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Bioactive lichen metabolites: alpine habitats as an untapped source

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Abstract Lichens are fungal and algal/cyanobacterial symbioses resulting in the production of specific metabolites. Some of these are forming an available biomass for phytochemical investigations, including the assessment of biological activities of the isolated compounds. The alpine or polar region are characterised by highly stressful environmental conditions for many organisms, but lichens are among the dominating organisms in these habitats. In the performant mutual protective system, lichen fungi often accumulate high amounts of metabolites with specific physicochemical properties (UV absorbents, hydrophobicity) which help the lichens to survive. Unique secondary metabolites and polysaccharides have been isolated and tested from these organisms. Even though this has been tested until now only with a low number of compounds so far, interesting activities have been recorded. We review here some of the antimicrobial, anti-inflammatory, antiproliferative and antioxidant activities properties described. Solutions with axenic biotechnological cultivation of each symbiotic partner and particularly the mycobiont to obtain the lichen secondary metabolites are challenging to overcome the limitations for the supply of these rare compounds. Additionally, these lichens appear to harbour a diversity of culturable microorganisms from which active compounds have also been isolated recently.

Keywords Bioactivity · Cold habitat · Natural compounds · Pharmacy · Symbiosis

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Introduction

Lichens, a major component of alpine and arctic vegetation, are self-supporting symbiotic associations formed by a fungus with one or several photoautotrophs (algae and/or cyanobacteria), as primary partners, and with other microorganisms as further colonizers. Since the fungal constituent usually dominates the association, lichens traditionally have been considered as a life style of fungi. The lichenous lifestyle is maintained by *c.* 18,800 known species (Feuerer and Hawksworth 2007). In contrast to many fungi that are embedded within their substrates, most lichens expose their vegetative parts at the substrate surface, enabling the photobiont to harvest energy from solar radiation. The compact light-exposed vegetative bodies of lichens, called thalli, are among the most complex and aesthetically pleasing morphologies

evolved by fungi during the past 600 million years (Yuan et al. 2005). Many lichens are highly extremotolerant which allows them to live as pioneers in the alpine zone and other cold environments. Life under these conditions correlates with the production of a variety of compound classes. Several of these are already found in plants or in other fungi, but about 80% reach highest diversity in lichens (Huneck and Yoshimura 1996). The valuation of these metabolites for medicinal purposes is generating an increasing interest as their activities are varied and sometimes significant. Only few lichen compounds are commercially available whereas the thousand known compounds are only partly or not at all investigated for their medicinal potential (Stocker-Wörgötter 2008). We review herein on the biological activities of some lichen compounds and focus on those encountered in lichen species growing in the polar or high mountain areas.

The alpine zone and lichens

The alpine zone is commonly recognised to correspond to the zone above the forest line with the nival zone at the upper limit (at about 2,800 m as in the North French Alps). The altitude may vary according to the latitudinal range and climate type resulting in some varied ecological features. In the Bavarian Alps, it is considered to start around 2,000 m in elevation compared to 4,700–5,000 m of the Andes of Southern Peru or Northern Bolivia (Troll 1973). Differences can also be determined by South or North exposure but such a zone is mainly characterised by an environmental harshness with a cold climate, drastic and rapid changes, lower oxygenated atmosphere and lower soil nutrient content, the mineral support increasing while the organic material is becoming scarce. To some extent, a correlation can be observed of altitudes and latitudes, although light regime varies across latitudes: the vegetation at a 2,000 m altitude for European Alps resembles the tundra vegetation, and that of 3,000 m altitude is similar to the one found in the High Arctic. Similar psychrophilic biological communities are shared by alpine and arctic habitats. There is also some evidence that microbial diversity is high in these habitats (Neufeld and Mohn 2005). The relative amount of microscopic fungi is increasing with altitude (Margesin et al. 2009) and recent analysis carried on subglacial sediment-rich ice from Arctic glaciers showed an unexpected high occurrence and diversity of filamentous *Penicillium* species (Sonjak et al. 2006). Similar richness in cold habitats has been observed for lichens (Asta 1984; Elvebakk and Bjerke 2006)

In arctic-alpine habitats, lichens are pioneer organisms. Often dominating as communities on rocks and stable soils, they form extensive biosurfaces a striking ability to survive in harsh conditions, in cases for several thousand years (Denton and Karlén 1973). Most lichens are therefore recognized by bare eye from a distance as they form bright colored marks on their substrates. Some lichens grow underneath the rock surface in the weathering rind as cryptoendolithic associations. Therefore, they are also particularly studied as models for life survival strategies in extreme terrestrial environments (Wynn-Williams and Edwards 2000; Edwards et al. 2003; de la Torre et al. 2007). Their resistance to extreme temperatures, desiccation and UV radiation stress is sustained by various biochemical processes and synthesis of protective molecules but above all to their capacity to survive in the stage of anhydrobiosis (Beckett et al. 2008). In lichens, all the control mechanisms respond with high sensitivity to excess light (Heber et al. 2000). In the cold environments, the symbiotic association allows a downshift of the photosynthetic gas exchange rates to optimum around 0°C while each of the photobiont or the mycobiont have a range optimum temperature above 15°C (Friedmann and Sun 2005). Such lichens are still active with some liquid water which can be found within the lichen thallus as combined with polyols, sugars or hydrated calcium oxalates, allowing low but functional respiration to temperature of a −20°C. The cellular and intracellular structures, which integrity are particularly exposed through freeze-thawing cycles, are preserved by polyols, polysaccharides, nucleotides, proteins and membrane lipids (Aubert et al. 2007). Extreme desiccation and irradiation increase the formation of ROS in the fungi and alga but protective mechanisms of the whole organism are highly more effective than those of the isolated partners (Kranner et al. 2005). The metabolic processes sustaining tolerance involve the gluthatione redox system and gluconate 6-P accumulation, which is of importance for reviviscence (Aubert et al. 2007). These mechanisms can also be involved to protect lichens from high UV irradiance (Bartak et al. 2004).

Other protective strategies as physical light scattering with oxalates or UV absorbers accumulated in the external layer such as xanthophylls, carotenoids (Singh et al. 2008) or other pigments (e.g., anthraquinones, melanins, chromones) may be involved to help them to tolerate such deleterious conditions. Some of these compounds such as dibenzofurans (e.g., usnic acid), depsides (e.g., atranorin), depsidones (e.g., lobaric acid) or shikiminate derivatives (e.g., calycin) are very commonly found in lichens (Fig. 1). Most of these secondary metabolites are accumulated as crystals on the external surfaces of hyphae (extrolites) in the upper cortex or in the internal medulla of the thallus. One or two of the cortex "lichen metabolites" are usually accumulated in higher amount. They may represent sometimes half of the 5–20% of the extractable material in the organic solvents.

Colourless substances of internal or basal thallus parts can vary, and chemical races are known for many species. Variation often occurs within substance classes (chemosyndromatic variation, Elix and Stocker-Wörgötter 2008). It has been controversially discussed for long whether the chemical races could represent separate species. Chemical variation is variably patterned in lichens and quantities of compounds can in some crustose species even vary among the areoles of a single thallus. Also, altitudinal gradients of chemical compound composition can sometimes be observed, e.g., in the crustose species *Dimelaena oreina*, which comprises 7 described chemotypes. Sampling across an altitudinal transect from 700 to 2,700 m revealed four chemotypes at lower elevations, but only two types at higher altitudes (Leuckert et al. 1981). To what extent this correlates with evolutionary patterns is not yet clear. In the search for new compounds such a chemical diversity can be considered as an opportunity. Alpine lichens offer an original material to investigate, particularly with fruticose or foliose species but also with some crustose species, at least when their macroscopic thalli can be scraped from their support. Lichen material for extraction in phytochemical studies needs to be gathered in dozens of grams (or from in vitro culture). Such studies will likely reveal a variety of further and uncommon compounds, but will be limited to species, which are easy to collect and available in large quantities. One example is presented in the following.

Cetraria islandica L. (Ach.): an alpine lichen

Cetraria islandica, commonly known also as "Islandic moss" is probably one of the best known alpine lichens used in folk medicine. The species develops extensive carpets composed of brownish cushions with more or less erect strap-like branches in boreal to subarctic tundra or above the tree-line in the Alps (see http://jlcheype.free.fr/imagesw/Lichens/Cetraria-islandica.htm). It preferentially occurs over acidic soil at windswept habitats, where the lichen is exposed to rapid and often drastic climatic fluctuations, ranging from overhydration to almost complete desiccation that is correlated also with extreme temperature changes. Besides typical lichen polysaccharides such as lichenan and isolichenan, *Cetraria islandica* contains several secondary metabolites, including the paraconic acids (chiral trisubstituted γ-butyrolactones bearing a carboxylic acid group in the β-position and a lipophilic alkyl chain in the γ-position) protolichesterinic acid (Fig. 2) and roccellaric acid (Horhant et al. 2007) or the depsidone fumarprotocetratric acid (and traces of protoceraric acid), and quite often reddish quinone-like compounds at the senescing bases. There is also a chemical gradient between the growing tips and the senescing basis: the tips contain significantly more paraconic acids, whereas the basis contains higher amounts of fumarprotocetraric acids than detected in the tips, as assessed by TLC (W. Obermayer, unpublished data). In the Kolyma Upland and the Badjal mountains of far Eastern Russia, lichens growing in the highly rigorous climate have changed their metabolism and appearance with regard to European species. For instance, *Cetraria islandica* var. *polaris* do not contain lichesterinic acids but is characterized by bright red thallus tips due to an accumulation of polyhydroxynaphtaquinoid pigments like islandoquinone (Stepanenko et al. 2002).

Protective compounds as a response to environment

Many lichen symbioses tolerate extreme environmental conditions unfavorable to the survival of the individual partners and higher accumulation of secondary protective metabolites is recognized as a response to environmental stress, such as high sun exposure (Gauslaa and Solhaug 2001). In field

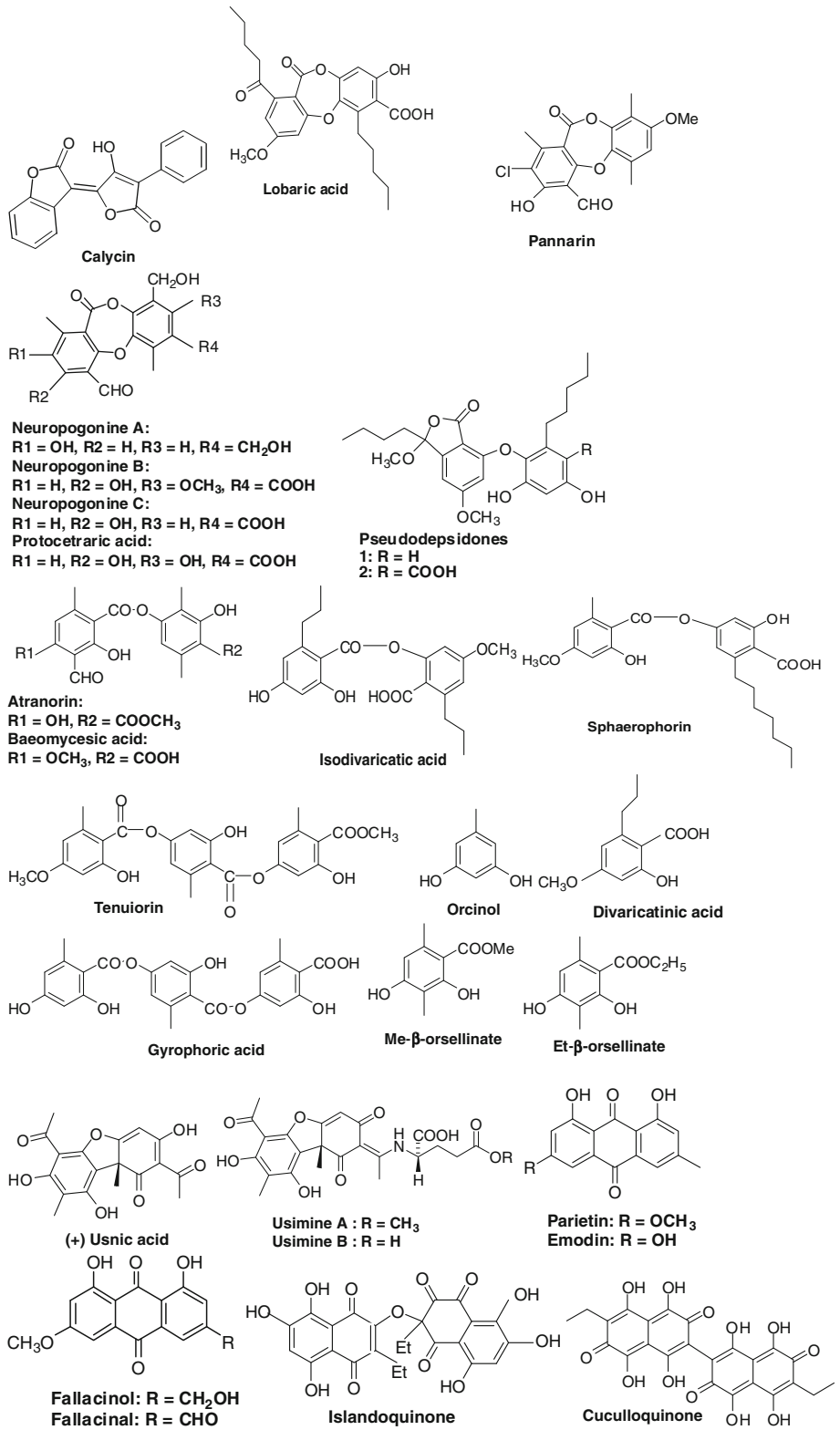

Fig. 1 Phenolic compounds from alpine lichen species with phototoprotective and/or biological activities

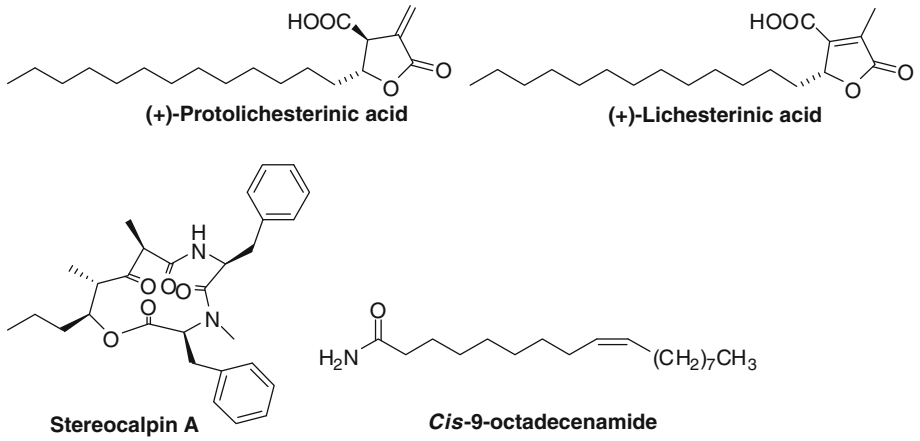

Fig. 2 Miscelleanous compounds from alpine lichen species with biological activities

experiments, the screening of "visible and UV" radiations on *Cetraria islandica* thalli during 3 months induced a 40% average decrease in the level of phenolic compounds, the biosynthesis of most of them being particularly influenced by UV-B radiations (Asta et al. 1999). Both the terricolous *Flavocetraria nivalis* and the crustose *Ophioparma ventosa* are common light-exposed species in the alpine zone and circumpolar areas. In these species, compound production is influenced by UV and photoactive radiation, particularly affecting production of usnic acid (Bjerke et al. 2002). Comparatively large quantities of some compounds, such as 12.7% of divaricatic acid in the *Ophioparma lapponicun* dry weight or 10% of gyrophoric acid (Fig. 1) in *Umbilicaria rossica* collected in mountains or permafrost areas of far East Russia, may indicate that they are stress-related compounds (Stepanenko et al. 2002). Seasonal changes in usnic acid accumulation in *Flavocetraria nivalis* (up between 4 and 8% of the thallus dry weight), both of Arctic-alpine habitat or Patagonian heathland, show the adaptability of lichens (Bjerke et al. 2005). In alpine zones of Chile or in Antarctica where the ozone layer is depleted, an increase of rhizocarpic acid accumulation was found to correlate with the increasing UV-B radiation levels (Rubio et al. 2002). In many alpine species, this shikimic acid derivative is synthesized as well as other shikimic acid derivatives (e.g., calycin) characterized by a conjugated lactone, suggesting a chemical acclimatization of high levels of irradiance. The presence of the UV-absorbing groups can be frequently observed in many cortical metabolites such as depsidones or usnic acid (Rancan et al. 2002; Fernandez et al. 2006) and the anthraquinonic parietin pigment (Fig. 1) synthesis is also described to be UV-B induced in *Xanthoria elegans* (Nybakken et al. 2004). In sunlit steppes on southern slopes of the Mongolian mountain taiga, green-algal lichens with either yellow or orange lichen substances (usnic acid, parietin, pulvinic acid derivatives) or melanin in the cortex dominate, probably because they efficiently absorb both ultraviolet radiations and visible light (Hauck et al. 2009). The cyanolichens (photobiont = cyanobateria ± green algae) are more particularly restricted to moist microsites, the foliose *Peltigera* and *Solorina* species are frequently encountered while gelatinous lichens (e.g., *Leptogium, Collema*) are less common. In such lichens, the protective UV compounds are mainly amino acid derivatives, such as the UV-B absorbing mycosporine collemin (Fig. 3) found in *Collema cristatum* (Torres et al. 2004). All these compounds are considered as UV filter candidates and studied for their photoprotective properties (Hidalgo et al. 2005). Indeed most of them reach the physicochemical criterions as UV filters (Rancan et al. 2002) and can be considered for preventive use against sunburns but also skin cancers, including the highly aggressive melanoma.

More ubiquitous protective compounds such as carotenoids and xanthophylls (e.g., asthaxanthin) are also commonly encountered in lichen species. The 22 species collected in the Himalayan region and analysed by Czeczuga and colleagues (1996) contained a variety of these compounds. It can also be frequently observed that paraconic acids corresponding

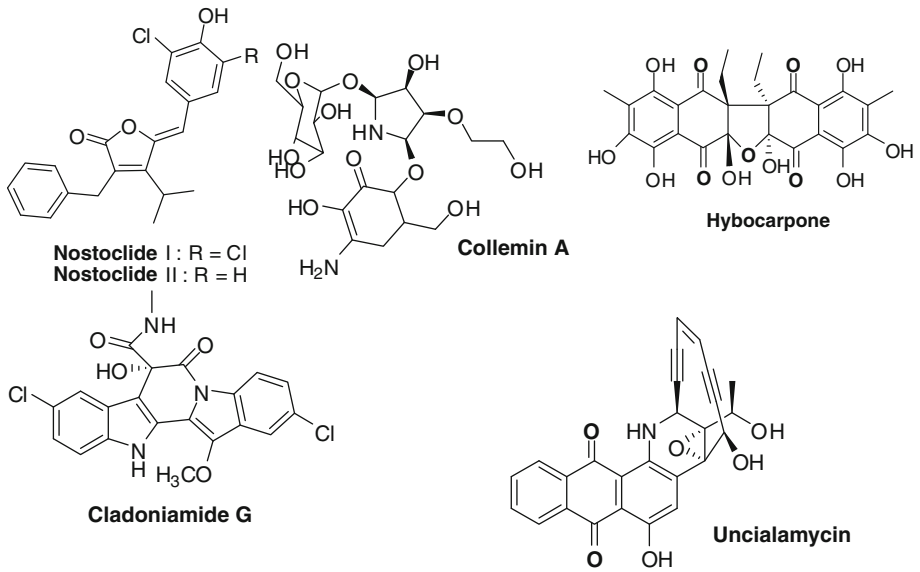

Fig. 3 Compounds from lichen-derived cultures (photobiont, mycobiont or an associated microorganism)

to butyrolactones which are substituted by a long carbon chain are commonly described in species found in alpine areas such as Ural Mountains (Rezanka and Guschina 2000, 2001) or in polar areas (Bodo and Molho 1980). Protolichesterinic acid and lichesterinic acids (Fig. 2) are the most common of these aliphatic acids and found abundant in *Cetraria islandica.* Some of these compounds are also described to form unusual macrolactone glycosides (Rezanka and Guschina 2001) and acetylenic lipids are also encountered in these lichens (Rezanka and Dembitsky 1999). Such compounds may account for a role in membrane integrity and favour liquid water maintain in low temperature conditions. Polyols and polysaccharides which may correspond to up to 57% of the extractable lichen compounds (Baron et al. 1991 cited in Olafsdottir and Ingolfdottir 2001; Podterob 2008) are also likely involved as freeze protectants. Interestingly, it can be noted that lichen derived antifreeze-proteins have also been used as food preservatives (see Oksanen 2006).

Lichen polysaccharides are high molecular weight compounds extractable with polar solvents, and generally with boiling water. Subsequently, the different types of polysaccharides can be separated according to their solubility in cold water (e.g., the soluble isolichenan compared to lichenan) or in alkaline versus acidic solutions, prior to precipitation with alcohols (e.g., methanol). Additionally various membrane filtration devices and gel filtration or ion exchange chromatography systems are used to separate lichen polysaccharides (Smestad Paulsen et al. 2002). Among the dozens of lichens studied for their polysaccharide content, some species are frequently found in cool montane to alpine zones. These are *Cladonia* species (Iacomini et al. 1985), *Cetraria islandica* (Ingolfsdottir et al. 1994b), *Thamnolia vermicularis* (Olafsdottir et al. 1999, 2007), *Peltigera* species (Fukuoka et al. 1968; Omarsdottir et al. 2006b) and *Umbilicaria* species (Nishikawa et al. 1969; Carbonero et al. 2006). They produce a variety of polysaccharides, including α- and β-glucans, galactomannanns and some heteroglycans, the β-glucans being often found in high amounts (Olafsdottir and Ingolfdottir 2001). The different structural types of lichen polysaccharides appear to be quite specific at the family level (e.g., pustulan for *Umbilicaria* species Carbonero et al. 2006 or for a given species such as thamnolan formed by *Thamnolia subuliformis,* the worm lichen (Olafsdottir et al. 1999).

Bioactivities of some lichen compounds found in alpine or polar regions

Lichen substances exhibit a great diversity of biological effects, including antimicrobial, anti-inflammatory, antioxidant, antiproliferative and cytotoxic

activities. Activities described from secondary lichen metabolites encountered in alpine or polar lichen species are given in Tables 1 and 2. Recent reviews have discussed the pharmaceutical potential of lichen substances (Huneck 1999; Muller 2001; Boustie and Grube 2005; Takahashi et al. 2005; Oksanen 2006; Podterob 2008; Muggia et al. 2009). There is a growing interest in the pharmaceutical properties of compounds derived from lichens. However, relatively few lichen substances have been screened in detail for biological activity and therapeutic potential, due principally to difficulties in obtaining them in quantities and purities sufficient for structural elucidation and pharmacological testing. Additionally, precise lichen determination is essential and requires taxonomic expertise. Consequently, very few marketed medicines contain lichen compounds or lichen extracts. One example of commercial success are the riminophenazine antibiotics, exemplified by clofazimine (Lamprene®), which were developed as antimycobacterial drugs (Reddy et al. 1999). Their synthesis followed from identification of the antituberculous activity of derivatives of diploicin, a depsidone produced by the overspread lichen *Diploicia* (*Buellia) canescens* (Nolan et al. 1948; Barry and Twomey 1950).

The alpine *Cetraria islandica* (Icelandic lichen, Lichen islandicus, or Islandic moss) is one of the rare lichen entering the formula of cold remedies [Broncholind® by MCM Klosterfrau (Köln, Germany) Isla-Moos® by Engelhard Arzneimittel (Niederdorfelden, Germany)]. The activity of *Cetraria* extracts is reported to be linked to the presence of polysaccharides as lichenan which helps to maintain hydration in human respiratory routes lowering the mucosal irritation. A small number of cosmetic, nutraceutical (http://www.iceherbs.is/ind_ensk.html), or pharmaceutical firms (e.g., Ichimaru Pharcos; Gifu, Japan) also manufacture products containing lichen substances or extracts. In any case, it should be taken into account that lichen compounds may have side effects particularly when misused. Allergenic reactions have been described for some (Thune and Solberg 1980; Hausen et al. 1993) as so as severe liver failures following about 500 mg/day ingestion of usnic acid in nutraceuticals marketed as weight-loss aids (Durazo et al. 2004; Neff et al. 2004). Thus, applications derived from activities described for lichen compounds have to be thoroughly studied, particularly in the antimicrobial, anticancer and anti-inflammatory domains.

Antibiotic and antifungal activities

The antibacterial properties of lichen extracts are known for long (Burkholder et al. 1945) and still assessed (Piovano et al. 2002; Rankovic et al. 2007; Paudel et al. 2008; Schmeda-Hirschmann et al. 2008; Micheletti et al. 2009). Gram-positive *Staphyloccocus aureus* and *Bacillus subtilis* were sensitive to methanolic extracts of four different Antarctic lichen species (Paudel et al. 2008). These Antarctic lichens were considered to be an enriched source of effective antibacterial agents. Three new depsidones isolated from a *Neuropogon* collected on the Antarctic Livingstone Island showed a moderate activity on a *Mycobacterium vaccae* strain (Ivanova et al. 2002). MICs values obtained from monoaromatic phenols (methyl beta-orsellinate, methyl and ethyl orsellinates) derived from various Icelandic species were found equal or higher than usual preservatives (methyl and propyl-*p*-hydroxybenzoates, *o*-cresol) (Ingolfsdottir et al. 1985). Usnic acid is one of the most common substances found in lichens and encountered in one enantiomeric form (+)-usnic acid in *Usnea* species, (−)-usnic acid in some *Cladonia* or *Alectoria* species, both isomers being, however, described to occur in two alpine species *Flavocetraria nivalis* and *Flavocetraria cucculata* (cited in Stocker-Wörgötter 2008). This substance and others may interfere with palatability or with the digestive flora of the gut of ruminants in the sub polar regions (Iacomini et al. 1985; Vegar Storeheier et al. 2002). Lichens known for their nutritional value as reindeer lichens (e.g., *Alectoria ochroleuca*, *Cladonia* spp., *Cetraria* spp.) species contain high amounts of usnic acid and, in fact, resistant microorganisms such as newly described *Eubacterium rangiferinum* (Clostridiales) have recently been isolated from the reindeer rumen (Sundset et al. 2008). Usnic acid has been used as antibiotic (e.g., Binan®, Usno®), and is still available as a topical antiseptic in some products (e.g., Gessato® shaving treatment from Italy, Camillen 60 Fudes spray and nail oil from Germany). It is suggested for application in medical devices, since usnic acid inhibits bacterial biofilm formation on polymer surfaces (Francolini et al. 2004). This compound or derivatives are valuable active compounds against serious pathogens such as vancomycin-resistant enteroccocci, methicillin-resistant *Staphylococcus aureus* (Elo et al.), mycobacteria (Ingolfsdottir et al. 1998) or

Table 1 Active phenolic compounds from alpine lichen species [values correspond to 50% Inhibitory Concentrations (IC_{50}), 50% Effective Doses (ED_{50}), 50% Lethal Doses (LD_{50}) or Minimal Inhibitory Concentrations (MIC)]

Structure type compound	Lichen species	Activity	References
Depsidones	*Stereocaulon alpinum*	Inhibition of platelet-type 12(S)-lipoxygenase (IC_{50} = 28.5 μM)	Bucar et al. (2004)
Lobaric acid	*Stereocaulon azoreum*	Inhibition of arachidonate 5-lipoxygenase (IC_{50} = 7.3 μM)	Ingolfsdottir et al. (1996)
	Stereocaulon sasakii	Inhibition of cyclooxygenase (IC_{50} = 29.2 μM)	
		Inhibition of DNA synthesis in T-47D, ZR-75-1 from breast carcinomas and K-562 ($14.5 < ED_{50} < 44.7$ μg/ml); inhibition of proliferation of mitogen-stimulated lymphocytes (ED_{50} = 24.5 μg/ml)	Ogmundsdottir et al. (1998)
		Significant inhibition of contractile activity of Guinea Pig *Taenia coli* at 5.8 μM and of cysteinyl-leukotrienes formation at 5.5 μM	Gissurarson et al. (1997)
		MIC values against *Mycobacterium aurum* ≥ 125 μg/ml	Ingolfsdottir et al. (1998)
		Non-competitive inhibition of protein tyrosine phosphatase 1B (PTP1B) (IC_{50} = 0.87 μM)	Seo et al. (2009)
		Inhibition of the polymerisation of tubulin (IC_{50} = 100 μM)	Morita et al. (2009)
		Inhibition of growth on fourteen cancer cell lines (IC_{50} # 12–65 μg/ml)	Ogmundsdottir et al. (1998), Haralsdottir et al. (2004)
Despidones	*Neuropogon* sp.	MIC values against *Mycobacterium vaccae* # 50 μg/ml	Ivanova et al. (2002)
Neuropogonines A–C			
Despidones	*Psoroma reticulatum, P. pulchrum, P. pallidum*	Inhibition of cell growth and induction of apoptosis in human prostate carcinoma DU-145 and human melanoma M14 cells (IC_{50} # 25 μM)	Russo et al. (2006, 2008)
Pannarin			
Pseudodepsidones 1 and 2	*Stereocaulon alpinum*	Inhibition of protein tyrosine phosphatase 1B (PTP1B) (1: IC_{50} = 6.86 μM; 2: IC_{50} = 2.48 μM)	Seo et al. (2009)
Depsides	*Stereocaulon alpinum*	MIC values against *Mycobacterium aurum* ≥ 125 μg/ml	Ingolfsdottir et al. (1998)
Atranorin	*St. ramulosum*	Moderate inhibition of protein tyrosine phosphatase 1B (PTP1B) (IC_{50} = 63.5 μM)	Seo et al. (2009)
	St. tomentosum		
	St. azoreum		
	Umbilicaria (Gyrophora) esculenta		
Depsides	*Thamnolia vermicularis* var. *subuliformis*	Weak inhibition of platelet-type 12(S)-lipoxygenase (at 100 μg/ml: 14.7 ± 2.76%)	Bucar et al. (2004)
Baeomycesic acid			
	Thamnolia subuliformis	Inhibition of 5-lipoxygenase from porcine leukocytes (IC_{50} = 8.3 μM); no activity against cyclooxygenase isolated from sheep seminal vesicle microsomes	Ingolfsdottir et al. (1997c)
		Inhibition of growth on fourteen cancer cell lines (IC_{50} > 22 μg/ml)	Ogmundsdottir et al. (1998), Haralsdottir et al. (2004)
Depsides	*Protousnea poeppigii*	Antileishmanial activities: 100% lysis at 100 μg/ml on *Leishmania amazonensis*, *L. brasiliensis*, *L. infantum*	Schmeda-Hirschmann et al. (2008)
Isodivaricatic acid		Antifungal activities against *Microsporum* and *Trichophyton* species (MIC = 50 μg/ml)	

Table 1 continued

Structure type compound	Lichen species	Activity	References
Depsides Sphaerophorin	*Sphaerophorus globosus*	Inhibition of cell growth and induction of apoptosis in human prostate carcinoma DU-145 and human melanoma M14 cells (IC_{50} # 30 μM)	Russo et al. (2006, 2008)
Tridepsides Tenuiorin	*Peltigera leucophlebia* *Peltigera aphthosa* *Lobaria linita* *Pseudocyphellaria crocata*	Inhibition of 5-lipoxygenase (IC_{50} = 59.6 μM) Reduction in [3H]-thymidine uptake of the pancreatic (PANC-1) (IC_{50} = 87.9 μM)— and colon (WIDR) (IC_{50} = 98.3 μM) cancer cells	Ingolfsdottir and Gudmundsdottir (2002)
Tridepsides Gyrophoric acid	*Umbilicaria* sp.	Low cytotoxicity against MM98 malignant mesothelioma cells, A431 vulvar carcinoma cells and HaCat keratinocytes	Burlando et al. (2009)
Orcinol derivatives Orcinol	*Umbilicaria esculenta*	Anti-inflammatory effect: inhibition of human synovial fluid phospholipase A2 (IC_{50} = 0.22 mM)	Kim et al. (1996)
Orcinol derivatives Divaricatinic acid	*Protousnea poeppigii*	Antileishmanial activities: 100% lysis at 100 μg/ml on *Leishmania amazonensis*, *L. brasiliensis*, *L. infantum* Antifungal activities against *Microsporum* and *Trichophyton* species (MIC = 100 or 50 μg/ml)	Schmeda-Hirschmann et al. (2008)
Orcinol derivatives Ethyl-β-orsellinate	*Umbilicaria vellea* (hydrolysis derivative from some depsides)	Antifungal and antibacterial activities	Min and Bae (1996)
Orcinol derivatives Me β-orsellinate	*Peltigera leucophlebia* *Stereocaulon* sp. *Umbilicaria* sp. (hydrolysis derivative from some depsides)	Antimicrobial activities: MIC values on various microorganisms between 30 and 500 μg/ml	Ingolfsdottir et al. (1985)
		Anti-inflammatory effect: inhibition of human synovial fluid phospholipase A2 (IC_{50} = 0.26 mM)	Kim et al. (1996)
		Inhibition of 5-lipoxygenase (IC_{50} = 41.6 μM)	Ingolfsdottir and Gudmundsdottir (2002)
Dibenzofuranes derivatives Usnic acid	*Usnea* and *Cladonia* sp. *Flavocetraria nivalis* *Flavocetraria cucculata* *Protousnea poeppigii*	A review of biological activities until 2002	Ingolfsdottir (2002)
		Moderate inhibition of protein tyrosine phosphatase 1B (IC_{50} A: 16.4 ± 0.4 μM)	Seo et al. (2008a)
		Moderate cytotoxic activity on various cancer cell lines (3LL, L1210, DU145, MCF7, K-562, U251) ($23.0 \leq IC_{50} \leq 105.4$ μM); apoptosis with activation of caspase 3 of murine leukaemia L1210 cells in a dose- and time-dependent manner	Bézivin et al. (2004), Bazin et al. (2008)
		P-53 independent cytotoxicity on p53 breast cancer cell lines MCF7, MDA-MB-231 and the lung cancer cell line H1299	Mayer et al. (2005)
		Significant cytotoxicity against MM98 malignant mesothelioma cells, A431 vulvar carcinoma cells and HaCat keratinocytes	Burlando et al. (2009)
		Antibiotic activities against vancomycin resistant enteroccocci (MIC ≤ 8 μg/ml)	Elo et al. (2007)
		Inhibition of bacterial (*Staphyloccocus aureus* and *Pseudomonas aeruginosa*) biofilm formation on polymer surfaces	Francolini et al. (2004)
		Antitrypanosoma activities: growth inhibition of culture epimastigotes with 5–30 μg/ml	De Carvahlo et al. (2005)
		Antiviral activities	Fazio et al. (2007)

Table 1 continued

Structure type compound	Lichen species	Activity	References
		Grazing deterrent	Nimis and Skert (2006)
		$LC_{50} < 1$ ppm against *Culex pipiens larvae*	Cetin et al. (2008)
		Antileishmanial activities: 100% lysis at 100 μg/ml on *Leishmania amazonensis*, *L. brasiliensis*, *L. infantum*	Schmeda-Hirschmann et al. (2008)
Dibenzofuranes derivatives Usimines A-C	*Ramalina terebrata**	Moderate inhibition of protein tyrosine phosphatase 1B (IC_{50} A: 15.0 ± 0.1, B: 27.7 ± 2.1, C: 23.2 ± 3.2 μM)	Seo et al. (2008a)
Anthraquinones Parietin (physcion)	*Xanthoria parietina*	Antifungal activity (MIC in the range 90–100 μg/ml);	Manojlovic et al. (1998)
		Virucidal effect against the arenaviruses Junin and Tacaribe	Fazio et al. (2007)
	Xanthoria parietina	Moderate cytotoxicity in HeLa, L-929 and K562 cells ($IC_{50} = 50$ μg/ml)	Ivanova et al. (2000)
		Antifungal activity (MIC in the range 90–100 μg/ml)	Manojlovic et al. (1998)
		Weak antibacterial activity against *Bacillus subtilis* ATCC 6633 (MIC > 200 μg/ml).	Ivanova et al. (2000)
Anthraquinones Fallacinal	*Xanthoria parietina*	Antifungal activity (MIC in the range 90–100 μg/ml)	Manojlovic et al. (1998)
Anthraquinones Emodin	*Xanthoria parietina*	Antifungal activity (MIC in the range 90–100 μg/ml)	Manojlovic et al. (1998)
	Caloplaca aurantia		
	Nephroma laevigatum		
Bis-naphthoquinones Cuculloquinone	*Flavoparmelia cucullata*	Antioxidant properties	Stepanenko et al. (2002)

* The lichen name initially given *Stereocaulon alpinum* has been corrected for *Ramalina terebrata* (correction by Seo et al. 2008a, J Nat Prod (2008) 71:1322)

Listeria monocytogenes (Tomasi et al. 2006). Some anthraquinone derivatives have also shown weak activity on *Bacillus subtilis* (Ivanova et al. 2000) but a more specific lichen compound, protolichesterinic acid exhibit a very interesting antibacterial activity against *Helicobacter pylori* (Ingolfsdottir et al. 1997b). This species is found responsible of ulcers and this antibiosis combined with a gel-forming protective effect of polysaccharides from the Islandic lichen may account for the traditional anti-ulcer use of *Cetraria islandica* (Ingolfsdottir et al. 1997b) or the experimental gastric-protective effect of an alcoholic extract reported in (Podterob 2008). (+)-Protolichesterinic acid which presents antibiotic activities against various bacteria (Borkowski et al. 1964; Ingolfsdottir et al. 1998; Turk et al. 2003), might also impair quorum sensing systems of bacteria (Riedel et al. 2008, preliminary data). Antiviral activities have been also reported (Pengsuparp et al. 1995; see Table 2).

Antifungal activities have been reported for parietin and other anthraquinone derivatives isolated from the foliaceous-crustose *Xanthoria parietina* (Manojlovic et al. 1998). More recently, extracts of the Andean lichens *Protousnea poeppigii* and *Usnea rigida* where found inactive against several yeast and *Aspergillus* strains but divaricatinic acid and the new isodivaricatic acid (Fig. 1) isolated from *P. poeppigii* displayed interesting activities against *Microsporum* and *Trichophyton* pathogen dermatophytes (Schmeda-Hirschmann et al. 2008).

Cytotoxic, antimutagenic and antitumor activities for potential anticancer agents

Usnic acid is the most ancient lichen compound also found in alpine species (*Cladonia, Flavocetraria*) and considered for antitumor activity with ten to hundred micromolar IC_{50} units on several cancer cell lines (Bazin et al. 2008). Apoptosis induction features have

Table 2 Active miscellaneous compounds from alpine lichen species (abbreviations as in Table 1)

Structure type Compound	Lichen species	Activity	References
α-Methylene-γ-lactone (+)-Protolichesterinic acid	*Cetraria islandica*	Inhibition of platelet-type 12(S)-lipoxygenase (IC_{50} = 77.0 μM)	Ingolfsdottir et al. (1994a, b), Bucar et al. (2004)
		Inhibition of 5-lipoxygenase (IC_{50} = 20.0 μM)	Ingolfsdottir (2000)
		Inhibition of DNA synthesis in T-47D, ZR-75-1 from breast carcinomas and K-562 (1.4 < IC_{50} < 24.6 μg/ml); inhibition of proliferation of mitogen-stimulated lymphocytes (IC_{50} = 8.4 μg/ml)	Ogmundsdottir et al. (1998)
		Inhibition of growth on fourteen cancer cell lines (IC_{50} # 1.5–24 μg/ml)	Ogmundsdottir et al. (1998), Haralsdottir et al. (2004)
		MIC values against *Mycobacterium aurum* ≥ 125 μg/ml	Ingolfsdottir et al. (1998)
		Inhibition of *Staphylococcus aureus* and *Mycobacterium tuberculosis* H37Rv at concns. of 39 or 100, and 125 and 90 γ/cc. medium.	Borkowski et al. (1964)
		MIC range of 16–64 μg/ml against *Helicobacter pylori*	Ingolfsdottir et al. (1997b), Ingolfsdottir (2000)
		Antimicrobial activity against *Escherichia coli, Staphylococcus aureus, Aeromonas hydrophila*, *Proteus vulgaris, Streptococcus faecalis*, *Bacillus cereus, Bacillus subtilis*, *Pseudomonas aeruginosa, Listeria monocytogenes*	Turk et al. (2003)
		Inhibition of the DNA polymerase activity HIV-1 RT, (IC_{50} = 24 μM)	Pengsuparp et al. (1995)
α-Methylene-γ-lactone derivatives: (+) and (−)-Lichesterinic acid	*Cetraria islandica*	Inhibition of platelet-type 12(S)-lipoxygenase (IC_{50} = 77.0 μM)	Ingolfsdottir et al. (1994a, b)
Cyclodepsipeptides: Stereocalpin A	*Stereocaulon alpinum*	1) Cytotoxicity against three human solid tumor cell lines (colon carcinoma cell line HT-29, IC_{50} = 6.5 μM, skin carcinoma cell line B16/F10, IC_{50} = 11.9 μM, liver carcinoma cell line HepG2, IC_{50} = 13.4 μM). 2) Weak inhibition of the activity of PTP1B (IC_{50} = 40.0 μM)	Seo et al. (2008b)
Alkamides: Cis-9-octadecenamide	*Stereocaulon alpinum*	Inhibition of cyclooxygenase from sheep seminal vesicle microsomes (IC_{50} = 64.3 μM)	Ingolfsdottir et al. (1997a)
Lactones Nostoclide I and II	Culture of *Nostoc* from *Peltigera canina*	Moderate cytotoxicity against the cell lines Neuro-2a CCL 131 and KB CCL17 (IC_{50} = 10 μg/ml)	Yang et al. (1993)
Mycosporines Collemin A	*Collema cristatum*	Photoprotective compound: prevented UV-B induced cell destruction in a dose-dependent manner, partially prevented pyrimidine dimer formation and completely prevented UV-B induced erythema when applied to the skin prior to irradiation	Torres et al. (2004)
Carotenoids	Undetermined lichen species from Himalaya	Protective role to photosynthetic pigments against the intense UV radiations	Singh et al. (2008)

been revealed for usnic acid on L1210 cell lines (Bézivin et al. 2004) through caspase 3 induction (Bazin et al. 2008) but in cellular tests as for in vivo experiments, the solubilisation of this substance appear to be of importance. 2-Hydroxypropyl-β-cyclodextrine was found to be suitable for solubilising usnic acid (Kristmundsdottir et al. 2002) and IC_{50} obtained on malignant cells are in the same range of the one obtained with a diaminooctane derivative (Bazin et al. 2008). A slight increase of its antitumor effect has been obtained with encapsulating this hydrophobic compound in microspheres (da Silva Santos et al. 2006). However, in vivo assays show (−)-usnic acid to have a weak, if any, antitumoral effect against Lewis Lung carcinoma and P388 leukemia (Kupchan and Kopperman 1975; Takai et al. 1979). As (+)-usnic acid was found active against Epstein-Barr Virus activation, it could therefore constitute a valuable candidate as antitumor promoters (Yamamoto et al. 1995) and the recent activities described in a p53-independent manner on three cancer cell lines led the authors to consider usnic acid as a non-genotoxic anti-cancer agent that makes it a potential candidate for novel cancer therapy (Mayer et al. 2005).

Series of depsides and depsidones isolated from Antarctic lichens were tested along with colchicine in cell cultures of lymphocytes (Correché and Carrasco 2002) or with usnic acid for their cytotoxic and apoptotic effects on hepatocytes (Correché and Carrasco 2002; Correché et al. 2004). Pannarin, 1′-chloropannarin and sphaerophorin were found more cytotoxic than colchicine and on primary cultures of hepatocytes, the depside sphaerophorin has higher cytotoxic effects than usnic acid while the depsidones salazinic acid, stictic acid, and psoromic acid displayed the more significant apoptotic activities. Pannarin and sphaerophorin are also reported to inhibit cell growth and to induce apoptosis in human prostate carcinoma DU-145 (Russo et al. 2006) and human melanoma M14 cells (Russo et al. 2008). Although active at higher doses than the anticancer alkaloid vinblastine, the depsidone lobaric acid was recently found to exhibit a remarkable inhibition of tubulin polymerization (Morita et al. 2009). This effect may be linked to the moderate but constant effect of lobaric acid (IC_{50} # 12–65 $\mu g\ ml^{-1}$) obtained on fourteen cancer cell lines while normal skin fibroblasts appear to be less sensitive (Ogmundsdottir et al. 1998; Haralsdottir et al. 2004). For some lichen compounds (i.e., gyrophoric, usnic acid) inhibiting HaCat keratinocytes at low concentrations, the antiproliferative activity was considered to be due to a cytostatic effect rather than a cytotoxic effect (Kumar and Muller 1999). Recent antiproliferative assays carried out on MM98 malignant mesothelioma cells, on A431 vulvar carcinoma cells compared to HaCat keratinocytes with (+)-usnic, salazinic, vulpinic, gyrophoric and evernic acids confirm the higher toxicity of usnic acid and afford interesting remarks about the disconnection of cell migration stimulation and mitosis inhibition (Burlando et al. 2009). The combination of usnic acid and gyrophoric acid, both used at subtoxic doses, was therefore stimulating keratinocyte tissue regeneration with possible use in wound healing (Burlando et al. 2009).

The antiproliferative activities of tenuiorin (a tridepside, as gyrophoric acid found in *Umbilicaria* species) and methyl orsellinate extracted from *Peltigera leucophlaebia* were tested on human breast (T-47D), pancreatic (PANC-1), and colon (WIDR) cancer cell lines; the former compound caused a weak-to-moderate effect on the pancreatic and colon cells, whereas methyl orsellinate was without effect (Ingolfsdottir and Gudmundsdottir 2002). A moderate cytotoxicity (IC_{50} # 0–13 μM) on three carcinoma cell lines has been recently described for stereocalpin A, a new cyclic depsipeptide (Fig. 2) isolated from *Stereocaulon alpinum* that was collected in Antarctica (Seo et al. 2008b).

A butyrolactone, protolichesterinic acid, present in *Cetraria islandica* was also found to act as antiproliferative against a series of fourteen cancer cell lines ($IC_{50} < 10$ μg/ml for most of them; Ogmundsdottir et al. 1998; Haralsdottir et al. 2004). Its activity against Ehrlich solid tumor has been confirmed, while other butyrolactone derivatives e.g., nephrosteranic acid had weak activities (Hirayama et al. 1980).

Lichen glucans do not exhibit antiproliferative activities with impressive IC_{50} values on cancer cells as exemplified by the galactomannose substituted α (1 → 3), α (1 → 4) glucan isolated from *Cladonia furcata* (IC_{50} # 500–800 μg/ml). Apoptosis induction and a telomerase activity diminution demonstrate their potential in anticancer adjuvants (Lin et al. 2003). Indeed, these lichen polysaccharides have been investigated in antitumor assays for 50 years

(see Boustie and Lohézic-Le Dévéhat 2008) including lichenan derivatives (Demleitner et al. 1991) and other structural features (Olafsdottir and Ingolfdottir 2001). Although the per os absorption of these high molecular weight compounds is poor, they are recognized to act on the immune system and are generally classified as Biological Response Modifiers (BRMs), more particularly stimulating the innate immunity through macrophage activation. These effects may result in a better defense of the organisms receiving these compounds with application as anti-tumor adjuvants but also promoting infectious resistance, and wound healing. Anti-tumor lichen PS have been characterized in in vivo tests as lichenan inducing highest scores for complete tumor regression when compared to isolichenan or pustulan (Fukuoka et al. 1968; Nishikawa et al. 1969). Thus, the polysaccharide sub-structure has to be considered, the reticuloendothelial system activation being observed with a heteroglycan (Ki-M-7) isolated from *Cetraria islandica* but not with the lichenan (3:7) (Ingolfsdottir et al. 1994b) and with *O*-acylated pustulan isolated from *Umbilicaria esculenta* (Nishikawa and Ohno 1981). In a recent study carried on the methanolic extracts of 8 polar lichens from Antarctica (Choi et al. 2009), the methanol extract of the crustose *Caloplaca regalis* was found to be the most active on rat peritoneal macrophages. Although the composition of the extract was not indicated, some lichen polysaccharides may have been be present along with the secondary metabolites to account for the tumoricidal activity. The macrophage activation resulting in TNF-α and NO production, was suggested to be mediated via the p38 MAPK and the NF-κB pathway (Choi et al. 2009).

Antiinflammatory activities

Some lichen compounds such as longissimone A have clearly demonstrated anti-inflammatory responses comparable to aspirin (Choudhary et al. 2005). The cyclooxygenase (COX) and lipoxygenase (LOX) pathways resulting in the production of prostaglandins and leukotrienes formation are involved in many inflammatory processes but also in tumor growth and promotion (Ara and Teicher 1996). Most assays have therefore been carried for these key enzymes, mainly with lichen compounds isolated from material collected in cold places as in Iceland. In a COX screening with depsides and depsidones, 4-*O*-methylcryptochlorophaeic acid ($IC_{50} = 0.34$ μM) was found to be the most active depside (Sankawa et al. 1982) and the monoaromatic phenol lichen compound methyl-β-orsellinate was also found to inhibit phospholipase A2 (Kim et al. 1996) and 5-LOX (Ingolfsdottir and Gudmundsdottir 2002). The trimeric depside tenuiorin isolated from *Peltigera aphthosa* (Ingolfsdottir and Gudmundsdottir 2002), the depsidones baeomycesic acid and lobaric acid, respectively isolated from *Thamnolia vermicularis* (Ingolfsdottir et al. 1997c) and *Stereocaulon alpinum* (Bucar et al. 2004) were also found active against 5-LOX. Although a dual inhibition of the inflammatory targets could result in more effective drugs, a selective inhibition of LOX with regard to COX, as for protolichesterinic acid (Ingolfsdottir et al. 1994a), can be of interest as the gastroprotective effect of prostaglandins would be theorically maintained. An alkamide, *cis*-9-octadecenamide (Fig. 2) isolated from *Stereocaulon alpinum*, also showed an inhibition of COX from the microsomes of sheep seminal vesicle (Ingolfsdottir et al. 1997a).

The anti-complementary activities of some PS lichens (Olafsdottir and Ingolfdottir 2001; Olafsdottir et al. 2003) may also result in an anti-inflammatory effect and particularly with the beta-glucans upregulating IL-10 secretion by the dendritic cells (Omarsdottir et al. 2006a). Recent in vivo experiments with sub cunaneously injected aqueous extracts of *Cetraria islandica* suggest the significant reduction of the BSA-induced arthritis in rats is related to the presence of lichenan (Freysdottir et al. 2008).

Antioxidant activities

Due to the harsh conditions in alpine or polar environments with sudden rehydration enhancing the production of reactive oxygen species (ROS), efficient protective mechanisms are expected to be encountered in such exposed lichens. The burst of intracellular ROS is accompanied by a decrease of water soluble low molecular-weight antioxidants such as gluthatione (Weissman et al. 2005b) and adjustment of enzymatic activities (Kranner et al. 2005; Weissman et al. 2005a). Although mainly hydrophobic, the polyphenolic nature of the major secondary metabolites of lichens is expected to afford

antioxidant properties. Cuculloquinone, a bisnaphthoquinone of *Flavocetraria cucullata* was found to inactivate DPPH to a 80% extent while the BHT that was used as a standard antioxidant was twofold less active (Stepanenko et al. 2002). A recent DPPH autoradiography assay with extracts of five lichens collected in Antarctica showed that 33–50% of the compounds were antioxidants with a 17–47 mg/g phenolic content in the lichen extracts (Bhattarai et al. 2008). However, the total phenolic content and antioxidant potency did not always correlate (Odabasoglu et al. 2005). Although reports on crude lichen extracts (e.g., Gulcin et al. 2002; Behera et al. 2003) are quite promising, the antioxidant properties of isolated compounds are not so impressive. For instance, two depsidones were found only slightly more active than the commercial quercetine in a superoxide scavenging assay with IC_{50} # 600 μM (Lohézic-Le Dévéhat et al. 2007) and none of the orcinol or orsellinate derivatives were as active as the commercial gallic acid to reduce DPPH (Lopes et al. 2008).

Products of axenically cultured mycobionts and photobionts

The main lichen partners can be dissociated to be cultivated separately, allowing a biotechnological approach for the metabolite production (Oksanen 2006). The mycobiont obtained from lichen spores or mechanical dissociation of the thallus has to be cultivated in aposymbiotic conditions, mainly on solid support and the growing rate is quite limited. However, lichen mycobionts synthesize significant quantities and variety of secondary metabolites only under permissive conditions, as has been demonstrated repeatedly in cultivation experiments (e.g., Hamada and Ueno 1987; Leuckert et al. 1990; Yamamoto et al. 1995; Hamada et al. 1996). Alpine lichen mycobionts were for example not growing at temperatures of 20°C and above (Yamamoto et al. 1987). Therefore, cultured mycobionts can produce new, interesting metabolites not encountered in nature, and synthesis of these novel products may be enhanced by varying the type and concentration of nutrients in the growth medium, or by simulating stress situations (ultraviolet irradiation, changes in thermal or osmotic conditions). For instance, different carbon sources in the culture medium can switch secondary metabolite biosynthesis from the polyketide pathway to the fatty acid biosynthetic pathway (Molina et al. 2003). Appropriate conditions are in some cases attributed to elevated osmotic conditions in vitro, since high levels of sugars, e.g., mannitol, often are needed to initiate secondary metabolite production in axenic fungal cultures. Alteration of secondary metabolite production was reported for the mycobiont of *Xanthoria elegans* grown on different media (Brunauer et al. 2007). Permissive conditions appear to include those mimicking the temporally changing conditions to which lichens are exposed in nature, since constant culture conditions often do not promote production of lichen-specific secondary metabolites (Stocker-Wörgötter 2008). In resynthesis experiments with *Cladia retipora* and *Dactylina arctica*, a complete thalli yielded typical lichen substances (Stocker-Wörgotter and Elix 2006), whereas resyntheses of *Lecanora rupicola* also produced additional substances, not found in the natural lichen, nor in the mycobiont cultures conditioned to produce the natural chemical diversity (Brunauer et al. 2006).

Secondary metabolite production by lichen photobionts warrants further investigations Among the very few such compounds reported are some with moderate cytotoxic activities: the nostoclides (Yang et al. 1993), corresponding to γ-butyrolactones, which are found in a *Nostoc* sp. (Fig. 3) from the lichen *Peltigera canina*. Microcystins, hepatotoxic cyclic heptapeptides were produced by a *Nostoc* sp. isolated from the lichen *Pannaria pezizoides* (Oksanen et al. 2004), and *β-N*-methylamino-L-alanine, a neurotoxic amino acid is produced by a *Nostoc* sp. from a *Peltigera* sp. (Cox et al. 2005). Further cryptophycins, peptolides with promising antineoplastic activities, are present in *Nostoc* strain ATCC53789, which was isolated from a lichen collected on Aaron Island in Scotland (Magarvey et al. 2006).

Secondary compounds from microbial associates of lichens

Lichens harbor not just the traditionally recognized cyanobacterial, algal, and fungal symbionts but also diverse lichen-inhabiting (lichenicolous and endophytic) fungi, as well as a plethora of bacteria. The

species diversity of these co-inhabiting fungi is well-studied: more than a thousand species parasitic for lichens have been documented (Lawrey and Diederich 2003). They can be producers of interesting metabolites in their own right. For example, ambuic acid and its acetyl derivative isolated from the endolichenic fungus *Pestalotiopsis* sp. inhabiting *Multiclavula* lichen species are active against *Staphylococcus aureus* (Ding et al. 2009). In the same way, the bisnaphtopyrone lichenicolin A isolated from an unidentified lichen-inhabiting fungus (He et al. 2005) was active against Gram-positive bacteria, including strains of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Morever, the new bioactive structures of preussomerins produced by endolichenic fungi are considered as lead compounds to be optimized by chemists (Weerapreeyakul et al. 2007). They were originally detected in the lichenicolous fungus *Microsphaeropsis* sp. (Seephonkai et al. 2002).

Gonzales et al. (2005) studied the biosynthetic potential of actinomycetes associated with lichens by DNA fingerprinting. High frequencies were obtained for PKS I (62.6%), PKS II (64.7%) and non-ribosomal peptide synthetases (58.5%). Associated bacteria in lichens from arctic habitats apparently had lower biosynthetic potential than those of tropical habitats. So far, species-rich and detailed studies of bacterial secondary metabolite biosyntheses from arctic-alpine species are still pending. Such studies could be highly interesting for pharmaceutical research. For example, a streptomycete isolate from a reindeer lichen (*Cladonia uncialis)* in British Columbia revealed uncialamycin as a new enediyne (Davies et al. 2005). Enedyines are cytotoxic compounds, and not surprisingly, uncialamycin shows strong antibacterial activity against both Gram-positive and Gram-negative human pathogens, including *Burkholderia cepacia* (MIC, 0.001 μg/ml) and *Staphylococcus aureus* (MIC, 0.0064 μg/ml). This strain also produces a series of cladoniamides (Fig. 3) corresponding to new alkaloids related to the indolocarbazole structural pattern (Williams et al. 2008). As staurosporine and rebeccamycin are two indolocarbazole heterosides used as lead compounds for new anticancer treatment, these Streptomyces metabolites are of high value for biogenetics and biotechnological production or for pharmacological tests. In addition, six new aminocoumarins, angucycline and a new butenolide were recently isolated from lichen-derived *Streptomyces* spp. (Cheenpracha et al. 2010; Motohashi et al. 2010).

The complex interaction between all these organisms remains unclear but we can assume that these compounds could be involved in defence and chemical communication pathways. Yet, associated bacteria might have been of profound evolutionary importance by contributing genetic material to lichen fungi. Schmitt and colleagues showed that lichen fungal genomes contain 6-methylsalicylic acid synthase-like genes which are related to bacterial genes. These genes could be responsible to contribute the basic phenolic units (orsellinic acid, resorcinol) for typical lichen compounds. The authors suggested that these genes could have been acquired by past horizontal transfer from bacterial genomes (Schmitt et al. 2008). Such horizontal transfer might be plausible, given the ubiquity of associated bacterial communities. Diverse and abundant bacteria have also been observed in some alpine and antarctic lichens (Grube et al. 2009; Selbmann et al. 2010).

Conclusions and future prospects

Investigations on the natural product composition of whole lichen thalli or lichen constituents, and their biosynthetic machineries, lag behind those of non-lichenous bacteria and fungi. The range of bioactivities identified to date, however, are quite promising for further research aiming at commercial production and exploitation of pharmaceutically interesting substances. The score of activities (with regard to the number of lichen or lichen-associated compounds tested) is in a good range for natural products (Cragg and Newman 2009). This is sustained by the structural diversity of the metabolites produced as a result of the symbiosis and magnified by the metabolic diversity of the hosted organisms. The extremophilic conditions under which alpine lichens thrive are also enhancing the chances to obtain new bioactive chemotypes. New compounds have therefore been reported recently from lichens collected from psychrophilic habitats. Usimines corresponding to natural new enamino derivatives of usnic acid have been reported from the polar lichen *Ramalina terebrata*: they exhibit a moderate inhibitory activity against the protein tyrosine phosphatase 1B (Seo et al. 2008a). This enzyme is a major non-transmembrane

phosphatase involved in human tissues as a negative regulator of the insulin-stimulated signal transduction pathways and a target for new type 2 antidiabetes treatment. Better activities are obtained with lobaric acid and other new pseudodepsidones isolated from *Stereocaulon alpinum* collected in the same Antarctic region (Seo et al. 2009).

A deeper investigation of arctic-alpine lichens can still reveal quite interesting discoveries. Recently, an arctic *Lecanora* (*griseofulva*) was described which contained (+)-griseofulvin (1) and (+)-dechlorogriseofulvin, as well as traces of alternariol (Elix and Øvstedal 2004). The presence of such antifungal spirobenzofuranones is unique in lichens so far (many lichens, though, are able to produce the griseofulvin precursor norlichenxanthone). These compounds are instead often produced by non-lichenized fungi (such as *Penicillium* and *Alternaria*). Interestingly, the recently described *Penicillium lanosum*, which has also been isolated from *Lecanora*, and other psychrophilic Penicillia are able to produce griseofulvin (Frisvad et al. 2005). Further studies are required in our opinion to evaluate whether unusual compounds are produced by lichens or their associated fungi. In any case we suppose that mold fungi with interesting secondary compounds can be isolated from lichens living in cold habitats.

For some potent active compounds the limitations for collection can be overcome through chemical synthesis or in vitro production as for hybocarbone, a naphtazarine-dimer derivative with potent activities on cancer cells ($IC_{50} = 1$ nM, MCF-7). Hybocarpone (Fig. 3) has been synthetised (Gray and Nicolaou 2004) and also isolated from a mycobiont culture of *Lecanora hybocarpa* (Ernst-Russel et al. 1999). Culturing approaches could be extended now to other lichen-associated microrganisms that produce compounds of interest (e.g., uncialamycin in Fig. 3). In the case, biotechnological approaches might be facilitated as most of the microorganisms allow high fermentation rates. Recent progress has been achieved for lichen cultivation particularly with synchrotron chambers where the natural environmental conditions can be reproduced and the metabolite production triggered with specific stresses (Stocker-Wörgötter 2008), while biotechnological approaches with lichen fungi are still in its infancy. These require the establishment of appropriate expression systems as previous work has not succeeded in production of lichen compounds so far (Chooi et al. 2008; Gagunashvili et al. 2009). It is anticipated that the genetic engineering and combinatorial biosynthesis approaches currently used to expand the repertoire of polyketides from "conventional" bacteria and fungi will soon become applicable to lichen PKS genes of (cyano-)bacterial and fungal origin. When these technological hurdles are solved we will be able to fully open the lichen's treasure chest of biosynthetic potential.

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References

Ara G, Teicher BA (1996) Cyclooxygenase and lipooxygenase inhibitors in cancer therapy. Prostaglandins Leukot Essent Fatty Acids 54:3–16

Asta J (1984) Flore et végétation lichéniques des étages alpin supérieur et nival des Alpes Nord-Occidentales françaises. Documents d'écologie Pyrénéenne 3–4:119–123

Asta J, Juge C, Gout E et al (1999) Lichens: models to study the adaptation to extrem high mountain environment. Bull Inf Ass Fr Lichénol Mémoires 3:131

Aubert S, Juge C, Boisson AM et al (2007) Metabolic processes sustaining the reviviscence of lichen *Xanthoria elegans* (Link) in high mountain environments. Planta 226:1287–1297

Baron M, Iacomini M, Fanta ES, Gorin PAJ (1991) Galactomannan, lichenan and isolichenan from the polysaccharide-rich lichen *Neuropogon aurantiaco-ater*. Phytochemistry 30(9):3125–3126

Barry VC, Twomey D (1950) Antituberculous substances. VI. Derivatives of diploicin. Proc R Irish Acad 53B:55–59

Bartak M, Hajek J, Vrablikova H et al (2004) High-light stress and photoprotection in *Umbilicaria antartica* monitored by chlorophyll fluorescence imaging and changes in zeaxanthin and glutathione. Plant Biol 6:333–341

Bazin MA, Le Lamer AC, Delcros JG et al (2008) Synthesis and cytotoxic activities of usnic acid derivatives. Bioorg Med Chem 16:8737–8744

Beckett RP, Kranner I, Minibayeva FV (2008) Stress physiology and the symbiosis. In: Nash TH (ed) Lichen biology. Cambridge University Press, Cambridge, pp 134–151

Behera BC, Adawadkar B, Makhija U (2003) Inhibitory activity of xanthine oxidase and superoxide-scavenging activity in some taxa of the lichen family *Graphidaceae*. Phytomedicine 10:536–543

Bézivin C, Tomasi S, Rouaud I et al (2004) Cytotoxic activity of compounds from the lichen: *Cladonia convoluta*. Planta Med 70:877–880

Bhattarai HD, Paudel B, Hong SG et al (2008) Thin layer chromatography analysis of antioxidant constituents of lichens from Antarctica. J Nat Med 62:481–484

Bjerke JW, Lerfall K, Elvebakk A (2002) Effects of ultraviolet radiation and PAR on the content of usnic and divaricatic acids in two arctic-alpine lichens. Photochem Photobiol Sci 1:678–685

Bjerke JW, Elvebakk A, Dominguez E et al (2005) Seasonal trends in usnic acid concentrations of Arctic, alpine and Patagonian populations of the lichen *Flavocetraria nivalis*. Phytochemistry 66:337–344

Bodo B, Molho D (1980) Structure des acides isomuronique et neuropogolique, nouveaux acides aliphatiques du lichen *Neuropogon trachycarpus*. Phytochemistry 19:1117–1120

Borkowski B, Wozniak W, Gertig H et al (1964) Bacteriostatic action of some compounds from lichen *Cetraria islandica* and of usnic acid. Dissertationes Pharmaceuticae 16: 189–194

Boustie J, Grube M (2005) Lichens, a promising source of bioactive secondary metabolites. Plant Genet Resour 3: 273–287

Boustie J, Lohézic-Le Dévéhat F (2008) Lichen extracts and cancer. In: Watson RR, Preedy VR (eds) Botanical medicine in clinical practice. CAB International, Trowbridge, pp 356–364

Brunauer G, Hager A, Krautgartner WD et al (2006) Experimental studies on *Lecanora rupicola* (L.) Zahlbr.: chemical and microscopical investigations of the mycobiont and re-synthesis stages. Lichenologist 38:577–585

Brunauer G, Hager A, Grube M et al (2007) Alteration in secondary metabolism of aposymbiotically grown mycobionts of *Xanthoria elegans* and culture resynthesis stages. Plant Physiol Biochem 45:146–151

Bucar F, Schneider I, Ogmundsdottir H et al (2004) Antiproliferative lichen compounds with inhibitory activity on 12(S)-HETE production in human platelets. Phytomedicine 11:602–606

Burkholder PR, Evans AW, McVeigh I et al (1945) Further studies on the antibiotic activity of lichens. Bull Torrey Bot Club 72:157–164

Burlando B, Ranzanto E, Volante A et al (2009) Antiproliferative effects on tumour cells and promotion of keratinocyte wound healing by different lichen compounds. Planta Med 75:607–613

Carbonero ER, Smiderle FR, Gracher AHP et al (2006) Structure of two glucans and a galactofuranomannan from the lichen *Umbilicaria mammulata*. Carbohydr Polym 63:13–18

Cetin H, Tufan-Cetin O, Turk OA, Tay T, Candan M, Yanikoglu A, Sumbul H (2008) Insecticidal activity of major lichen compounds, (-) and (+) usnic acid, against the larvae of house mosquito, *Culex pipiens* L. Parasitol Res 102:1277–1279

Cheenpracha S, Vidor NB, Yoshida WY, Davies J, Chang LC (2010) Coumabiocins A−F, aminocoumarins from an organic extract of *Streptomyces* sp. L-4-4. J Nat Prod 73: 880–884

Choi H-S, Yim JH, Lee HK et al (2009) Immunomodulatory effects of polar lichens on the function of macrophages in vitro. Mar Biotechnol 11:90–98

Chooi YH, Stalker DM, Davis MA et al (2008) Cloning and sequence characterization of a non-reducing polyketide synthase gene from the lichen *Xanthoparmelia semiviridis*. Mycol Res 112:147–161

Choudhary MI, Saima Jalil A, Atta-ur-Rahman (2005) Bioactive phenolic compounds from a medicinal lichen, *Usnea longissima*. Phytochemistry 66:2346–2350

Correché ER, Carrasco M (2002) Cytotoxic screening activity of secondary lichen metabolites. Acta Farm Bonaerense 21:273–278

Correché ER, Enriz RD, Piovano M et al (2004) Cytotoxic and apoptotic effects on hepatocytes of secondary metabolites obtained from lichens. ATLA 32:605–615

Cox PA, Banack SA, Murch SJ et al (2005) Diverse taxa of cyanobacteria produce β-N-methylamino-L-alanine, a neurotoxic amino acid. Proc Natl Acad Sci 102:5074–5078

Cragg GM, Newman EDJ (2009) Nature: a vital source of leads for anticancer drug development. Phytochem Rev 8:313–331

Czeczuga B, Obermayer W, Upreti DK, Sharma LR (1996) Carotenoids in lichens in various regions of the Himalayas. J Hattori Bot Lab 80:323–330

da Silva Santos NP, Nascimento SC, Wanderley MSO et al (2006) Nanoencapsulation of usnic acid: an attempt to improve antitumour activity and reduce hepatotoxicity. Eur Pharm Biopharm 64:154–160

Davies J, Wang H, Taylor T et al (2005) Uncialamycin, a new enediyne antibiotic. Org Lett 7:5233–5236

De Carvahlo EAB, Andrade PP, Silva NH, Pereira EC, Figueiredo RCBQ (2005) Effect of usnic acid from the lichen *Cladonia substellata* on *Trypanosoma cruzi* in vitro: an ultrastructural study. Micron 36:155–161

de la Torre R, Garcia-Sancho L, Horneck G (2007) Adaptation of the lichen *Rhizocarpon geographicum* to harsh high-altitude conditions: relevance to a habitable Mars. Eur Space Agency SP-1299:145–150

Demleitner S, Kraus J, Franz G (1991) Synthese und antitumoraktivitat von Licheninderivaten. Pharm Unserer Zeit 20:120

Denton GH, Karlén W (1973) Lichenometry: its application to Holocene moraine studies in Southern Alaska and Swedish Lapland. Arctic Alpine Res 5:347–352

Ding G, Li Y, Fu S et al (2009) Ambuic acid and torreyanic acid derivatives from the endolichenic fungus *Pestalotiopsis* sp. J Nat Prod 72:182–186

Durazo FA, Lassman C, Han SHB et al (2004) Fulminant liver failure due to usnic acid for weight loss. Am J Gastroenterol 99:950–952

Edwards HGM, Newton EM, Wynn-Williams DD (2003) Molecular structural studies of lichen substances II: atranorin, gyrophoric acid, fumarprotocetraric acid, rhizocarpic acid, calycin, pulvinic dilactone and usnic acid. J Mol Struct 651–653:27–37

Elix JA, Øvstedal DO (2004) A new *Lecanora* species from the Arctic with a remarkable chemistry. Graphis Scripta 15: 57–59

Elix JA, Stocker-Wörgötter E (2008) Biochemistry and secondary metabolites. In: Nash TH III (eds) Lichen biology. Cambridge University Press, Cambridge, pp 353–363

Elo H, Matikainen J, Pelttari E (2007) Potent activity of the lichen antibiotic (+)-usnic acid against clinical isolates of vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. Naturwissenschaften 94:465–468

Elvebakk A, Bjerke JW (2006) The Skibotn area in North Norway—an example of very high lichen species richness far to the north. Mycotaxon 96:141–146

Ernst-Russel MA, Elix JA, Chai CL et al (1999) Hybocarpone, a novel cytotoxic naphthazarin derivative from mycobiont cultures of the lichen *Lecanora hybocarpa*. Tetrahedron Lett 40:6321–6324

Fazio AT, Adler MT, Bertoni MD, Sepúlveda CS, Damonte EB, Maier MS (2007) Lichen secondary metabolites from the cultured lichen mycobionts of *Teloschistes chrysophthalmus* and *Ramalina celastri* and their antiviral activities. Z Naturforsch C 62:543–549

Fernandez E, Quilhot W, Rubio C et al (2006) Effects of UV radiation on usnic acid in *Xanthoparmelia microspora* (Müll. Arg. Hale). Photochem Photobiol 82:1065–1068

Feuerer T, Hawksworth DL (2007) Biodiversity of lichens, including a world-wide analysis of checklist data based on Takhtajan's floristic regions. Biodivers Conserv 16:85–98

Francolini I, Norris P, Piozzi A et al (2004) Usnic acid, a natural antimicrobial agent able to inhibit bacterial biofilm and formation on polymer surfaces. Antimicrob Agents Chemother 48:4360–4365

Freysdottir J, Omarsdottir S, Ingolfsdottir K et al (2008) In vitro and in vivo immunomodulating effects of traditionally prepared extract and purified compounds from *Cetraria islandica*. Int Immunopharmacol 8:423–430

Friedmann EI, Sun H (2005) Communities adjust their temperature optima by shifting producer-to-consumer ratio, shown in lichens as models: I. hypothesis. Microb Ecol 49:523–527

Frisvad JC, Larsen TO, Dalsgaard PW et al (2005) Four psychrotolerant species with high chemical diversity consistently producing cycloaspeptide A, *Penicillium jamesonlandense sp. nov., Penicillium ribium sp. nov., Penicillium soppii* and *Penicillium lanosum*. Int J System Evol Microbiol 56:1427–1437

Fukuoka F, Nakanishi M, Shibata S et al (1968) Polysaccharides in lichens and fungi. II. Antitumor activities on sarcoma-180 of the polysaccharide preparations from *Gyrophora esculenta* Miyoshi, *Cetraria islandica* (L.) Ach. var. *orientalis* Asahina, and some other lichens. Gann 59:421–432

Gagunashvili AN, Daviðsson SP, Jónsson ZO et al (2009) Cloning and heterologous transcription of a polyketide synthase gene from the lichen *Solorina crocea*. Mycol Res 113:354–363

Gauslaa Y, Solhaug KA (2001) Fungal melanins as a sun screen for symbiotic green algae in the lichen *Lobaria pulmonaria*. Oecol 126:462–471

Gissurarson S, Sigurdsson S, Wagner H, Ingolfsdottir K (1997) Effect of lobaric acid on cysteinyl-leukotriene formation and contractile activity of Guinea Pig *Taenia coli*. J Pharmacol Exp Ther 280:770–773

Gonzales I, Ayuso-Sacido A, Anderson A et al (2005) Actinomycetes isolated from lichens: evaluation of their diversity and detection of biosynthetic gene sequences. FEMS Microbiol Ecol 54:401–415

Gray D, Nicolaou KC (2004) Total synthesis of hybocarpone and analogues thereof. A facile dimerization of naphthazarins to pentacyclic systems. J Am Chem Soc 126: 607–612

Grube M, Cardinale M, Vieira de Castro J et al (2009) Species-specific structural and functional diversity of bacterial communities in lichen symbiosis. ISME J 3:1105–1115

Gulcin I, Oktay M, Kufrevioglu OI et al (2002) Determination of antioxidant activity of lichen *Cetraria islandica* (L) Ach. J Ethnopharmacol 79:325–329

Hamada N, Ueno T (1987) Depside from an isolated lichen mycobiont. Agric Biol Chem 51:1705–1706

Hamada N, Miyagawa H, Miyawaki H et al (1996) Lichen substances in mycobionts of crustose lichens cultured on media with extra sucrose. Bryologist 99:71–74

Haralsdottir S, Guolaugsdottir E, Ingolfsdottir K et al (2004) Anti-proliferative effects of lichen-derived lipoxygenase inhibitors on twelve human cancer cell lines of different tissue origin in vitro. Planta Med 70:1098–1100

Hauck M, Juergens S-R, Willenbruch K et al (2009) Dissociation and metal-binding characteristics of yellow lichen substances suggest a relationship with site preferences of lichens. Ann Bot 103:13–22

Hausen BM, Emde L, Marks V (1993) An investigation of the allergic constituents of *Cladonia stellaris* (Opiz)Pous& Vezda (silver moss, reindeer moss or reindeer lichen). Contact Derm 28:70–76

He H, Bigelis R, Yang HY et al (2005) Lichenicolins A and B, new bisnaphthopyrones from an unidentified lichenicolous fungus, strain LL-RB0668. J Antibiot 58:731–736

Heber U, Bilger W, Bligny R et al (2000) Phototolerance of lichens, mosses and higher plants in an alpine environment: analysis and photoreactions. Planta 211:770–780

Hidalgo ME, Bascunan L, Quilhot W et al (2005) Spectroscopic and photochemical properties of the lichen compound lobaric acid. Photochem Photobiol 81:1447–1449

Hirayama T, Fujikawa F, Kasahara T et al (1980) Anti-tumor activities of some lichen products and their degradation products. Yakugaku Zasshi 100:755–759

Horhant D, Le Lamer AC, Boustie J et al (2007) Separation of a mixture of paraconic acids from *Cetraria islandica* (L.) Ach. employing a fluorous tag-catch and release strategy. Tetrahedron Lett 48:6031–6033

Huneck S (1999) The significance of lichens and their metabolites. Naturwissenschaften 86:559–570

Huneck S, Yoshimura I (1996) Identification of Lichen substances. Springer, Berlin, p 493

Iacomini M, Schneider CL, Gorin PAJ (1985) Comparative studies on the polysaccharides of *Cladonia alpestris* (reindeer moss), *Cladonia confusa* and *Cladonia amaurocraea*. Carbohydr Res 142:237–251

Ingolfsdottir K (2000) Bioactive compounds in Iceland moss. In: Paulsen BS (ed) Bioactive carbohydrate polymers, vol 44. Kluwer Academic Publishers, Dordrecht, pp 25–36

Ingolfsdottir K (2002) Molecules of interest – usnic acid. Phytochemistry 61:729–736

Ingolfsdottir K, Gudmundsdottir GF (2002) Effects of tenuiorin and methyl orsellinate from the lichen *Peltigera leucophlebia* on 5-/15-lipoxygenases and proliferation of malignant cell lines in vitro. Phytomedicine 9:654–658

Ingolfsdottir K, Bloomfield SF, Hylands PJ (1985) In vitro evaluation of the antimicrobial activity of lichen metabolites as potential preservatives. Antimicrobial Agents Chem 28:289–292

Ingolfsdottir K, Breu W, Huneck S et al (1994a) In vitro inhibition of 5-lipoxygenase by protolichesterinic acid from *Cetraria islandica*. Phytomedicine 1:187–191

Ingolfsdottir K, Jurcic K, Fischer B et al (1994b) Immunologically active polysaccharide from *Cetraria islandica*. Planta Med 60:527–531

Ingolfsdottir K, Gissurarson SR, Müller-Jakic B, Breu W, Wagner H (1996) Inhibitory effects of the lichen metabolite lobaric acid on arachidonate metabolism *in vitro*. Phytomedicine 2(3):243–246

Ingolfsdottir K, Gissurarson SR, Nenninger A et al (1997a) Biologically active alkamide from the lichen *Stereocaulon alpinum*. Phytomedicine 4:331–334

Ingolfsdottir K, Hjalmarsdottir K, Sigurdsson MA et al (1997b) In vitro susceptibility of *Helicobacter pylori* to protolichesterinic acid from the lichen *Cetraria islandica*. Antimicrobial Agents Chem 41:215–217

Ingolfsdottir K, Wiedemann B, Birgisdottir M et al (1997c) Inhibitory effects of baeomycesic acid from the lichen *Thamnolia subuliformis* on 5-lipoxygenase in vitro. Phytomedicine 4:125–128

Ingolfsdottir K, Chung GA, Skulason VG et al (1998) Antimycobacterial activity of lichen metabolites in vitro. Eur J Pharm Soc 6:141–1444

Ivanova V, Schlegel R, Grafe U (2000) 2-Methoxy-4, 5, 7-trihydroxy-anthraquinone, a new lichen metabolite produced by *Xanthoria parietina*. Pharmazie 55:785–786

Ivanova V, Aleksieva K, Kolarova M et al (2002) Neuropogonines A, B and C, new depsidon-type metabolites from *Neuropogon* sp., an antarctic lichen. Pharmazie 57: 73–74

Kim J-W, Song K-S, Yoo I-D et al (1996) Two phenolic compounds isolated from *Umbilicaria esculenta* as phospholipase A2 inhibitors. Han'guk Kyunhakhoechi 24: 237–242

Kranner I, Cram WJ, Zorn M et al (2005) Antioxidants and photoprotection in a lichen as compared with its isolated symbiotic partners. Proc Natl Acad Sci 102:3141–3146

Kristmundsdottir T, Aradottir HA, Ingolfdottir K et al (2002) Solubilization of the lichen metabolite (+)-usnic acid for testing in tissue culture. Pharm Pharmacol 54:1447–1452

Kumar S, Muller K (1999) Lichen metabolites. II. Antiproliferative and cytotoxic activity of gyrophoric, usnic and diffractaic acid on human keratinocyte growth. J Nat Prod 62:821–823

Kupchan S, Kopperman H (1975) Usnic acid: tumor inhibitor isolated from lichens. Experientia 31:625

Lawrey JD, Diederich P (2003) Lichenicolous fungi: interactions, evolution, and biodiversity. Bryologist 106:81–120

Leuckert C, Buschardt A, Hertel H (1981) Die Verteilung der Chemotypen von *Dimelaena oreina* (Lichenes) auf verschiedene Hohenstufen an einem Transekt im Vinschagau (Sudtirol, Italien). Nova Hedwigia 34:623–631

Leuckert C, Ahmadjian V, Culberson CF et al (1990) Xanthones and depsidones of the lichen *Lecanora dispersa* in nature and of its mycobiont in culture. Mycologia 82: 370–378

Lin X, Cai Y-G, Li Z-X et al (2003) Structure determination, apoptosis induction and telomerase inhibition of CFP-2, a novel lichenin from *Cladonia furcata*. Biochem Biophys Acta 1622:99–108

Lohézic-Le Dévéhat F, Tomasi S, Bernard A et al (2007) Stictic acid derivatives from the lichen *Usnea articulata* L. and their antioxidant activities. J Nat Prod 70: 1218–1220

Lopes TIB, Coelho RG, Yoshida NC et al (2008) Radical-scavenging activity of Orsellinates. Chem Pharm Bull 56:1551–1554

Magarvey NA, Beck ZQ, Golakoti T et al (2006) Biosynthetic characterization and chemoenzymatic assembly of the cryptophycins. Potent anticancer agents from cyanobionts. ACS Chem Biol 1:766–779

Manojlovic NT, Solujic S, Sukdolak S et al (1998) Anthraquinones from the lichen *Xanthoria parietina*. J Serb Chem Soc 63:7–11

Margesin R, Jud M, Tscherko D et al (2009) Microbial communities and activities in alpine and subalpine soils. FEMS Microbiol Ecol 67:208–218

Mayer M, O'Neill MA, Murray KE et al (2005) Usnic acid: a non-genotoxic compound with anti-cancer properties. Anticancer Drugs 16:805–809

Micheletti AC, Beatriz A, de Lima DP et al (2009) Constituintes químicos de Parmotrema lichexanthonicum Eliasaro & Adler—isolamento, modificações estruturais e avaliação das atividades antibiótica e citotóxica. Quim Nova 32:12–20

Min T-J, Bae K-G (1996) Structure and antibiotic activities of phenolic compounds from *Umbilicaria vellea*. Kor J Chem Soc 40(9):623–629

Molina MC, Crespo A, Vicente C et al (2003) Differences in the composition of phenolics and fatty acids of cultured mycobiont and thallus of *Physconia distorta*. Plant Physiol Biochem 41:175–180

Morita H, Tsuchiya T, Kishibe K et al (2009) Antimitotic activity of lobaric acid and a new benzofuran, sakisacaulon A from *Stereocaulon sasakii*. Bioorg Med Chem Lett 19:3679–3681

Motohashi K, Takagi M, Yamamura H, Hayakawa M, Shin-ya K (2010) A new angucycline and a new butenolide isolated from lichen-derived *Streptomyces* spp. J Antibiot 63:545–548

Muggia L, Schmitt I, Grube M (2009) Lichens as treasure chests of natural products. Sim News 59:85–97

Muller K (2001) Pharmaceutically relevant metabolites from lichens. Appl Microbiol Biotechnol 56:9–16

Neff GW, Reddy KR, Durazo FA et al (2004) Severe hepatotoxicity associated with the use of weight loss diet supplements containing ma huang or usnic acid. J Hepatol 41:1062–1064

Neufeld JD, Mohn WW (2005) Unexpectedly high bacterial diversity in arctic tundra relative to boreal forest soils, revealed by serial analysis of ribosomal sequence tags. Appl Environ Microbiol 71:5710–5718

Nimis PL, Skert N (2006) Lichen chemistry and selective grazing by the coleopteran *Lasioderma serricorne*. Environ Exp Bot 55:175–182

Nishikawa Y, Ohno H (1981) Studies on the water-soluble constituents of lichens. IV. Effect of the antitumor lichenglucans and related derivatives on the phagocytic activity of the reticuloendothelial system in mice. Chem Pharm Bull 29:3407–3410

Nishikawa Y, Takeda T, Shibata S et al (1969) Polysaccharides in lichens anf fungi. III. Further investigation on the structures and the antitumor activity of the polysaccharides from

Gyrophora esculenta Miyoshi and *Lasallia papulosa* Llano. Chem Pharm Bull 17:1910–1916

Nolan TJ, Algar J, McCann EP et al (1948) Chemical constituents of lichens found in Ireland *Buellia canescens*. III. Constitution of diploicin. Sci Proc R Dublin Soc 24A: 319–334

Nybakken L, Solhaug KA, Bilger W et al (2004) The lichens *Xantoria elegans* and *Cetraria islandica* maintain a high protection against UV-B radiation in Arctic habitats. Oecol 140:211–216

Odabasoglu F, Aslan A, Cakir A et al (2005) Antioxidant activity, reducing power and total phenolic content of some lichen species. Fitoterapia 76:216–219

Ogmundsdottir HM, Zoega GM, Gissurarson SR et al (1998) Anti-proliferative effects of lichen-derived inhibitors of 5-lipoxygenase on malignant cell-lines and mitogen-stimulated lymphocytes. J Pharm Pharmacol 50:107–115

Oksanen I (2006) Ecological and biotechnological aspects of lichens. Appl Microbiol Biotechnol 73:723–734

Oksanen I, Jokela J, Fewer DP et al (2004) Discovery of rare and highly toxic microcystins from lichen-associated cyanobacterium *Nostoc* sp. strain IO-102-I. Appl Environ Microbiol 70:5756–5763

Olafsdottir ES, Ingolfdottir K (2001) Polysaccharides from lichens: structural characteristics and biological activity. Planta Med 67:199–208

Olafsdottir ES, Omarsdottir S, Smestad Paulsen B et al (1999) Rhamnopyranogalactofuranan, a new immunologically active polysaccharide from *Thamnolia subuliformis*. Phytomedicine 6:273–279

Olafsdottir ES, Omarsdottir S, Paulsen BS et al (2003) Immunologically active O6-branched (1–3)-b-glucan from the lichen *Thamnolia vermicularis var. subuliformis*. Phytomedicine 10:318–324

Omarsdottir S, Olafsdottir ES, Freysdottir J (2006a) Immunomodulating effects of lichen-derived polysaccharides on monocytes-derived dentritic cells. Int Immunopharmacol 6:1642–1650

Omarsdottir S, Petersen H, Barsett H et al (2006b) Structural characterisation of a highly branched galactomannan from the lichen *Peltigera canina* by methylation analysis and NMR-spectroscopy. Carbohydr Polym 63:54–60

Omarsdottir S, Freysdottir J, Olafsdottir ES (2007) Immunomodulating polysaccharides from the lichen *Thamnolia vermicularis* var. *subuliformis*. Phytomedicine 14:179–184

Paudel B, Bhattarai HD, Lee HG et al (2008) Antibacterial potential of Antarctic lichens against human pathogenic gram-positive bacteria. Phytother Res 22:1269–1271

Pengsuparp T, Cai L, Constant H et al (1995) Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. J Nat Prod 58:1024–1031

Piovano M, Garbarino JA, Giannini FA et al (2002) Evaluation of antifungal and antibacterial activities of aromatic metabolites from lichens. Bol Soc Chil Quim 47:235–240

Podterob AP (2008) Chemical composition of lichens and their medical application. Pharm Chem J 42:582–588

Rancan F, Rosan S, Boehm K et al (2002) Protection against UVB irradiation by natural filters extracted from lichens. J Photochem Photobiol B 68:133–139

Rankovic B, Misic M, Sukdolak S (2007) Evaluation of antimicrobial activity of the lichens *Lasallia pustulata, Parmelia sulcata, Umbilicaria crustulosa,* and *Umbilicaria cylindrica*. Microbiol 76:723–727

Reddy VM, O'Sullivan JF, Gangadharam PR (1999) Antimycobacterial activities of riminophenazines. J Antimicrob Chemother 43:616–623

Rezanka T, Dembitsky V (1999) Novel brominated lipidic compounds from lichens of central Asia. Phytochemistry 51:963–968

Rezanka T, Guschina IA (2000) Glycosidic compounds of murolic, protoconstipatic and allo-murolic acids from lichens of central Asia. Phytochemistry 54:635–645

Rezanka T, Guschina IA (2001) Macrolactone glycosides of three lichen acids from *Acarospora gobiensis*, a lichen of central Asia. Phytochemistry 58:1281–1287

Riedel K, Boustie J, Eberl L et al (2008) Effect of lichen secondary metabolites on bacterial functions and biofilm formation. Planta Med 74:960

Rubio C, Fernandez E, Hidalgo ME et al (2002) Effects of solar UV-B radiation in the accumulation of rhizocarpic acid in a lichen species from alpine zones of Chile. Bol Soc Chil Quim 47:213–217

Russo A, Piovano M, Lombardo L et al (2006) Pannarin inhibits cell growth and induces cell death in human prostate carcinoma DU145 cells. Anticancer Drugs 17: 1163–1169

Russo A, Piovano M, Lombardo L et al (2008) Lichen metabolites prevent UV light and nitric-oxide mediated plasmid DNA damage and induce apoptosis in human melanoma cells. Life Sci 83:468–474

Sankawa U, Shibuya M, Ebizuka Y et al (1982) Depside as potent inhibitor of prostaglandin biosynthesis: a new active site model for fatty acid cyclooxygenase. Prostaglandins 24:21–34

Schmeda-Hirschmann G, Tapia A, Lima B et al (2008) A new antifungal and antiprotozoal depside from the Andean Lichen *Protousnea poeppigii*. Phytother Res 22:349–355

Schmitt I, Kautz S, Lumbsch HT (2008) 6-MSAS-like polyketide synthase genes occur in lichenized ascomycetes. Mycol Res 112:289–296

Seephonkai P, Isaka M, Kittakoop P et al (2002) Evaluation of antimycobacterial, antiplasmodial and cytotoxic activities of preussomerins isolated from the lichenicolous fungus *Microsphaeropsis* sp. BCC 3050. Planta Med 68:45–48

Selbmann L, Zucconi L, Ruisi S et al (2010) Culturable bacteria associated with Antarctic lichens: affiliation and psychrotolerance. Polar Biol 33:71–83

Seo C, Sohn JH, Park SM et al (2008a) Usimines A-C, bioactive usnic acid derivatives from the Antarctic Lichen *Stereocaulon alpinum*. J Nat Prod 71:710–712

Seo C, Yim JH, Lee HK et al (2008b) Stereocalpin A, a bioactive cyclic depsipeptide from the Antarctic lichen *Stereocaulon alpinum*. Tetrahedron Lett 49:29–31

Seo C, Sohn JH, Ahn JS et al (2009) Protein tyrosine phosphatase 1B inhibitory effects of depsidone and pseudodepsidone metabolites from the Antarctic lichen *Stereocaulon alpinum*. Bioorg Med Chem Lett 19:2801–2803

Singh J, Upreti DK, Bajpai R et al (2008) Effect of altitudinal changes on photosynthetic pigment concentration in some cryptogams. J Ecophys Occup Health 8:107–110

Smestad Paulsen B, Olafsdottir ES, Ingolfdottir K (2002) Chromatography and electrophoresis in separation and

characterization of polysaccharides from lichens. J Chromatogr A 967:163–171
Sonjak S, Frisvad JC, Gunde-Cimerman N (2006) *Penicillium* mycobiota in arctic subglacial ice. Microb Ecol 52:207–216
Stepanenko LS, Krivoshchekova OE, Skirina IF (2002) Functions of phenolic secondary metabolites in lichens from far east Russia. Symbiosis 32:119–131
Stocker-Wörgötter E (2008) Metabolic diversity of lichen-forming ascomycetous fungi: culturing, polyketide and shikimate metabolite production, and PKS genes. Nat Prod Rep 25:188–200
Stocker-Wörgotter E, Elix JA (2006) Morphogenetic strategies and induction of secondary metabolite biosynthesis in cultured lichen-forming Ascomycota, as exemplified by *Cladia retipora* (Labill.) Nyl. and *Dactylina arctica* (Richards) Nyl. Symbiosis 41:9–20
Sundset MA, Kohn A, Mathiesen SD et al (2008) *Eubacterium rangiferina*, a novel usnic acid-resistant bacterium from the reindeer rumen. Naturwissenschaften 95:741–749
Takahashi K, Kinoshita K, Yamamoto Y et al (2005) Chemical constituents from lichens for pharmaceutical and industrial uses. Folia Cryptogam Est 41:109–114
Takai M, Uehara Y, Beisler JA (1979) Usnic acid derivatives as potential antineoplastic agents. J Med Chem 22:1380–1384
Thune PO, Solberg PO (1980) Photosensitivity and allergy to aromatic lichen acids, compositae oeoresins and other plant substances. Contact Derm 6:64–71
Tomasi S, Picard S, Lainé C et al (2006) A solid-phase synthesis of polyfunctionalized natural products: application to usnic acid, a bioactive lichen compound. J Comb Chem 8:11–14
Torres A, Hochberg M, Pergament I et al (2004) A new UV-B absorbing mycosporine with photo protective activity from the lichenized ascomycete *Collema cristatum*. Eur J Biochem 271:780–784
Troll C (1973) High mountain belts between the polar caps and the equator: their definition and lower limit. Arctic Alpine Res 5:19–27
Turk OA, Meral Y, Merih K et al (2003) The antimicrobial activity of extracts of the lichen *Cetraria aculeata* and its protolichesterinic acid constituent. Z Naturforsch C 58: 850–854
Vegar Storeheier P, Mathiesen SD, Tyler NJC et al (2002) Nutritive value of terricolous lichens for reindeer in winter. Lichenologist 34:247–257
Weerapreeyakul N, Anorach R, Khuansawad T et al (2007) Synthesis of bioreductive esters from fungal compounds. Chem Pharm Bull 55:930–935
Weissman L, Garty J, Hochman A (2005a) Characterization of enzymatic antioxidants in the lichen *Ramalina lacera* and their response to rehydration. Appl Environ Microbiol 71:6508–6514
Weissman L, Garty J, Hochman A (2005b) Rehydration of the lichen *Ramalina lacera* results in production of reactive oxygen species and nitric oxide and a decrease in antioxidants. Appl Environ Microbiol 71:2121–2129
Williams DE, Davies J, Patrick BO et al (2008) Cladoniamides A-G, tryptophan-derived alkaloids produced in culture by *Streptomyces uncialis*. Org Lett 10:3501–3504
Wynn-Williams DD, Edwards HGM (2000) Adaptation of the lichen *Rhizocarpon geographicum* to harsh high-altitude conditions: relevance to a habitable Mars. Planet Space Sci 48:1065–1075
Yamamoto Y, Mizuguchi R, Takayama S et al (1987) Effects of culture conditions on the growth of Usneaceae lichen tissue cultures. Plant Cell Physiol 28:1421–1426
Yamamoto Y, Miura Y, Kinoshita Y et al (1995) Screening of tissue cultures and thalli of lichens and some of their active constituents for inhibition of tumor promoter-induced Epstein-Barr virus activation. Chem Pharm Bull 43:1388–1390
Yang X, Shimiazu Y, Steiner JR et al (1993) Nostoclide I and II, extracellular metabolites from a symbiotic cyanobacterium, *Nostoc* sp., from the lichen *Peltigera canina*. Tetrahedron Lett 34:761–764
Yuan X, Xiao S, Taylor TN (2005) Lichen-like symbiosis 600 million years ago. Science 308:1017–1020