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Lichens as a potential natural source of bioactive compounds: a review

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Abstract Biological activity of material whether known in folk medicine or observed in planned screening program has been the starting point in the drug research. The general pattern is the isolation of active principles, elucidation their structures, followed by attempts for modulation of its activity potential by chemical modification. Lichens are valuable plant resources and are used as medicine, food, fodder, perfume, spice, dyes and for miscellaneous purposes throughout the world. Lichens are well known for the diversity of secondary metabolites that they produce. Compounds isolated from various lichen species have been reported to display diverse biological activities. Here we review the medicinal efficacy of lichen substances, which intends to explore the pharmaceutical potential of lichen substances.

Keywords Lichen · Lichen substances · Natural product · Bioactivity

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Introduction

The use of herbal medicine is a traditional way to cure ailments and has been applied for more than five millennia in several civilizations. Even today, plant materials continue to play a major role in primary health care as therapeutic agents in many developing countries. For example, *Ocimum sanctum* and *Azadirachta indica* are known since ages to cure diseases. Besides using herbal remedies to treat many diseases natural products have contributed enormously to the development of important therapeutic drugs used currently in modern medicine. The major challenge today is the discovery of plants with promising activities and isolation of active principles. Not only plants belonging to the angiosperm but also lower plants like, bryophytes and lichens have potential healing/curing power.

Throughout the ages, lichens have been used for various purposes, in particular as dyes, perfumes and remedies in folk medicines. In Indian spice market lichens are sold by name of 'Chharila', which consists of mixture of two or more species of *Parmelia*, *Usnea longissima*, *Ramalina subcomplanata* and *Heterodermia tremulans*. Chharila has astringent, resolvent, laxative and carminative properties and is also supposed to possess aphrodisiac property. The smoke of chharila is believed to relieve headache. The powdered drug is applied to wounds besides functioning as a good cephalic snuff. Different genera of lichens are used in curing many ailments. Species of

Evernia, Peltigera, Parmelia, Cladonia, Rocella and *Pertusaria,* were used to control fever, diarrhoea, infections, skin diseases, epilepsy, convulsions and as purgative (Kumar et al. 1996). *Peltigera caninna* is a tonic and used against liver ailments because of its high methionine content (Subramanian and Ramakrishnan 1964).

Medicinal properties of lichens are mentioned in the Ayurvedic system of therapy as they are useful in diseases of blood, heart, bronchitis, scabies, leprosy, enlarged spleen, burning sensation, bleeding pile, thirst, vomiting, asthma while in Unani System lichens find use in curing inflammations, stomach disorder, dyspepsia, vomiting, pain in liver, amenorrhea, vesicular calculus. Their powder is applied to wounds (Kirtikar and Basu 1984). The fame of many lichens derives from the 'Doctrine of Signature'. These doctrines rely on the concept of 'like affects like'. *Parmelia sulcata* Taylor was a remedy for cranial maladies; *Peltigera canina* was used for treating rabies. *Peltigera apthosa* (L.) Wild, the thallus of which is dotted with wart like tuberoses was recommended for children who suffered from 'Thrush' (Upreti 1994). They have tremendous curative power. The antibiotic aspect of lichens has greatly increased its medicinal importance. This review focuses on the biological activities of the various lichen species along with the individual chemical classes of lichen metabolites responsible for diverse biological activity and their potential pharmaceutical use.

Unique characteristics and chemical composition of lichens

Lichens are stable, self-supporting, mutualistic symbionts involving fungus and microalga and/or a cyanobacterium. They are among the slowest growing plants. The growth rate of 1 cm/year is considered to be high. They have the remarkable ability to tolerate adverse atmospheric condition. Another peculiarity of lichen is the presence of secondary metabolites such as depsides and dibenzofuran (Asahina and Shibata 1954; Culberson 1969; Huneck and Yoshimura 1996), so called lichen substances (Fig. 1). According to their chemical structures, most lichen substances are phenolic compounds (orcinol and β-orcinol derivatives), dibenzofurans (e.g. usnic acid), depsides (e.g. barbatic acid), depsidones (e.g. salazinic acid), depsones (e.g. picrolichenic acid), lactones (e.g. protolichesterinic acid, nephrosterinic acid), quinones (e.g. parietin), and pulvinic acid derivatives (e.g. vulpinic acid).

Biosynthetic pathways involved in the synthesis of lichen substances

Lichens apparently involved diverse biosynthetic pathways to produce the variety of compounds (Table 1) mainly polymalonate, shikimic acid and mevalonic acid pathways (Boustie and Grube 2005).

(1) *Polymalonate pathway:* Lichen secondary metabolites synthesized via polymalonyl pathway belong to unique class of chemical compounds mainly, depsides and depsidones. These compounds are synthesized by fungal partner, only when it is in association with alga (lichen symbiosis). These compounds play an important role in successful symbiotic association of lichens.

(2) *Shikimic acid pathway:* Lichen substances synthesized via shikimate pathway are mainly pulvinic acid and terphenylquinone. These compounds are obtained by fusion of two phenylpyruvate units. These chemicals widely occur in the lichen family Stictaceae.

(3) *Mevalonic acid pathway:* Mevalonic acid pathway mainly results in the synthesis of terpenes. Sesquiterpenes have not been reported in lichens yet. Diterpenes are also rare (till now 16α-Hydroxycuarene and Nephrene have been isolated from lichens. Triterpenes are abundant in lichens, 20 different triterpenes have been derived from different species of lichens. Zeorin is the main tripene in various species of lichens.

Role of lichen substances

Secondary products from lichens can comprise of up to 20% of the dry weight of thallus although 5–10% is more common. The physiological cost in energy and carbon used to produce these compounds suggests that they have important role in defense mechanism (Dayan and Romagini 2001, 2002). More than 50% lichen substances are synthesized to sustain

Fig. 1 Lichen substances

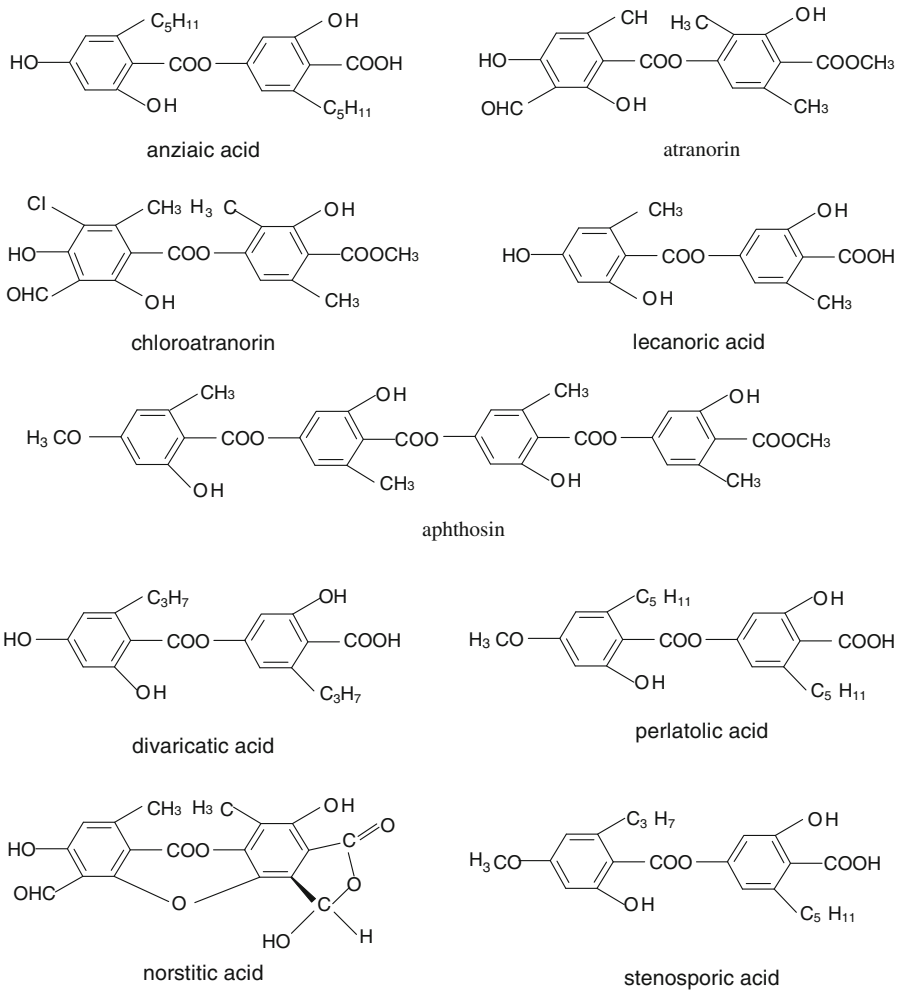

Table 1 Biosynthetic pathways involved in the synthesis of lichen substances

	Biosynthetic pathways	Lichen substances
1	*Acetyl polymalonyl pathway*	Depside, Depsidones, Chromone, Xanthone, Dibenzofuran, Emodin, Anthraquinone and Androcrocin
2	*Shikimic acid pathway*	Pulvinic acid and its derivative Terphenylquinone
3	*Mevalonic acid pathway*	Terpene

and protect the symbiotic association from various abiotic and biotic factors. Although more than 800 lichen substances are known and their structures have been elucidated (Huneck 2001), many others remain to be characterized. The over-riding interest in these compounds has been in respect to their potential source as prospective pharmacophores (González-Tejero et al. 1995; Huneck 1999).

Biological activities of lichen substances

Secondary metabolites from lichens, especially polymalonyl derived polyketides, have been found to exhibit manifold biological activities in various screenings (Huneck 1999; 2001; Müller 2001). Compounds synthesized via polymalonyl pathway are composed of two or three orcinol and β-orcinol

type phenolic units joined by ester, ether and C–C bond. These phenolic structures could constitute a mechanism of defense against oxidative stress (Hidalgo et al. 1994). The orcinol and β-orcinol derivatives (depsides, depsidones, and dibenzofuran) are especially interesting as they presumably play a role in the establishment of the lichen symbiosis and probably in the interaction between the symbionts and their environments (Armaleo 1995).

Various chemicals have been isolated from different lichen species. Secondary metabolite chemistry of *Xanthoria elegans, Lecanora rupicola, Graphis scripta and G. desquamescens* has been carried out by (Brunauer et al. 2006, 2007; Miyagawa et al. 1994). Lichen acids, mainly atranorin, evernic, physodic and usnic acids, are powerful inhibitors of some metabolic enzymes, interestingly related to polyamine metabolism, such as arginase, arginine decarboxylase, ornithine decarboxylase, etc. (Legaz et al. 2001; Matsubara et al. 1997, 1998; Kinoshita et al. 2002).

Lichen polysaccharides have been receiving much attention for their biological activities, specially antitumor, immunostimulatory, and antiviral properties (Olafsdottir and Ingólfsdottir 2001). Depsidones and fatty acids were present in *Parmelia stygia* (Mischenko et al. 1984). Several species of stictaceae were studied and characterized for their constituents by two-dimensional TLC method (Culberson and Johnson 1976). Aslan et al. (2006) revealed the antioxidant and antimicrobial properties of the lichens *Cladonia foliacea*, *Dermatocarpon miniatum*, *Everinia divaricata*, *Evernia prunastri*, and *Neofuscella pulla*. Secondary metabolites of some lichens were separated by HPLC method (Feige et al. 1993). Carotenoids were isolated from the members of the genera *Cladonia, Lobaria, Nephroma, Stereocaulon* and *Sticta* (Czeczuga et al. 1988). The chemical constitution and activities of different lichens have been enlisted in Table 2.

Potentially active depside and depsidone compounds

The structural diversity of depsides and their occurrence in lichens has evoked considerable interest in their biological activities. Many depsides reported in literature have been found to possess important physiological properties. The antioxidant property has been reported in depsides isolated from various lichen species. It has been found that depsidones are more efficient antioxidants than depsides. The higher efficiency of the depsidones could be related to a larger incorporation into lipidic microdomains (Hidalgo et al. 1994). Bridging at the phenolic group in the *p*-position can increase the antioxidant activity of phenols due to more efficient overlap of the substitute orbital within the aromatic π system (Burton et al. 1985). Depsidones have an ether linkage in addition to the ester linkage of the depsides, resulting in a rigid polycyclic system. Therefore, they are based on an 11*H*-dibenzo[*b*,*e*][1,4]dioxepin-11-one ring system. This chemical feature was shown to be important for the inhibitory activity of this class of lichen metabolites against HIV-1 integrase (Neamati et al. 1997). Depsidone and depside compounds such as pannarin, 10-chloropannarin and sphaerophorin, tested in cell cultures of lymphocytes, were shown to have a higher cytotoxic effect than colchicine (Correché et al. 2002). The depsidones salazinic acid, stictic acid and psoromic acid were the most apoptotic active derivatives among 15 lichen compounds evaluated on primary cultures of rat hepatocytes (Correché et al. 2004).

Depsides like barbatic and diffractic acids are potential biologically active compounds. Barbatic acid impairs PS II functioning in higher plants while diffractic acid has fungicidal properties (Dayan and Romagini 2001, 2002; Takahagi et al. 2006). Inhibition of photosystem II in tobacco cells by barbatic acid while inhibition of growth of lettuce seedling by diffractic and barbatic acids have been reported by Nishitoba et al. (1987). Lichen acids are known to show antifungal activity (Halama and Van Haluwyn 2004). The inhibition of gastric mucosal lesion, oxidative stress and neutrophil-infiltration in rats by diffractic acid has been studied by Bayir et al. (2006). Diffractic and usnic acids are known to show moderate inhibiting activity towards arachidonate 5-lipoxygenase, antiproliferative activity and antisporiatic properties (Kumar and Müller 1999a, b, c). Atranorin isolated from *Pseudoevernia furfuracea* shows trypsin inhibition mechanism (Proksa et al. 1994). Polysaccharide (GE-3-S) characterized from *Umblicaria esculenta* shows anti-HIV activity (Hirabayashi et al. 1989). Orsellinic acid derivatives from *Evernia prunastri* are nematocidal (Ahad et al. 1991).

Table 2 Chemical constituents and biological activity of lichen species

S. no.	Lichen species	Compounds characterized	Activity	Reference
	Cladoniaceae			
1	*Cladonia*	Usnic acid and other lichen acids	Antibiotic	Vartia (1973)
2	*Cladonia arbuscula* (Wallr.) Rabenh	(+)-usnic acid	Antimycobacterial activity	Ingólfsdóttir et al. (1998)
3	*Cladina stellaris*	Usnic acid, Perlatolic acid, Atranorin		Falk et al. (2008)
4	*Cladonia* sp.	44 phenolic lichen substances		Huovinen (1987)
	Cladina sp.			
5	*Cladonia leptoclada*	(–) usnic acid	Anti tumor	Kupchan and Kopperman (1975)
6	*Heterodea muelleri* (Hampe) Nyl.	Usnic acid, Diffractic acid and barbatic acid	UV-C stress and cold temperature stress	Hager et al. (2008)
	Stictaceae			
7	*Pseudocyphellaria glabra* and *P. homoeophylla*	Usnic acid	Antimicrobial, Antiviral and Cytotoxic	Perry et al. (1999)
	Lecanoraceae			
8	*Lecanora hybocarpa*	A dimer of naphthazarin, the highly substituted pentacyclic hybocarpone	Potent cytotoxic against a murine mastocytoma cell line, with an IC_{50} value of 0.27 μM	Ernst-Russell et al. (1999)
	Lobariaceae			
9	*Lobaria pulmonaria*	Depsidones and melanins	Light screening pigments	McEvoy et al. (2007a)
10	*Pseudophellaria nudata* (Zahlbr.) D.J. Galloway.	Phenolics, depsides, triterpenes		Cuellar et al. (2008)
	Nephromataceae			
11	*Nephroma arcticum*	Usnic acid	UV Screening	McEvoy et al. (2007b)
12	*N. laevigatum*	Hypericin derivative	Anti-HSV-1	Cohen et al. (1996)
	Pannariaceae			
13	*Erioderma chilense*	Depsidones 1-chloropannarin & pannarin	Antioxidant	Quilhot et al. (1983); Hidalgo et al. (1994)
	Parmeliaceae			
14	*Alectoria ochroleuca*	Vulpinic and (+) (–) usnic acid	Antifungal,	Lauterwein et al. (1995)
15	*Cetraria islandica*	Fumaroprotocetraric and protocetraric acid	Inhibit HIV-1 reverse transcriptase	Pengsuparp et al. (1995)
	C. ericetorum			
16	*Evernia prunastrii* (L.) Ach.	Orcinol, orsellic acid, orcinol monomethyl ether, everninic acid, evernyl 3,5-dimethoxy toluene, methyl evernate, ethyl evernate, usnic acid, evernic acid and atranorin	Used in perfumery	Heide et al. (1975)
17	*Flavoparmelia caperata*	Polysaccharide (PC 2)	Long term potentiation enhancement	Smriga et al. (1996)

Table 2 continued

S. no.	Lichen species	Compounds characterized	Activity	Reference
18	*Hypotrachyna revoluta*	8′-methylmenegazziaic acid	Radical scavenging (RSA)	Papadopoulou et al. (2007)
19	*Lethariella canariensis*	Atranol, chloroatranol, methyl β-orsellinate methyl hematommate ethyl hematommate	Phytotoxicity and Antioxidative	Toledo Marante et al. (2003)
20	*Parmelia caperata*	Four orsellinic acid derivatives, n-octacosanol, β-sitosterol, 3-D-glucopyranoside		Saraswathy et al. (1990)
21	*P. loxodes* and *P. verruculifera*	Orcinol type depside		Culberson and Johnson (1976)
22	*P. stenophylla*	68 fatty acid		Dembitsky et al. (1992)
	P. scortea			
	P. sulcata			
23	*Parmelia stygia*	Fumaroprotocetraric acid depsidones	Smooth muscle relaxant	Mischenko et al. (1984)
24	*Peltigera apthosa*	Tenuiorin, methyl gyrophorate, methyl evernate, methyl lecanorate, methyl orsellinate, 4-O- methyl gyrophoric and evernic acid		Maass (1975)
25	*Protousnea poeppigii* (Nees & Flot.) Vain.	Isodivaricatic acid, 5-propylresorcinol, divaricatic acid, usnic acid	Antifungal & antiprotozoal	Schmeda-Hirschmann et al. (2007)
26	*Pseudevemia furfuracea*	Physodic acid, chloroatranorin, atranorin, and olivetoric acid	Antimicrobial	Türk et al. (2006)
27	*Protousnea* sp.	Resorcinol derivative	Tyrosinase inhibition	Kinoshita et al. (1994)
28	*Pseudoevernia furfuracea*	D-Usnic acid, evernic acid and atranorin	Allergic	Goncalo (1987)
	Evernia prunastri			
	Pertusariaceae			
29	*Thamnolia subuliformis*	Rhamnopyranosyl galactofuranan	Immunilogically active	Olafsdottir et al. (1999)
	Ramalinaceae			
30	*Ramalina almquisii*	D-Protolichesterinic acid and nephrosternic acid	Anti-tumor	Hirayama et al. (1980)
31	*R. farinacea* (L.) Ach.	(+)-Usnic acid, evernic and obtusatic acid		Rastogi and Mehrotra (1993)
32	*R. farinacea*	(+)-Usnic Acid, Norstictic Acid, and Protocetraric Acid	Antimicrobial	Tay et al. (2004)
33	*R. subcomplanata*.	Secondary metabolites	Antibacterial	Kumar et al. (1995)
34	*Roccella belangeriana* (Awasthi)	Chloroform extract	Antibacterial	Karthikaidevi et al. (2009)
	Stereocaulaceae			
35	*Stereocaulon alpinum* Laur	Lobaric acid	Inhibit 5-lipoxygenase from porcine leukocytes, with an IC_{50} value of 7 μM	Ingólfsdóttir et al. (1996)

Table 2 continued

S. no.	Lichen species	Compounds characterized	Activity	Reference
36	*Stereocaulon ramulosum*	Methyl haematommate	Antifungal	Hickey et al. (1990)
	Stictaceae			
37	*Pseudocyphellaria glabra* and *P. homoeophylla*	Usnic acid	Antimicrobial, Antiviral and Cytotoxic	Perry et al. (1999)
	Teloschistaceae			
38	*Caloplaca* species	Anthraquinone	Broad-spectrum antifungal and antibacterial properties	Manojlovic et al. (2005)
39	*Xanthoria parietina*	Parietin	UV-protecting agent	Solhaug et al. (2003)
	Thelotremataceae			
40	*Diploschistes muscorum*	Secondary metabolites	Oxidative stress	Cuny et al. (2004)
	Umbilicariaceae			
41	*Gyrophora exculenta*	Secondary metabolites	Inhibitory effect on cyclooxygenase activity of prostaglandin H_2 synthase	Min et al. (1996)
42	*Umbilicaria mammulata*	Secondary metabolites	Low temperature stress	Stocker-Wörgötter (2001a)
43	*U. Antarctica*	Gyrophoric acid, lecanoric acid, and methyl orsellinate	Inhibition of PTP1B	Seo et al. (2009)
	Usneaceae			
44	*Usnea campestris*	Usnic acid	Anti-fungal & anti-bacterial	Gutkind et al. (1981)
45	*U. diffracta*	Diffractaic acid usnic acid	Analgesic & antipyretic	Okuyama et al. (1995)
46	*U. diffracta*	Diffractaic acid usnic acid	Anti-inflammatory	Otsuka et al. (1972)
47	*U. diffracta*	Decarboxy stenosporic acid	*Staphyrococcus aurens*	Yamamoto et al. (1998)
48	*U. longissima*	Usnic acid, depside	Photosystem II inhibition	Endo et al. (1998)
49	*U. longissima*	Usnic acid	Plant growth inhibition	Nishitoba et al. (1987)
50	*U. longissima*	Lichesterinic, (+)- usnic and evernic acid	Epstein-Barr virus activation inhibition	Yamamoto et al. (1995)
51	*U. misaminensis*	Usnic acid	Smooth muscle relaxant	Mustafa et al. (1995)
52	*U. venosa*	D-Usnic acid, barbatic acid and norstictic acid		Rastogi and Mehrotra (1991)

Broad spectrum antibiotic compounds

Dibenzofuran, usnic acid is a molecule with wide spectrum of activities (Ingólfdóttir 2002; Cardarelli et al. 1997; Lauterwein et al. 1995; Huovinen and Lampero, 1989; Kupchan and Kopperman 1975; Duman et al. 2008). Usnic acid is known to be present in three forms, i.e. (−)-usnic acid, (+)-usnic acid and isousnic acid (Shibata and Taguchi 1967). Both (−) and (+)-usnic acid are biologically important. Photo system II inhibition is shown by usnic acid (Inoue et al. 1987). Usnic acid is also a non-genotoxic compound with anticancer properties (Mayer et al. 2005). Derivatives of usnic acid are also reported to be antineoplastic (Takai et al. 1979). (−)-usnic acid isolated from *Alectoria ochroleuca* has shown antifungal activity (Proksa et al. 1996).

UV screening compounds

Lichen are also known to synthesize, UV-B-absorbing cortical pigments, like brown melanic compounds in *Lobaria pulmonaria* and orange parietin in *Xanthoria aureola*, which act as uv filter and protects the inner algal layer from harmful effects of uv radiation. These compounds are produced by the mycobiont and induced by UV-B radiation. UV-B has been reported to induce production of usnic acid (Solhaug et al. 2003; McEvoy et al. 2006; Nybakken and Julkunen-Tiitto 2006). Low temperature also can set off an increased production of secondary metabolites, as reported by Stocker-Wörgötter (2001a). According to Swanson and Fahselt (1997) and Begora and Fahselt (2001), UV-A irradiation alone causes the production of higher amount of phenolic compounds in lichens than exposed to both UV-A and UV-B radiation.

Pulvinic acid derivatives

Apart from compounds synthesized via polymalonyl pathway, other compounds synthesized via mevalonate and shikimate pathways are potentially active. Vulpinic acid is also known to possess antimicrobial activity against aerobic and anaerobic microorganisms. It also induces uncoupling of oxidative phosphorylation (Abo-Khatwa et al. 1996).

Hydroxybenzoic acid derivatives

Esters of 4-hydroxybenzoic acid such as methylparaben are used as preservatives in the pharmaceutical preparations. As these agents are rapidly hydrolyzed in vivo to the corresponding acid which is then conjugated and excreted, their toxicity is generally low (Wilson et al. 1998).

Sterol compounds

Due to different types of pharmacological activities like antiinflammatoy, antiulcerogenic, antibacterial, antifungal, antirheumatic activities, the vast majority of steroids play an important role in the field of medicines. It has been reported that sterols may also play a pivotal role in the membrane permeability and perhaps influence the transport of materials from algae to fungi in lichens. In general C_{28} sterols predominate in fungi while C_{29} sterols are found in algae (Lenton et al. 1973). NMR spectral analysis of sterols is an aid to characterize the structure (Thompson et al. 1972). Sterols have been isolated and characterized from *Xanthoria parientina* (Safe et al. 1975), *Pseudoevernia furfuracea* (Wojciechowski et al. 1973) and *Lobaria pulmonaria*, *L. scrobiculata* and *Usnea longissima* (Safe et al. 1975). Brassicasterol, lichesterol, poriferasterol, β-sitosterol have been reported from *Ramalina africana* (Shukla et al. 2004).

The above-mentioned activities clearly indicate the potential of lichen compounds for pharmaceutical purposes, but some properties of lichens still need consideration. Their slow growth, both in nature and in axenic cultures, may be regarded as a major problem for the production of metabolites. However, culture conditions of lichen mycobionts can be optimized in order to support the synthesis of interesting secondary compounds. Much progress has been achieved recently by specifically addressing these issues (Stocker-Wörgötter 1998, 2001b, 2002a, b, Stocker-Wörgötter and Elix 2004).

Further manifold biological activities of lichen metabolites have now been recognized, but their therapeutic potential has not yet been fully explored. In particular, the depsides and depsidones isolated from lichens are of special interest because of their antiinflammatory, antiproliferative and anti-HIV activities.

Conclusion

Most of the preliminary information on biological activity and potential use of lichens and/or their metabolites are derived from their ethno-botanical lore and 'Doctrine of Signatures'. But the recent work on the biochemical and physiological activities associated with the individual components of lichen extract reveals tremendous potential of these compounds for mankind. With the aid of modern equipments and methodologies, isolation and characterization of active compounds and elucidation of mechanism of action has become easier.

Chemical structure of most of the lichen substances is simple which facilitates synthesis of these compounds in the laboratory. This practice would provide large amounts of material without affecting ecosystem. In addition, many of these compounds can be used as precursors based on their particular mechanism of action and can then be optimized in the laboratory to fit specific applications. Appropriate chemical modification may increase the stability and reduce the toxicity of the natural products and could lead to an increase in their potency.

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