



REVIEW ARTICLE

Lichen-derived secondary metabolites: Ethnobotanical insights and pharmacological prospects

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Abstract

Lichens, symbiotic associations of fungi and photosynthetic algae, are rich sources of bioactive compounds with significant ecological functions and considerable pharmacological potential. This review provides an integrated overview of the morphological, ethnobotanical, structural and functional diversity of lichen metabolites. Most lichen species produce structurally diverse secondary metabolites with antimicrobial, anticancer, antioxidant, anti-inflammatory and enzyme-inhibitory effects. Despite centuries of traditional use, challenges persist in isolating individual metabolites because of their complex thallus structure, low solubility and sensitivity to conventional extraction methods. However, modern advancements, including axenic cultivation, genome mining, molecular networking and next-generation analytical technologies, have enabled the discovery of previously undetectable metabolites and provided deeper insights into their biosynthetic pathways. Advancing lichen research by combining traditional knowledge with modern biotechnological innovations will be pivotal for identifying new, sustainable therapeutic molecules that meet emerging global healthcare demands.

Keywords: ethnobotany; lichens; mycobiont; photobiont; secondary metabolites; symbiotic association

Introduction

Lichens are stable and ecologically significant symbiotic organisms composed of 2 main partners: fungi and algae. The fungal component or mycobiont, typically belongs to the Ascomycetes, Basidiomycetes, Phycomycetes, or Deuteromycetes, whereas the photosynthetic partner, or photobiont, is either a green alga (Chlorophyta) or a cyanobacterium (Cyanophyta). The mycobiont usually establishes the structural framework and protects against environmental stresses, while the photobiont contributes organic carbon and, in some cases, fixed nitrogen, ensuring the metabolic balance of the association (1). Lichens are broadly distributed across diverse terrestrial ecosystems and play a vital role in mineral cycling (2). Lichen symbiosis represents one of the most successful and stable mutualistic relationships in nature, persisting for more than 600 million years and contributing significantly to the stability of terrestrial ecosystems (3, 4).

Lichens are highly sensitive to environmental changes, particularly those related to air pollution. Their growth is hindered when sulfur dioxide (SO₂) levels in the atmosphere exceed 50–60 µg/m³. In addition to SO₂, exposure to other contaminants such as fluoride, nitrogen oxides, hydrocarbons, heavy metals and particulate matter can adversely affect lichen physiology, leading to discoloration, reduced growth and even mortality. Therefore, lichens are widely recognized as reliable bioindicators for assessing air

pollution and environmental health (5). This high environmental sensitivity also modulates the secondary metabolite composition of lichens, resulting in chemical profiles that closely mirror their growth conditions, an essential factor for obtaining consistent, high-quality biomass in pharmacological research and natural product development.

Beyond their ecological indicator role, lichens have evolved remarkable biochemical defense mechanisms that enable them to thrive in extreme environmental conditions, including arid deserts, alpine regions, rocky coastlines and polar habitats. These adaptive responses are largely attributed to the synthesis of secondary metabolites, a diverse group of chemically unique compounds, such as depsides (DE), depsidones (DEPs), dibenzofurans (DBF) and usnic acid (UA) derivatives, which provide protection against ultraviolet radiation, microbial pathogens and oxidative stress (6). The exploration of natural sources for novel bioactive compounds has increasingly highlighted lichens as promising candidates for drug discovery. Their documented therapeutic relevance positions them as valuable non-timber forest resources with significant biomedical potential (7). Although more than 20000 lichen species have been identified globally, only a small subset has undergone rigorous chemical and biological characterization, leaving much of their metabolic diversity and therapeutic capacity unexplored. This limitation underscores the necessity for expanded biochemical

profiling and mechanistic pharmacological studies to fully elucidate and harness their value in modern drug research (8).

Morphological characteristics of lichens

Lichens exhibit remarkable morphological diversity, a feature that enables them to thrive across a wide range of diverse ecological habitats, from arid deserts to polar tundras and humid forests. Their structural variations play a crucial role in adapting to environmental stresses, such as temperature extremes, moisture fluctuations and variations in light intensity (9). Based on their macroscopic growth forms, lichens are categorized into 3 major types: fruticose, foliose and crustose (10).

Fruticose lichens possess a complex, 3-dimensional and often shrubby or filamentous thallus that extends freely from the substrate, as seen in *Usnea* species. Foliose lichens, on the other hand, display broad, leaf-like thalli with distinct upper and lower surfaces, loosely attached to the substrate except at specific points; examples include *Umbilicaria* and *Lobaria* species. Crustose lichens form thin, tightly adherent crusts on rocks, bark, or soil, lacking a lower cortex, which makes separation from their substrate difficult; *Rhizocarpon* species are typical representatives. Beyond these major types, several intermediate or specialized morphologies have been identified, such as leprose (powdery), filamentous (hair-like), squamulose (scaly), gelatinous (mucilaginous due to cyanobacterial photobionts) and byssoid (cottony) forms. These variations highlight the evolutionary adaptability of lichens and their ability to colonize extreme and unique environments (11). Fig. 1 illustrates representative examples of the selected lichen species.

Ethno-botanical roles of lichens

Lichens hold a long-standing place in traditional and ethnomedicinal practices worldwide, reflecting their cultural, nutritional and therapeutic significance. Various cultures, including those in China, Japan, India, Iceland and several other European countries, have historically recognized and utilized ethnolichens as integral components of traditional healing systems. In traditional medicine, lichen preparations have been used to treat a wide range of ailments, including skin infections, respiratory disorders, digestive problems, liver ailments, hemorrhoids, wounds and gynecological conditions (13). In addition, various traditional groups worldwide have used lichens as valuable sources of food and fodder, natural dyes, aromatic substances and spices (14, 15).

Lichens and their bioactive components have long been utilized in traditional and modern medicinal practices for their therapeutic efficacy against a broad spectrum of diseases. *Evernia furfuracea* is one of the earliest recorded lichens used by humankind, with archaeological evidence indicating its identification in ancient Egyptian remains from the 18th Dynasty (1700–1600 BC), suggesting its significance as a medicinal and aromatic substance in early civilizations (16). Lichens have been conventionally used in the treatment of various diseases, including dysentery, bronchitis, hemorrhoids and tuberculosis (TB) and serve as stomachic, antidiabetic and hemostatic agents (17, 18). In addition to their traditional uses, lichens exhibit a wide range of biological activities, including anticancer, antimicrobial, antiallergenic, antiviral, anti-inflammatory, antipyretic, hepatoprotective, analgesic, antinociceptive, anthelmintic, neuroactive, antioxidant and enzyme-inhibitory properties, as well as anti-herbivore and plant-growth-inhibitory activities (19). The initial investigations primarily identified the antioxidant and

antigenotoxic properties of lichen extracts (20). Over time, the focus has extended to include antimicrobial, enzyme-inhibitory, immunomodulatory and anti-inflammatory potentials. Nevertheless, *in vivo* studies are limited, typically in fish and rodents (21). Thus, lichens represent a promising yet underexplored reservoir of pharmacologically active compounds with significant potential for development into modern therapeutic agents. These diverse traditional uses are underpinned by a vast array of unique bioactive secondary metabolites, which are discussed in the following sections. Fig. 2 displays the overall pharmacological properties of the lichen extracts.

Bioactive compounds and pharmacological potential

Lichens possess remarkable biochemical diversity, producing a variety of unique bioactive compounds that contribute to their nutritional and medicinal significance. Despite their long-standing use in traditional practices, scientific exploration of their edible and therapeutic potentials remains relatively limited. Lichens produce 2 distinct categories of metabolites: primary and secondary. Their therapeutic applications are attributed to their bioactive secondary metabolites and their ability to store carbohydrates. These secondary metabolites, often produced via unique biosynthetic pathways not found in higher plants, include DE, DEPs, DBF and related compounds. Such compounds are known for their wide range of biological activities, including antimicrobial, antioxidant, antiviral, anti-inflammatory and cytotoxic effects (13). Primary metabolites produced by lichens are vital for their growth and survival and include essential biomolecules such as amino acids, proteins, polysaccharides, carotenoids and various vitamins (22).

Extensive studies have revealed that lichens are rich reservoirs of chemically diverse metabolites, many of which are structurally unique and exclusive to these symbiotic organisms. The major classes of these bioactive compounds include DE and their esters (e.g., atranorin and barbatic acid), DEPs (e.g., salazinic and lobaric acid), phenolic compounds (e.g., orcinol and β -orcinol derivatives), depsones (e.g., picrolichenic acid), polysubstituted benzenes, anthraquinones (e.g., physcion), DBFs (e.g., UA), terpenoids, steroids, xanthenes, aliphatic acids, quinones (e.g., parietin), pulvinic acid derivatives (e.g., vulpinic acid), lactones (e.g., nephrosterinic acid) and specific lichen-derived polysaccharides. Many of these metabolites are unique to lichens and rarely occur in other organisms (23, 24).

Most secondary metabolites in lichens are synthesized through 3 principal biosynthetic routes: the acetyl-malonate (also referred to as the polyketide pathway), mevalonate and shikimate pathways. Among these, the acetyl-malonate pathway is the most prominent, yielding a wide range of biologically active compounds, including DE, DEPs, DBF, anthraquinones, chromones and xanthenes, which have been extensively studied for their pharmacological properties (25). Notable metabolites synthesized via this pathway include lecanoric, gyrophoric, evermic, atranorin, thamnolic, protocetraric, fumarprotocetraric, stictic, UA, lepralic, thiophanic and umbilicaric acid.

The mevalonate pathway primarily contributes to the synthesis of terpenes, carotenoids and steroids. To date, researchers have identified over 20 distinct triterpene compounds in lichens (26). In contrast, the shikimic acid pathway, commonly found in both microorganisms and plants, serves as a key route for the production of essential primary metabolites, including aromatic amino acids



a) Fruticose lichen e.g. *Letharia vulpina*



b) Foliose lichen e.g. *Flavoparmelia caperata*



c) Crustose lichens e.g. *Lecidella elaeochroma*



d) Squamulose lichen e.g. *Placidium arboreum*



e) Leprose lichen e.g. *Chrysothrix xanthina*



f) Gelatinous lichen e.g. *Collema bachmanianum*



g) Filamentous lichen e.g. *Ephebe lanata*



h) Bysoid lichen e.g. *Roccellinastrum neglectum*

Fig. 1. Different forms of lichens with examples (12).

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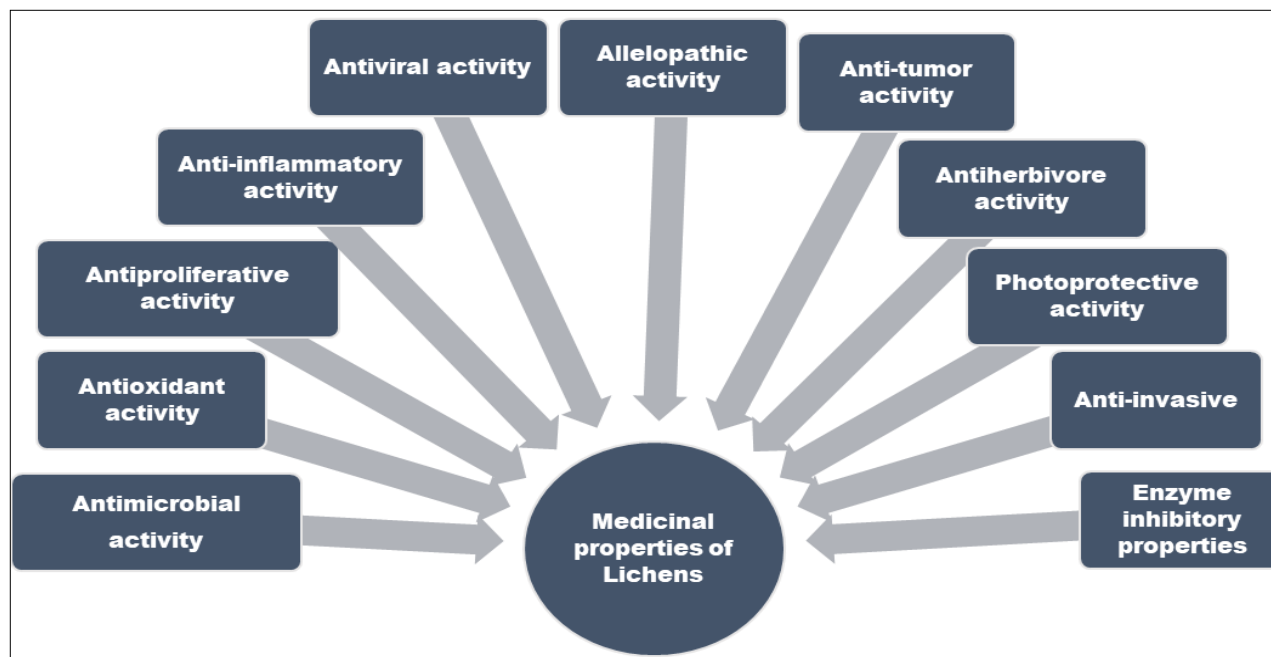


Fig. 2. Medicinal applications of lichen.

pathway is particularly associated with the formation of pulvinic acid and terphenylquinone pigments, which protect lichens from ultraviolet radiation and oxidative stress (28). Representative chemical structures of these lichen metabolites are illustrated in Fig. 3, highlighting their structural diversity and functional significance.

These structurally diverse natural compounds have been reported to exhibit a broad spectrum of bioactivities, many of which align with the traditional medicinal uses and therapeutic claims associated with lichens (15, 29, 30). Ongoing phytochemical investigations have shown that different lichen species synthesize distinct sets of bioactive molecules, each characterized by unique structural features (31). These bioactive compounds are largely responsible for the antibacterial, antiviral, antimycobacterial, anti-protozoal, anti-inflammatory, analgesic, immunostimulatory and antipyretic properties of lichens (32). The remarkable chemical diversity and corresponding therapeutic applications of lichen-derived metabolites, as well as their roles in ethnomedicine across

cultures, are summarized in Table 1, providing a comprehensive overview of their pharmacological potential and reinforcing the significance of lichens as a rich source of bioactive natural products.

Advances in lichen metabolite extraction and analysis

Secondary metabolites derived from natural sources frequently exhibit potent biological activities. Due to the growing threat of antibiotic resistance, the search for new antimicrobial agents from natural sources has become increasingly important (57). Although lichens have long been studied for their pharmacologically relevant compounds, isolating individual secondary metabolites and developing efficient extraction methods remain challenging. Their complex symbiotic structure, comprising fungal and algal or cyanobacterial partners enveloped in a robust extracellular matrix, restricts the availability of internal metabolites. Furthermore, many lichen-derived compounds exhibit poor solubility, which complicates their extraction and analysis (58).

Recent advancements, including axenic cultivation, targeted metabolite synthesis, molecular network techniques, advanced

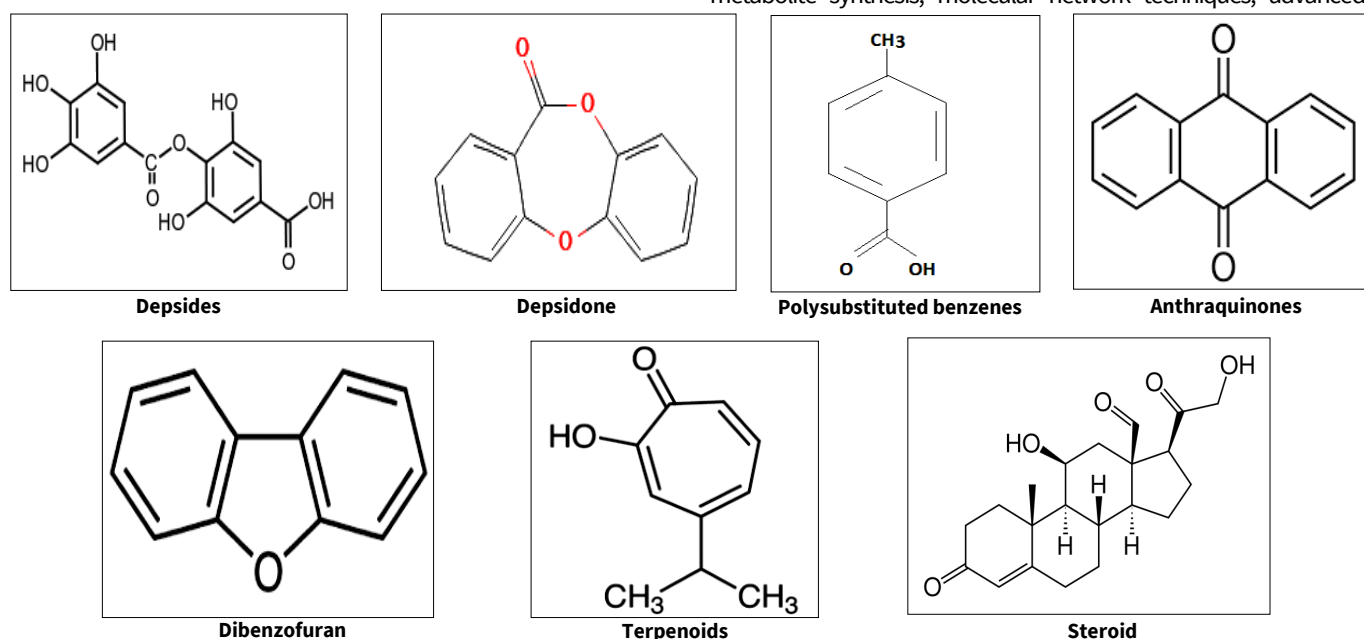


Fig. 3. Molecular structure of some secondary metabolites produced by lichens.

Table 1. Bioactive compounds produced by lichens and their application in ethnomedical fields

Sl.No	Species of lichen	Bioactive compounds	Medical applications	References
1	<i>Acarospora gobiensis</i>	Gobienines A-C, Acarogobien A and B,	Antibacterial and antioxidant properties	(33)
2	<i>Acroscyphus sphaerophoroides</i>	Gyrophoric acid, Skyrin, Graciliformin, Rugulosin	Antibacterial and antioxidant properties	(34)
3	<i>Alectoria ochroleuca</i>	UA, Atranorin, Virensic acid, Ethyl hematommate, 2-methoxypsoromic acid and Olivetoric acid	Antibacterial, antifungal, anticancer and antioxidant properties	(35)
4	<i>Arthothelium awasthii</i>	Barbatic acid	Antibacterial and antioxidant properties	(36)
5	<i>Cetraria islandica</i>	Protolichesterinic acid, UA, Butyrolactone, Perlatolic acid	Antimicrobial, antioxidant, anticancer, antidiabetic and immunomodulatory effects	(37)
6	<i>Cladonia sp</i>	Fumarprotocetraric acid, UA, Perlatolic acid, Squamatic acid	Anticancer, antimicrobial, antigenotoxic and antioxidant properties	(38)
7	<i>Dermatocarpon miniatum</i>	Mycosporines	Antioxidant, antibacterial and photoprotective properties	(38)
8	<i>Diploschistes scruposus</i>	Polyphenols	Antioxidant and antibacterial properties	(39)
9	<i>Everniastrum cirrhatum</i>	Atranorin	Antimicrobial, antioxidant and anti-obesity properties	(40)
10	<i>E. prunastri</i>	Evernic acid	Antibacterial, neuroprotective, anti-inflammatory, cytotoxic and antioxidant properties	(41)
11	<i>Flavocetraria nivalis</i>	UA	Antimicrobial and antioxidant properties	(42)
12	<i>Flavoparmelia caperata</i>	UA	Wound healing, antimicrobial and anti TB properties	(43)
13	<i>Heterodermia diademata</i>	Atracric acid	Antifungal, anti-lipoxygenase and anticancer properties	(44)
14	<i>Hypogymnia physodes</i>	Physodic acid, 3-hydroxyphysodic acid, 2'-O-methylphysodic acid, Protocetraric acid, Chloroatranorin, Usnic acid and Atranorin	Antimicrobial, cytotoxic, antioxidant, treating Alzheimer's and Parkinson's disease	(23)
15	<i>Lasallia sp</i>	Depside, tridepsides, polyglucans and anthraquinones.	Antimicrobial, anticancer and antioxidant properties	(23)
16	<i>Lethariella sp</i>	UA	antioxidant, anticancer and anti-inflammatory effects	(45)
17	<i>Letharia vulpina</i>	Vulpinic acid	Antibacterial, anti-angiogenic, antiproliferative and antioxidant property	(42)
18	<i>Lobaria sp</i>	Retigeric acid B, Rhizonyl alcohol, Thelephoric acid	Antioxidant, antibacterial, antifungal, neuro protective and anti-inflammatory properties	(38)
19	<i>Ochrolechia sp</i>	Variolaric acid, Gyrophoric acid	Antibacterial, anti-tumor, anticancer, antiviral, anti-inflammatory and antiproliferative properties	(46)
20	<i>Parmelia sp</i>	Salazinic acid	Antioxidant, antibacterial, antifungal and anti-inflammatory properties	(42)
21	<i>Parmotrema sp</i>	Parmosidone F, Tsavoene A	Antioxidant, antibacterial, antifungal, antiviral and anti-Alzheimer's disease properties	(47)
22	<i>Protousnea magellanica</i>	Divaricatic acid, Sekikaic acid	Antibacterial, antiviral, anticancer and antioxidant properties	(48)
23	<i>P. furfuracea</i>	Olivetoric acid, Physodic acid, Physciosporin	Antioxidant, antimicrobial, antifungal and enzyme-inhibiting properties	(49)
24	<i>Psoroma sp</i>	Vicanicin, Pannarin, Psoromic acid	Anti-proliferative and antioxidant property	(50)
25	<i>Ramalina sp</i>	UA, Sekikaic acid, Parietin, Ramalin, Stereocalpin A and B	Reduce inflammation, antimicrobial and anticancer activity	(51)
26	<i>Rinodina sp</i>	Atranorin, Variolaric acid, Sphaerophorin	Antibacterial, anti-inflammatory, antioxidant and anticancer activity	(52)
27	<i>Rhizocarpon geographicum</i>	Psoromic acid; UA, Rhizocarpic acid	Anti-proliferative activity	(53)
28	<i>Solorina crocea</i>	Solorinic acid, Norsolorinic acid, Averantin, Depsides	Antimicrobial, cytotoxic and antioxidant properties	(35)
29	<i>Sphaerophorus globosus</i>	Sphaerophorin, UA	Anti-proliferative activity and antioxidant activity	(50)
30	<i>Stereocaulon alpinum Laurer</i>	Lobaric acid	Antioxidant, anticancer, antimicrobial activity and anti TB properties	(54)
31	<i>Thamnotia sp</i>	UA	Anti-inflammation, antimicrobial, antioxidant and anticancer properties	(38)
32	<i>Umbilicaria sp</i>	Gyrophoric acid, UA, Lecanoric acid	Anti-cancer, antimicrobial, anti-inflammatory, anti HIV, and antioxidant properties	(55)
33	<i>Usnea sp</i>	Norstictic acid, Psoromic acid, Protocetraric acid, Barbatic acid, Diffraetic acid	Anti-inflammation; anticancer, anti TB, antioxidant and cytotoxic properties	(47)
34	<i>Xanthoparmelia coreana</i>	Norstictic acid, Stictic acid	Antibacterial, anticancer antioxidant properties and treating sexual dysfunction	(56)
35	<i>Xanthoria sp</i>	Parietin	Cytotoxicity activity, anti-viral, anti-inflammatory, enzyme inhibition, antioxidant, antibacterial properties, cardiovascular and gastrointestinal protection	(35)

bioinformatics, phylogenetics and modern genetic tools, have begun to overcome these barriers and enhance our understanding of lichen metabolomics and their evolutionary biosynthetic pathways (24). Innovative strategies, such as one strain many compounds (OSMAC), genome mining and molecular networking, now enable the activation of cryptic biosynthetic gene clusters in lichen symbionts, expanding the discovery of novel bioactive compounds (59). Recent studies employing genome mining and comparative genomics have identified biosynthetic gene clusters and potential regulatory elements in the lichen-forming fungi, *Evernia prunastri* and *Pseudevernia furfuracea*. Notably, the non-reducing polyketide synthase (NR-PKS) gene in *P. furfuracea* was found to synthesize depside-lecanoric acid, a compound not previously reported from natural lichen thalli (60).

In addition, emerging extraction technologies, such as Soxhlet extraction, microwave-assisted extraction and supercritical fluid extraction, have improved metabolite recovery from lichen biomass (61–63). However, challenges remain in degrading thermolabile metabolites under high temperatures and harsh solvent conditions (59). Therefore, the use of potent organic solvents, such as acetone, benzene, ethanol and chloroform, must be carefully optimized to preserve compound integrity (7). As a sustainable alternative, volatile natural deep eutectic solvents (VNADES) have gained attention for their efficiency in extracting lichen compounds while minimizing the use of toxic solvents. They comprise volatile and easily evaporated components such as menthol, thymol and camphor. VNADES allows residue-free extraction and effective recovery of sensitive metabolites, including polyphenols, alkaloids, flavonoids and lichen acids, without their degradation (6).

For metabolite identification, advanced analytical tools such as liquid chromatography tandem mass spectrometry (LC-MS/MS) and nuclear magnetic resonance (NMR) spectroscopy, coupled with chromatography, have demonstrated high sensitivity and precision, particularly for compounds like UA (64, 65). The integration of MS/MS-based molecular networking with comprehensive spectroscopic analyses, including Gauge-Independent Atomic Orbital (GIAO) NMR shift calculations, has facilitated the discovery and structural elucidation of novel pigments in lichens (66). Additionally, several MS-based metabolomic approaches, including electron ionization-mass spectrometry (EI-MS), high-performance liquid chromatography-diode array detector-mass spectrometry (HPLC-DAD-MS), electrospray ionization-mass spectrometry fragmentation patterns (HESI-MS/MS) and liquid chromatography-diode array detector-tandem mass spectrometry (UPLC-PDA-MS/MS), have significantly contributed to the identification of new lichen compounds and enhanced insights into their complex biochemical systems (59).

Furthermore, imaging techniques such as Raman microscopy provide time-resolved insights into the spatial distribution of key compounds within lichens (65). Using Fourier-transform infrared (FTIR) imaging and Raman microscopy, researchers have successfully localized UA in various lichen species (67). Moreover, nanotechnology has emerged as a promising tool for enhancing the extraction efficiency and therapeutic delivery of lichen metabolites. Nanoencapsulation strategies, employing liposomes, cyclodextrins, or metallic nanoparticles, have improved the bioactivity, stability and controlled release of key compounds, such as UA, while reducing cytotoxicity (68). These advancements have

significantly enhanced the therapeutic potential of lichen-derived metabolites.

To fully harness the pharmacological potential of lichens, future research should prioritize comprehensive pharmacological screening, toxicity evaluation and preclinical validation of unexplored metabolites. Careful optimization of extraction parameters, including solvent type, temperature and duration, is essential to maximize yield while maintaining metabolite integrity. The integration of advanced analytical platforms with next-generation computational tools continues to redefine lichen chemistry, leading to the discovery and detailed characterization of numerous novel bioactive compounds.

Limitations of the present review

Although this review provides a comprehensive overview of the ecological, ethnobotanical, chemical and pharmacological significance of lichens, it is limited by the availability and heterogeneity of existing literature. Many lichen species remain poorly studied and data on their bioactive metabolites are unevenly distributed across taxa, regions and analytical methods. Most pharmacological evidence is restricted to *in vitro* studies, with few *in vivo* investigations or clinical evaluations, which limits the translation of these findings to therapeutic applications. Additionally, variations in extraction procedures, environmental influences on metabolite composition and the limited number of genome-sequenced lichenized fungi constrain the depth of comparative biochemical and biosynthetic analysis. Therefore, the conclusions drawn must be interpreted in light of these knowledge gaps.

Conclusion

Lichens are a remarkable yet underutilized reservoir of structurally diverse bioactive compounds, many of which exhibit notable pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory and anticancer activities. Secondary metabolites, such as UA, atranorin, lobaric and psoromic acids, contribute significantly to these therapeutic effects, supporting the long-standing traditional use of lichens in ethnomedicine across cultures. Despite substantial *in vitro* evidence, the lack of comprehensive *in vivo* studies and clinical validation continues to hinder the translation of these findings into viable human therapeutic applications. Modern biotechnological advancements have enhanced the potential to discover novel compounds and improve their bioavailability in the human body. Future advancements will require targeted interdisciplinary strategies, including combining metagenomics of the lichen holobiont with integrated metabolomic profiling to uncover cryptic biosynthetic gene clusters, applying genome mining, molecular networking and structure-activity relationship (SAR)-based computational modelling to accelerate lead identification and developing axenic or symbiont-engineered cultivation systems to enhance metabolite yield. Moreover, incorporating nanotechnology-driven drug-delivery approaches may improve the bioavailability and therapeutic efficacy of key metabolites. By integrating these modern biotechnological tools with ethnobotanical insights, lichens can be positioned as sustainable, non-timber bioresources capable of contributing meaningfully to the next-generation natural drug discovery.

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Authors' contributions

SDK involved in conceptualization, literature survey, manuscript drafting and critical revision of the article. DKS contributed to data collection, organization of literature and preparation of figures and tables. SM contributed to writing the sections on phytochemistry and medicinal properties of lichens. DMD assisted in reference formatting and manuscript editing. NG provided inputs on biotechnological and pharmacological aspects and proofreading. TS was involved in formatting and checking of overall content, figures and tables. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interest to declare.

Ethical issues: None

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used OpenAI's ChatGPT and Quillbot to assist in improving the language, grammar and readability of the manuscript, without generating any original scientific ideas or data.

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