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MINI-REVIEW

Ecological and biotechnological aspects of lichens

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Abstract Lichens and the partners from three different kingdoms are both taxonomically and physiologically a very diverse group, which makes them interesting from both ecological and biotechnological points of view. A lichen is a mutual ecophysiological innovation in many extreme environments in which symbiosis seems to protect the partners. Lichen's ability to grow in harsh environments can be advantageous, resulting in important ecological niches, or disadvantageous when lichens occupy and cause biodeterioration of cultural monuments. Recently, new candidate compounds for drugs, UVB protection, and antifreeze proteins for frozen foods were discovered. Lichens were also found to have potential in bioplastic degradation and prevention of desertification. Nevertheless, there is still large potential for further industrial screening and research on lichen products. Due to improved culture techniques of isolated symbionts, increased knowledge of their secondary metabolism and improved methods for solubilizing lichen metabolites, the screening and activity tests can be implemented more easily today than in the past.

Keywords Lichen · Green algae · Cyanobacteria · Fungi · Symbiosis · Natural product

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Introduction

A lichen is a symbiotic life form between a wide range of fungi, algae, or cyanobacteria, or possibly of all three (Hawksworth et al. 1995; Nash 1996a). The genetic and phenotypic diversity of the organisms involved in lichen symbiosis represents a valuable source for commercially interesting compounds. Lichens and their natural products have a long tradition of being used for decorations, brewing and distilling, perfume and dying industry, food, and natural remedies (Llano 1948; Richardson 1975, 1988; Fahselt 1994; Elix 1996; Kumar and Müller 1999a; Ingolfsdottir et al. 2000; Choudhary et al. 2005; Ingolfsdottir 2002; Müller 2001; Stocker-Wörgötter 2005). With modern technology, the potential of discovering and utilizing useful metabolites has increased. This paper provides a brief overview of the partners in lichens, their ecophysiology, and lichen secondary metabolites. The more practical aspects of the prevention of lichen-caused weathering of glass and rocks and the latest applications involving lichens are also described.

Lichen symbiosis

> A lichen is an ecologically obligate, stable mutualism between an exhabitant fungal partner and an inhabitant population of extracellularly located unicellular or filamentous algal or cyanobacterial cells.
>
> (Hawksworth et al. 1995).

The lichen symbiosis probably evolved around 400–600 million years ago (Yuan et al. 2005). Lichens can be considered as ecosystems where the interaction of partners results in behavior and life forms that are not

found in the isolated partners (Nash 1996a; Tehler 1996; Kranner et al. 2005; Vrablikova et al. 2006; Fig. 1). Lichens are not regarded as a taxonomic group, but lichen taxonomy is based on the taxonomy of the fungal partner, the mycobiont (Tehler 1996). In a course of evolution, about 13,000 extant fungal species (Hawksworth 2001) have specialized in gaining their carbon and about 1,500 species also in gaining their nitrogen from a photosynthesizing partner (photobiont; Hawksworth et al. 1995). Nearly 19% of all fungi are lichenized (Lutzoni et al. 2001; Hawksworth et al. 1995). The fungal diversity alone offers a great metabolic potential for new ecological and biotechnological discovery.

More than 98% of lichenized fungal species belong to phylum Ascomycota, a few to orders of phylum Basidiomycota and some to Mitosporic fungi (Hawksworth et al. 1995; Tehler 1996). Most of the lichenized fungi (mycobionts) form lichen symbiosis with green alga (Chlorophyta; Lewis and McCourt 2004), only about 10% with cyanobacteria, and 3% with both green alga and cyanobacteria (Tschermak-Woess 1988; Hawksworth et al. 1995; Honegger 1996a). Most of the tripartite lichen thalli consist of lichen fungi and green alga (Chlorophyta; Lewis and McCourt 2004), while the cyanobacteria are spatially separated from alga in internally or externally occurring fungal compartments called cephalodia (Büdel and Scheidegger 1996). Some mycobionts can also change their photosynthesizing partner from green alga to cyanobacterium and vice versa and this leads to changes in thallus morphology. This behavior was suggested to be due to an environmental adaptation and related to ecological compatibility of the photobiont (Honegger 1996a; Stenroos et al. 2003).

Out of the 55 cyanobacterial genera (previously classified as blue-green algae) described in the *Bergey's manual* (Castenholz 2001), 12 to 13 cyanobacterial genera were reported from lichen symbiosis (Tschermak-Woess 1988; Rai 1990). These and nearly 30 green algal genera form from lichen symbioses (Tschermak-Woess 1988; Friedl and Büdel 1996), which is substantially fewer than the taxonomic diversity of lichen fungi. The fungi and the photobiont may not in many cases require a specific partner (for cyanobacteria, see Rikkinen et al. 2002; Lohtander et al. 2003; O'Brien et al. 2005; for green algae, see DePriest 2004; Yahr et al. 2006). Future studies with careful evaluation of cyanobacterial taxonomy (Oren 2004) and carefully chosen DNA markers should result in a clearer picture of the taxonomic diversity of lichen bionts. There are challenges in finding appropriate DNA markers that have descended directly from a common ancestor that provide sufficiently but not too much nucleotide variation and have conserved sites for primer design (Oksanen et al. 2004a; Sánchez-Baracaldo et al. 2005).

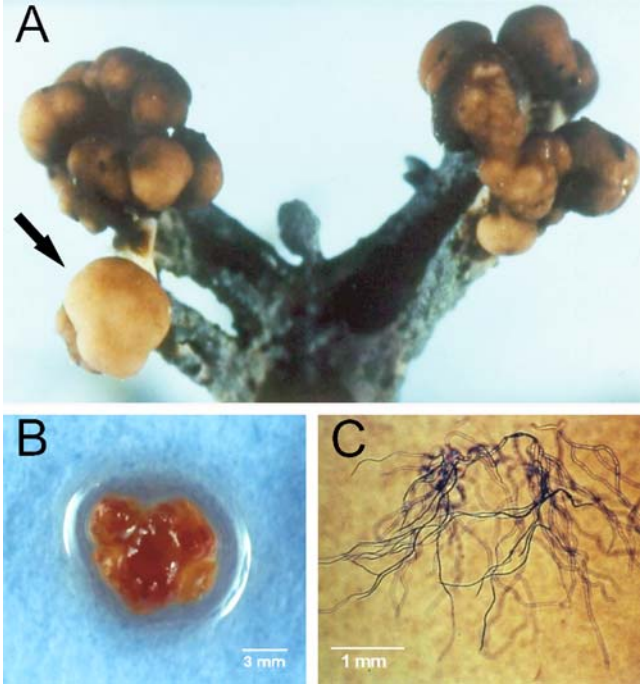

Fig. 1 **a** Lichen species *Cladonia furcata* with fruiting bodies (*arrow*), **b** *C. furcata* spore-derived mycobiont, 3 weeks old, on Lilly–Barnett 1.8% agar medium with 2% glucose, and **c** mycobiont of *C. furcata* in liquid L–B medium with 4% adonitol. Photos from E. Stocker

Ecology of lichens

In general, three major life forms of lichen thallus are recognized, crustose (crust-like biofilm), foliose (leaf-like), and fruticose (branched tree-like, shrubby, pendulous; Fig. 1a) thalli (Hawksworth et al. 1995; Büdel and Scheidegger 1996). The fourth type, gelatinous thallus, is restricted to some cyanobacterial lichens (Büdel and Scheidegger 1996). Even without roots, lichens can efficiently extract nutrients (phosphorus, magnesium, calcium, potassium, sulfur, and iron) from recalcitrant surfaces (Richardson 1975). Rhizinae on lichen thalli may have a function in the uptake of nutrients. Lichens often grow in habitats with extreme light, dryness, or temperature, which are less favorable or unsuitable for higher plants (Kershaw 1985; Vrablikova et al. 2006).

Both mycobiont and the algal photobiont may participate in seasonal photoacclimation in green algal lichens (Vrablikova et al. 2006). The light (Vrablikova et al. 2006) and desiccation (Kranner et al. 2005) tolerance is greater in the lichen symbiosis than in its isolated partners. Lichens adapted to open habitats tolerate extreme desiccation and UV exposure via their screening cortical pigments (Nybakken et al. 2004; Gauslaa 2005; Vrablikova et al. 2006) by preventing the formation of or by scavenging free radicals. In isolated

partners, the photoprotective machineries and biochemical reactive oxygen species scavenging are damaged by desiccation (Kranner et al. 2005).

Lichen thalli are poikilohydrous, which means that their water status passively follows the atmospheric humidity (Nash 1996a; Kappen 2000). The presence of water rapidly activates lichen metabolism (Nash 1996a,b; Schlensog et al. 2004). Recovery of the photosynthetic apparatus after the dark winter takes only minutes in Antarctic lichens, whereas in mosses it is a longer process (Schlensog et al. 2004). Incredible adaptations enable some cold-adapted green algal lichens to activate their photosynthesis at −20°C with water vapor obtained from snow. Photosynthetic activity can be high by at 0°C (Kappen et al. 1996; Kappen 2000; Richardson 2002). Certain strategies increase the fitness of some lichen over others in dry habitats (cited in Richardson 2002). The right choice of the photobiont, the water holding structures, and a tolerance to osmotic stress are some of the survival strategies (cited in Rundel 1988; Richardson 2002). While green algae in lichens are able to activate their photosynthesis with water vapor, cyanobacteria in lichens need liquid water (cited in Rundel 1988; Richardson 2002). This explains why green algal lichens survive in dryer habitats than cyanobacterial lichens, which in humid tropics represent nearly half of the known lichen species (cited in Richardson 2002). Some cyanobacterial lichen species with gelatinous polysaccharides-containing thalli and green algal lichens with cushious water-storing thalli are able to extend their daily metabolism compared to thin, easily drying lichen species (cited in Richardson 2002).

Growing lichen partners

Lichens reproduce either with fungal spores (Büdel and Scheidegger 1996; Murtagh et al. 2000) that have to find a suitable photobiont or by vegetative propagules including both partners (Büdel and Scheidegger 1996). Crustose lichens grow slowly, ≤0.87 mm/year (Karlen and Black 2002; Sancho and Pintado 2004); other growth forms from 0.06 to 36.5 mm/year Richardson 1975). Slow growing crustose lichens, often *Rhizocarpon geographicum*, were used as natural chronometers. The technique termed lichenometry can determine the relative age of geomorphological objects (Karlen and Black 2002; Sancho and Pintado 2004). Lichenometry was suggested as a valuable tool for monitoring climate change in the maritime Antarctic (Sancho and Pintado 2004).

Many lichenized fungi and their photobionts can be grown in single cultures, and lichen can be resynthesized from these (Stocker-Wörgötter 2001; Brunauer and Stocker-Wörgötter 2005; Fig. 1). Some fungi, algae, and cyanobacteria isolated from lichens are available from culture collections, e.g., American Type Culture Collection (ATCC) and Culture Collection of Algae at the University of Göttingen. Growth of lichen fungi is slow and variable between different fungi; a culture generated from hypnal fragments might at best yield 10 g fresh weight after 1 year. (Stocker-Wörgötter and Elix 2004) and in a case of a fast-growing fungi, e.g., >100 mg dry weight after 10 weeks (Crittenden, unpublished data; Fig. 2). This growth rate is achieved with modern culture techniques incorporating improvements in nutrient media, and culture chambers (Stocker-Wörgötter and Elix 2004; Stocker-Wörgötter 2005; Fig. 2).

In contrast, the photobionts from lichens grow relatively quickly (Friedl and Büdel 1996; Oksanen et al. 2004a,b). Most of the cyanobacteria grow fast in fermenters (Oksanen et al. 2004a,b). Only a few of over a hundred *Nostoc* strains, cultured by the author, grew slowly (perhaps a few grams a year) and could not be suitable for commercial applications.

There is a long way to go in the development of lichen fungi for industrial use (Stocker-Wörgötter and Elix 2004). To Dr. Stocker-Wörgötter (personal communication) and the author's knowledge, there are as yet no reports of lichen fungi grown in bioreactors. Lichens can be collected from the field for applications (Stocker-Wörgötter 2005). However, intensive lichen harvesting is not a sustainable solution because lichen populations recover extremely slowly (Olofsson 2006). The development of bioreactors for cultures and genetic manipulation would facilitate large-scale production of lichen metabolites.

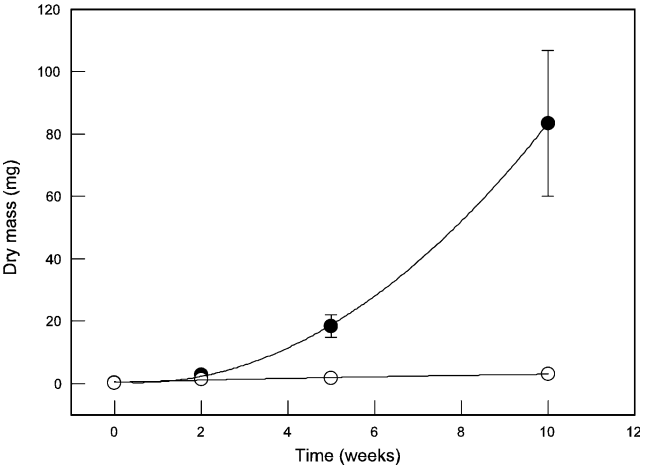

Fig. 2 Growth curves for lichen-forming fungi in axenic liquid batch culture using filtered malt–yeast extract as the growth medium. *Upper curve*, *Pyrenula macrospora*, a fast-grow species; *lower curve*, *Ochrolechia parella*, a slow-growing species. Plotted points are mean values (n=8–12)±1 SEM. The mycelia used for inoculation were derived from polyspore cultures. Data from L. Turbin and P. D. Crittenden, unpublished data

Land restoration

The fact that with only about 1–2% biomass of the angiosperm plant *Gunnera* its symbiotic cyanobacterium *Nostoc* is able to meet plant's nitrogen needs (Adams 2000; Osborne and Sprint 2002) highlights the ecological significance of cyanobacteria in lichens and their impact in nitrogen cycling in nutrient-poor environments where nitrogen leaks from growing and degrading lichens (Nash 1996c).

Prevention of desertification and restoration of desertificated lands could be aided by focusing land restoration on biological soil crusts comprised of mosses and nitrogen-fixing cyanobacterial lichens (Bowker et al. 2005). The latter may also play an important role in increasing soil water-holding capacity and nutrient availability. In one patent it is proposed that lichens could be combined with plant seeds and adapted to extremes and sand-fixing liquid mixture, which is sprayed on to desertificated land (Yang 2002; Table 1).

Lichen caused weathering

Lichens erode substrate surface both biogeophysically and biogeochemically when growing on rock stones, on buildings, on statues, rock carvings, and on glass (Richardson 1975; Drewello and Weissmann 1997; Piervittori et al. 2004; Adamo and Violante 2000). In physical weathering fungal hyphae penetrate voids in lithotypes of the rock up to depth of 10 mm (Favero-Longo et al. 2005). During wetting, expansion of lichen thalli in cracks deteriorates rocks (Richardson 1975). Lichen chemicals that play a role in weathering are low molecular weight organic carboxylic acids (oxalic, citric, gluconic, and lactic acids) that can act as chelators and as corrosive agents (Adamo and Violante 2000; Kiurski et al. 2005). Other agents are CO_2 (Drewello and Weissmann 1997) and polyphenolic compounds of low solubility in water (Adamo and Violante 2000). One of the weathering mechanisms in lichens may also be the modification of the mineral substrate to form secondary crystals (Adamo and Violante 2000) shown with unlichenized fungi (Adeyemi and Gadd 2005). According to Adeyemi and Gadd (2005), the presence of glucose plays an important role in the capacity of fungi to weather minerals. In weathering, lichen growth form and adhesion to the substrate may be less important than physiological (metabolic) activity and the nature of the substrate (Adamo and Violante 2000). Lichens have provided a good model system for studying biological weathering of minerals (Banfield et al. 1999).

Since the 1940s, there were several attempts to find materials and coatings incorporating biocides that could be used to control lichens (Drewello and Weissmann 1997). Historical glass and mineral materials were treated with phenol compounds and derivatives of imidazole and triazole, which are also used for fungal diseases in humans. Carboxylic acids or sodium chloride added to acetic acid were also used against lichens (Kashimoto 2003). Concrete was treated with the lichen secondary metabolite, usnic acid, as a 0.5% solution to prevent the growth of the lichens and cyanobacteria (Sugiyama et al. 1997). In addition, CuO powder and Cu slag was used in ceramic roof tile production to minimize textural faults, which enhance biological growth (Kiurski et al. 2005).

The growing interest to biodegradable materials may lead to studies on the capability of lichens to degrade materials. Some lichen fungi and lichen-associated unlichenized fungi and bacteria are able to degrade bioplastic poly-3-hydroxy-butyric acid (Lee et al. 2005).

Lichens as environmental indicators

Lichens adsorb and are sensitive to heavy metals (Garty 2001). *Coccomyxa* photobiont species were more sensitive to metals than *Trebouxia* species and this may affect the habitat preference of lichens containing these green algae (Guschina and Harwood 2006).

Lichens are used in environmental monitoring of industrial pollution (Garty 2001). Monitoring methods include quantification of lichen populations, examination of lichen morphology, and heavy metal analyses of natural or transplanted thalli (Garty 2001; Krasnogorskaja et al. 2005). The emission of ethylene is one of the measures of air pollution stress even though ethylene biosynthesis and its control in lichen are not fully understood (see contrary views of Ott et al. 2000; Lurie and Garty 1991; Oksanen 2004). A new method for environmental monitoring involves the reduction of triphenyltetrazolium chloride to colored triphenyl formazan in lichen (Bačkor and Fahselt 2005). This measure of lichen dehydrogenase activity indicates environmental stress in lichens and their isolated bionts. Some lichen species are also indicators of the conservation value of forests as their occurrence correlates to forest continuity (Hedenås and Ericson 2000).

Lichen metabolites

Lichenologists have studied lichen chemistry for the past hundred years and have found over 800 compounds (cited in Müller 2001) considered as secondary metabolites (Elix 1996). Polyketide-derived aromatic compounds include, e.g., depsides and depsidones, dibenzofurans, anthraquinones, xanthones, and naphthaquinones. Compounds from other

pathways result in, e.g., esters, terpenes, steroids, terphenylquinones, and pulvinic acid (Fahselt 1994; Cohen and Towers 1995; Elix 1996; Müller 2001; Brunauer and Stocker-Wörgötter 2005; Stocker-Wörgötter 2005). Most of the products are restricted to lichens and of these, depsides and depsidones occur most commonly (Fahselt 1994; Elix 1996). Parasite parasymbionts (Honegger 1996b) can also be a source of natural products and may affect the metabolism of lichens (Blanco et al. 2002). One isolated lichenicolous fungus LL-RB0668 produced two new antibacterial bisnaphthopyrones (He et al. 2005).

Despite some patents (Table 1) and two extensive surveys under the direction of Dr. Y. Yamamoto (Nippon Paint) and Dr. P. D. Crittenden (in collaboration with Xenova), industry has not recently exploited lichens for new natural products (Miao et al. 2001; Stocker-Wörgötter 2005; Richardson, personal communication). One reason for this is that lichens and lichen fungi grow slowly in culture (Stocker-Wörgötter and Elix 2004; Behera et al. 2006). There has also been no success in enhancing the expression of ketides in their natural or surrogate hosts (Stocker-Wörgötter and Elix 2004). Secondly, low predictability in the production of target compounds in many cases may present a problem (Stocker-Wörgötter and Elix 2004; Stocker-Wörgötter 2005). Thirdly, because lichens are not commonly consumed by humans, the lichen-derived compounds may need extensive risk assessment. It is well documented that many lichens can cause allergic reactions such as dermatitis (Richardson 1975, 1988; Fahselt 1994; Ingolfsdottir 2002).

Most lichen secondary metabolites are of fungal origin (Elix 1996) and are exported outside the fungal cells to be found on cell surfaces as crystals in different parts of the thallus. They often accumulate in the upper cortex or in specialized structures such as fruiting bodies (Fahselt 1994; Elix 1996). The primary (polysaccharides) and secondary lichen compounds showed bioactivities from nematocidal, antimicrobial, cytotoxic, antimutagenic, and antiproliferative to immununostimulatory effects (Fahselt 1994; Elix 1996; Müller 2001; Ingolfsdottir 2002; Haraldsdóttir et al. 2004; Pramyothin et al. 2004; Choudhary et al. 2005; Schepetkin and Quinn 2006; Table 1). There are single lichen species that have many of these activities (Choudhary et al. 2005). When *Usnea barbata* is used together with extracts from the plant *Hypericum perforatum* (Schempp et al. 2005) it was claimed to heal various forms of dermatitis, skin aging, acne, rosacea, and *Pityrosporum* yeast infection. Choudhary et al. (2005) have determined a structure of an antiinflammatory but noncytotoxic phenolic compound, longissiminone A, from *Usnea longissima*.

Lichens that were rinsed with acetone to extract lichen substances were more palatable to generalist snail herbivore than untreated lichens (Gauslaa 2005). Thus, some lichen substances may effectively protect lichens against herbivores (Müller 2001; Gauslaa 2005). Extracts of *Parmelia cirrhatum*, *Evernia prunastri*, and *Hypogymnia physodes* also showed antifungal activity ranging from slight to strong against some plant pathogens (Shahi et al. 2003; Halama and van Haluwin 2004). However, it is important to study the environmental effects of these lichen substances before their use as pesticides or fungicides.

Some lichens, including cyanobacterial lichen species *Nephroma arcticum*, contain antifreeze proteins (AFPs) that were patented by Unilever for their property of modifying ice crystal growth because AFPs have a freezing point that is lower than melting point and can inhibit recrystallization (Berry et al. 2001; Sidebottom et al. 2004). With these properties, AFPs maintain homogenized food textures even when frozen. Patents describe various ways to obtain the protein: extracting from lichens collected from the natural habitat or expressed, e.g., in culture. Good Humor Breyers Ice Cream (Unilever) may be the first ones to use AFPs in the manufacture of commercial milk-containing frozen confections. A lichen-originated AFP may be the "ice structuring protein found in nature" they mentioned in their web site in March 2006.

Bioactive metabolites from mycobionts

The medicinal bioactivities of one of the common lichen metabolite, usnic acid, were reviewed by Ingolfsdottir (2002) (Table 1). In high doses it can be hepatotoxic (Han et al. 2004; Pramyothin et al. 2004; Durazo et al. 2004). In isolated rat hepatocytes (+)-usnic acid resulted in induced loss of cell membrane integrity that lead to the destruction of mitochondrial respiration and oxidative phosphorylation besides also stimulating respiration (Pramyothin et al. 2004). As usnic acid efficiently stimulates cellular energy metabolism (Pramyothin et al. 2004), it was incorporated into weight loss products. One dietary supplement incorporating sodium usnate was associated with severe chemical hepatitis in seven persons (Favreau et al. 2002). Pure usnic acid has caused liver failure (Durazo et al. 2004). One hazardous weight loss product containing usnic acid is on the online market (National Food Agency Finland 2006). In the European Union (EU), regulations based on an EU Directive allow the sale of dietary supplements without a permit or scientific evidence, indeed, even US regulations are limited (Bent and Ko 2004).

The (−)-usnic and evernic acids were shown to have antifungal activities toward some plant pathogens (Halama and van Haluwin 2004). Terragen Discovery (Davies et al. 2002) has patented a method involving usnic and vulpinic acids for the inhibition of eukaryotic protein kinases. The (+)-usnic acid attached to polymers was shown to kill cells

Table 1 Metabolites and their applications and ecological innovations involving lichen thalli as whole, lichen-originated fungi, or cyanobacteria

Metabolites and innovations	Bioactivity/application	Reference
Originated from lichen thallus/lichen fungi		
α-Glucan	Effects on macrophages	Reviewed by Schepetkin and Quinn (2006)
Antifreeze proteins	Maintaining milk containing frozen confections homogenized	Berry et al. (2001): patent appl. WO0183534; Sidebottom et al. (2004): patent appl. US6774210
Atranorin	Inhibition of leukotriene B_4 biosynthesis in leukocytes	Kumar and Müller (1999b)
Beta-1,6-D-glucan	Antitumor and analgetic activities	Stepanenko et al. (1998): patent appl. RU2121839
Compounds from *Cladonia* sp.	Antimicrobial: for packages of frozen food	Savvateeva et al. (2002): patent appl. RU2162637
Compounds from *U. barbata*	Healing human skin diseases	Schempp et al. (2005): patent appl. WO2005099728
Cytochrome P450 enzyme of lichen fungus	Oxidizing an alkyl group in specific levels	Pacey (2002): patent appl. JP2002034585
Diffractaic acid	Inhibition of leukotriene B_4 biosynthesis in leukocytes, antiproliferative	Kumar and Müller (1999a,b)
Evernic acid	Fungicidal: total/strong growth inhibition of plant pathogens	Halama and van Haluwin (2004)
Extracts of *Graphis* spp., others in Graphidaceae	Inhibition of tyrosinase and xanthine oxidase, scavenging of superoxide	Behera et al. (2006) and references therein
Extracts of *P. cirrhatum*, *E. prunastri*, *H. physodes*	Fungicidal: total/strong growth inhibition of plant pathogens	Halama and van Haluwin (2004); Shahi et al. (2003)
Extracts of *Ramalina farinacea*	Antiviral: reduced lenti- and adenoviral infectivity	Esimone et al. (2005)
Extracts of *Xanthoria elegans*, *Acanthosis nigricans*	Cancer chemoprevention	Ingolfsdottir et al. (2000)
Extract/purified compound from *Collema*	For 80% UVB protection: UV absorbency 220–425 nm	Claes et al. (2005): patent appl. US2005129630
Gyrophoric acid	Antiproliferative effect (cytostatic) on human keratinocytes	Kumar and Müller (1999a)
Heteroglycans (acidic)	Effects on macrophages	Reviewed by Schepetkin and Quinn (2006)
Lichen extracts	Prevention of estrogen formation from estrogen precursors	Ingolfsdottir et al. (2000)
Lobaric acid from *Stereocaulon alpinum*	Antiproliferative on human cancer cells	Haraldsdóttir et al. (2004)
Longissiminone A from *U. longissima*	Antiinflammatory	Choudhary et al. (2005)
Methyl-β-orcinol carboxylate	Against methicillin-resistant *S. aureus* (MRS)	Anonymous (1993): patent appl. JP5271064
Methyl-β-orcinol carboxylate	Against pathogenic fungi-resistant to polyene and azole antibiotics	Garg et al. (2004): patent appl. CA2521055

Protein active synergistic enzyme	Human and veterinary medicines	Yang and Yang (2001): Patent CN1289844
Protolichesteric acid	Inhibition of leukotriene B_4 biosynthesis in leukocytes	Kumar and Müller (1999b)
Protolichesteric acid from *Cetraria islandica*	Antiproliferative on human cancer cells	Haraldsdóttir et al. (2004)
Usnic acid	Against lichens and cyanobacteria	Sugiyama et al. (1997): Patent JP2728238
Usnic acid	Antimicrobial, antiprotozoal, antiviral, antiproliferative, antiinflammatory, antipyretic, analgesic	Reviewed by Ingolfsdottir (2002)
Usnic acid	Hepatotoxic nutritional additives for weight loss	Favreau et al. (2002); Durazo et al. (2004); National Food Agency Finland (2006)
Usnic acid	Eukaryotic protein kinases inhibition	Davies et al. (2002): Patent US6455270
(+)-Usnic acid	Against bacterial biofilm formation on medical devices	Francolini et al. (2004)
(−)-Usnic acid	Induction of human apoptotic cell death	Bézivin et al. (2004)
(−)-Usnic acid	Fungicidal: total/strong growth inhibition of plant pathogens	Halama and van Haluwin (2004)
Vulpinic acid	Eukaryotic protein kinases inhibition	Davies et al. (2002): Patent US6455270
Ecological innovations		
Degradation of poly-3-hydroxy-butyric acid	Degradation of bioplastic	Lee et al. (2005)
Input of nutrients-, water-, and soil-holding capacity	Prevention of desertification and land restoration	Yang (2002): Patent CN1374425; Bowker et al. (2005)
Lichenometry	Monitoring climate change in the maritime Antarctic	Sancho and Pintado (2004)
Reduction of triphenyl–tetrazolium chloride	Indication of environmental stress: dehydrogenase activity	Bačkor and Fahselt (2005)
Simplified lichenoindication method	Evaluation of atmospheric pollution by observing morphology of lichens	Krasnogorskaja et al. (2005): Patent RU2260934
Lichen originated cyanobacteria		
Biologically active protein	Medicine, nutritional additives, environmental protection	Yu et al. (1997): Patent CN1149625
Cryptophycin derivative	Pesticide, drug: antiproliferative	Sesin (1989): Patent US4845085; Trimurtulu et al. (1994); Biondi et al. (2004); D'Agostino et al. (2006)
Microcystins	Inhibitors of eukaryotic protein phosphatases 1&2A, tumour promoters	Oksanen et al. (2004b)

of the bacterium *Staphylococcus aureus*, and change the morphology of a biofilm of the bacterium *Pseudomonas aeruginosa* (Francolini et al. 2004). This system may provide a method for inhibiting bacteria from forming biofilms on medical devices. Methyl-β-orcinol carboxylate extracted from lichen was patented for use against methicillin-resistant *S. aureus* (MRS; Anonymous 1993) and more recently against human pathogenic fungi that are resistant to polyene and azole antibiotics (Garg et al. 2004).

While all P450 enzymes of hemoprotein enzyme superfamily are suitable for oxidizing an alkyl group bonded directly or through a linkage to a sulfonamide moiety, certain microorganisms are capable of oxidation in specific levels. One of these is lichen fungus *Syncephalastrum racemosum* strain ATCC 18192 (Pacey 2002). Innovation reduces steps required to synthesize molecules of medicinal interest.

Lichens are rich in pigments (Kappen 2000; Friedl and Büdel 1996; Elix 1996: Nybakken et al. 2004; Vrablikova et al. 2006), which may differ with the seasonal amount of irradiance (Vrablikova et al. 2006). The pigments can screen UVB as shown for melanins and parietin (Nybakken et al. 2004; Vrablikova et al. 2006). There is a patent (Claes et al. 2005) for using natural extract or a purified compound from the cyanobacterial lichen *Collema* with an UV absorbency of 220–425 nm that gives 80% protection against UVB irradiation. Some lichens (e.g., *Heterodermia obscurata* and *Nephroma laevigatum*) contain anthraquinones that can be used in dyes (Cohen and Towers 1995; Müller 2001) and as catalysts in wood pulp production and in the paper industry.

Recently, there was a renewed interest in low molecular weight molecules from lichens, such as polyketides as drugs and for pharmaceutical products (Stocker-Wörgötter 2005). Polyketides were studied with mass spectrometry and NMR (Su et al. 2003). New synthetic approaches applying asymmetric methods with transition metal or organocatalysts should enable the engineering of structurally diverse compounds (Seitz and Reiser 2005). Kristmundsdóttir et al. (2005) have managed to enhance the water solubility of depsides and depsidones to test them in common pharmacological models. Esimone et al. (2005) described a viral vector-based assay for screening bioactive compounds from lichens. Genetic engineering, cloning, and homologous or heterologous expression may facilitate the environmentally sound large-scale production of lichen natural products (Miao et al. 2001). However, up to the present, there was no successful expression of lichen ketides in prokaryotic or eukaryotic hosts (Brunauer and Stocker-Wörgötter 2005). DOE Joint Genome Institute (US Department of Energy) plans to sequence genome of first lichen fungus *Xanthoria parietina* and the availability of genome sequences of lichen partners should enable faster development of genetic and proteomic methods.

Control of fungal biosynthetic pathways

Recently, the control mechanisms of biosynthetic pathways in secondary metabolism of some lichens were studied but are far from fully understood (Brunauer and Stocker-Wörgötter 2005; Stocker-Wörgötter 2005; Behera et al. 2006). It is not clear why certain secondary metabolites are, or are not, synthesized in aposymbiotic lichen fungi (Brunauer and Stocker-Wörgötter 2005). Besides the growth medium and the growth state of the fungi, factors such as temperature and UV exposure or the presence of the algal partner affect the secondary metabolism of lichen fungi (Stocker-Wörgötter 2001, 2005; Stocker-Wörgötter and Elix 2004; Brunauer and Stocker-Wörgötter 2005; Behera et al. 2006). Culture conditions can determine whether fatty acid biosynthesis predominates over the polyketide synthesis. In fungal cultures of *Dactylina arctica*, an active polymalonyl pathway is found in the early growth stages, while other pathways resulting in more complex end products, such as tridepsides, are active in later developmental stages after a cold treatment at −23°C for 3 weeks (Stocker-Wörgötter 2005). Spore-derived cultures of the *Bunodophoron patagonicum* produced depsides and dibenzofurans, while fragment-derived cultures lacked dibenzofuran production (Stocker-Wörgötter and Elix 2004). The fungi of lichen species *Lecanora rupicola* grew very slowly in culture, and did not produce detectable amounts of lichen substances such as atranorin and lecanoric acid, until the fungus was resynthesized with its algal partner. Even then, some of the original metabolites identified in the voucher specimen could not be detected (Brunauer and Stocker-Wörgötter 2005).

Bioactive metabolites from photobionts

Marine and freshwater cyanobacteria produce a wide range of peptides and other bioactive compounds and are a rich source of mixed peptide–polyketides (Burja et al. 2001). Twenty metabolites with commercially promising bioactivity, such as anticancer, antibiotic, antifungal, and antiviral activities, were reported from seven *Nostoc* strains, the genus most common in terrestrial cyanobacterial symbioses. The most commonly isolated bioactive compounds are microcystins, most of which are potent inhibitors of eukaryotic protein phosphatases 1 and 2A. So far, a single lichen-associated *Nostoc* sp. strain IO-102I (Oksanen et al. 2004b) was shown to produce microcystins. Screening of over 1,000 cyanobacterial strains for antitumor activity revealed only a single *Nostoc* sp. strain GSV 224 from a lichen that showed strong cytotoxic activity with its cyclic peptide cryptophycin A (dioxadiazacyclohexadecenetetrone). This peptide was also found from another lichen-

originated *Nostoc* sp. strain ATCC 53789 (Trimurtulu et al. 1994). A synthetic compound, structurally related to this cryptophycin, has a potent antiproliferative effect by destabilizing microtubules during mitosis (D'Agostino et al. 2006). When used for treating human ovarian cancer, it resulted in considerable disease stabilization. The antimitotic cryptophycin could also possibly be used as pesticide but its cytotoxicity to the nontarget organisms has to be studied (Sesin 1989; Biondi et al. 2004). This is necessary because the cryptophycin-producing *Nostoc* sp. strain ATCC 53789 had antifungal (toward nine pathogenic fungi), insecticidal (toward *Helicoverpa armigera*), and cytotoxic (toward *Artemia salina*) activities (Biondi et al. 2004).

Carotenoids are commercially important natural pigments that occur in cyanobacteria, one of the model organisms used in genetic engineering of carotenoid production (Lee and Schmidt-Dannert 2002). Moreover, the common green algal lichen symbiont and free-living green algae *Trentepohlia* is rich with carotenoid pigments (Friedl and Büdel 1996). It is likely that lichen-originated green alga and cyanobacteria could be a source for the production of compounds with useful properties.

Perspectives

Recent innovations involving lichen metabolites include AFPs for frozen foods, new antibiotics against bacteria and fungi, pesticides for agriculture and concrete materials, active biological proteins from cyanobacteria as nutritional additives, enzymes for specific enzymatic oxidation, and compounds for UVB protection. Most were patented as the idea of using lichens for land restoration and for preventing desertification. It remains to be seen whether such innovations will be successful on a commercial scale. Hepatitis in humans caused by consumption of herbal remedies containing usnic acid reminds us of the importance of testing of lichen metabolites for toxicity.

The innovations in the present paper focus mainly on compounds derived from lichen thallus, isolated fungi, and on lichen cyanobacteria. No patent involving green algae from lichens was approved so far. With current culturing techniques, lichen fungi can be screened industrially for potentially useful natural products. However, the technique for the rapid growth of lichen fungi in bioreactors and genetic expression of metabolites are needed for large-scale production. Protein expression and genetic engineering are likely to succeed sooner than recombinant techniques with polyketide complexes. The genome sequencing of the first lichen fungus will open a new era in lichenology. It will facilitate a wide range of other approaches such as comparative genomics, genomic engineering, transcriptomics, and proteomics.

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