Inventum Biologicum: *An International Journal of Biological Research*
2025, Vol. 5, Issue 1, pp. 36-42

Inventum Biologicum

Journal homepage: www.journals.worldbiologica.com/ib

Review paper

A Comprehensive Review on Secondary Metabolite of Lichens

Chandranshu Bhushan [a], **Salman Khan** [a], **Saumya Singh** [a], **Ekta Singh** [a], **Charvi Mishra** [a], **Avinash Pratap Singh** * [a]

[a]*Microbiology and Plant Pathology Laboratory, Department of Botany, C.M.P. Degree College, University of Allahabad, Prayagraj-211002, India*

ARTICLE INFO

Keywords

Lichen
Secondary metabolite
Medicinal property
Antioxidant

DOI
10.5281/ib-1932825

***Corresponding author**
Avinash Pratap Singh
✉ **Email**
avinashsinghau@gmail.com

ABSTRACT

Unique organisms and lichen-forming fungi produce physiologically active compounds with a wide range of actions, including cytotoxic, antimycobacterial, antiviral, anti-inflammatory, analgesic, antipyretic, and antiproliferative properties. Nevertheless, very few lichen compounds have been examined for their biological and medicinal properties in medicine. This is undoubtedly a result of the challenges involved in species identification, bulk quantity collection, and isolation of pure chemicals for testing and structural determination. This involves synthesizing natural products or their derivatives for testing, extracting targeted chemicals, or using axenic cultures to produce new or authentic substances. Synthetic antioxidants that are often utilized are thought to have harmful and cancer-causing properties. As a result, there is an increasing interest in discovering novel natural resource antioxidants that are free of unwanted effects. Numerous in vitro investigations on plants, macromycetes, micro- and macroalgae, and lichens have provided compelling evidence that their antioxidant-capable elements can protect biological systems from oxidative stress. Because natural antioxidants have a preventive effect against oxidative stress and physiological dysfunction, their use is crucial. Lichens have piqued our interest in the search for novel natural antioxidant sources. Secondary metabolites, mainly phenols, which are well recognized for their antioxidant properties, are abundant in lichens.

1. Introduction

A stable and resilient relationship between fungi, mycobionts, and their photoautotrophic, algae companions, or photobionts, is known as lichen. In unique organisms, lichen-forming fungi produce physiologically active compounds with a wide range of actions, including cytotoxic, antimycobacterial, antiviral, anti-inflammatory, analgesic, antipyretic, and antiproliferative properties. Nevertheless, very few lichen compounds have been examined for their biological properties and possible medical applications. This is undoubtedly a result of the challenges involved in species identification, bulk quantity collection, and the isolation of pure chemicals for testing and structural determination.

One-fifth of all fungi maintain a lichen-forming habit, which appears to be a successful type of fungal symbiosis. Include only a small number of basidiomycetes but over 40% of ascomycetes. Worldwide, approximately 18,500 types of lichens have been acknowledged and described. Thus, they may thrive in a variety of occasionally harsh ecological settings. At severe altitudes (up to 7400 m) or polar latitudes, lichens can be found under extremely dry and frigid conditions. Notwithstanding this wide variety of ecological adaptations, the

majority of lichens are susceptible to shifts in their preferred ecological circumstances and find it difficult to thrive in non-native environments. In natural areas where lichens are prevalent, they frequently enhance their habitat with a vibrant element. The unique character of many lichens is caused by the enormous buildup of various secondary chemicals, often known as "lichen substances." In addition to being small, they also indicate chemically intricate molecules. In addition to the readily apparent crystallized and non-crystallized colours deposited in the lichen's vegetative body's top surface layers, Additionally, colourless chemicals are prevalent and mostly located in the thalli's interior regions.

2. Diversity of Secondary Elements in Lichens

The majority of lichen substances are classified as phenolic compounds (orcinol and b-orcinol derivatives), dibenzofuranes, usnic acids (for example, usnic acid), depsides (for example, barbatic acid), depsidones (for example, salazinic acid), depsones (for example, picrolichenic acid), lactones (e.g., protolichesterinic acid, nephrosterinic acid), quinones (for example, parietin), and derivatives of pulvinic acid (for example, vulpinic acid). It appears that lichens have developed a variety of biochemical routes to generate this range of chemicals, primarily polymalonate, shikimic acid, and mevalonic acid. To create this variety of molecules, lichens appear to have developed a variety of biosynthetic routes, primarily the polymalonate, shikimic acid, and mevalonic acid pathways (Huneek, et al., 1995). These species also include a few odd groups of elements, including the cyclic depsipeptide arthogalin, as well as other substances generated from amino acids, including the cytotoxic scabrosin esters that were separated from *Xanthoparmelia scabrosa* (Ernst, et al., 1999). Additionally, uncommon characteristics can be found in binding with other substances, such as sugars, in the form of different intramolecular configurations or residues of common chemical groups. Several unique compounds have been identified, including monotetrahydrofuranic acetogenin derivatives (Rezanka, et al., 2004), brominated acetylenic fatty acids and brominated depsidones (Rezanka, et al., 1999).

3. Antioxidant Activities of Lichen Secondary Metabolites

Water–methanol (90:10 v/v) Thin layer chromatography (TLC) was used to examine extracts of five polar lichen species from King George Island: *Stereocaulon alpinum, Ramalina terebrata, Caloplaca* sp., *Lecanora* sp., and *Caloplaca regalis.* This was followed by the DPPH (2,2-diphenyl-1-picrylhydrazyl) spray approach. According to experimental findings, active antioxidants make up 33–50% of the main ingredients of the test extracts (Bhattarai,et al., 2008& Bhattarai,et al., 2008). Certain depsides, like atranorin (derived *from Placopsis sp*.) and divaricatic acid (derived from *Protousnea malacea*), as well as depsidones, like pannarin (derived from *Psoroma pallidum*) and 10-chloropannarin (derived from *Erioderma chilense*), exhibit antioxidant activity (Hidalgo, et al., 1994). Depsidones are the most efficient secondary chemicals in inhibiting β-carotene oxidation and homogenate auto-oxidation in rat brains. Both sphaerophorin (depside) and pannarin (depsidone) suppress superoxide anion production in vitro, with pannarin being more effective (Hidalgo, et al., 1994). Similarly, a thiobarbituric acid reactive species assay in mouse lung tissue revealed that fumarprotocetraric acid, which is generated by the lichen *Cladonia verticillaris*, has a strong antioxidant capacity.

Several types of lichen metabolites have been evaluated for their antioxidant activity (Thadhani, et al., 2011) using in vitro superoxide radical (SOR), nitric oxide radical, and 2,2-diphenyl-1-picrylhydrazil radical scavenging tests. In comparison to the standard, propyl gallate (IC50¼ 106.0~1.7μmol), the despsides sekikaic acid and lecanoric acid demonstrated encouraging antioxidant activity in the SOR assay, with IC50 values of 82.0~0.3 μmol and 91.5~2.1 μmol, respectively, and depsidone lobaric acid displaying an IC50 value of 97.9~1.6 μmol. Compared to the conventional rutin (IC50¼ 86.8~1.9μmol), methyl-β-orcinol carboxylate, one of the most prevalent mononuclear phenolic compounds, was shown to be a strong NO scavenger (IC50 ¼ 84.7 ~ 0.1 μmol).

The impact of six lichen metabolites (diffractaic acid, lobaric acid, usnic acid, vicanicin, variolaric acid, and protolectinic acid) on the quantity of ROS (reactive oxygen species) in three human cancer cell lines: HeLa (cervical adenocarcinoma), MCF-7 (breast adenocarcinoma), and HCT-116 (colon carcinoma) (Brisdelli, et al., 2013).

Some stictic acid derivatives showed extremely high superoxide anion scavenging activity and moderate antiradical activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) test (Lohézic, et al., 2007).

Six Umbilicaria species were used to examine the antioxidant qualities of methanolic extracts and lichen acids (gyrophoric, lecanoric, and umbilicaric acids) (Buçukoglu, et al.,2013). The antioxidant capacity was assessed using an experiment using 2,2-diphenyl-1-picrylhydrazyl (DPPH) to scavenge free radicals. The methanolic extracts demonstrated moderate DPPH radical-scavenging efficiency. Among the lichen acids, umbilicaric acid showed the highest antioxidant activity with an inhibition of 68.14%.

In addition to the previously described metabolites, 80-methylstictic acid, 80-methylmenegazziaic acid, stictic acid, 80-ethylstictic

acid, and atranorin, four new β-orcinol metabolites, hypotrachynic acid, deoxystictic acid, cryptostitinolide, and 80-methylconstictic acid, were isolated for the first time from tissue extracts of the lichen *Hypotrachyna revoluta* (Papadopoulou, et al.,2007). Comprehensive spectroscopic investigations were performed to elucidate the structures of these novel metabolites. The findings demonstrated that molecules with an extra hydroxyl group on the aromatic ring, such as 80-methylmenegazziaic acid and atranorin, were the most active; when the hydroxyl of C-3 was swapped out for an aldehyde moiety, the activity was halved. Lastly, when the methylene of the γ-lactone ring was replaced by a hydroxy or methoxy moiety, the scavenging activity of the metabolites with an aldehyde group at C-3 appeared to be significantly decreased, as seen in the cases of deoxystictic acid, stictic acid, and 80-methylstictic acid. BHT, a common antioxidant, was twice as potent as cuculloquinone, a bisnaphthoquinone of Flavocetraria cucullata, which has been reported to inactivate DPPH by 80% (Stepanenko, et al., 2002).

The antioxidant effects of *Evernia prunastri* and *Pseudevernia furfuracea* lichens and their main metabolites, evernic acid and physodic acid, resulted in uneven antioxidant success in terms of superoxide anion radical scavenging, reducing power, free radical scavenging, and physodic acid. It was discovered that the acid worked best (Kosanić, et al.,2013).

4. Evolutionary Patterns of Secondary Chemistry in Lichenized Ascomycotina

The fungus often forms secondary products of lichens, as evidenced by the presence of secondary chemicals in cultivated mycobionts and their lack of algae (Ahmadjian, et al.,1961). It has been proposed that these ascomycetous lineages might have ancestral traits, such as the capacity to create lichen symbioses and the abundance of secondary chemicals. The genetic potential for producing secondary metabolites was proposed to be preserved, even though certain species (such as Eurotiomycetes and groups in Chaetothyriomycetes; (Lutzoni, et al., 2001) may have "secondarily" lost a lichen habit over evolution. Lecanoromycetes and Arthoniomycetes are two sizable lineages of primarily lichenized fungi that have developed separately. Although each of these groups has some distinct compounds that are not present in the others, they also share some other compounds (and in some cases, with other non-lichenized fungal groups).

5. Genes Involved in the Production of Secondary Metabolites

Clusters of sequentially set-up genes regulate the production of secondary fungal products (Keller, et al.,1997). Concatenation of C2-units by polyketide synthases (PKS) is the first important phase in the synthesis of polyketides. These enzymes generate secondary metabolite core structures. Multifunctional proteins (fungal type I PKSs) with a single, frequently applied ketoacyl synthesis domain that progressively condenses fungal PKS genes encoding C2-units. A gene from *Xanthoria parietina* was linked to alleles that encode for the generation of aflatoxins or equivalent mycotoxins (Grube, et al.,2003) using a heterologous primer technique. It seems fair to assume that this gene represents an anthraquinone-producing polyketide synthase since anthraquinones are precursors of these mycotoxins and because the upper cortex of *Xanthoria* contains crystallized anthraquinone parietin. One PKS gene is preferentially transcribed by heterologous primers that are currently available. gene or a small number of genes from a subset of paralogs in lichen genomes; therefore, there are three ways to find more PKS genes:

- Cloning PCR products were made with primers that are not specific for different paralogs (Schmitt, et al.,2005).
- Amplifying with more specific primers for specific Paralog lineages
- Screening lichen mycobiont genomic libraries using PKS gene probes (Lawrey, 1986).

A lichen phage library contains orotidine 50-monophosphatase, which is responsible for decarboxylating orotidylic acid to uridylic acid using hybridization techniques for *Solorina crocea* (Lawrey., 1995).

6. Bioactive Compounds and Potential Medicinal Uses

Lichen's diverse range of biological activities is generally linked to their unique ecological conditions (Lawrey.,1986, Lawrey.,1995& Rikkinen,1995). They produce metabolites with antimicrobial and deterrent effects and can occasionally be extremely toxic to specific animals. Potential of compounds as pharmaceuticals (Müller., 2001& Yamamoto., 2000). Lichens have also been utilized in traditional medicine for centuries; many features of usnic acid have been described, and in certain countries, commercial products based on their presence are available for local antiseptic action (Ingolfsdottir., 2002). Although usnic acid, like many other lichen chemicals, can induce allergic responses, its insufficient usage in nutraceuticals (approximately 500mg daily administered orally to lose weight) has recently been linked to mild hepatotoxicity. In Asian nations, lichens are still used in traditional and alternative medicine (*Benalu tehw*) for various indications (Saklani, et al.,1992). Iceland moss (¼ *Cetraria islanÿdica*) is included in the European

Pharmacopoiea (2005), and its suggested applications match a *tonicum amarum* and as a cough treatment. Because of its lung-like appearance, *Lobaria pulmonaria* has also been used for cough treatment. It is still used in homoeopathies such as *Sticta pulmonaria.* Some Indian lichens have antifungal properties (Shahi, et al.,2000& Shahi, et al.,2001& Shahi, et al., 2003), and there is much data on how lichens are used ethnobotanically by many of India's ethnic groups. Based on current knowledge, the pharmacological and other biological actions of lichens and lichen compounds can be categorized into the following groups.

6.1 Antibiotic activity

In the 1950s, many lichen chemicals and extracts were tested for antibacterial activity, and in several instances, their action against mycobacteria and gram-positive organisms was verified (Stoll, et al.,1950). The ability of UA to combat harmful Gram-positive bacteria in vitro has been demonstrated, and it has been utilized in toothpaste, mouthwash, and topical treatments. Furthermore, the substance was found to be effective against anaerobic bacteria such as *Clostridium perfringens* and Bacteroides species (Lauterwein, et al., 1995). Given that Iceland moss is used to heal duodenal and stomach ulcers, it is significant that a component It has been demonstrated that the lichen's protolichesterinic acid has in vitro action against *Helicobacter pylori* (Ingolfsdottir, et al., 1997). Serious clinical complications have recently resulted from the rise of drug-resistant bacterial species such as tubercular mycobacteria. Lichens are an intriguing source of chemicals, and as the search expands to additional sources, new antimicrobial agents are urgently required.

6.2 Antitumor and antimutagenic activity

A few lichen compounds with antitumor and antimutagenic properties have been partially studied, and dibenzofuran-usnic acid has an antitumor action against Lewis's lung cancer and P388 leukemia) and has been linked to apoptotic induction and mitosis inhibition. Protolichesterinic acid, a butyrolactone, was also shown to be antiproliferative against Ehrlich solid tumors and leukemia cells K-562 (IC50¼ 20 mg/ml), whereas derivatives of nephrosteranic acid showed weak activity (Hirayama, et al., 1980). Physodalic acid, lichen glucans, polyphonic acid (terphenyl quinone) and its derivatives (Cain., 1961& Cain., 1966), and depsidone. This approach has also been used to study lichenin derivatives (Demleitner., et al., 1991) and other substances. Regarding novel secondary metabolites from lichens that have cytotoxic properties against cancer cell lines, *Xanthoparmelia scabrosa's* original N-containing complex structures (scabrosin esters) (IC50¼ 0.27mM p-815), Recent descriptions have identified a naphthazarin-derived dimer (hybocarpone) isolated from a mycobiont culture of *Lecanora hypocarbia* (IC50¼ 1nM, MCF-7) and an uncommon indenone naphthopyrone euplectin from *Flavoparmelia euplecta* (IC50 ¼ 0.58 mM, P-815) (Ernst-Russell, et al., 1999& Ernst-Russell, et al., 1999).

Phaerophorin, 10-chloropannarin, pannarin, and other depsidone and depside series have been shown to have greater cytotoxic effects than colchicine in lymphocyte cell cultures (Correche, et al., 2002). Of the 15 lichen compounds tested on primary cultures of rat hepatocytes, salazinic acid, stictic acid, and psoromic acid were the most apoptotically active derivatives (Correche, et al., 2004).

Table 1 Anticancer activity of lichen secondary metabolite

Lichen name	Bioactive molecule	Anticancer method	Year of report
Lecanora atra	Atranorin	In-vitro- MTT In-vivo- using male BALB/c mice	2011
U. aurantiaca	Salazinic acid	In-vitro- MTT In-vivo- using Albino wistar rats	2019
Flavocentraria cucllate	Usnic acid	In-vitro- MTT In-vivo- using Swiss albino mice	2014

6.3 Antiviral activity

Certain anthraquinone chemicals such as emodin and its derivatives, which are also found in higher plants, have demonstrated antiviral activity in vitro and are thought to be of interest against human cytomegalovirus (Wood, et al., 1990). The inhibitory action of 17 depsides and depsidones against HIV integrase has been investigated, and pharmacophores made from virforensic acid have enabled the selection of several strong inhibitors. It was also discovered that butyrolactone protolichesterinic acid, extracted from *Cetraria islandica*, inhibited HIV-RT (Pengsuparp, et al., 1995). Four depsides, and most importantly (p)-usnic acid, were found to be effective against EBV activation and may therefore be good options for antitumor promoters (Yamamoto, et al., 1995). In terms of high-molecular-weight substances, a sulfate (GE-3-S) made by treating GE-3, partly acetylated (Kosanić, et al., 2013) Glucan from the lichen *Umbilicaria esculenta* with chlorosulfonic acid prevented HIV's cytopathic impact in vitro (Hirabayashi, et al., 1989).

6.4 Enzyme inhibitory activities

Lichen acids, primarily atranorin, evernic, physodes, and usnic acids are potent inhibitors of several metabolic enzymes that are connected to polyamine metabolism, including arginase, arginine decarboxylase,

Table 2 Antiviral activity of lichen secondary metabolites

Lichen name	Bioactive molecule	Name of Virus	Year of report
Roccella montagenei	Orcinol	Anti-herpes simplex virus-1	2023
Parmelia perlata	Usnic acid	Respiratory syncytical virus type 1 RSV	2009
Ramalina farinacea	Psoromic acid	Herp's simplex virus type 1	2019

and ornithine decarboxylase. Certain lichen extracts and chemicals have also been shown to inhibit lipoxygenase. Certain lichen compounds have anti-inflammatory, analgesic, and antipyretic properties (Okuyama, et al., 1995), as well as local anesthetic effects. These properties may be linked to the inhibition of prostaglandin biosynthesis (Sankawa, et al., 1995) and leukotriene B4 biosynthesis (Kumar, et al., 1999). Natural lichen extracts (behera) inhibit tyrosinase, an enzyme involved in melanin formation, and xanthine oxidase, a crucial enzyme in hyperuricemia. In several instances, it was discovered that the cultivated lichen tissue was superior to the test standards employed. It has been possible to identify tyrosinase inhibitors such as divinyl or diphenylmethane derivatives and synthesize more powerful derivatives (Matsubara, et al., 1998).

Table 3 Enzyme inhibitory activity of lichen secondary metabolite

Lichen name	Bioactive molecule	Anticancer method	Year of report
Caloplaca boatorina	Atranorin	In-vitro- MTT In-vivo- using male BALB/c mice	2010
Physcia aipolia	Salazinic acid	In-vitro- MTT In-vivo- using Albino wistar rats	2014
Flavoparmelia caperata	Usnic acid	In-vitro- MTT In-vivo- using Swiss albino mice	2015

7. Conclusion

Although other lichen characteristics still need to be considered, the aforementioned actions clearly show the potential of lichen chemicals for pharmacological purposes. Both in nature and in axenic cultures, lichen's sluggish development might be seen as a significant issue for metabolite production. Nonetheless, it is possible to enhance the synthesis of intriguing secondary chemicals by optimizing the growth of lichen mycobionts.

However, a lichen thallus's high chemical content (extraction typically produces 5–25% of dried lichen material) could be enough. both for direct crystallizations and for testing, even though many situations call for particular solubilization efforts. Since direct crystallization makes it easier to isolate and characterize molecules and for their derivatization and semisynthetic investigations, this might be useful for therapeutic applications. Parallel to this, advancements in the study of the rich genetic heritage of polyketide synthase genes might transform their application in upcoming biotechnological strategies, such as the creation of chimeric molecules and heterologous expression in rapidly developing hosts.

References

1. Ahmadjian, V. & Reynolds, J. T. (1961) Production of biologically active compounds by isolated lichenized fungi. Science 133, 700 –701.
2. Bhattarai, H. D., Paude, B., Lee, H. S. et al (2008a) Antioxidant activity of Sanionia uncinata, a polar mass species from King George Island, Antarctica. Phytother Res 22, 1635–1639.
3. Bhattarai, H. D., Paudel, B., Hong, S. G. et al (2008b) Thin layer chromatography analysis of antioxidant constituents of lichens from Antarctica. J Nat Med 62, 481–484.
4. Brisdelli. F., Perilli. M., Sellitri. D. et al (2013) Cytotoxic activity and antioxidant capacity of purified lichen metabolites: an in vitro study. Phytother Res 27, 431–437.
5. Buçukoglu, T. Z., Albayrak, S., Halici, M. G., & Tay, T. (2013). Antimicrobial and Antioxidant Activities of Extracts and Lichen Acids Obtained from Some U mbilicaria Species from C entral A natolia, T urkey. Journal of food processing and preservation, 37(6), 1103-1110.
6. Cain, B. F. (1961). Potential antitumour agents. Part I. Polyporic acid series. Journal of the Chemical Society Abstracts, 936 – 940.
7. Cain, B. F. (1966). Potential anti-tumour agents. Part IV. Polyporic acid series. Journal of the Chemical Society Section C, Organic, 1041 –1045.
8. Correche, E., Carrasco, M., Giannini, F., Piovano, M., Garbarino, J., & Enriz, D. (2002). Cytotoxic screening activity of secondary lichen metabolites. *Acta Farmaceutica Bonaerense*, *21*(4), 273-278.
9. Correché, E. R., Enriz, R. D., Piovano, M., Garbarino, J., & Gómez-Lechón, M. J. (2004). Cytotoxic and apoptotic effects on hepatocytes of secondary metabolites obtained from lichens. Alternatives to Laboratory Animals, 32(6), 605-615.
10. Demleitner, S., Kraus, J. & Franz, G. (1991). Synthese und Antitumoraktivitat von Licheninderivaten. Pharmazie in unserer Zeit 20, 120.
11. Ernst-Russell, M. A., Elix, J. A., Chai C. L., Willis, A. C., Hamada, N. & Nash T. H. (1999). Hybocarpone, a novel cytotoxic naphthazarin derivative from mycobiont cultures of the lichen Lecanora hybocarpa. Tetrahedron Letters 40, 6321– 6324.
12. Ernst-Russell, M. A., Elix, J. A., Chai, C. L., Hockless, D. C., Hurne, A. M., & Waring, P. (1999). Structure revision and cytotoxic activity of the scabrosin esters, epidithiopiperazinediones from the lichen Xanthoparmelia scabrosa. *Australian Journal of Chemistry*, *52*(4), 279-283.

13. Grube, M. & Blaha, J. (2003). On the phylogeny of some polyketide synthase genes in the lichenized genus Lecanora Mycological Research 107, 1419 – 1426.
14. Hidalgo, M. E., Ferna´ndez, E., Quilhot, W. et al (1994). Antioxidant activity of depsides and depsidones. Phytochemistry 37, 1585–1587.
15. Huneck. S., & Himmelreich, U. (1995). Arthogalin, a cyclic depsipeptide from the lichen *Arthothelium galapagoense*. *Zeitschrift fu¨rNaturforschung*, B. Chemical Sciences 50, 1101–1103
16. Hirabayashi. K., Iwata. S., Ito. M., Shigeta. S., Narui. T., Mori, T. & Shibata. S. (1989). Inhibitory effect of a lichen polysaccharide sulfate, GE-3-S, on the replication of human immunodeficiency virus (HIV) in vitro. Chemical and Pharmaceutical Bulletin 37, 2410–2412.
17. Hirayama, T., Fujikawa, F., Kasahara, T., Otsuka, M., Nishida, N. & Mizuno, D. (1980). Anti-tumor activities of some lichen products and their degradation products. Yakugaku Zasshi 100, 755 –759.
18. Ingolfsdottir. K., (2002). Molecules of interest: usnic acid. Phytochemistry 61, 729 –736.
19. Ingolfsdottir, K., Hjalmarsdottir, M. A., Guðjo´nsdo´ttir, G. A., Brynjolfsdo´ttir. A., Sigurðsson, A. & Steingrı´msson O´. (1997). In vitro susceptibility of Helicobacter pylori to protolichesterinic acid from Cetraria islandica. Antimicrobial Agents and Chemotherapy 41, 215– 217.
20. Keller, N. P. & Hohn, T. M. (1997). Metabolic pathway gene clusters infilamentous fungi. Fungal Genetics and Biology 21, 17– 21
21. Kosanić, M., Manojlović, N., Janković, S., Stanojković, T., & Ranković, B. (2013). Evernia prunastri and Pseudoevernia furfuraceae lichens and their major metabolites as antioxidant, antimicrobial and anticancer agents. Food and chemical toxicology, 53, 112-118.
22. Kumar, S. & Muller, K. (1999). Lichen metabolites. I. Inhibitory action against leukotriene B4 biosynthesis by a non-redox mechanism. Journal of Natural Products 62. 817 – 820.
23. Lauterwein, M., Oethinger, M., Belsner, K., Peters, T. & Marre. R. (1995). In vitro activities of the lichen secondary metabolites vulpinic acid, (þ)-usnic acid and (2)-usnic acid against aerobic and anaerobic microorganisms. Antimicrobial Agents and Chemotherapy 39, 2541– 2543.
24. Lawrey, J. D. (1986). Biological role of lichen substances. The Bryologist 89,11– 122.
25. Lawrey, J.D. (1995) The chemical ecology of lichen mycoparasites. Canadian Journal of Botany 73(Suppl. 1) 603 – 608.
26. Lohézic-Le Dévéhat, F., Tomasi, S., Elix, J. A., Bernard, A., Rouaud, I., Uriac, P., & Boustie, J. (2007). Stictic acid derivatives from the lichen Usnea articulata and their antioxidant activities. Journal of natural products, 70(7), 1218-1220.
27. Lutzoni, F., Pagel, M., & Reeb, V. (2001). Major fungal lineages are derived from lichen symbiotic ancestors. Nature, 411(6840), 937-940.
28. Matsubara, H., Miharu, K., Kinoshita, K., Koyama, K., Ye, Y., Takahashi, K., Yoshimura, I., Yamamoto, Y., Miura, Y. & Kinoshita, Y. (1998) Inhibitory effect of lichen metabolites and their synthetic analogs on melanin biosynthesis in cultured B-16 mouse melanoma cells. Natural Product Sciences 4, 161–169.
29. Miao, V., Coëffet-LeGal, M. F., Brown, D., Sinnemann, S., Donaldson, G., & Davies, J. (2001). Genetic approaches to harvesting lichen products. TRENDS in Biotechnology, 19(9), 349-355.
30. Müller, K. (2001). Pharmaceutically relevant metabolites from lichens. Applied microbiology and biotechnology, *56*, 9-16.
31. Okuyama, E., Umeyama, K., Yamazaki, M., Kinoshita, Y., & Yamamoto, Y. (1995). Usnic acid and diffractaic acid as analgesic and antipyretic components of Usnea diffracta. Planta medica, 61(02), 113-115.
32. Papadopoulou, P., Tzakou, O., Vagias, C., Kefalas, P., & Roussis, V. (2007). β-Orcinol Metabolites from the Lichen Hypotrachyna revoluta. Molecules, 12(5), 997-1005.
33. Pengsuparp, T., Cai, L., Constant, H., Fong, H. H., Lin, L. Z., Kinghorn, A. D., Pezzuto, J. M., Cordell, G. A., Ingo´lfsdo´ttir, K., Wagner, H. & Hughes, S. H. (1995). Mechanistic evaluation of new plant-derived compounds that inhibits HIV-1 reverse transcriptase. Journal of Natural Products 58, 1024– 1031.
34. Rezanka, T., Temina, M., Hanus, L. & Dembitsky, V. M. (2004). The tornabeatins, four tetrahydro-2-furanone derivatives from the lichenized ascomycete *Tornabea scutellifera* (With.) J. R. Laundon. Phytochemistry 65, 2605– 2612.
35. Rezanka, T. & Dembitsky, V. (1999). Novel brominated lipidic compounds from lichens of central Asia. Phytochemistry 51, 963– 968.
36. Rezanka, T. & Gushina, I. A. (1999). Brominated depsidones from *Acarospora gobiensis*, a lichen of Central Asia. Journal of Natural Products 62, 1675–1677.
37. Rikkinen. J., (1995). What's behind the pretty colours? A study on the photobiology of lichens. Bryobrothera 4, 1–239.
38. Saklani, A., & Upreti, D. K., (1992) Folk uses of some lichens in Sikkim. Journal of Ethnopharmacology 27, 229 – 233.
39. Sankawa, U., Shibuya, M., Ebizuka, Y., Noguchi, H., Iitaka, Y., Endo, A., & Kitahara, N. (1982). Depside as potent inhibitor of prostaglandin biosynthesis: a new active site model for fatty acid cyclooxygenase. Prostaglandins, 24(1), 21-34.
40. Schmitt, I., Martin, M. P., Kautz, S., & Lumbsch H, T. (2005). Diversity and evolution of secondary metabolite encoding genes in the Pertusariaceae. Phytochemistry (in press).
41. Shahi, S. K., Shukla, A. C., Uperti, D. K., & Dikshit. A., (2000). Use of lichens as antifungal drugs against superficial fungal infections. Journal of Medicinal and Aromatic Plant Sciences 22(4A)/23(1A), 169 –172.
42. Shahi, S. K., Shukla, A. C., Dikshit, A. & Upreti, D. K., (2001). Broad spectrum antifungal properties of the lichen. *Heterodermia leuocomela*. Lichenologist 33, 177 – 179.
43. Shahi, S. K., Patra, M., Dikshit, A., & Upreti, D. K. (2003). *Parmelia cirrhatum*: a potential source of broad spectrum natural antifungal. Phytotherapy Research 17, 399 –400.

44. Sinnemann, S. J., Andrésson, Ó. S., Brown, D. W., & Miao, V. P. (2000). Cloning and heterologous expression of Solorina crocea pyrG. Current Genetics, 37, 333-338.
45. Stoll, A., Brack, A. & Renz, J. (1950). Die Wirkung von Flechtenstoffen auf Tuberkelbakterien und auf einige andere Mikroorganismen. Schweizer Zeitschrift fu¨r Allgemeine Pathologie und Bakteriologie 13, 729 –751
46. Stepanenko, L. S., Krivoshchekova, O. E., & Skirina, I. F., (2002). Functions of phenolic secondary metabolites in lichens from Far East Russia. Symbiosis (Philadelphia, *PA)*, *32*(2), 119-131.
47. Thadhani, V. M., Choudhary, M. I., Ali, S. et al (2011). Antioxidant activity of some lichen metabolites. Nat Prod Res 25, 1827–1837.
48. Wood, S., Huffman, J., Weber, N., Andersen, D., North, J., Murray, B., Sidwell, R. & Hughes, B. (1990). Antiviral activity of naturally occurring anthraquinones and anthraquinone derivatives. Planta Medica 56, 651 – 652.
49. Yamamoto, Y., (2000). Screening of biological activities and isolation of biological-active compounds from lichens. Shokubutsu no Kagaku Chosetu 35, 169 –179.
50. Yamamoto, Y., Miura, Y., Kinoshita, Y., Higuchi, M., Yamada, Y., Murakami, A., Ohigashi, H. & Koshimizu, K. (1995). Screening of tissue cultures and thalli of lichens and some of their active constituents for inhibition of tumor promoterinduced Epstein-Barr virus activation. Chemical and Pharmaceutical Bulletin 43, 1388 –1390.