelia caperata	Protocetraric acid	0.062¶		
Parmelia conspresa	Stictic acid	0.5¶		
Lecanora muralis	NS	0.5†		Karagöz et al., 2009
Cladonia furcata	NS	0.39*		
Peltigera polydactyla	NS	0.5†		
Ramalina farinacea	NS	0.5†		
Umbilicaria vellea	NS	0.1†		
Xanthoria elegans	NS	0.5†		
Xanthoparmelia tinctina	NS	0.5†		
Anaptychia ciliaris	NS	0.5†		
Lecanora frustulosa	Divaricatic acid, Zeorin	3.12*,1.56¶		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	0.78*,¶		
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	742*, 3025*, 8460‡	*Listeria monocytogenes*	Türk et al., 2003
Ramalina farinacea	Usnic acid, Norstictic acid Protocetraric acid	0.013*		Tay et al., 2004
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	3.9*,§,‡, 0.12ǁ, 2.9 □		Yılmaz et al., 2004
Cladonia crispatula	Depsides, Usnic acid	NS	*Mybobacterium smegmatis*	Khanuja et al., 2007
Flavoparmelia caperata	NS	0.25§		Gupta et al., 2007
Heterodermia leucomela	NS	0.5§		
Lecanora flavidorufa	NS	>1.0§		
Leptogium pedicellatum	NS	>1.0§		
Lobaria isidiosa	NS	>1.0§		
Phaeophyscia hispidula	NS	>1.0§		
Rimelia reticulata	NS	0.5§		
Stereocaulon foliolosum	NS	0.5§		
Everniastrum cirrhatum	NS	0.5§		
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	425*, 1215§,1165‡	*Staphylococcus aureus*	Türk et al., 2003

(*Continued*)

Table 1. (*Continued*).

Lichen	Active compound	MIC values	Test microbes	References
Usnea barbata	NS	0.1*, ¶		Madamombe & Afolayam, 2003
Ramalina farinacea	Usnic acid, Norstictic acid Protocetraric acid	0.013*		Tay et al., 2004
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	7.8*,3.9§, 15.6‡, 0.97ǀ, 0.73 □		Yılmaz et al., 2004
Usnea ghattensis	Usnic acid	0.005-0.01¶		Behera et al. 2005
Alectoria sarmentosa	Alectrosarmentin	NS		Khanuja et al., 2007
Cladonia furcata	Fumarprotocetraric acid	0.062¶		Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	0.125¶		
Parmelia conspresa	Stictic acid	0.5¶		
Anaptychia ciliaris	NS	0.5†		Karagöz et al., 2009
Peltigera praetextata	NS	0.5†		
Rhizoplaca melanophthalma	NS	0.5†		
Umbilicaria vellea	NS	0.1†		
Xanthoria elegans	NS	0.5†		
Xanthoparmelia tinctina	NS	0.5†		
Xanthoria parietina	NS	0.25†		
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	0.78*, ¶		Ranković et al., 2010
Lecanora frustulosa	Divaricatic acid, Zeorin	1.56*, 0.78¶		
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	0.6¶		Swathi et al., 2010
Cladia aggregata	Barbatic acid	0.1‡		Martins et al., 2010
Xanthoparmelia somloensis	NS	0.7-0.9*, ¶		Zambare et al., 2010
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	1480*, 6050§, 8460‡	*Streptococcus faecalis*	Türk et al., 2003
Ramalina farinacea	Usnic acid, Norstictic acid Protocetraric acid	0.013*		Tay et al., 2004
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	3.9*,0.97§,‡,0.24ǀ,0.73 □		Yılmaz et al., 2004
Xanthoparmelia somloensis	NS	0.7-0.9*, ¶	*S. pyogenes (Group A)*	Zambare et al., 2010
		0.7-0.9*,¶	*S. agalactiae (Type B)*	
Usnea barbata	NS	0.1*, ¶	*Micrococcus viradans*	Madamombe & Afolayam, 2003
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	0.4¶	*S. epidermindis*	Swathi et al., 2010

*Acetone extract, ¶Methanol extract, §Ethanol extract, †Aqueous extract, ‡Diethyl ether extract, ǀChlorofrom extract, □Petroleum ether extract, #Not specified.

petroleum ether extracts of *Parmelia sulcata* containing salazinic acid demonstrated antifungal activity against *Aspergillus niger, Aspergillus fumigatus,* and *Penicillium notatum* (Candan et al., 2007). Parietin and anthraquinone isolated from methanol extracts of *Caloplaca cerina* (Ehrh. ex Hedwig) Th.Fr. (Teloschistaceae) displayed a significant antifungal activity (Manojlovic et al., 2005). Extracts of Andean lichens *Protousnea poeppigii* (Nees and Flot.) Vain. (Parmeliaceae) and *Usnea florida* var. *rigida* Acharius demonstrated antimicrobial activity against the pathogenic fungi *Microsporum gypseum*, *Trichophyton mentagrophytes* and *T. rubrum*. Acetone extracts of three lichen species - *Evernia prunastri*, *Hypogymnia physodes* and *Cladonia portentosa*—were investigated for antifungal activity against eight plant pathogenic fungi: *Pythium ultimum*, *Phytophthora infestans*, *Rhizoctonia solani*, *Botrytis cinerea*, *Colletotrichum lindemuthianum*, *Fusarium solani*, *Stagonospora nodorum* and *Ustilago maydis* (Halama & Van, 2004). Manojlovic et al. (2000) isolated anthraquinones from *Xanthoria* lichen species possessing antifungal activity. A potent fingitoxic compound, lecanoric acid, was isolated from *Parmotrema tinctorum* lichen and tested against the fungus *Cladosporium sphaerospermum* (Gomes et al., 2002). Antifungal activities have been reported for the lichen substance anthraquinone parietin from *Caloplaca cerina* (Manojlovic et al., 2005) and for divaricatinic acid, isodivaricatic acid, usnic acid, and 5-propylresorcinol compounds from Andean lichens *Protousnea poeppigii* and *Usnea rigida* (Schmeda-Hirschmann et al., 2008). Antifungal activities were tested on *Aspergillus, Botrytis, Fusarium, Mucor, Penicillium* and *Tricoderma* species with low MIC values (0.00625-6.25 mg/mL) indicating high activity (specificity) of these lichen extracts against fungal pathogens. The lichen active compounds reported to possess antifungal activity—divaricatic acid, zeorin, lecanoric acid, lichenic acid, atranorin, salanizic acid,

Table 2. Antibacterial activity of lichen species against Gram-negative bacteria.

Lichen	Active compound	MIC values	Test microbes	References
Cetraria aculeata	Protolichesterinic acid	212*, 607[§], 2330[‡]	*Aeromonas hydrophila*	Türk et al., 2003
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	3.9*[,§,‡,ǂ], 46.8 [□]		Yılmaz et al., 2004
Parmelia caperata	Protocetraric acid	0.062[¶]	*E. nterobacter cloaceae*	Ranković & Mišić, 2008
Cladonia furcata	Fumarprotocetraric acid	0.062[¶]		
Parmelia conspresa	Stictic acid	0.5[¶]		
Ochrolechia androgyna,	Lecanoric acid	0.062[¶]		
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	0.78*, 1.56[¶]		Ranković et al., 2010
Lecanora frustulosa	Divaricatic acid, Zeorin	1.56*, 0.78[¶]		Ranković et al., 2010
Cetraria aculeata	Protolichesterinic acid	850*, 1215[§], 2330[‡]	*Escherichia coli*	Türk et al., 2003
Usnea barbata	NS[#]	0.5*		Madamombe & Afolayam, 2003
Stereocaulon vesuvianum	Atranol	NS		Khanuja et al., 2007
Cladonia furcata	Fumarprotocetraric acid	0.062[¶]		
Parmelia caperata	Protocetraric acid	0.062[¶]		
Ochrolechia androgyna,	Lecanoric acid	0.125[¶]		
Parmelia caperata	Protocetraric acid	0.125[¶]		
Parmelia conspresa	Stictic acid	0.5[¶]		
Anaptychia ciliaris	NS	0.5[†]		Karagöz et al., 2009
Peltigera polydactyla	NS	0.5[†]		
Peltigera praetextata	NS	0.5[†]		
Ramalina farinacea	NS	0.5[†]		
Umbilicaria vellea	NS	0.1[†]		
Xanthoria elegans	NS	0.5[†]		
Xanthoparmelia tinctina	NS	0.5[†]		
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	-		Ranković et al., 2010
Lecanora frustulosa	Divaricatic acid, Zeorin	-		
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	0.7[¶]		Swathi et al., 2010
Parmelia caperata	Protocetraric acid	0.062[¶]	*Klebsiella pneumonia*	Ranković & Mišić, 2008
Parmelia conspresa	Stictic acid	0.25[¶]		
Cladonia furcata	Fumarprotocetraric acid	0.031[¶]		
Ochrolechia androgyna,	Lecanoric acid	0.062[¶]		
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	0.78*, 1.56[¶]		Ranković et al., 2010
Lecanora frustulosa	Divaricatic acid, Zeorin	1.56*, 0.78[¶]		
Cetraria aculeata	Protolichesterinic acid	1480*,3025[§], 8460[‡]	*Pseudomonas aeruginosa*	Türk et al., 2003
Usnea barbata	NS	5.0*		Madamombe & Afolayam, 2003
Everniastrum cirrhatum	Atranorin, Protolichesterinic acid, Salazinic acid	0.8[¶]		Swathi et al., 2010
Usnea barbata	NS	5.0*	*Proteus vulgaris*	Madamombe & Afolayam, 2003
Cetraria aculeata	Protolichesterinic acid	1480*, 6050[§],8460[‡]		Türk et al., 2003
Ramalina farinacea	Usnic acid, Norstictic acid Protocetraric acid	0.013*		Tay et al., 2004
Cladonia foliacea	Usnic acid, Atranorin, Fumarprotocetraric acid	3.9*[,§,‡,ǂ], 46.8 [□]		Yılmaz et al., 2004
Usnea barbata	NS	0.1*[,¶]	*E. faecalis*	Madamombe & Afolayam, 2003
Cetraria islandica	Protolichesterinic acid	NS	*Helicobacter pylori*	Khanuja et al., 2007

*Acetone extract, [¶]Methanol extract, [§]Ethanol extract, [†]Aqueous extract, [‡]Diethyl ether extract, [ǂ]Chlorofrom extract, [□]Petroleum ether extract, [#]Not specified.

protolichesterinic acid, fumarprotoacetraric acid, protocetraric acid, stictic acid and usnic acid—are summarized in Table 3.

Antiviral activities of lichens

Antiviral properties have been attributed to various lichen substances. Anthraquinones, especially the polyphenolic and/or polysulphonate substituted types, have been shown to exhibit potent antiviral properties (Schinazi et al., 1990; Sydiskis et al., 1991). Cohen et al. (1996) isolated anthraquinones, bianthrones and hyperacin derivatives from lichens whose antiviral activities were positively correlated with an increasing substitution of chlorine in the anthraquinone structure. It is plausible to suggest that

Table 3. Antifungal activity of lichen species.

Lichen	Active compound	MIC values	Test microbes	References
Cladonia furcata	Fumarprotocetraric acid	0.25¶	*Aspergillus flavus*	Ranković & Mišić, 2008
Ochrolechia androgyna	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	1.0¶		
Lecanora frustulosa	Divaricatic acid, Zeorin	-		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	3.12¶		
Cladonia furcata	Fumarprotocetraric acid	0. 25¶	*A. fumigates*	Ranković & Mišić, 2008
Ochrolechia androgyna	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	1.0¶		
Parmelia conspresa	Stictic acid	1.0¶		
Lecanora frustulosa	Divaricatic acid, Zeorin	12.5¶		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	3.12¶		
Everniastrum cirrhatum	Atranorin, Salanizic acid Protolichesterinic acid,	NS#		Swathi et al., 2010
Usnea subfloridans	NS	0.00625§	*A. niger*	Ekong et al., 2008
Everniastrum cirrhatum	Atranorin, Salanizic acid Protolichesterinic acid,	NS		Swathi et al., 2010
Melanelia sp	NS	NS	*Botryosphaeria dothidea*	Oh et al., 2006
Nephromopsis pallescens	NS	NS		
Umbilicaria proboscidea	NS	NS		
Ramalina conduplicans	NS	NS	*Botrytis cinerae*	Oh et al., 2006
Lecanora frustulosa	Divaricatic acid, Zeorin	12.5*, 3.12¶		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	3.12¶		Ranković et al., 2010
Evernia prunastri, Hypogymnia physodes, Cladonia portentosa	Lichenic acid	NS		Halama & Van, 2004
Cladonia furcata	Fumarprotocetraric acid	0.125¶		Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.062¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	0.5¶		
Cladonia furcata	Fumarprotocetraric acid	0.125¶	*Candida albicans*	Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.062¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	0.5¶		
Lecanora frustulosa	Divaricatic acid, Zeorin	6.24¶		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	3.12¶		
Parmotrema tinctorum	Lecanoric acid	NS	*Cladosporium sphaerospermum*	Gomes et al., 2002
Evernia prunastri, Hypogymnia physodes, Cladonia portentosa	Lichenic acid	NS	*C. lindemuthianum*	Halama & Van, 2004
Nephromopsis asahinae	NS	NS	*Diaporthe actinidiae*	Oh et al., 2006
Parmelia laevior	NS	NS		
Evernia prunastri, Hypogymnia physodes, Cladonia portentosa	Lichenic acid	NS	*Fusarium solani*	Halama & Van, 2004
Parmelia furfuracea	Usnic acid	NS	*Fusarium moniliforme*	Khanuja et al., 2007
Cladonia furcata	Fumarprotocetraric acid	0. 25¶	*Fusarium oxysporum*	Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	1.0¶		
Lecanora frustulosa	Divaricatic acid, Zeorin	12.5¶		
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	3.12¶		
Cladonia furcata	Fumarprotocetraric acid	0. 25¶	*Mucor mucedo*	Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	1.0¶		

(*Continued*)

Table 3. (*Continued*).

Lichen	Active compound	MIC values	Test microbes	References
Lecanora frustulosa	Divaricatic acid, Zeorin	12.5¶		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	3.12¶		
Cladonia furcata	Fumarprotocetraric acid	0.125¶	*Paecilomyces variotii*	Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	0.5¶		
Lecanora frustulosa and	Divaricatic acid, Zeorin	6.25¶		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	1.56¶		
Cladonia furcata	Fumarprotocetraric acid	0. 25¶	*Penicillium purpurescens*	Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	1.0¶		
Parmelia conspresa	Stictic acid	1.0¶		
Lecanora frustulosa	Divaricatic acid, Zeorin	NS		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	6.25¶		
Cladonia furcata	Fumarprotocetraric acid	0. 25¶	*Trichoderma harsianum*	Ranković & Mišić, 2008
Ochrolechia androgyna,	Lecanoric acid	0.125¶		
Parmelia caperata	Protocetraric acid	0.5¶		
Parmelia conspresa	Stictic acid	0.5¶		
Lecanora frustulosa	Divaricatic acid, Zeorin	3.12§		Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	6.25§		
Pertusaria sp.	NS	NS	*Pestalotiopsis dothidea*	Oh et al., 2006
Ramalina sp	NS	NS	*Phythium sp.*	
Ramalina conduplicans	NS	NS	*Sclerotium cepivorum*	
Ramalina sinensis	NS	NS	*Rhizoctonia solani*	
Vulpicida	NS	NS	*Rhizoctonia solani*	
Evernia prunastri, Hypogymnia physodes, Cladonia portentosa	Lichenic acid	NS	*Phytophthora infestans*	Halama & Van, 2004
Cladonia portentosa	Lichenic acid	NS	*P. ultimum*	
Evernia prunastri, Hypogymnia physodes, Cladonia portentosa	Lichenic acid	NS	*Rhizoctonia solani*	
Evernia prunastri, Hypogymnia physodes, Cladonia portentosa	Lichenic acid	NS	*Stagonospora nodorum*	
Cladonia portentosa	Lichenic acid	NS	*Ustilago maydis*	
Lecanora frustulosa	Divaricatic acid, Zeorin	NS	*Penicillium verrucosum*	Ranković et al., 2010
Parmeliopsis hyperopta	Divaricatic acid, Zeorin	6.25¶		

*Acetone extract, ¶Methanol extract, ᶜEthanol extract, #Not specified.

similar manipulations could improve the antiviral effects of the nascent compounds in crude lichen extracts. Plant polysaccharides have also been shown to exhibit potent antiviral activities, especially against enveloped viruses (Hosoya et al., 1991; Premanathan et al., 1999). Esimone et al. (2007) reported that the crude polysaccharide fraction (CPF) of a *Parmelia perlata* lichen extract targeted the enveloped positive-sense RNA virus (yellow fever virus) but was inactive on non-enveloped RNA viruses (poliomyelitis and IBDV). However, an empirical conclusion to this effect could only be substantiated after further screening of CPF against several other enveloped viruses and after detailed molecular elucidation studies. Usnic acid isolated from *Teloschistes chrysophthalmus* (L.) Th. Fr. (Teloschistaceae) and parietin isolated from *Ramalina celastri* demonstrated antiviral activity against the arena viruses Junin and Tacaribe (Fazio et al., 2007). Recently, Praveen-Kumar et al. (2010a) reported an antifungal activity of microlichen *Ramalina hossei* H. Magn & G. Awasthi. The aqueous extracts and the ethanolic extracts prepared from the lichen species *Xanthoria parietina* and *Xanthoparmelia tinctina* were evaluated for antiviral activity against human parainuenza virus type 2(HPIV-2) and cytotoxic activity towards Vero cells. The EC_{50} of the ethanol extract of *X. tinctina* for HPIV-2 replication was 20 μg/mL, and for aqueous extract was 22.5 μg/mL (Karagöz & Aslan, 2005). *In vitro* antiviral activities of lichen extracts were reported for human cytomegalovirus (Wood et al., 1990), HIV (Hirabayashi et al., 1989; Neamati et al., 1997), HIV-RT (Pengsuparp et al., 1995), and Epstein-Barr virus (Yamamoto et al., 1995). Lichenan, a structural component of the mycosymbiont cell wall (Honegger & Haish 2001), contained a linear {1→3, 1→4} β-D-glucan linkage (Tvaroska et al., 1983)

that inhibited symptom development and virus accumulation in four greenhouse-grown *Nicotiana* spp. infected by a tobacco mosaic virus (Stubler & Buchenauer, 1996).

Anticancer activities of lichens

Some lichen substances like usnic acid, cristazarin, protolichesterinic acid, polyporic acid, depsidone and lichenin have been investigated for antitumor effects on tumor cells—melanoma B-16 (Khanuja et al., 2007), P388 leukaemia (Takai et al., 1979), K-562 leukaemia (Hirayama et al., 1980), Ehrlich solid tumor (Cain, 1966) and lymphocyte (Correche et al., 2002) cells. *In vitro* anticancer activities of lichen extracts have been evaluated according to the cell proliferation assay (Tokiwano et al., 2009) in three cancer cell lines: human pancreatic (PANC-1) (Ingolfsdottir et al., 2002), prostate (DU-145) (Russo et al., 2006) and breast (MCF7) (Bogo et al., 2010) cancer cell lines.

The anticancer properties of lichen extracts have been studied for many years. Extracts from the lichen *Collema flaccidum* showed significant anticancer activity in the crown gall tumor inhibition test. The purified inhibitors were identified as colleflaccinosides and bisanthraquinone glycosides (Rezanka & Dembitsky, 2006). Extracts containing depsidone pannarin exhibited similar anticancer activities by inducing cell death in human prostate carcinoma DU-145 cells (Maier et al., 1999; Russo et al., 2006) and cell apoptosis in human melanoma M14 cells (Russo et al., 2006; 2008). Tenuiorin (a tridepside) and methyl orsellinate extracted from *Peltigera leucophlaebia* inhibited cell proliferative activities on human breast (T-47D), pancreatic (PANC-1) and colon (WIDR) cancer cell lines (Ingolfsdottir et al., 2002). Usnic acid showed inhibitory effects on the cell growth and proliferation of two different human cancer cell lines—the breast cancer cell line T-47D and the pancreatic cancer cell line Capan-2 (Einarsdottir et al., 2010). Lecanoric acid, a secondary metabolite from *Parmotrema timctorum*, exerted anticancer activities against HEp-2 larynx carcinoma, MCF7 breast carcinoma, 786-0 kidney carcinoma and B16-F10 murine melanoma cell lines (Bogo et al., 2010).

The antitumor and cytotoxic activities of some lichen constituents in different cell systems have been reviewed by Huneck (2001) and Ingolfsdottir et al. (1997). Crude extracts from various lichen species were screened for their cytotoxic activities and some of them were found to be cytotoxic in different cancer cell lines (Perry et al., 1999; Bezivin et al., 2003). Usnic acid exhibited an antiproliferative effect on human leukemia cells (K562) and endometrial carcinoma (Ishikawa, HEC-50) cells (Carderelli et al., 1997; Kristmundsdottir et al., 2002). A lichen-derived polysaccharide CFP-2 reduced the viability of HL-60 and K562 cells due to apoptotic pathway and telomerase activity, suggesting its possible therapeutic potential against cancer (Lin et al., 2003). Protolichesterinic acid isolated from *Cetraria islandica* L. (Ach.) inhibited growth of malignant cell lines (Ogmundsdottir et al., 1998). Antiproliferative effects of several lichen compounds in human platelets were ascribed to their inhibitory activities on 12(S)-HETE which plays role in carcinogenesis and metastasation (Bucar et al., 2004). Zeytinoglu et al. (2004) reported genotoxic/antigenotoxic and cytotoxic activities of extracts from *C. aculeata* in bacterial and mammalian cell systems. Pannarin inhibited cell growth and induced cell death in human prostate carcinoma DU-145 cells (Maier et al., 1999). The orcinol derivatives, tenuiorin and methyl orsellinate, present in extracts of *Peltigera leucophlebia* (Nyl.) Gyeln (Peltigeraceae), exhibited *in vitro* inhibitory activity against 15-lipoxygenase from soybeans. On this account, tenuiorin and methyl orsellinate were further tested for antiproliferative activity on cultured human breast, pancreatic and colon cancer cell lines. Bianthraquinone glycosides, colleflaccinosides isolated from *Collema flaccidum* (Ach.) Ach. (Collemataceae), collected in Israel and Russia, were reported to have antitumor activity (Rezanka & Dembitsky, 2006).

Anti-insecticidal activities of lichens

Killing larvae of mosquitoes is a successful way of minimizing mosquito population in breeding grounds before they reach adult stage (Vinayaka et al., 2009). The most commonly used insecticidal agents are currently based on synthetic chemicals; however, their repeated use has been reported for widespread development of chemical resistance and public concern over possible health problems associated with food and environment (Bonning & Hammock, 1992). Phytochemicals contain many bioactive ingredients which offer an alternative source of insect-control agents and that have little or no harmful effect on non-target organisms and the environment. It is observed that the methanol extract of *R. conduplicans* was active against mosquito larvae (Vinayaka et al., 2009). Extracts from lichen *Letharia vulpine* showed potent insecticidal activities against *Spodoptera ornithogalli* and *S. littoralis* (Khanuja et al., 2007). Bioassays with (–)- and (+)-usnic acids against larvae of *Culex pipiens* revealed that the LC_{50} values were 0.8 and 0.9 ppm, respectively (Cetin et al., 2008).

Enzyme inhibition activities of lichens

Lichen substances like usnic acids, resorcinol derivatives and atranorin were found to be potent enzyme inhibitors of ornithine decarboxylase and arginine decarboxylase that affect the polyamine metabolism (Boustie & Grube, 2005). Atranoin (from *Psedevernia furfuracea*) and resorcinol (from *Protousnea* spp.) were reported for trypsin and tyrosinase inhibition, respectively (Khanuja et al., 2007). Inhibition of tyrosinase (for melanin biosynthesis) and xanthine oxidase (for hyperuricaemia) with lichen extracts were reported by various researchers (Higuchi et al., 1993; Behera et al., 2005; Kim & Cho, 2007; Verma et al., 2008).

Tyrosinase or polyphenol oxidase (monophenol, odiphenol: oxygen oxidoreductase; EC 1.14.18.1) is a copper enzyme that catalyzes two different reactions using molecular oxygen (Sanchez-Ferrer et al., 1995): the hydroxylation of mono-phenols to *o*-diphenols (monophenolase activity) and the oxidation of the *o*-diphenols

to *o*-quinones (diphenolase activity). This enzyme is widely distributed in plants, microorganisms and animals where tyrosinase is responsible for melanization. In humans, the melanization is influenced by several mechanisms such as anti-oxidation, direct tyrosinase inhibition, melanin inhibition of migrated cells and hormonal activities (Prota & Thomson, 1976; Pawelek & Korner, 1982). Tyrosinase inhibitors have been frequently used in cosmetics as depigmenting agents for hyperpigmentation (Funasaka et al., 2000). A concerted effort has been made to search for naturally occurring tyrosinase inhibitors from various organisms, many of them being largely free from harmful adverse effects (Sasaki & Yoshizaki, 2002).

Umbilicaria esculenta extracts strongly inhibited disaccharide hydrolytic enzymes of mold and mammalian origin (Lee & Kim 2000). A glucosidase inhibitory activity by extracts of *Parmelia austrosinensis* and *Parmelia praesorediosa* was also reported (Lee & Kim, 2000). Anti-inflammatory, analgesic and antipyretic activities of lichen substances (Okuyama et al., 1995) were evidenced by inhibition of lipoxygenase (Ingolfsdottir et al., 2002), prostaglandin (Sankawa et al., 1982) and leukotriene B4 biosyntheses (Kumar & Muller, 1999).

Antioxidant activities of lichens

Many lichen extracts have been reported for antioxidant properties due to their phenolic content. Antioxidant agents inhibit and prevent reactive oxygen species, which can cause degenerative diseases. Natural antioxidants are preferred over many synthetic antioxidants, which can be toxic, for therapeutic applications. Jayaprakasha and Rao (2000) examined the antioxidant properties of methyl orsellinate, atranorin, osellinic acid and lecanoric acid. Bhattarai et al. (2008) reported stronger antioxidant activities in extracts from Antarctic lichens than from lichens native to temperate or tropical regions. Phenolic constituents from the lichen *Parmotrema stuppeum* (Nyl.) Hale (Parmeliaceae) including methyl orsenillate, orsenillic acid, atranorin and lecanoric acid showed moderate antioxidant activity (Jayapraksha & Rao, 2000). An animal study reported antioxidant activities of lichen *Cetraria islandica* (Gülçin et al., 2002).

Antioxidant activities as assessed by DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical and ABTS [2,2′-azinobis-(3-ethylbenzothiazoline-6-sulfonate)] radical scavenging capacities were determined and compared with those of commercial standards BHA (butylated hydroxyanisole) and Trolox [(±)-6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid] (Paudel et al., 2008; Gülçin et al., 2002; Kekuda et al., 2009). Many researchers reported antioxidant activity of lichen extracts based on lipid peroxidation inhibition and total phenol content (Behera et al., 2005; Odabasoglu et al., 2005; Yucel et al., 2007; Islas et al., 2008; Özen & Kinalioğlu, 2008; Verma et al., 2008; Vinayaka et al., 2009; Manojlovic et al., 2010; Praveen-Kumar et al., 2010b). Stactic acid derivatives (β-orcinol depsodomes) were obtained from usnea articulate lichens with potential antioxidant activity (Dévéhat et al., 2007). Lichens produce a number of secondary metabolites—polysaccharides and/or phenolic compounds—that are known to exhibit such properties (Liu et al., 1997; Hidalgo et al., 1994; Sanchez-Moreno et al., 1999; Germano et al., 2002; Duh et al., 1999; Okamoto et al., 1992; Suzuki et al., 1992).

The antioxidant activity has been evaluated based on DPPH free radical scavenging, reducing power, superoxide anion radical scavenging and lipid peroxidation inhibition. Methanol has been used as the most efficient and suitable solvent for extraction of bioactive compounds with antioxidant activities from lichens, hence, most antioxidant activity assays have been performed on methanol extracts (Table 4). The lichens *Peltigera canina, Peltigera praetextata, Sticta nylanderiana, Ramalina*

Table 4. Antioxidant activity of lichen extracts in different solvents.

Lichen	Solvent	DPPH radical scavenging (%)	Reducing power capacity	Superoxide anion radical scavenging activity (%)	Lipid peroxidation inhibition	References
Cetraria islandica	Acetone	35.0	0.042	36.0	NS	Kosanić & Ranković, 2011
Lecanora atra		94.7	0.11	84.5	NS	
Parmelia pertusa		40.0	0.038	32.0	NS	
Pseudoevernia furfuraceae		87.27	0.08	52.0	NS	
Umbilicaria cylindrica		40.0	0.038	30.0	NS	
Xanthoparmelia somloensis		76.6	NS[#]	NS	85.0	Zambare et al., 2010
Usnea ghattensis	Methanol	89.6	NS	67.0	89.6	Varma et al., 2008
Ramalina conduplicans		85.4	NS	NS	NS	Vinayaka et al., 2009
Bryoria confusa		10.5	0.14	NS	49.6	Heng et al., 2010
Bryoria himalayensis		29.3	0.24	NS	74.6	
Bryoria lactinea		23.1	0.21	NS	74.6	
Bryoria poeltii		28.5	0.24	NS	82.4	
Cetrelia olivetorum		9.5	0.15	NS	NS	
Cetraria islandica		20.8	0.28	NS	65.4	

(*Continued*)

Table 4. (*Continued*).

Lichen	Solvent	DPPH radical scavenging (%)	Reducing power capacity	Superoxide anion radical scavenging activity (%)	Lipid peroxidation inhibition	References
Cetraria laevigata		29.7	0.19	NS	79.8	
Cetrariopsis wallichiana		21.2	0.15	NS	40.9	
Cladia aggregata		21.9	0.25	NS	83.9	
Cladonia amaurocraea		32.1	0.21	NS	80.9	
Cladonia cervicornis		29.6	0.22	NS	77.1	
Cladonia corymbescens		17.1	0.19	NS	78.7	
Cladonia macilenta		19.3	0.25	NS	79.3	
Cladonia rangiferina		22.9	0.24	NS	78.7	
Cladonia squamosissma		25.2	0.22	NS	78.3	
Coccocarpia erythroxyli		21.5	0.28	NS	79.0	
Evernia mesomorpha		14.2	0.16	NS	80.7	
Everniastrum cirrhatum		32.4	0.70	NS	77.2	
Everniastrum rhizodendroideum		34.2	0.85	NS	69.8	
Hypogymnia hypotrypella		24.8	0.29	NS	80.3	
Hypogymnia taiwanalpina		40.9	0.38	NS	82.4	
Lethariella cladonioides		26.9	0.32	NS	41.2	
Lethariella zahlbruckneri		18.1	0.26	NS	NS	
Lobaria isidiophora		31.0	0.28	NS	NS	
Lobaria kurokawae		37.3	0.31	NS	72.0	
Lobaria orientalis		38.3	0.32	NS	NS	
Lobaria retigera		25.3	0.13	NS	NS	
Lobaria yunnanensis		29.2	0.16	NS	NS	
Menegazzia terebrata		48.6	0.31	NS	85.3	
Nephromopsis pallescens		15.2	0.13	NS	NS	
Nephromopsis stracheyi		16.6	0.18	NS	NS	
Nephromopsis yunnanensis		26.4	0.17	NS	13.5	
Oropogon secalonicus		17.8	0.14	NS	NS	
Peltigera canina		84.9	0.66	NS	84.9	
Peltigera praetextata		87.8	1.04	NS	85.4	
Pilophorus aciculare		23.2	0.15	NS	7.0	
Ramalina intermedia		53.2	0.36	NS	78.8	
Ramalina sinensis		20.6	0.19	NS	NS	
Sticta nylanderiana		90.4	1.48	NS	85.5	
Tuckneraria ahtii		20.4	0.18	NS	40.7	
Tuckneraria pseudocomplicata		34.5	0.30	NS	54.6	
Umbilicaria indica		25.4	0.20	NS	15.0	
Umbilicaria sinoccidentalis		24.7	0.20	NS	29.5	
Umbilicaria thamnodes		17.3	0.15	NS	NS	
Umbilicaria yunnana		21.9	0.19	NS	NS	
Usnea longissima		25.4	0.19	NS	31.8	
Cetraria islandica		49.0	0.058	42.0	NS	Kosanić & Ranković, 2011
Lecanora atra		93.32	0.1	69.0	NS	
Parmelia pertusa		48	0.042	60.0	NS	
Pseudoevernia furfuraceae		57.88	0.06	50.0	NS	
Umbilicaria cylindrica		50.0	0.06	51.0	NS	
Parmotrema pseudotinctorum		89.41	0.776	NS	NS	Praveen Kumar et al., 2010b
Xanthoparmelia somloensis		65.0	NS	NS	81.0	Zambare et al., 2010
Cetraria islandica	Water	30.0	0.02	10.0	NS	Kosanić & Ranković, 2011
Lecanora atra		93.23	0.09	55.0	NS	
Parmelia pertusa		30.0	0.02	7.31	NS	
Pseudoevernia furfuraceae		33.91	0.02	30.0	NS	
Umbilicaria cylindrica		40.0	0.02	23.0	NS	

[#]Not specified.

conduplicans, Usnea ghttensis and *Parmotrema pseudotinctorum* all had more than 85% DPPH scavenging activity. Furthermore, as shown in Table 4, the methanol extracts of lichens showed the highest activities of reducing power, superoxide radical scavenging and lipid peroxidation inhibition.

Bioactivities of lichen mycobionts

As described in the previous sections, lichens and their metabolites have various biological activities such as antimicrobial, antifungal, antiviral, antiprotizoal, antiproliferative, antioxidant and anti-inflammatory (Behera et al., 2005; Halama & Van, 2004; Ingolfsdottir, 2002; Müller, 2001; Perry et al., 1999; Yamamoto et al., 1998). Dembitsky & Tolstikov (2003) proposed that this phenomenon may be due to the presence of halogenated compounds in the lichen mycobiont. Haloginated compounds are phenol-based molecules synthesized in lichens and other organisms (Neidleman & Geigert, 1986) by the enzyme haloperoxidase in presence of hydrogen peroxide and halide ions (Cl^-, Br^-, I^-) (Grifin, 1990). Hence, the use of isolated lichen mycobionts, lichen-forming fungi (LFF), may overcome, owning to their faster growth and metabolite production, disadvantages that impede commercialization of LFF-derived bioactive compounds. Examples of LFF include *Pyrenula japonica*, *Pyrenula pseudobufonia* (Tanahashi et al., 1999). Wei et al. (2008) isolated 94 LFF from lichen species, collected from China and Korea, that showed a promising antimicrobial activity against the plant pathogenic fungus *Colletotrichum acutatum*, a causal agent of anthracnose on hot pepper. Hur et al. (2003) reported on the isolation (from *Heterodermia* lichen species), cultivation and antifungal activity of a LFF against 14 fungal species. Table 5

Table 5. Antifungal activities of lichen-forming fungi.

Lichen	Test microorganisms	Reference
Melanelia sp.	*Botryosphaeria dothidea*	Oh et al., 2006
Nephromopsis asahinae	*Diaporthe actinidiae*	
Nephromopsis pallescens	*Botryosphaeria dothidea*	
Parmelia laevior	*Diaporthe actinidiae*	
Pertusaria sp.	*Pestalotiopsis dothidea*	
Ramalina conduplicans	*Botrytis cinerae, Sclerotium cepivorum*	
Ramalina sinensis	*Rhizoctonia solani*	
Ramalina sp.	*Phythium* sp.	
Umbilicaria proboscidea	*Botryosphaeria dothidea*	
Vulpicida	*Rhizoctonia solani*	
Amandinea punctata, Anaptychia palmatula, Anzia opuntiella, Bacidia schweinitzii, Bryoria confuse, Bryoria himalayensis, Caloplaca flavorubescens, Cetrelia braunsiana, Cladonia furcata,Cladonia gracilis, Cladonia metacorallifera, Cladonia coniocraea,Cladonia yunnana, Cladonia macilenta, Cladonia coccifera, Cladonia cervicornis, Cladonia pleurota, Cetrelia braunsiana, Cetrelia japonica, Cladonia squamosissima, Cladonia rangiferina, Cladonia scabriuscula, Everniastrum cirrhatum, Gymnoderma coccocarpum, Heterodermia japonica, Heterodermia hypoleuca, Heterodermia microphylla, Hypogymnia delavayi, Hypogymnia pseudoenteromorpha, Hypogymnia pruinosa, Hypogymnia hengduanensis, Hypotrachyna osseoalba, Icmadophila ericetorum, Lecanora argentata, Megalospora tuberculosa, Melanelia olivacea, Menegazzia terebrata,Menegazzia pseudocyphellata, Myelochroa aurulenta, Myelochroa irrugans, Myelochroa galbina, Myelochroa aurulenta, Myelochroa indica, Myelochroa entotheiochroa, Nephromopsis yunnanensis, Nephromopsis pallescens, Nephromopsis ornate, Nephromopsis asahinae, Nephromopsis pseudocomplicata, Parmelia laevior, Parmelia adaugescens, Parmelia pseudolaevior, Parmelia omphalodes, Parmotrema austrosinense, Parmelia simplicior, Parmotrema ultralucens, Pannaria leucosticte, Phaeophyscia limbata, Phaeophyscia exornatula, Phaeophyscia melanchra, Physcia caesia, Phaeophyscia exornatula,Phaeophyscia hirtella, Physcia stellaris, Physcia stellaris, Phaeophyscia melanchra, Punctelia borreri, Pyxine endochrysina, Pyxine consocians, Ramalina conduplicans, Ramalina exilis, Ramalina intermedia, Ramalina litoralis, Ramalina pertusa, Ramalina sp., Ramalina complanata, Ramalina yasudae, Ramalina almquistii, Ramalina sinensis, Ramalina roesleri, Rimelia clavulifera, Rimelia reticulate, Stereocaulon commixtum, Tephromela atra, Tuckneraria pseudocomplicata, Umbilicaria esculenta, Umbilicaria proboscidea, Umbilicaria kisovana, Umbilicaria yunnana, Usnea longissima, Usnea orientalis, Nephromopsis pallescens, Xanthoparmelia hirosakiensis, Xanthoria elegans	*Colletotrichum acutatum*	Wei et al., 2008

(*Continued*)

Table 5. (*Continued*).

Lichen	Test microorganisms	Reference
Heterodermia sp.	*Bipolaris coicis, Botryosphareia dothidea, Botrytis cinerea, Cercospora kikuchii, Collectotricum coccodes, Collectotricum gloeosporioides, Collectotricum orbiculare, Fusarium graminearum, Magnaporthe grisea, Pestalotiopsis longiseti, Phomopsis mali, Phomopsis soje, Rhizoctonia solani, Sclerotinia sclerotiorum*	Hur et al., 2003
Acarospora cervina, Bacidia rubella, Cladonia coniocraea, Cladonia furcata, Cladonia pyxidata, Diploschistes scruposus, Evernia prunastri, Hypogymnia physodes, Lasallia pustulata, Lecania hyaline, Lecanora argentata, Lecidella elaeochroma, Melanelia fuliginosa, Neofuscelia pulla, Parmelia saxatilis, Parmelia sulcata, Parmelina tiliacea, Physconia distorta, Protoparmeliopsis muralis, Ramalina fastigiata, Ramalina pollinaria, Sarcogyne regularis, Umbilicaria hirsute, Xanthoparmelia conspersa, Xanthoparmelia stenophylla	*Collectotrichum acutatum C. coccodes C. gloeosporioides*	Jeon et al., 2009

Table 6. Cultivation media for production of bioactive compounds from lichen-forming fungi (Stocker & Hager, 2008).

Lichen-forming fungi	Medium	Bioactive compounds produced
Cetraria islandica	Lilly & Barnett Medium (LB)*, S4%	Protocetraric acid, fumarprotocetraric acid, confumarprotocetraric acids, succin-protocetraric acid (protolichesterinic acid)
Cladonia bellidiflora	Malt Yeast Extract[#] Medium (MY)	Bellidiflorin, graciliformin
Lobaria fendleri	Murashige & Skoog[§] Medium (MS)	Gyrophoric and 4-*O*-methylgyrophoric acid
Solorina crocea	Mix medium*	Solorinic and disolorinic acids, hybocarpone
Haematomma stevensiae	Sabouraud 4% glucose agar (S4)*	Haematommone, russulone
Heterodeamuelleri	LB+Soil extract*, MS, Sabouraud 2% glucose agar (S2)*	Diffractaic acid, barbatic acid
Evernia divaricata	LB+Bark extract*	Divaricatic acid
Umbilicaria mammulata	Potato Dextrose Agar (PDA)	Gyrophoric acid
Lecanora rupicola	LB	Lecanoric acid, sordidone, eugenitol, atranorin (haematommic acid)
Neuropogon sphacelatus	LB	Usnic acid
Xanthoria elegans	LB	Parietin, 1-*O*-methylparietin, emodin, 1-*O*-methylemodin, teloschistin, teloschistin monoacetate, 1-*O*-methylphyscionbisanthrone, physcion-bisanthrone
Cryptothecia rubrocincta	LB 4% erythriol	Chiodectonic acid, confluentic acid
Cladonia furcata	LB 4% ribitol	Chrysophanol
Haematomma persoonii	LB 4% ribitol, 4% sorbitol	Isosphaeric acid, chloroatranorin, sphaerophorin, russulone
Protousnea magellanica	LB, S4%	Usnic acid, sekikaic and subsekikaic acid, 40 -*O*-demethylsekikaic and 40 -*O*-demethylsub-sekikaic acids
Ramalina peruviana	Liquid LB	Atranorin, sekikaic acid
Lobaria spathulata	MS	Methylorsellinate, lecanoric and gyrophoric acids, telephoric acid (shikimic acid pathway)
Bunodophoron patagonicu	MS 4% sucrose	Isopatagonic and 2-*O*-methylisopatagonic acid (depsides), ascomatic and norascomatic acid (dibenzofurans)
Cladonia salmonea	MY	Usnic acid, salazinic acid, rhodocladonic acid
Xanthoparmelia flavescentireagens	MY, MS, LB, PDA	Usnic acid, norlobaridone, loxodin, divaricatic acid
Stereocaulon ramulosum	MY, S4%	Perlatolic acid, stenosporic acid, divaricatic acid

[¶]Lilly & Barnett, 1951; [#]Yamamoto, 1990; [§]Murashige & Skoog 1962; *Stocker & Hager, 2008.

contains a list of LFF with promising antifungal activities. Only a few reports are available on antibacterial activities of LFF in literature. For example, an antibacterial activity of LFF from *Nephromopsis pallescens* lichen against *Helicobacter pylori* was recently reported by Luo et al. (2011).

Pharmaceutical and biotechnological uses of LFF require large quantities of fungal materials for extraction. Most lichen fungi can be cultured in liquid and semiliquid media. Most of the lichen end products that are formed in the fermentation media are a mix of substances that need further purification using chemical separation methods like selective extraction, preparative chromatography, etc. Table 6 shows a selection of nutrient media that have been used to induce biosynthesis of LFF-based bioactive compounds. However, to date, progress in evaluation of lichen-derived fungi for antifungal activity against plant pathogenic fungi in order to develop less harmful and

safer protectants (e.g., as novel agrochemicals) has been slow. The LFF have shown promising antifungal activities, however, more research needs to be done to reveal the full potential of biological activities from LFF.

Conclusions

Despite their broad spectrum of biological activities, lichens have for long been overlooked by mycologists and agro-chemists, mainly due to their slow growth in nature and difficulties in their artificial cultivation. Because of that, the stage of large-scale industrial production of lichen metabolites has not been reached yet. More research and development is required to develop, optimize and scale-up promising lichen-based technologies of high industrial and national importance. The biopharmaceutical industry would benefit though the commercialization of biotechnologies aimed at production of natural anti-oxidants, anti-microbial, anti-insecticidal, antipyretic, and anti-cancer agents. Lichens hold great potential that needs to be fully explored and utilized for the benefit of human health and our society.

Declaration of interest

The authors report no conflicts of interest.

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