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Review Article

An overview of the therapeutic potential of understudied lichen species for novel drug discovery

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Abstract
Due to the emergence of new diseases, drug discovery is an ever-exciting field of science. Researchers have shifted their focus from chemical-based medicines to drugs of natural origin and their structural synthetic analogues to solve the problem of developing antibiotic resistance and the detrimental impacts of existing chemical medications. Lichens are still one of the least explored natural sources for drug discovery. These slow-growing forms are a rich source of some exceptional secondary metabolites known collectively as lichenochemicals. The significant proportion of these lichenochemicals are bioactive compounds with multiple pharmacological properties, including antimicrobial, anticancer, free radical scavenging, anti-inflammatory, antidiabetic and neuroprotective abilities and are also high in nutritional values, making this uncanny combination of algae and fungi, together with their metabolites, so well renowned in traditional and indigenous medicine. Although only oral knowledge was available about them earlier, studies over the last few decades have isolated and identified some unique bioactive compounds with high medicinal values, making lichen biology one of the most interesting and promising areas of pharmacological research. More than half of the lichen species and phytochemicals are yet to be explored. However, lichen-derived vitamin D3 is the only vegan source of vitamin D3. Likewise, studies have shown that lichenochemicals can significantly reduce the problem of antibiotic resistance developed by microorganisms. Advanced techniques in identification and isolation, combined with bioinformatics, predictive software, and databases, have greatly aided in understanding lichen chemistry. This review summarizes the use of lichens in drug discovery with a highlight on recent breakthroughs in lichen biology.

Keywords: Antibiotic resistance, Antimicrobial, Drug discovery, Lichenochemicals, Lichens

INTRODUCTION

Lichens are one of the most intriguing members of the living world. The term “lichen” comes from Greek, referring to the growth seen on the bark of olive trees. Around 300 BC, Theophrastus, known as the Father of Botany, introduced this term to categorize this specific group of plants. Lichens are complex symbiotic structures consisting of a fungal partner, usually from the Ascomycetes and sometimes the Basidiomycetes, and a photosynthetic partner, or photobiont, which can be either a Cyanobacteria or Chlorophyte algae and sometimes may even contain both types of photobionts (Puginier *et al.,* 2024). In this mutualistic relationship, the photobionts provide carbohydrates from photosynthesis to the fungi, offering a protective microenvironment against various stresses. Modern research has revealed that these composite organisms do not only consist of algae and fungi, as previously thought but may also include yeast, bacteria, protists and even viruses (Petrzik *et al.,* 2019; Grimm *et al.,* 2021; Tagirdzhanova *et al.,* 2023). This unique algal-fungal combination has been a part of everyday life since time immemorial; and there is evidence that humans have used it for food and medicine since ancient times. They are versatile organisms that thrive in diverse environments and are often recognized as pioneer species due to their ability to colonize and establish in new habitats (Porada *et al.,* 2018). These tiny plant-like members have made their presence known in almost every habitat, from moist evergreen forests to cold deserts. More than 20,000 lichen species have been identified worldwide, with 10% belonging to India; spanning over six different lichen vegetation zones. They can be terricolous (soil), saxicolous (stone), corticolous (trees), humicolous (humus), lignicolous (decaying wood), ramicolous (twigs), folicolous (leaves), muscicolous (mosses), or calcicolous (lime plates) depending on the substrate in which they grow (Bhagarathi *et al.,* 2022). Surprisingly, lichens have been discovered growing on animals and insects in some cases (Puginier *et al.,* 2024). Researchers have discovered lichen growth in Galapagos male tortoises. Similarly, they have been identified from lacewig insect larvae, which aids in camouflage and, in return, the insects help in the dispersal of asexual spore-like lichen structures for reproduction (Fang *et al.,* 2020; Upreti *et al.,* 2015).

Lichens are broadly classified based on their structure. They have a thallus-like main body and rhizines, hair-like attachments to the substratum. Sometimes, the attachment is made possible by holdfast an extension of lichen thallus itself. Foliose (leaf-like), Squamulose (pebble-like), Crustose (crust-like) and Fruticose (free-standing) are the four major lichen growth forms (Devkota *et al.,* 2017). Lichens are extremely sensitive to pollution, particularly air pollution, as they get their nutrients directly from the air. Because they are extremely sensitive to flurides, oxides, hydrocarbons, and vehicle exhaust, they are widely used as biomonitoring agents in modern science. Lichens can function remarkably as a sensitive and accumulative biomonitor. Aside from that, lichens are used in geomorphic studies to determine the age of substrates (Abas 2021).

Lichens are always self-sufficient in terms of nutrition. The phycobiont (algae or cyanobacteria), is strictly photosynthetic. Meanwhile the non-photosynthetic partner, the mycobiont (fungus), absorbs moisture and inorganic salts and protects algal cells by arranging themselves over them, thus defining the shape of lichen (Sanders and Masumoto, 2021). Lichens are said to be homomereous when a number of algal cells are more than fungal cell and heteromerous when fungal cells are seen higher in number. They are also highly resistant to predators due to the presence of unique secondary metabolites. Only a few insects and moths have been observed to feed on them. At the same time, they are an important food source for reindeer and caribou in northern areas (Abas, 2021).

Lichens play an inevitable role in indigenous medicine. Their extracts and powders, both crude and purified, are used to treat a variety of ailments. The medicinal properties are attributed to secondary metabolites specific to them because they produce particular bioactive components that neither the algal nor fungal components produce (Adenubi *et al.,* 2022). Ongoing research focuses on lichen-based drug discovery, particularly to combat antibiotic resistance. Lichen-based Vitamin D3 is one of the major breakthroughs in this field. More research on lichen substances will assist us in realizing their full potential as a source of drug discovery (Ljubic *et al.,* 2020; Arora and Philippidis, 2023).

LICHENS IN TRADITIONAL MEDICINES

Research on the potential uses of lichens in pharmaceutics and medicine expanded significantly in recent years. Various communities utilized lichens in multiple ways, particularly in traditional medicine across temperate and arctic regions. Edible lichens, rich in nutrients, had a long history of consumption as folk food and medicine in countries such as India, Japan, China, and several European nations (Crawford, 2019).

In the Nepal Himalaya, seven species of lichens from four families (*Parmeliaceae*, *Physciaceae*, *Ramalinaceae*, and *Usneaceae*) and six genera (*Heterodermia*, *Everniastrum*, *Parmotrema*, *Ramalina*, *Thamnolia*, and *Usnea*) were recorded for their medicinal uses (Devkota *et al.,* 2017). Similarly, in China, species like *Lobaria*, *Peltigera*, and *Usnea* were employed to treat various infectious ailments affecting the skin and digestive system (Yang *et al.,* 2021). In the USA, *Usnea*, *Cladonia*, and *Cladina*are the most traditionally used lichen species; in Europe, *Cetraria*, *Cladonia*, *Peltigera*, *Usnea* and *Lobaria* were predominantly used for medicinal purposes. Similarly, species like, *Usnea*, *Parmotrema*, and *Ramalina* were reportedly utilized for their digestive, antifungal, and anti-inflammatory properties in Africa (Crawford and S. D, 2019). Almost all cultures are known to use lichens for medicinal purposes, but there is little evidence to support the use of lichens in Australia (Adenubi *et al.,* 2022). More and more lichen families and subspecies are being discovered as taxonomy advances, making it difficult to determine which lichen is mentioned in available folk literature. Lichens were also considered sacred, and were used for spiritual and healing purposes. The same lichen has been used for different medical purposes in different continents. The lichen family *Parmeliaceae* is the most widely used in food and medicine and it includes the most commonly used medicinal lichens, *Usnea* and *Parmotrema*. The most commonly used lichen species as a part of indigenous medicine in India are listed below in Table 1:

Chharila –Incredible lichen mix

Chharila is a medicinal powder that is typically made by combining edible lichen species from the Parmeliaceae family. Although the mix primarily consists of *Parmotrema* species like *Parmotrema perlatum* and *P. nilgherrense*, other species, such as *Usnea bailey* and *U. subsordita* are occasionally included (Kumar *et al.,* 2023). Because of its proven benefits, pharmaceutical companies are now marketing it as a health mix; it is also accepted as a spice due to its distinct aroma and taste (Dwarakanath *et al.,* 2022). The main ingredient *Parmotrema,* also known as stone flower in India. Studies have shown that stone flowers are rich in proteins, glucose, phenols, Vitamin A, and Vitamin C, all of which are vital for health. It can also be used as astringent and has sedative and diuretic properties that can treat bronchitis, vomiting, toothache, arthritis and other inflammations (Kumar *et al.,* 2016). Table 2 shows the proven health benefits of chharila.

Phytochemical profile

Lichens produce a diverse range of aromatic and aliphatic compounds. Their secondary metabolites include amino acid derivatives, sugar alcohols, aliphatic acids, macrolytic lactones, monocyclic aromatic compounds, quinines, chromones, xanthones, dibenzofurans, depsides, depsidones, depsones, terpenoids, steroids, carotenoids, and diphenyl ethers. These low molecular compounds are known to comprise about 20% of dry weight of lichens (Adenubi *et al.,* 2022). Lichen secondary metabolites are unique, occurring only in algal-fungal combinations. These compounds have antibacterial, antifungal, antiviral, anticancer, neuroprotective, antidiabetic, wound healing, and photoprotective activities. Lichens synthesize secondary metabolites through three primary biosynthetic pathways: the shikimic acid pathway, the mevalonic acid pathway, and the acetate-malonate pathway (Nayaka and Haridas, 2020). Each pathway involves a series of complex enzymatic reactions that convert simple precursor molecules into structurally diverse and biologically active compounds.

Shikimic acid pathway

Shikimic acid pathway is essential for the production of aromatic compounds. It starts with the condensation of phosphoenolpyruvate (PEP) and erythrose-4-phosphate to form 3-deoxy-D-arabino-heptulosonate-7-phosphate (DAHP). DAHP undergoes a series of enzymatic transformations to produce shikimic acid, which

Table 1. Lichen species used in traditional Indian medicine

Sl. No.	Species name	Medicinal use	Referance
1	*Cladina mitis*	used for respiratory and hepatic health	O'Neill *et al.,* (2017).
2	*Usnea bailey*	ingredient in Charila, restores respiratory health	O'Neill *et al.,* 2017.
3	*Parmotrema reticulatum*	medicine for respiratory problems	O'Neill *et al.,* 2017
4	*Usnea sikkimensis*	used against lung diseases, strengthens hair, wound healing	O'Neill *et al.,* 2017; Pradhan and Badhola 2008; Biswas 1956
5	*Canoparmelia ecarperata*	medicine for cough and cold	Singh *et al.,* 2012
6	*Ramalina sinensis*	treats cough and cold	Singh *et al.,* 2012
7	*Parmotremasancti-angelii*	treats skin diseases	Brij Lal and Upreti 2005.
8	*Usnea longissima*	repairs bone fractures	Brij Lal and Upreti 2005, Sharma 2006
9	*Parmotrema nilgherrense*	releive stomach and kidney related issues, good for menstrual health	Kumar and Upreti 2001
10	*Usnea subsordida*	ingrediant in Charila, restores respiratory health	Shah 1998
11	*Stereocaulon himalayense*	used against urinary infections	Sharma 1997
12	*Hypotrachyna cirrhata*	medicine to treat headache and cold	Biswas 1947
13	*Parmotrema perforatum*	medicine for diuresis	Biswas 1947

Table 2. Health benefits of *Chharila*

Sl. No.	Ailments	Effect or Mode of action	References
1	Chronic gastritis	Inhibits *H.Pylori*	Gehlot *et al.,* 2016
2	Diabetes	Flavanoids and phenols	Patil *et al.,* 2011
3	Liver health	Hepatoprotective constituents	Shailajan *et al.,* 2014
4	Yellow fever	Antiviral activity	Goyal *et al.,* 2016
5	Arthritis	Anti-inflammatory property	Diwakar *et al.,* 2019
6	Kidney health	Reduce creatinine and uric acid	Goyal *et al.,* 2018
7	Reduce Cholesterol	Phenolic constituents	Rahman, 2014
8	Contraceptive	Reduce sperm density and motility	Patel *et al.,* 2018, Tanwar *et al.,* 2015
9	Wound healing	Antimicrobial and anti-inflammatory properties	Panicker *et al.,* 2018
10	Head ache	Soporific and sedative nature	Chauhan *et al.,* 1999

serves as a precursor for aromatic amino acids like phenylalanine, tyrosine, and tryptophan. These amino acids are further modified to produce a variety of secondary metabolites, including flavonoids and alkaloids (Singh, 2023).

Mevalonic acid pathway

The mevalonic acid pathway, also known as the isoprenoid pathway, is responsible for synthesizing terpenes and steroids. This pathway begins with the condensation of acetyl-CoA molecules to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA), which is then reduced to mevalonic acid. Mevalonic acid is phosphorylated and decarboxylated to produce isopentenyl pyrophosphate (IPP), a crucial building block for isoprenoids. IPP can be polymerized and cyclized to form various terpenes and steroids, contributing to lichen secondary metabolites' structural and functional diversity (Sveshnikova and Piercey, 2021; Singh 2023).

Acetate-malonate pathway

The acetate-malonate pathway, also known as the polyketide pathway, is the most prevalent route for producing lichen secondary metabolites. This pathway involves the iterative condensation of acetyl-CoA and malonyl-CoA units to form polyketide chains. These chains undergo cyclization, reduction, and oxidation reactions to produce various polyketides, such as usnic acid, depsides, and depsidones. Polyketides are known for their diverse biological activities, including antimicrobial and anti-inflammatory properties (Singh, 2023; Nayaka and Haridas, 2020).

These biosynthetic pathways highlight the intricate and highly regulated processes that lichens use to produce their unique and bioactive secondary metabolites and are outlined in Fig. 1. Usnic acid (Varlı *et al.,* 2024; Shukla *et al.,* 2010), retigeric acid (Liu *et al.,* 2018; Francolini *et al.,* 2004), evernic acid (Lee *et al.,* 2021; Chang *et al.,* 2012), Squamatic acid, atranorin, gyrophoric acid, norstictic acid (Wang *et al.,* 2023; Mohammadi *et al.,* 2022; Gökalsın and Sesal 2016), salazinic acid, stictic acid, physodic acid (Killari *et al*., 2023; Delebassée *et al.,* 2017), vulpinic acid, ramalin, physciosporin, tumudulin (Cansaran *et al.,* 2021) etc. are few among the mostly studied bioactive compounds in lichenology. Understanding these pathways provides insights into lichens' ecological roles and opens up possibilities for biotechnological applications in drug discovery and development. Table 3 shows major lichenochemicals and their respective chemical classes.

Pharmacological profile

Lichens have high pharmacological value due to unique secondary metabolites found nowhere else. The plethora of compounds like polyketides, depsides, depsidones, and usnic acid have bestowed lichen extracts with antimicrobial, anti-inflammatory, antioxidant, anticancer, antidiabetic, neuroprotective and photoprotective activities. For instance, usnic acid has been extensively studied for its antimicrobial properties, showing effectiveness against a range of bacterial and fungal pathogens (Wang *et al.,* 2022). Additionally, lichen-derived compounds like atranorin and physodic acid exhibit significant antioxidant activities, which help scavenge free radicals and protect cells from oxidative stress (Simko *et al.,* 2022; Cardile *et al.,* 2022). Compounds like usnic acid, atranorin, lecanoric acid, norstictic acid, lobaric acid, stictic acid, ramalin, gyrophoric acid, salazinic acid, and fumarprotocetraric acid have been recognized for their strong anticancer effects. These substances act through various pathways, such as inducing cell cycle arrest, promoting apoptosis and necrosis, and inhibiting angiogenesis. These mechanisms highlight their potential as promising candidates for developing new anticancer treatments (Murugesan *et al.,* 2023; Mohammadi *et al.,* 2022). Metabolites such as fumarprotocetraric acid and usnic acid have also been recognized for their neuroprotective properties (Fernández *et al.,* 2017; Erfani *et al.,* 2020). The biological activities of prominent lichen metabolites are shown

Table 3. Substance class of major Lichen secondary metabolites

Sl. No.	Lichenochemical	Substances class	References
1	Gyrophoric acid	Depsides	Mohammadi *et al.,* 2022
2	Vulpinic acid	Methyl ester derivative	Sahin *et al.,* 2019
3	Tumidulin	Carbonyl compound	Poulsen-Silva *et al.,* 2023
4	Squamatic acid	Carbonyl compound	Majchrzak *et al.,* 2022
5	Physodic acid	Depsidone	Türk*et al.,* 2014
6	Norsticstic acid	Depsidone	Garlick *et al.,* 2012
7	Ramalin	Hydrazide	Paudel *et al.,* 2011
8	Retigeric acid	Terpenoids	Liu *et al.,* 2013
9	Atranorin	Depsides	Wang *et al.,* 2023
10	Usnic acid	Dibenzofuran	Erfani *et al.,* 2020

in Table 4 and the overall biological pharmacological applications of lichen metabolites are summarized in Fig. 2.

Nutritional profile

Many Asian and European lichens are edible and have traditionally been used as a medical and nutrient source. These folklore claims are also supported by modern research. Because of their high fiber content, they are excellent for intestinal health. Lichens are a good source of protein, and their high potassium and low sodium content make them beneficial for preventing hypertension. Lichens contain essential amino acids in higher concentrations than the “ideal protein” standard, with phenylalanine at 140%, leucine at 109%, tryptophan at 291%, and valine at 183%. Additionally, they are rich in minerals such as potassium (800 – 5497 ppm), iron (311 – 19579 ppm), and calcium (2130 – 17190 ppm) making them superior to many staple food commodities in terms of mineral content (Rethinavelu *et al.,* 2023). Lichen is the only known vegan source of vitamin D (Benedik, 2022). They are also known for having high iron content. Food industries reduce the natural bitterness of lichens through various processes while also enhancing their volatile flavor components thus making lichens more suitable for creating new food formulations. Although commonly used as a spice and flavour enhancer, more research is needed to prove their potential benefits, as the bioavailability of these nutrients in the human body must also be considered. *Usnea, Parmotrema*, *Cladina, Lobaria*, *Ramalina*, *Evernia*, *Parmelia*, *Peltigera* (Dobrescu *et al.,* 1993; SalinRaj *et al.,* 2014; Huang *et al.,* 2018; Malhotra *et al.,* 2007; Wang *et al.,* 2021; Hussain *et al.,* 2021; Aoussar *et al.,* 2020) etc contain the most of the edible lichen species.

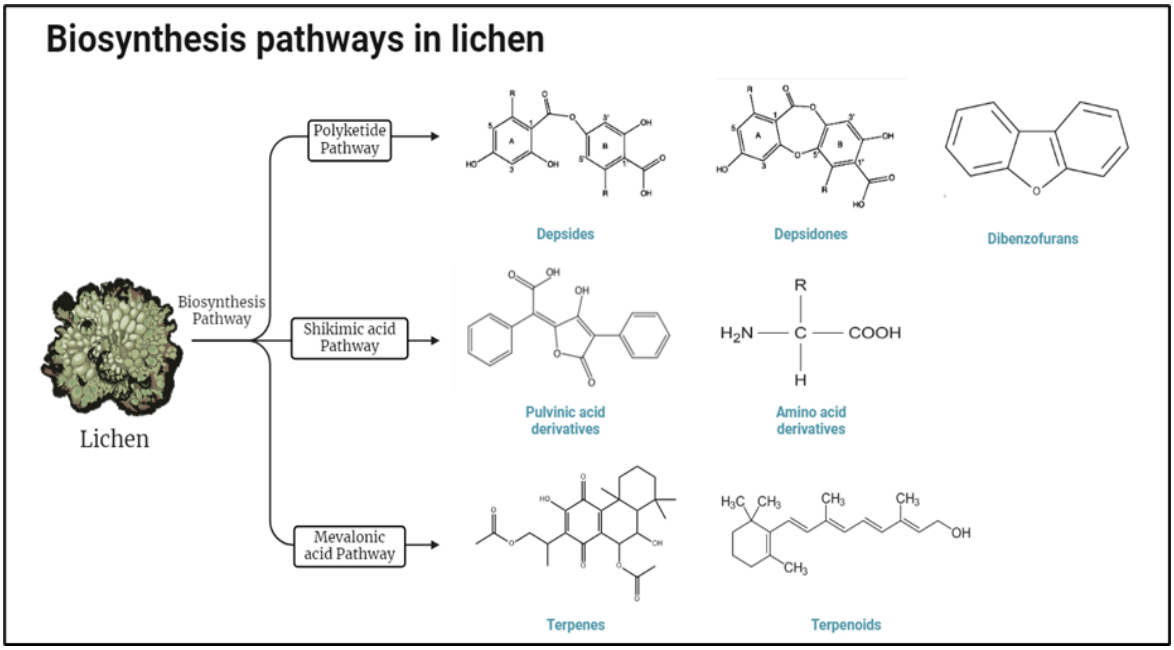

Fig. 1. *Biosynthesis pathways in lichens*

Extraction and identification of lichen metabolites

One of the most critical steps in lichen-based drug discovery is extracting and identifying lichen compounds. Lichen extraction yields are high in both conventional and non-conventional methods. Cold percolation, soxhlet extraction, maceration, as well as microwave \ ultrasound-assisted and supercritical fluid extraction, are all currently in use (Mohammadi *et al.,* 2020). Among the various solvents used for lichen extraction, ethanol, methanol, and acetone in optimal temperatures give high yield, even though aqueous extracts are always preferred for medicinal purpose. The widely used technique for identifying lichen secondary metabolites from crude extracts is Thin-layer chromatography (TLC). Individual compounds are purified using column chromatography, which can then be identified using Gas chromatography-mass spectrometry (GC-MS) (Leela *et al.,* 2017; Poulsen-Silva *et al.,* 2023). Innovations in Nuclear Magnetic Resonance (NMR) spectroscopy and X-ray crystallography have further enhanced the structural elucidation of complex lichen compounds (Syed *et al.,* 2019). The new omics approach has made identifying secondary metabolites even easier. Secondary metabolites that were previously unknown can now be easily identified by recognizing their Biosynthetic Gene Clusters (BGC's) (Singh *et al.,* 2021). MIPS-CGN and MIDDAS-MN are popular tools for determining BGC in fungal genomes. Databases such as Pubchem, ChemSpider, ChEBI, etc. , are commonly used to identify secondary metabolites easily (Weber *et al.,* 2016; Kalra *et al.,* 2020).

ADVANCES IN LICHEN PHARMACOLOGY

In the past few decades, lichen biology has expanded. Identification of novel bioactive compounds has led to more research revealing their unique pharmacological benefits. Lichen secondary metabolites are proven to be good therapeutic agents can tackle the emerging antibiotic resistance problem. Different biological effects exhibited by lichen metabolites are depicted in Fig. 3. Recent advances in lichen pharmacology are discussed below:

Antimicrobial activity

Recent, studies reveal the antimicrobial and antioxidant activities of *Pseudevernia furfuracea*, *Lobaria pulmonaria*, *Cetraria islandica*, *Evernia prunastri*, *Stereocaulon tomentosum*, *Xanthoria elegans* and *Umbilicaria hirsute* (Kello *et al*., 2023). Another study examined the impact of five Usnea species, including *Usnea baileyi*, *U. diffracta*, *U. glabrata*, *U. longissima* and *U. rubicunda* against multidrug-resistant ESKAPE pathogens, such as *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter cloacae* (Dela *et al.,* 2023). The Usnea species demonstrated promising in vitro inhibitory activities against these bacteria. The antioxidant activities of usnic acid are also reported from extracts of different lichens (Maulidiyah *et al.,* 2023).

Table 4. Biological activities of Lichen secondary metabolites

Sl. No.	Secondary metabolite	Biological activity	References
1	Salazinic acid	Antidiabetic	Pham *et al.,* 2021
2	Gyrophoric acid	Anticancer	Mohammadi*et al.,* 2022
3	Diploschistesic acid	Antimicrobial	Sedrpoushan*et al.,* 2022
4	Evernic acid	Neuroprotective, Anti-inflammatory	Lee*et al.,* 2021
5	Mycosporine	Photoprotective, Antioxidant	Geraldes *et al.,* 2021
6	Barbatic acid	Schistosomicidal	Silva *et al.,* 2020
7	Vulpinic acid	Antioxidant	Sahin *et al.,* 2019
8	Physciosporin	Anticancer	Taş*et al.,* 2019
9	Lobaric acid	Anti-inflammatory	Chang*et al.,* 2012
10	Psoromic acid	Anti-herpetic	Hassan *et al.,* 2019
11	Tumidulin	Anticancer	Yang *et al.,* 2018
12	Usnic acid	Antibacterial, Antifungal, Antiviral	Erfani*et al.,* 2020
13	Squamatic acid	Anticancer	Majchrzak *et al.,* 2017
14	Perlatolic acid	Herbicidal	Peres *et al.,* 2016
15	Retigeric acid	Antifungal	Lee *et al.,* 2012
16	Norstictic acid	Antimicrobial	Ranković *et al.,* 2012
17	Vicanicin	Anticancerous	Russo *et al.,* 2012
18	Ramalin	Anti-inflammatory, Antioxidant	Paudel *et al.,* 2011
19	Scabrosin	Antibacterial, Antifungal	Liu*et al.,* 2019
20	Atranorin	Antibacterial, Wound healing	Gaikwad *et al.,* 2023
21	Parietin	Photoprotective	Mendili *et al.,*2024

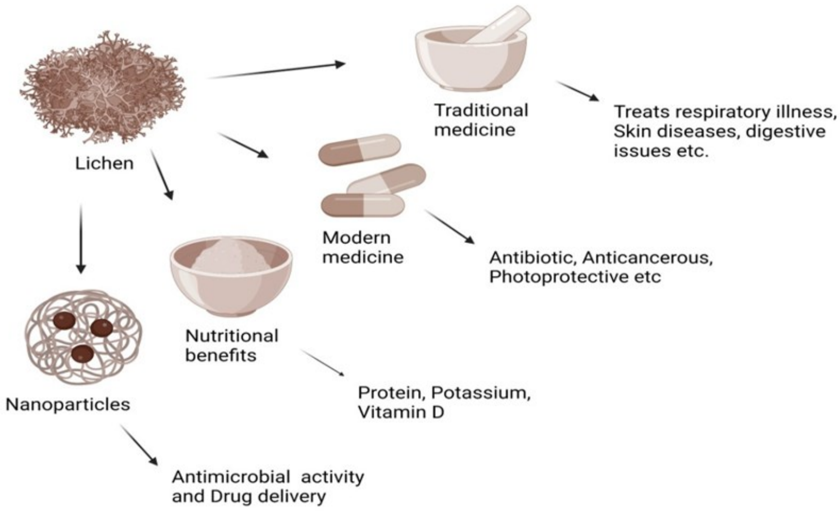

Fig. 2. *Pharmacological applications of lichens*

Anti- proliferative activity

A large fraction of lichenochemicals are well known for their anticancerous activities. Atranorin, physodic acid, evernic acid and gyrophoric acid were evaluated for their antiproliferative activity along with some crude lichen extracts (Kello *et al.,* 2023). Similarly crude extracts of *Parmelia vagans* were effective against cancer in human cell line studies (Bondarenko *et al.,* 2022).

Photoprotective activity

Lichen species are known for their impressive photoprotective abilities, largely due to the production of unique secondary metabolites. Compounds like usnic acid, atranorin, and parietin protect lichens from harmful ultraviolet (UV) radiation (Radice *et al.,* 2016). Recent research has shown that these metabolites effectively absorb and dissipate UV light, preventing photoinhibition and oxidative stress in lichen photobionts. For example, studies on *Parmotrema* and *Usnea* species have demonstrated that their extracts and isolated compounds (methyl β-orcinol carboxylate and salazinic acid) act as effective UV filters, comparable to commercial sunscreens (Nguyen *et al.,* 2021). Similarly, lichen derived compounds vulpinic acid and gyrophoric acid has proven their photoprotective activity against UV radiation in human keratinocytes (Varol *et al.,* 2016). Additionally, lichens use non-photochemical quenching mechanisms and antioxidant systems to mitigate the effects of excess light energy and Reactive Oxygen Species (ROS), further enhancing their photoprotective capabilities. These findings highlight the potential of lichens as a source of natural photoprotective agents, which could be used to develop new sunscreens and other skincare products. Incorporating lichen-derived compounds into commercial applications offers a sustainable alternative to synthetic UV filters and leverages the evolutionary adaptations of lichens to extreme environmental conditions.

Toxicity of lichens

Although most lichenochemicals are known to benefit humans, it is imperative to note that lichens also contain potentially harmful secondary metabolites. Traditional medical practitioners used to choose lichens for medical purposes based on their colour to determine whether they possess toxic chemicals or not (Sujetovienė, 2015). Lichens accumulate toxins easily, but studies have revealed that they are far below the levels required to cause human toxicity and can be easily removed by traditional pretreatment methods (Zhao *et al.,* 2020). There are research reports on the accumulation of heavy metals by various lichen species in polluted cities (Singh *et al.,* 2018). Studies on Iceland lichen and Reindeer lichen revealed that without pretreatment methods, their toxins were lethal enough to kill rats. It was also observed in autopsy reports that the lead content in their kidneys was high, which was proportional to the lead content in Lichens (Airaksinen *et al.,* 1986). Also, some studies on usnic acid have revealed that, although it has a lot of benefits, it can cause allergic dermatitis and drug-induced liver injury in some patients (Wang *et al.,* 2022). Presence of irritative compounds like vulpinic acid and protolichesterinic acid makes some lichen species unfit for consumption (Sahin *et al.,* 2019; Poulsen *et al.,* 2023). Certain lichen species sometimes harbor cyanobacteria that produce microcystins, potent toxins causing liver damage in humans and animals (Thakur and Chander, 2021). Lichen-derived compounds are actively researched for their pharmacological benefits despite the potential risks. This underscores the importance of thoroughly evaluating the toxicological profiles of lichens to ensure they can be safely used in therapeutic applications.

Lichen-based nanoparticles

Lichen bioactive compounds are undoubtedly therapeutically important, but like any other natural compound, it

Table 5. Lichen based nanoparticles prepared from different species

Sl. No.	Lichen Species	Nanoparticles prepared (NPs)	Biological activity	References
1	*Lobaria pulmonaria, Ramalinafari-nacea, Everniaprunastri*	AgNPs	Antibacterial, Antioxidant	Salah *et al.,* 2022
2	*Parmotremaaustrosinense*	TiNps	Antimicrobial	Ali *et al.,* 2022
3	*Pseudeverniafurfuracea, Lobariapulmonaria*	AgNPs	Antibacterial Antioxidant	Goga *et al.,* 2021
4	*Ramalina sinensis*	FeONps	Antibacterial	Safarkar *et al.,* 2020
5	*Xanthoriaparietina, Flavopuncteliaflaventior*	AgNPs	Antibacterial Cytotoxic	Alqahtani *et al.,* 2020
6	*Lecanora muralis*	SiO_2Nps, ZnONps	Antimicrobial	Abdullah *et al.,* 2020
7	*Protoparmeliopsismuralis*	AgNps, CuNps	Antibacterial	Alavi *et al.,* 2019

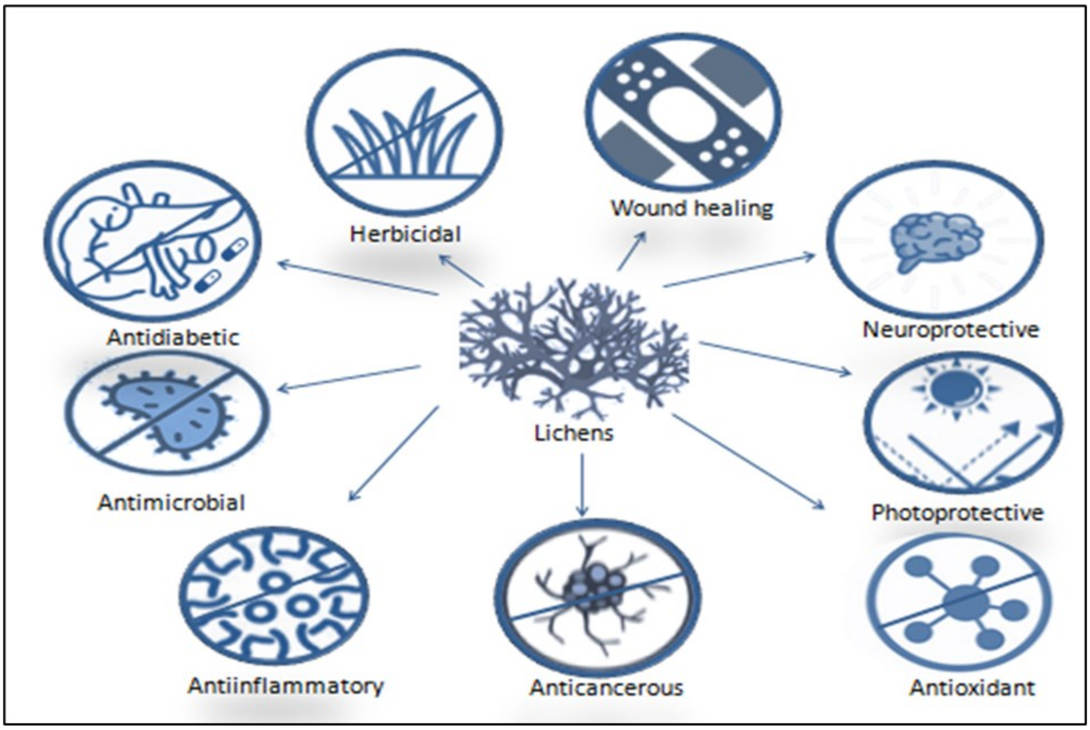

Fig. 3. *Biological effects of lichen secondary metabolites*

is difficult to deliver them to the target site effectively; researchers are developing lichen nanoparticles to address this issue. Lichen bioactive compounds have been shown to be excellent capping agents and reducing agents. These nanoparticles are more effective than lichen metabolites alone. Silver, Gold, Titanium, Cadmium, Iron, Zinc and Copper nanoparticles are synthesized using different lichens through biogenic synthesis (Rattan *et al.,* 2021). Table 5 shows major nanoparticles synthesized using lichen extract.

Future prospective

The future of lichen metabolites in drug discovery is highly promising, with ongoing research continually revealing their extensive pharmacological potential. Advances in biotechnology and molecular biology facilitate the identification and synthesis of these compounds, addressing the challenges posed by their slow growth and complex cultivation. Researchers are delving deeper into the diverse bioactive properties of lichen metabolites, such as their antimicrobial, anti-inflammatory, and anticancer activities, which hold significant promise for developing novel therapeutics. Furthermore, integrating metagenomic approaches and biosynthetic gene cluster analysis is paving the way for more efficient and sustainable production methods. These advancements ensure that these valuable compounds can be harnessed for future medical applications. The continued exploration and innovation in this field are expected to unlock new, effective treatments derived from lichens, significantly contributing to the advancement of drug discovery. Additionally, the potential for discovering new bioactive compounds through high-throughput screening and bioinformatics tools further enhances the prospects of lichen metabolites, making them a vital resource for future pharmaceutical developments.

Conclusion

Lichens and their metabolites are among the least studied members in pharmacology. Even though lichen research has gained prominence in recent decades, many lichen species and their metabolites have yet to be thoroughly investigated. Further exploration and advancement is essential to develop and refine potential lichen-based technologies like lichen-based nanoparticles. The potential medicinal qualities of lichens would assist in the treatment of various neurological disorders, cancer, and diabetes conditions and their antimicrobial and antifungal capabilities can be used to solve the problem of developing antimicrobial resistance. Lichens have enormous potential, which must be thoroughly studied and exploited to improve human health and society.

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Conflict of interest

The authors declare that they have no conflict of interest.

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