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Lichentherapy: Highlights on the Pharmaceutical Potentials of Lichens

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Review Article

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Abstract

Lichens exist in every continent and have a history of being used as food, medicine, a source of dyes and animal feed. Lichens are now being used as natural indicators of climate change and for air quality monitoring worldwide. Lichens play an important role in many ecosystems and exist as a symbiotic association between fungi and algae or cyanobacteria. This symbiosis results in the production of unique secondary metabolites known as lichen substances, which arise within the thalli and are typically in crystal form on the surface of the fungal hyphae. Recently, lichens and their secondary metabolites have been receiving increased attention due to their nutritional value and pharmaceutical potential. This review aims to highlight on the importance and variety of common lichen substances (secondary metabolites). Finally, the commercialization of lichens is growing but, in the future, metabolic and biotechnological approaches can be used as an alternative product to overcome the limited availability of biologically active, commercially valuable and medicinally important secondary metabolite components.

Keywords: Lichens; Pharmaceutical Activities; Biological Activities

Abbreviations: BHA: Butylated Hydroxyanisole.

Introduction

Lichens play an important role in many ecosystems and exist as a symbiotic association between fungi and algae or cyanobacteria. This symbiosis results in the production of unique secondary metabolites known as lichen substances, which arise within the thalli and are typically in crystal form on the surface of the fungal hyphae. Recently, lichens and their secondary metabolites have been receiving increased attention due to their nutritional value and pharmaceutical potential [1]. Lichens can grow on a range of surfaces from rocks to existing as epiphytes on trees or leaves [2]. The majority of described lichens are terrestrial, although a few are marine and have the ability to adapt to water and saline stress. Lichens are an excellent example of a symbiotic relationship between members belonging to two unrelated separate kingdoms (fungi and algae), which results in the collection of secondary metabolites. These metabolites can be fungal originated, algal originated or unique compounds not produced by either fungi or algae individually [3].

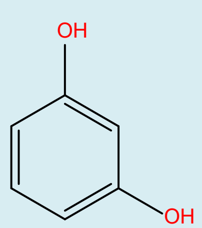
The vegetative component of lichen is called the thallus and this can be subdivided into four main categories. Foliose: A leaf-like thallus, attached to the substrate at various points. Crustose: A thallus that is flattened against the substrate and its lower surface is entirely attached. Fruticose: the thallus is mainly composed of pendulous or, less commonly, upright branches and is attached at a single point. Squamulose: In which the thallus begins like foliose lichen, but subsequently develops erect branches named podetial [4-7]. Mostly lichens secondary metabolites have yielded a wide range of interesting compounds with biological activities from antimicrobial to anticancer. Further, the nutritional value of lichens is identified alongside a role in environmental monitoring, and several commercialized lichen-based products are located. Lichens are found on every continent and have a history of use as food, medicine, dyes, and livestock feed [1].

Approximately there are 13,500 lichen species around the world. Lichens have a history of medicinal use and beneficial claims have been correlated, to some extent, with their polysaccharide content [8]. The unique biochemical compounds produced by lichens have made them useful for people in traditional cultures as a food source, for dyes, and as medicines [9]. Lichens grow on all continents and species distribution is influenced by a range of variables, including both climate and aspect. It is estimated that lichens are the dominant vegetation on 8% of the earth's terrestrial surface. Hence, lichens are a part of many food webs; including humans, vertebrates, and invertebrates. Lichens are used as a regular food source in Africa, America, Asia, and Europe [10-12]. Lichens are a valuable source of many natural classes with varying biological potentials including antiviral, antifungal, analgesic, antipyretic, antioxidant, and anticancer effects. Lichens produce a wide array of biologically active primary (intracellular) and secondary (extracellular) metabolites [13,14]. More than 1000 metabolites were extracted from lichens, some of these compounds are exclusively produced by lichens, while others were commonly observed in fungal extracts and those of higher plants [15]. The pharmaceutical potential of lichens is high and several companies are now attempting to commercialise these unique attributes [14]. This review aims to highlight on the importance and variety of common lichen substances (secondary metabolites), which are investigated along with their historical and modern applications, use in health research.

Bioactive Compounds and Medicinal uses of Lichens

Various lichens are well known as producers of many secondary metabolites with noticeable biological activities [16-18]. Although, many lichens are edible; other lichens are found to have some toxic substances. Different compounds produced by lichens are classified into separate groups:

- Aliphatic substances (such as acids, polyhydric alcohols, zeorin compounds, etc.);
- Aromatic substances (such as depsides, depsidones, diphenyleneoxide derivatives, quinones, xanthone derivatives, triterpenes, tetronic acids, and nitrogen-containing compounds, etc.); and
- (3) Carbohydrates (mainly polysaccharides). Up to date, about 350 different secondary metabolites produced from lichens have been identified. The majority of lichen's secondary metabolites water-insoluble and thus these metabolites can be extracted by organic solvents. Among the important substances that have been produced by lichens and identified are depsides (e.g., diffractic acid), dibenzofurans, lactones (e.g., protolichessterinic acid), phenolic compounds (e.g., atranol and resorcinol), pulvinic acid derivative (e.g., vulpinic acid), and usnic acids (e.g., usnic acid). Other lichen substances have been also frequently studied including atranorin, lecanoric acids, stictic acid, and pannarin [19-21]. Figure 1 presents the chemical structures of some lichens compounds.



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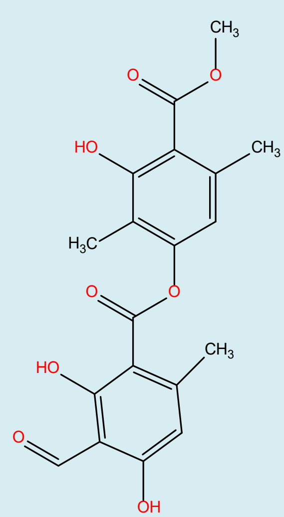

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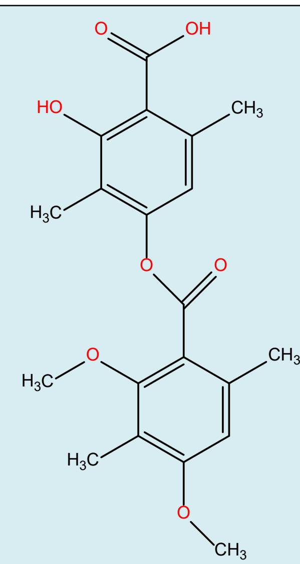

Diffractic acid

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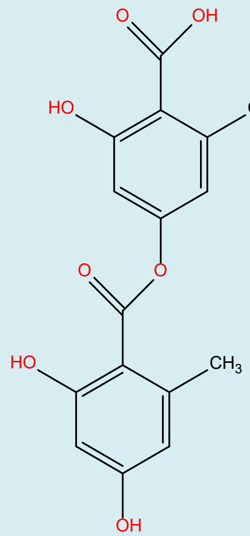
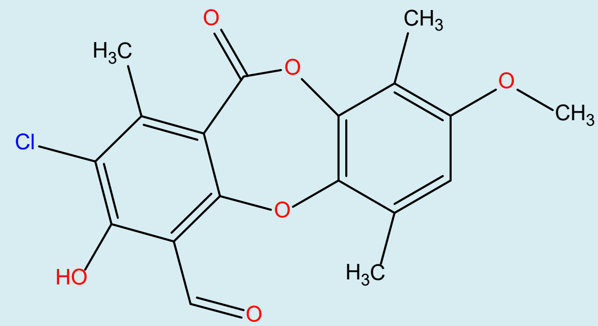
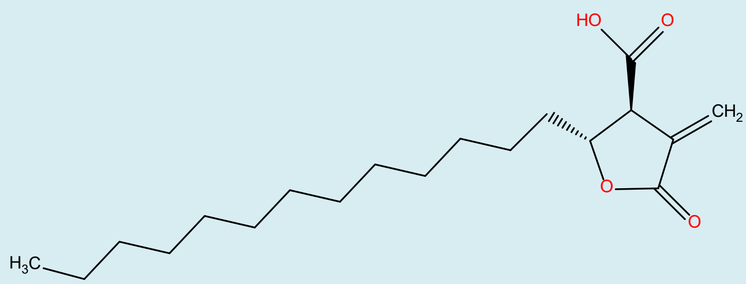


Lecanoric acid



Pannarin



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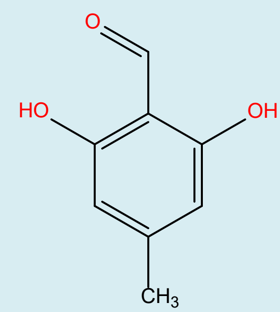
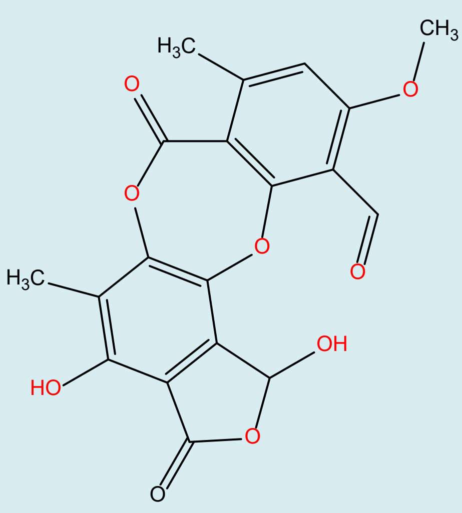
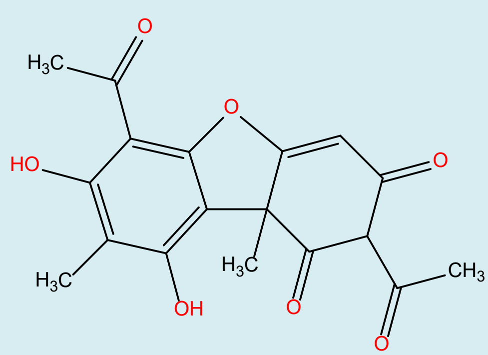


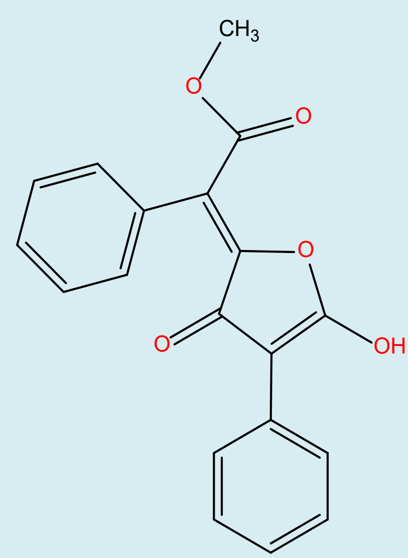
Resorcinol



Stictic acid



Usnic acid



Vulpinic acid

Figure 1: The chemical structures of some common lichens compounds.

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Lichens have been known since ancient times for their medical importance. Many lichens were reported to show their effectiveness against restoring lost hair, rabies jaundice, and coughs [22]. During middle age, lichens gained a great value among the herbals used by practitioners. Moreover, lichens are still valuable and important in the modern pharmaceutical industry due to their biological activities [20]. Among the lichens that have gained importance by the people of Northern California is *Letharia vulpina* (L.) Hue. (Parmeliaceae), this lichen had been used to treat stomach diseases [23]. Another species named *Dictyonema* was widely consumed by the Waorani as a hallucinogen [24]. However, *Alectoria usneoides* was used in Arabian medicine for the treatment of enlarged spleen (splenomegaly). *Usnea* sp. gained a great value for its demulcent properties where it was used in treatments of inflammation of the oral and pharyngeal mucosa. Also, *Usnea filipendula* Stirt had been used for treatment of cuts and wounds [25]. The Decoction of *Pseudoevernia furfuracea* (L.) Zopf. (Parmeliaceae) has been consumed in Alfacar and Viznar in respiratory ailments. Other lichens also have been used to treat some kidney-related problems such as *Ramalina bourgeana* Mont. ex Nyl. (Ramalinaceae) that has been consumed as a diuretic and it has been also used to dissolve kidney stones [26].

Numerous commercial pharmacological products containing lichen substances have been developed in many countries all over the world. For example, lichen extracts or substances have been applied in many pharmaceuticals, cosmetics, and neutraceutical products in Japan (Figures 2 & 3). Icelandic lichens have been consumed in cold remedies formulation under the trade names of Broncholind (MCM Klosterfrau Vertriebsgesellschaft mbH, Germany) and Isla-Moos® (Engelhard Arzneimittel GmbH & Co. KG, Germany). Moreover, usnic acid has been used in some antiseptic products in Italy such as 'Gessato™ shaving' and in Germany such as 'Camillen 60 Fudes spray and nail oil [27].

Figure 2: *Usnea* sp. Family Parmeliaceae, Collected by: Tilson; Locality United States, Virginia, Abingdon, USA. Hosted by; http://mycoportal.org).

Figure 3: *Dirinaria applanata* (Photographs taken by Waill A. Elkhateeb, Locality: Hakozaki Higashi-ku Fukuoka-shi Japan).

Different Biological Activities of Lichens

As mentioned before, lichens have highly valued due to their ability to produce a wide variety of vital biologically active primary and secondary metabolites [28-30]. Among the primary metabolites are amino acids, carotenoids, polysaccharides, polyols, and vitamins, etc. Lichenan and isolichenan, are examples of cell wall polysaccharides and both have taxonomic significances. Moreover, the carotenoid compounds produced by lichens have been studied for evolutionary relationships investigation. On the other side, lichen's secondary metabolites, which are usually named lichen acids, are mainly produced by the mycobiont, the secreted onto lichen's hyphae surface either in crystals or amorphous forms. Many studies reported that these secondary metabolites show important biological activities such as antiinflammatory, analgesic, antipyretic, plant growth inhibitory, antibiotic, antimycobacterial, antiviral, enzyme inhibitory, antiproliferative, and cytotoxic effects, as well as many other important biological activities [31].

Antibacterial Activities of Lichens

The development of resistance to many antibiotics as well as many antimicrobial agents has been a serious problem worldwide [32]. Many pathogenic microbes cause serious threats to human health and more effort have been directed toward this issue. Thus, new alternatives for fighting the spread of infection due to the development of antibiotic-resistant microbes are required. Discovering new natural products are proposed as a new strategy to overcome antibiotic-resistant problems [33,34]. Some lichens-derived substances have exerted antibacterial [35] and interestingly about 50 % of all lichens have been reported to exhibit promising antibiotic activities [27,36]. Burkholder, et al. [37] was the first to conduct a research on lichens as antibacterial agents. Usnic acid is among the lichens-derived products

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that have been reported as a strong antimicrobial agent [38]. Additionally, usnic acid as well as others including evernic acid and vulpinic acid can inhibit the growth of various Gram-positive bacteria such as *Bacillus subtilis* and *Bacillus megaterium*, as well as *Staphylococcus aureus*; however, they did not show any effect against Gram-negative bacteria including *Escherichia coli* nor *Pseudomonas aeruginosa* [35]. Salazinic acid obtained from acetone, chloroform, diethyl ether, methanol and petroleum ether extracts of *Parmelia sulcata* has also been reported for its antibacterial activity against various species such *as Aeromonas hydrophila*, *Bacillus subtilis*, *Bacillus cereus*, *Listeri monocytogenes, Proteus vulgaris, Staphylococcus aureus, Streptococcus faecalis, Candida albicans Candida glabrata, and Yersinia enterocolitica* [39]. Moreover, the ethanol, diethyl ether, and acetone extracts of *Cetraria aculeate* showed the presence of protolichesterinic acid that exhibits antibacterial activity against some bacteria belonging to both Gram-negative and Gram-positive groups [40]. These bacteria include *Bacillus*, *Candida*, *E. coli*, *Kleibsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Staphylococcus aureus*, and *Yersinia* species [41-47].

Antifungal Activities of Lichens

Many lichens have shown their ability to inhibit fungal growth. The lichens produce many active compounds that possess antifungal activity. These compounds include: atranorin, salanizic acid, stictic acid, usnic acid, divaricatic acid, zeorin, lecanoric acid, lichenic acid, protolichesterinic acid, fumarprotoacetraric acid, and protocetraric acid. Both acetone and methanol extracts of *Parmelia sulcata* Taylor, *Umbilicaria crustulosa* (Ach.) Frey and *Lasallia pustulata* (L.) Méret have been reported to contain selective antifungal agents [47]. Additionally, usnic acid together with 5-propylresorcinol, divaricatinic acid, and isodivaricatic acid showed their ability to inhibit fungal growth [48]. Salazinic acid was extracted from *Parmelia sulcate* by various solvents such as acetone, diethyl ether, methanol, chloroform, and petroleum ether. Salazinic acid exhibits antifungal activity against some fungi species such as *Aspergillus fumigatus*, *Aspergillus Niger*, and *Penicillium notatum* extracts of containing [39]. Moreover, the methanol extract of *Caloplaca cerina* (Ehrh. ex Hedwig) Th.Fr. was reported to contain both parietin and anthraquinone that exhibit promising antifungal activities [49].

Acetone extracts obtained from the three lichen species - *Cladonia portentosa, Evernia prunastri*, and *Hypogymnia physodes*- also displayed antifungal activity against many plant pathogenic fungi including *Botrytis cinerea*, *Colletotrichum lindemuthianum*, *Fusarium solani*, Pythium *ultimum*, *Phytophthora infestans*, *Rhizoctonia solani*, *Stagonospora nodorum,* and *Ustilago maydis* [50]. A powerful antifungal agent named lecanoric acid was isolated from a lichen species '*Parmotrema tinctorum'*, this is an antifungal agent is very effective against *Cladosporium sphaerospermum* [19].

Antiviral Activities of Lichens

Antiviral activities have been attributed to many lichens-derived compounds. Anthraquinones, particularly, the polyphenolic and polysulphonate substituted compounds, have been proved to exert promising antiviral properties [51,52]. A previous study reported by Cohen, et al. [53], showed that some lichen-derived compounds such as anthraquinones, hyperacin as well as bianthrones showed antiviral properties. Moreover, the antiviral activity was found to be directly related to the increase in the chlorine substitution in the anthraquinone structure. Since many plants originated polysaccharides exhibit potent antiviral activities, in particular against enveloped viruses [54-56], it was essential to evaluate the antiviral activities of the polysaccharides derived from various lichens. The studies reported that crude polysaccharide isolated from *Parmelia perlata* lichen showed a potent antiviral activity towards yellow fever virus (the enveloped positive-sense RNA virus), however, it was not active against non-enveloped RNA viruses such as IBDV and poliomyelitis.

Parietin isolated from *Ramalina celastri* and usnic acid derived from *Teloschistes chrysophthalmus* (L.) Th. Fr. displayed potent antiviral activity against the arenaviruses, Tacaribe and Junin [57]. It worth mentioning that both the aqueous and the ethanolic extracts of lichen species *Xanthoparmelia tinctina* and *Xanthoria parietina* and were tested for their antiviral activity against human parainuenza virus type 2 (HPIV-2) and cytotoxic activity against Vero cells. *Xanthoparmelia* tinctina ethanol extract showed antiviral activity against HPIV-2 where the half-maximal effective concentration (EC_{50}) for the virus replication was 20 μg/mL, and for aqueous extract, the EC_{50} was found to be 22.5 μg/mL [58]. Lichenan is a structural polysaccharide of the mycosymbiont cell wall [59]. It is composed of a linear (1→3, 1→4) β-d-glucan linkage [60]. Interestingly, lichenan protects greenhouse-grown various *Nicotiana* species from the virus accumulation and symptom development caused by a tobacco mosaic virus [61].

Insecticidal Properties of Lichens

Iinsecticidal agents based on synthetic chemicals are the most commonly used agents against insects. However, these agents show many drawbacks due to the development of chemical resistance resulted from their repeated use. Another serious issue is the development of many health problems due to the bad effect of these agents on food and the environment [62]. One of the successful ways for

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getting rid of the mosquito population in breeding grounds before they reach the adult stage is achieved by killing the larvae of mosquitoes [63]. The studies reported that several phytochemicals contain compounds that may be used as alternative sources for harmful synthetic chemicals-based control agents. Extract obtained from lichen species '*Letharia vulpine'* showed a strong insecticidal effect against *Spodoptera littoralis* and *Spodoptera ornithogalli* [20]. The results also showed that usnic acids isolated from lichens also show insecticidal effects against *Culex pipiens* larvae [64].

Antioxidant Activities of Lichens

Antioxidants are compounds that inhibit the oxidation process. Oxidation is a chemical reaction that results in the production of free radicals which lead to undesired chain reactions and that finally ends in cell damage and degenerative diseases. Natural antioxidants are a better choice for therapeutic use over synthetic antioxidants that could be toxic or have serious side effects. Numerous lichen extracts have demonstrated antioxidant properties due to their phenolic compounds and/or polysaccharides that are well known to exhibit antioxidant properties [65,66]. The extracts from Antarctic lichens were reported to display antioxidant activities that were more potent than those obtained from lichens native to tropical regions [32]. However, the phenolic components obtained from the lichen *Parmotrema stuppeum* (Nyl.) Hale such as atranorin, methyl orsenillate, orsenillic acid, and lecanoric acid showed moderate antioxidant activity [67]. A previous study reported antioxidant activity of lichen *Cetraria islandica*[68], where that antioxidant activity was assessed by DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical, reducing power, and superoxide anion scavenging activities capacities and compared to positive controls such as BHA (butylated hydroxyanisole) and α-tocopherol, quercetin [68]. Also, it was reported that stactic acid derivatives obtained from *Usnea articulate* lichens displayed potent antioxidant activity [69]. Other lichens interestingly showed antioxidant activities with more than 85% DPPH scavenging activity. These lichens included *Peltigera canina*, *Peltigera praetextata*, *Parmotrem pseudotinctorum Ramalina conduplicans*, *Sticta nylanderiana*, and *Usnea ghttensis* [70].

Antitumor Activities of Lichens

The effect of lichen extracts on tumors has been extensively studied for many years. Some lichen derived compounds such as cristazarin, usnic acid, depsidone, lichenin, protolichesterinic acid, and polyporic acid exhibited antitumor activities against various tumor cells such as P388 leukemia [71], melanoma B-16 [20], Ehrlich solid tumor [72], K-562 leukaemia [73], and lymphocyte cells [74]. *Collema flaccidum* extract revealed anticancer activity when evaluated in the crown gall tumor inhibition test. It was reported that colleflaccinosides and bisanthraquinone glycosides were the inhibitors [75]. Also, extracts containing depsidone pannarin showed anticancer activities by inducing cell apoptosis in human melanoma M14 cells, causing cell death in human prostate carcinoma DU-145 cells [76,77].

Usnic acid which is among the important metabolites produced by lichens had an antiproliferative effect on endometrial carcinoma (Ishikawa, HEC-50) cells and human leukemia cells (K562) [78,79]. The polysaccharides derived from lichens also play a role in the antitumor activities of lichens.A lichen-derived polysaccharide named CFP-2 was able to reduce the viability of K562 and HL-60 cancer cells due to telomerase activity and apoptotic pathway, indicating that this polysaccharide could be a promising therapeutic agent against various types of cancer [80].

Methyl orsellinate and tenuiorin that have been isolated from *Peltigera leucophlaebia* lichen showed their ability to inhibit the proliferative of different cell lines including pancreatic (PANC-1), human breast (T-47D), and colon (WIDR) [38]. Lecanoric acid is a secondary metabolite isolated from *Parmotrema timctorum* lichen. This metabolite showed anticancer activities against MCF7 breast carcinoma, 786-0 kidney carcinoma, and HEp-2 larynx carcinoma, as well as B16-F10 murine melanoma cell lines [81]. The anticancer properties of other lichens derived substances have been also reported by Huneck [82], Ingolfsdottir, et al. [83] and Elkhateeb, et al. [84].

Conclusion

Lichens are a generous source of novel compounds that can be investigated for their potential biological activities. This review presents some lichen-derived substances that exhibit a huge array of important biological activities. Many secondary metabolites isolated from lichens showed antibacterial, antifungal, antiviral, insecticidal, antioxidant as well as antitumor activities. Furthermore, the properties of these lichen-derived substances make them of great value to be applied in many pharmaceutical industries. At the same time, it is well known that lichens are slow-growers, and the exploitation of their valuable secondary metabolites could threaten the survival of lichens. Thus, improving the culture methods and adjusting the growing conditions might extensively improve the production of these secondary metabolites without being at risk of the extinction of the natural communities.

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