Review Article

An Overview on Pharmaceutical Applications of Lichen Secondary Metabolites

Renjini A.S*[1], Celestin Baboo R.V[2], Sirajudheenm.K[3], Saranya S Mohan[1], Sarika P.V[1]
[1]M Pharm student, Jamia Salafiya Pharmacy College Pulikkal, Malappuram District, Kerala, India.
[2] Professor and Head, Department of Pharmacognosy, Jamia Salafiya Pharmacy College Pulikkal, Malappuram District, Kerala, India.
[3] Principal, Jamia Salafiya Pharmacy College Pulikkal, Malappuram District, Kerala, India.
***Corresponding author's E-mail:** 2017renjinias1@gmail.com

Received: 10-01-2024; **Revised:** 28-02-2024; **Accepted:** 05-03-2024; **Published on:** 15-03-2024.

ABSTRACT

Lichens are complex symbiotic organisms comprising cyanobacteria, fungi, and algae. They produce a wide variety of secondary metabolites, many of which have shown beneficial properties in various fields including medicine. Pharmaceutical use of lichen secondary metabolites. An overview thorough search was conducted in several databases, including Scopus, Embase, Cochrane, and PubMed. The search terms used included Lichen, Lichen secondary metabolites, Lichen pharmaceutical application, antimicrobial agents from lichens, bioactive secondary metabolites from the likens, and anticancer activity of lichens. The study included all publications published in English. Lichens produce compounds such as usnic acid, which exhibit antimicrobial and antiviral properties. Usnic acid has been shown to have inhibitory effects against bacteria, fungi, and viruses. It has been studied for its potential in the management of hyperproliferative skin conditions and tumor growth. The lichens contain secondary metabolites with potent antioxidant properties. These compounds can scavenge free radicals, chelate catalytic metals, and act as oxygen scavengers, thereby obstructing oxidation. Lichen-derived antioxidants can be used to protect food from oxidative lipid degradation and to maintain food quality. Lichen secondary metabolites have shown potential for various medicinal activities, including anti-cancer, anti-inflammatory, anti-hepatotoxic, enzyme inhibitory, and anti-tumoral effects. Different lichen compounds have demonstrated cytotoxic activity against human cancer cell lines and inhibition of specific enzymes involved in inflammatory processes.

Keywords: Lichen, cyanobacterium, secondary metabolites, biodeterioration, cancer therapy, antimicrobial, antioxidant, usnic acid.

INTRODUCTION

Lichens are created when a fungal partner and photosynthetic partner, such as algae or cyanobacteria, form a symbiotic relationship. More than 800 lichen products and more than 17,000species of lichen are known to be used for a variety of purposes, including drying, pollutant monitoring, fragrance, floral decorating, as well as food and medical purposes[1] component that is used in both scent, and the medicine used was usnic acid. They lack both leaves and roots. or flowers, they directly absorb airborne contaminants, nutrients, water, and other factors. They are not appropriately used and are built up in thetissues. Stones are protected from environmental factors by a thick coating of lichens, which suggests that they may act as a protective coating, especially in adverse situations[2]. Lichens can bioaccumulate certain pollutants, and are extremely sensitive to them. One illustration of how pollutionaffects lichens is the decline in lichen species caused by the breakdown of symbiotic interactions. Lichens are therefore employed as bioindicators based on the types of lichens that are present or absent in the environment. Foliose (leaf-like) lichen is an aqueous extract of the lichen species, Lobariapulmonaria. It is bright green, wet, and pale brown when dried[3].

Lichens are frequently used in folk medicine to treat a variety of illnesses, including eczema and respiratory, pulmonary, and arthritic conditions[4]. In addition to being utilized in food and cosmetics, it also serves as an anti-inflammatory and antiulcerogenic agent. Lichens havebeen used in medicine since ancient times. For example, Lobaria pulmonaria, *Cetraria islandica*, and Cladonia species have been shown to be useful for the treatment of pulmonary tuberculosis. Many organisms, including humans, rely heavily on lichens as food. They are employed in the manufacture of alcohol, paints, and the pharmaceutical and perfume industries. Lichens produce a variety of bioactive secondary metabolites, some of which are utilized in medicinal research[5]. Numerous lichen extractshave been used in various folk remedies, and screening of lichens has revealed the frequent presence of metabolites with antibiotic, antimycobacterial, antiviral, antitumor, analgesic, and antipyretic properties. In Turkish folk medicine, certain lichen species are used as stomachics and anti-diabetic medications[6].

Many mammals are protected from harmful bacteria by antibiotic secondary metabolites produced by lichen-forming fungus[7]. The initial analysis of lichen antibacterial activities was conducted by Burkholder et al. According to *Cetraria islandica*, which is used for cough treatment, several lichens exhibit ethnopharmacological effects. Human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT) DNA polymerase activity was significantly inhibited by the aliphaticalpha-methylene gamma-lactone derived from lichens (Figure 1).

Figure 1: Lichen

Lichens have been used in tribal medicine to treat various diseases. These lichens contain secondary metabolites, including antibiotics, antimycobacterial, antiviral, antitumor, analgesic, and antipyretic as well as antiproliferative, antioxidant, and anti-HIV properties[8]. According to previous reports, lichens and their secondary metabolites have great potential as antifungal sources. Metabolites from lichens exhibit anti-hervivoore activity[9]. Lichens produce metabolites that are toxic to the nematodes, snails, and insects. Lichens have long been used in traditional medicine to treat a variety of ailments, including eczema and respiratory, pulmonary, and arthritic conditions. In addition to food, they have been used in cosmetics. Lichen creates aromatic compounds that effectively block UV rays and shield photobionts from harmful irradiation. Secondary metabolites from lichens are involved in metal homeostasis, sensitivity to heavy metal build-up, and pollution tolerance. Lichens are symbiotic organisms composed of one or more photosynthetic partners (photobionts) and a fungal partner (mycobiont). Green algae, cyanobacteria, or both may be photobionts[10]. The photobiont belongs to the Chlorophyta or Cyanobacteria division, whereas the fungus most usually represents the Ascomycota division and, less frequently, the Basidiomycota division. According to recent investigations, approximately 18500 species of lichens.

Ascomycota make up the majority (98%) of the fungal partners in lichen, with Basidiomycota and Anamorphic fungi rounding out the group. An estimated 21% of mushrooms have the capacityto function as mycobionts. Lichens are formed by a partnership between approximately 40 species, 25 algae, and 15 cyanobacteria that participate in photosynthetic processes. From polar to tropical locations, plainsto the highest mountains, and wet to dry environments, lichens can be found in a variety of habitats[11]. According to Molnar and Farkas, the majority of lichens are terrestrial; however, certain species can be found in freshwater streams and some marine intertidal zones. The three main growth formsexhibited by lichens are crustose, foliose, and fruticose. Crustose lichens are encrusting forms that cover and penetrate the surface of their habitat, and cannot be removed without disintegration. Foliose lichenshave leafy lobes that spread over the surface of a horizontal layer[12]. Fruticose lichens,on the other hand, have shrubby shapes with numerous branches and can be manually scraped from the surface. Lichens create metabolites to endure harsh circumstances, and these metabolites are useful for creating new biotechnologies. Lichens have been used as a source of colorants, cosmetics, and medicines since ancient times because of their capacity to synthesize a vast variety of distinctive chemical compounds; for example, Xanthoria parietina and Letharia vulpine have been used to treat jaundice and digestive illnesses, respectively, while *Parmelia sulcata* has been used to treat respiratory diseases.

METHODS

One of the most effective ways for fungi to meet their carbohydrate needs is lichensymbiosis. with lichen-forming species, making up approximately one-fifth of all known fungal species. More than 40% of all Ascomycota species currently recognized are lichenized[13]. From the poles to the tropics, they are found in almost all terrestrial habitats, from xeric settings to freshwater and marine (littoral) aquatic habitats. In 8% of the world's land area, lichens predominate, notably in arctic, alpine,and coastal settings, where water vapor and fog are common. Their almost universal capacity to colonize different substrates serves as another indicator of ecological success[14]. They can develop on or within the bark of trees, rocks, or vascular plants, especially in the tropics, on wood, soil, mosses, leaves, and other lichens, as well as on man-made substrates such as concrete, glass, metals, and plastics.

Reproduction of Lichens

The transmission of fungal and photosynthetic partners from one generation to the next is necessary for lichen reproduction [15]. The process of finding a compatible photobiont and resynthesizing by fungal spores after germination is known as de novo lichen symbiosis (horizontal transmission of the photobiont) if the mycobiont reproduces sexually. In cases where the mycobiont reproduces asexually, the photobiont is typically passed on to the following generation along with themycobiont by specialized vegetative propagules (such as Soredia or Isidia) or via thallus fragments carrying both symbionts (vertical transmission of the photobiont). This is because the most prevalent mechanism of reproduction for the fungal partner appears to be sexual reproduction[16].

Types of Lichen Species

Lichens can grow in several ways. The most basic lichens were loosely combined fungalcrusts, algae, and hyphae. Others are more intricate, with leafy or shrubby shapes that resemble small trees and have specialized structures linked to them[17]. Encrusting lichens, also known as crustose or crustaceous lichens, cover and encrust the surface of their habitats. However, they cannot be removed from the surfacewithout disintegration. In all A thallus or lichenized stroma, the fungus that develops is like lichens and may include special secondary chemicals. When using rocks as their substrate, lichens are generally considered saxicolous species that fall into one of three categories: crustose, foliose, or fruticose, depending on how they cling to their substrate. Foliose lichens have leafy lobes that cover the surface of a horizontal layer. They are held in place by root-like threads and are easily removed using a knife. Fruticose lichens are shrubby lichenswith many branches. These were easily removed from the surface by hand. The filamentous (hair-like) lichens were distinct. They are composed of chains of algal cells enveloped in fungal hyphae. Powdery lichens of leprosy, a peculiar subgroup of lichens known as lichens, have never been seen to generate fruiting bodies. These lichens have not yet been fully recognized or at least not yet givencomplete scientific names, which is necessary to correctly identify fungi[18]. These mushrooms lack an outside brain and an inner brain. Instead of a cortex, these fungihave an algal cell layer and occasionally a weakened medulla. Squamulose lichens have a section of their thallus raised off the substrate to generate "squamules," which are composed of tiny scale-like structures and lack a lower cortex. Overall, they resemble crustose lichens, which lacka bottom cortex but have an upper cortex. Cyanobacteria create polysaccharides in gelatinous lichens that retain and absorb water. There are several gradations of shapes between these three major groupings, and lichens may not always neatly fall into one of these artificial categories[19].

Distribution of Lichens

Lichens can thrive in a variety of settings, and abiotic factors, including temperature,humidity, wind speed, and light accessibility, can affect their development[20]. An essential part of lichen thalli, which can play several symbiotic roles, is lichen-associated microorganisms. Related bacteria that were exposed to lichen-borne Alphaproteo bacteria were examined using barcoded pyrosequencing bases. The investigated bacteria were found to be closely related to the Rhizobiales lineage, known as nitrogen fixers, which are associated with lichens[21]. Due to their resistance, lichens may live in deserts that freeze and scorch tundra. It is proposed that their capacity for drying survival and intricate chemistry play key roles in their accomplishment. Lichens can completely dry out when moisture is not available and lose all of their body water without perishing [22]. Lichen thalli are poikilohydrous, which means that their waterstatus reacts to changes in air humidity in order to immediately start up the lichen metabolism. After along, gloomy winter, Antarctic lichens may restore their photosynthetic apparatus[23] in just a few minutes. Researchers have found that lichens, as micro-ecosystems, are tolerant to three extreme conditions: total dehydration, exceptionally low temperature (-196°C), and hypoxia. Specific pathways allow lichens to cope with these stress conditions through ecological stability. Lichens require liquid water for cyanobacteria. Thallus dehydration may survive at temperatures as low as -196°C/77 K. Furthermore, under anoxic conditions, it may produce molecular hydrogen both in the light and the dark. Molecular hydrogen might then be used as fuel to meet the space's increased demand for efficient and pollution-free energy. There is very little flora and a very harsh temperature in Antarctica. Researchers have found that lichens, as micro-ecosystems, are tolerant to three extreme conditions: total dehydration, exceptionally low temperature (-196°C), and hypoxia[24]. Specific pathways allow lichens to cope with these stress conditions through ecological stability. Lichens require liquid water for cyanobacteria. Thallus dehydration may survive at temperatures as lowas -196°C/77 K. Furthermore, under anoxic conditions, it may produce molecular hydrogen both in thelight and dark. Molecular hydrogen might then be used as fuel to meet the space's increased demand for efficient and pollution-free energy. There is very little flora and a very harsh temperature in Antarctica. Poikilohydric lichen[25] is a type of lichen that can persist for a long timein a water-deficient environment and restore physiological activity under certain circumstances. A gene in lichens that makes them resistant to drought can be used to understand the operation of another creature that can combat water shortages wherever in the world. The results of various studies have indicated that the antioxidant capacity of lichens plays a major role in their ability to endure drought. In previous studies, dryingand rehydrating three lichens with drought resistance to heat stress sedated the redox state of reduced and oxidized glutathione.

Secondary Metabolites

Lichens produce a variety of beneficial secondary metabolites, some of which are employed in pharmacy medical sciences[26]. Usnic acid is a naturally occurring substance that is often present in lichen species of the genus Usnea. Usnic acid is a potent lichen compoundused in medicinal preparations. In addition toits analgesic and antipyretic properties, it has antimicrobial and antiviral properties. This substance inhibits bacterial and eukaryotic cellmultiplication in vitro. Higher plant cells are among the biological systems in which antimitotic and antiproliferative effects have been demonstrated. Additionally, the pharmacological potential of usnic acid has been examined in the management of tumor growth and its therapeutic promise for hyperproliferative skin conditions such as parasite infestations and psoriasis. Usnic acid does not appear to have any overt harmful effects according to mouse pharmacokinetic studies. A class of organic compounds known as pulvinic acids includes compounds with a-alkylidenebutenolide ring structure[27]. They were separated from several lichens and fungi.

Lichens with different biological characteristics produce a wide range of secondary metabolites.Up to 20% of the dry weight of lichens consists of these complexes, mostly small-molecule metabolites. The secondary metabolite concentration of lichen thalli ranges from 0.1 to 10%, and on rare occasions,it can even exceed 30% of the dry weight of the thallus[28]. The three main routes for production of secondary metabolites in lichens are acetylpolymalonyl, mevalonic acid, and shikimic acid. More than 800 secondary metabolites have been identified in lichen. The significance of lichens as a source of novel natural products has been confirmed by the ongoing development of lichen-derived chemicals. For a long time, the pharmaceutical industry has paid little attention to lichens because of their sluggish growth and challenges in laboratory cultivation. For the same reason, it is challenging to find pure lichen metabolites in sufficient quantities to evaluate their biological actions. Basic elements such as proteins, pigments, and vitamins are produced by the fundamental metabolic pathways of lichens. Many different classes of compounds comprise lichen secondary metabolites, such as aliphatic acids, sugar alcohols, quinines, chromones, xanthones, dibenzofurans, depsides, depsidones, depsones, terpenoids, steroids, carotenoids, and diphenyl ethers. Basic elements such as proteins, pigments, and vitamins are produced by the fundamental metabolic pathways of lichens. Many different classes of compounds comprise lichen secondary metabolites, such as aliphatic acids, sugar alcohols, quinines, chromones, xanthones, dibenzofurans, depsides, depsidones, depsones, terpenoids, steroids, carotenoids, and diphenyl ethers.

Application of Lichens

In addition to being used as food and cosmetics, lichens have long been used in folk medicine to cure a variety of ailments, including eczema and respiratory, pulmonary, and arthritic illnesses[29]. The use of several lichens is covered in the following sections.

Activity on human cancer cell

Four human cancer cell lines are cytotoxicly affected by extracts of lichen species that arefoliaceous or drusy[30]. All four chronic myelogenous leukemia cell lines, cK-562, glioblastoma cellline U251, prostate cancer cell line DU145, and breast adenocarcinoma cell line MCF7 are examples of cancer cell lines. Among these, extracts of *Cladonia convoluta, Cladonia rangiformis, Parmelia caperata, Platismatia glauca*, and *Ramalina cuspidata* showed noteworthyeffects, particularly on human cancer cell lines.

Antioxidants

Free radicals are crucial for many chemical reactions that occur inside cells, but they can also have negative consequences that might harm cells. The search for natural antioxidant alternatives is important because synthetic antioxidants are frequently harmful. It has been discovered that lichens contain a range of secondary lichen chemicals, which are potent antioxidants [31]. Antioxidants can obstruct the oxidation process by interacting with free radicals, chelating unbound catalytic metals, and acting as oxygen scavengers. Phenolic antioxidants serve as metal chelators and free radical terminators. Lichens produce antioxidants that protect food from oxidative lipid degradation and maintain food quality. Consequently, antioxidants are crucial in the food sector[32]. In the food industry, synthetic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and tert-butylhydroquinone (TBHQ) are used. However, BHA and BHT have also been linked to carcinogenesis and liver damage. In Turkish traditional medicine, *Cetraria islandica* is well known for treating ailments, such as hemorrhoids, pneumonia, dysentery, and tuberculosis. The main physiologically active secondary metabolites of C. *islandica* are thought to belactone, fumarprotocetric acid, and -orcinol depsidone. High antimicrobial activity was demonstrated by the secondary metabolites from C. According to the antioxidant activity of *C. islandica* aqueous extract enhanced with increasing extract concentrations (from 50 to 500 g) applied to linoleic acid emulsion[33].

Classification of Lichen

Lichens are a unique class of organisms that depend on symbiosis for survival[34]. This cooperativelink between fungi (mycobiont) and green algae or cyanobacteria[35] (photobionts)[36]. In addition, lichens contain related bacteria[37], yeasts [38], and other fungi [39], which together create a varietyof complicated relationships. The intriguing new growth forms of lichens that are produced as a result of this symbiotic mode of existence are unlike those of any other closely related species, their known forebears, or even their solitary bionts[40]. Lichens are widely distributed and can be found growingon a variety of surfaces, including rocks, walls, gravestones, roofs, tree bark, soil, etc. They are referredto as the group of terrestrial organisms for this reason. These creatures, which are found in symbiotic relationships between an alga and a fungus partner, different colors, shapes, sizes and forms. Lichens were discovered some 400 million years ago, according to records. For growth and development, these terrestrial creatures need a clean environment with enough air[41]. Lichens can also be found on gravestones, buildings, and many other surfaces in addition to rocks. During specific occasions, theseorganisms are also seen on tiny branchlets, as flat, leaf-like structures, as particles that resemble powder, and in a variety of different shapes. Lichens are divided into various categories based on theirdistinguishing characteristics. *Crustaceae Lichens*: Crustose lichens lack distinct lobes and are flat and thin. They are frequently found tightly clinging to stones, boulders, barks, and tree trunks. The two outstanding specimens of crustose lichens are *Haematomma puniceum* and *Graphic scripta*[42]. Foliose Lichens: Compared to other lichen types, foliose lichens are more appealing. They have a flatshape, are large, smooth, and resemble leaves; they are frequently wrinkled and twisted. It has a clearupper surface and a bottom surface. With the aid of the rhizoid, this species of lichen is typically discovered adhering to rocks and twigs[43]. Among them are Cetraria, Cluiudhuria, Parmelia, and Xanthoria are example of a foliose lichens[44]. Fruticose lichens: These are thin, widely branching lichens are the most significant types[45]. The fruticose lichens are larger, more appealing growths that protrude from rocks, leaves, and tree branches. Ramalina and Cladonia in the woods. CorticolousLichens: These lichens grow on tree bark. Saxicolous: These lichens grow on rocks or stones. Marine:These lichens can be seen growing on siliceous rocks close to the seashores[46]. Freshwater: Lichensof this type can be found growing on the hard siliceous rocks in freshwater[47]. Terricolous: These types of lichens are found growing on the soil, therefore also called the terrestrial lichens[48].

Based on their internal structure

- Heteromerous lichens
- Homoiomerous lichens[49]

Based on their fungal partner

- Ascolichens
- Basidiolichens
- Hymenolichens[50]

Based on the fungal components present

- Ascolichene: Its fungal partner is belonging to Ascomycetes.
- Basidiolichens: Its fungal partner is belonging to Basidiomycetes[51].
- Deuterolichens: Its fungal partner is belonging to Deuteromycetes and they are sterile and it does not produce spores.

Based on the external form or thallus organization

- Crustose lichens: They are thin and flat lichen and it can be found on the surface and itcan be removed by crumbling the surface[52].

Eg-Lecanora, Graphis, Haematomma

- Foliose lichens: It has lobes and it is dorsiventrally flattened, leafy lichens. It is attached to sumstratum by hairy rhizoids known as rhizines[53].

Eg-Collema, Peltigera, Parmelia.

- Fruticose lichens: It is also known as s shrubby lichens. These are having cylindrical, branched and erect thallus. It is attached to substratum by basal mucilaginous disc[54].Eg-Usnea, Alectoria, Cladonia

Identification of Lichen

Usnea subfloridana

It is found on trees, twigs and rocks. Tolerant to air pollution. Growth type is fruticose. It has bushy thallus with many branches [55]. At the base of the main stem, it is black in colour[56]. Remaining is yellow-green or grey-green in colour.

Oakmoss

It is grey-green coloured foliose lichen and its growth type is fruticose[57]. It is found ascrossing on wood such as branches, fences, tree trunks and twigs. It is used in perfumery[58].

Common greenshield lichen

It is found on the bark of trees and on the rocks[59]. It looks pale grey when it is dried andyellow green in wet.

Hammered shield lichen

It is grey-white in colour with brown tips. It is also called as powdered shield,waxpaperlichen[60].

Monks'hood lichen

It is used for monitoring the air pollution. It has moderate sensitivity to sulphur dioxide and heavy metals[61]. It has grey-green thallus with white powdery reproductive structure on theunderside of outer edges.

Dog lichen

It is found on soil, woodlands and in sandy places[62].

Umbilicaria cylindrica

It has grey-brown upper surface and dark grey-black spots. It is commonly found in NorthernScotland[63].

Sea ivory

It is fruticose species. It can be seen on rocks and walls on the coastline. It is tolerant of saltspray[64].

Importance of Lichen

Lichen is used for the treatment of eczema, respiratory diseases, pulmonary diseases and also in arthritis[65].

Activity on human cancer cell lines

Fruticulous lichen species has cytotoxic effect on human cancer cell lines[66]. The four cancer cell lines are Ck-562: chronic myelogenous leukaemia, the U251: glioblastoma, the DU145: prostate carcinoma and the MCF7: breast adenocarcinoma[67]. The extract from Cladonia convolute, *Cladonia rangiformis*, *Parmelia caperata* are having activities on human cancer cell lines[68].

Antioxidant

Lichens contain different type of secondary lichen substances having antioxidant activities[69]. Antioxidant interfere with oxidation process by reacting with free radicals. It chelates free catalytic metals and also it acts as oxygen scavengers [70]. The antioxidants produced by lichens are used to preserve food qualiy from deterioration of lipid. *Ceteria islandica* is Turkish folk medicine used for the treatment of hemorrhoids, bronchitis, dysentery, and tuberculosis[71].

Used as food

Oakmoss lichen are used to make jelly. *Cladonia rangiferina* used to make brandy[72].

Lichens as dyes

Lichens are widely used as the source of valuable purple dye[73]. Dyes are extracted by boilingthe lichen in water and also by fermenting the lichens in ammonia[74]. Wolf lichen is the widely used lichen dye among the native people of North America[75].

Cosmetics and perfumes

Lichen[76] Evernia prunastri is used to make perfume[77]. The thallus of Usnea has the power for retaining scent[78]. So, it is widely used in perfumery[79].

Potential Medicinal Activities of Lichens[80]

Lichens are symbiotic organisms made up of cyanobacteria, fungi, and algae[81]. Fungi that generate lichens produce a wide range of secondary metabolites, many of which are distinctive[82]. A total of about 1050 lichen compounds, including those present in cultures, have been identified thanks to advancements in analytical tools and experimental methodologies[83]. Lichen secondary chemicals play a variety of putative biological activities in addition to their position in chemotaxonomyand systematics[84]. These roles include photoprotection against strong radiation as well as, antiviral,anticancer, antibacterial, Lichens, which were initially discovered in the planet's most adverse environments, have numerous medical applications that researchers might take use of secondary metabolites are also known as lichen acids since they are created by mycobionts and spread throughoutthe environment[85]. In the form of crystals or amorphous material on the surface of lichens[86]. Lichen acids possess a variety of biological properties, including antioxidant, anticancer, enzyme inhibitory, antiviral, antifungal, antidiabetic, allelopathy, antipyretic, crop growth inhibitory, cytotoxic, anti-hepatotoxic, and antiproliferative qualities[87]. Secondary metabolites are typically referred to as lichen acids because they are produced by mycobionts and disperse over the surface of lichens as amorphous or crystalline. Lichen acids include various antiherbivore, and antioxidant action.

Anti-oxidant activity

Pharmacological hobby of lichens lies of their potential to produce bioactive secondarymetabolites, being maximum of them phenolic compounds with reactive hydroxyl companies that confer antioxidant potential via numerous mechanisms[88]. Lichens appear like a promising supply of phenolic compounds within the discovery of natural product exerting antioxidant activity. Lichens were discovered to incorporate an expansion of secondary lichen substance with robust antioxidant hobby[89]. Those are materials have high potential to scavenge poisonous loose radicals because of their phenolic organization. A few depsides, like atranorin (isolated from Placopsis sp) and divaricatic acid (isolated from *Protousnea malacea*), as well as depsidones, such pannarin (isolated from Psoroma pallidum), have antioxidant properties. All those secondary compounds prevented betacarotene and auto-oxidation in rat brain homogenate, but depsidones were shown to be more potent [90]. Observed that both sphaerophorin (depside)and pannarin (depsidone) inhibited superoxide anion formation *in vitro*, pannarin being extra green[91]. Phenolic antioxidant feature as free radical terminatory and steel chelators the antioxidant produced by means of lichens can be used to keep foodsatisfactory from oxidative deterioration of lipid[92]. One of the distinctive bioactivities of lichens is anti-oxidant activity, which is mostly caused by secondary compounds containing phenolic devices. The most often used antioxidants include those produced synthetically, such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), tertbutylhydroquinone (TBHQ), and propyl gallate (PG)[93]. Lichen extracts include a wide variety of antioxidant, which changed into confirmed in man research, loose radical scavenging by DPPH become considered, and in some of them, the discount inelectricity or superoxide anion scavenging hobby were additionally tested.

Table 1: Antioxidant activity of lichen secondary metabolites

Lichen name	Bioactive molecule	*In-vitro* and *In-vivo* anticancer method	Year of report
Lecanora atra	Atranorin	*In-vitro*- microculturetetrazolam test (MTT) *In-vivo*- using male BALB/c mice	2011
U.aurantiaca	Salazinic acid	*In-vitro*- MTT method *In-vivo*- using Albino wistar rats.	2019
Flavocetraria cucullata	Usnic acid	*In-vitro*- MTT method *In-vivo*- using Swiss albino mice	2014

ANTI TUMOUR ACTIVITY

The antitumor potential of several lichen compounds has been partially investigated. It was discovered that the dibenzofuran (--)-usnic acid, which has antitumor effects against Lewis Lung cancer and P388 leukaemia, is involved in mitotic inhibition and apoptosis induction[94]. Protolichesterinic acid, a derivative of butyrolactone, has been demonstrated to be effective as an antiproliferative againstEhrlich solid tumour and leukaemia cells K-562 (IC50 14 20 mg/ml).New lichen secondary metabolitesthat exhibit cytotoxic activity against tumour cell lines, original N-containing complex structures (scabrosin esters) isolated from *Xanthoparmelia scabrosa* (IC_{50}=0.27µM, p-815),an unusual indanone naphthopyrone euplectin from *Flavoparmelia euplecta* (IC_{50}=0.58µM ,P-815), and a naphthazarin - derived dimer (hybocarpone) isolated from a mycobiant culture of *Lecanora bybocarpa* (IC_{50}=1Nm, MCF-7), have been recently described. A number of prediction studies were conducted on extracts from lichens from different nations.

Table 2: Anticancer activity of lichen secondary metabolites

Lichen name	Bioactive molecule	*In-vitro* and *In-vivo* anticancer method	Year of report
Lecanora atra	Atranorin	*In-vitro*- microculturetetrazolam test (MTT) *In-vivo*- using male BALB/c mice	2011
U.aurantiaca	Salazinic acid	*In-vitro*- MTT method *In-vivo*- using Albino wistar rats.	2019
Flavocetraria cucullate	Usnic acid	*In-vitro*- MTT method *In-vivo*- using Swiss albino mice	2014

Table 3: Antiviral activity of lichen secondary metabolites

Lichen name	Bioactive molecule	Antiviral activity (Name of Virus)	Year of report
Roccella montagnei	Orcinol	Anti-herpes simplex virus-1	2023
Parmelia perlata	Usnic acid	Respiratory syncytial virus type 1 RSV	2009
Ramalina Farinacea	Psoromic acid	Herps simplex virus typr 1	2019

Antiviral activity

The secondary metabolites usnic acid and parietin are purified using chromatographic methods using the *Teloschistes chrysophthalmus* extract. Purified products of usnic acid and parietin were utilised, respectively, to exert virucidal and antiviral effects on the Junin and *Tacaribe arena* viruses. To check the activity against the traits that render the virus inactive, the experiment (virucidal assay) was carried out directly on the virus nucleus. Seventeen depsides and depsidones have been examined for their inhibitory activity against HIV integrase and pharmacophores derived from virsenic acid allowed selection of various potent inhibitors[95].

Additionally, it was discovered that the butyrolactone, protolichesterinic acid, isolated from *Centraria islandica*, inhibits HIV-RT. Since four depsides, especially (+)-usnic acid, were proven to be effective against EB Vactivation, they could make excellent candidates for antitumor promoters.

ANTIFUNGAL ACTIVITY

Numerous scientists have examined the antifungal activity of extracts and secondary metabolites derived from lichen thalli against various species of dermatophytes, including *Epidermophyton floccosum*, which causes smooth skin mycosis, *Microsporum canis, M. audouinii*, *M. nanum*, and *M. gypseum*, which causes mycosis of the scalp and hairy skin. *Trichophyton rubrum, T. mentagrophytes [footfungus], T. tonsurans, and T. violetum* [hairy and smooth skin mycoses]. Additionally, the Clinical and Laboratory Standards Institute has given a standard procedure for cultivating and evaluating the activity of lichen compounds against dermatophytes[96].

Extracts of lichen are used to combat Fusarium species of mould. Lichen extracts from 51corticolous, terrecolous, and saxicolous lichen species were collected, and secondary chemicals were tested against a variety of fungi, including Fusarium acuminatum, *F. avenacuem, F. udum, F. solani,* and *F. oxysporum*. The best antifungal activity was demonstrated by secondary metabolites such as 2-hydroxy -4-methoxy-3,6-dimethylbenzoic acid, atranorin, Lecanoric, and (+)usnic acids. These sportsmight try to compete with fungicides' ability, such fucytosine and fuconozole. Statistics from original studies revealed that lichen extracts have powerful antifungal properties.

The pathogenic fungi *Fusarium oxysporum* and *F. avenacuem* were susceptible to the antifungal activity of secondary lichen metabolites isolated using acetone and ethanol from *Cetraria islandica, Cladonia mitis, C. rangiferina, Pseudevernia furfuracea,* and *usnea dasopoga*. Fumarprotocetraric, Salazinic, and usnic acids, as well as atranorin, were the most effective extracts atpreventing the growth of fungus mycelia. Alcoholic extracts from *Clodonia mitis* and *Cetraria rangiferina* both significantly reduced the growth of the two Fusarium representatives (*Fusarium oxysporum* and *F. avenacuem*), more so than extracts from the combined thalli of the two terricolous taxa. The secondary metabolites of lichen displayed a stronger inhibitory capacity, demonstrating theirability to compete with widely used antifungal drugs.

Anti-Hepatotoxic activity

The primary human health issue brought on by excessive alcohol intake is liver cirrhosis. Alcohol consumption causes hepatocytes to produce more NADH/NADP, which prevents mitochondrial fatty acid -oxidation and increases lipid transfer from the small intestine to the liver, leading to abnormal fat accumulation[97]. The use of reindeer lichen (*Cladonia rangiferina*) for the treatment of fever, liver conditions, arthritis, convulsions, TB, and constipation has already been documented. Alcohol-related liver and tissue damage can be lessened by using the reindeer lichen extract. Potential anti-cancer. The pharmaceutical industry now places a great deal of emphasis onsecondary lichen metabolites; cervical cancer therapy sings them follow the Collemataceae family of lichens, which comprises the active components bianthraquinone, colleflaccinosides, and glycosides, is made up of several lichens, *Collema flaccidum* in particular. According to previous studies, the acetone extract from *Usnea barbata* (usnic acid) lichen possesses potent anti-cancer action against human melanoma and human colon carcinoma cell lines with IC_{50} values of 12.72 and 15.66 g/ml. Another study found that the active component usnic acid and its derivative usen amines, which are extracted from the lichen Us- nea longissimi, can induce the death of HepG2 cells[98]. According to a different study, HCT-116 and SW-480 cell lines are most sensitive to the ethyl acetate and acetone extracts of the lichens *Pseudevernia furfuracea* and *Platismatia glauca*, respectively (IC_{50}=21.21.3) and 51.30.8g/mL).

Table 4: Antifungal activity of lichen secondary metabolites

Lichen name	Bioactive molecule	*In-vitro* and *In-vivo* anticancer method	Year of report
Variospora dolomiticola	Atranorin	*In-vitro*- microculture tetrazolam test (MTT) *In-vivo*- using male BALB/c mice	2015
Caloplaca lacteal	Salazinic acid	*In-vitro*- MTT method *In-vivo*- using Albino wistar rats.	2016
Flavoplaca citrina	Usnic acid	*In-vitro*- MTT method *In-vivo*- using Swiss albino mice	2019

Table 5: Anti hepatotoxic activity of lichen secondary metabolites

Lichen name	Bioactive molecule	*In-vitro* and *In-vivo* anticancer method	Year of report
Reindeer lichen	Atranorin	*In-vitro*- microculturetetrazolam test (MTT) *In-vivo*- using male BALB/c mic	2012
Lichen rangiferinus	Salazinic acid	*In-vitro*- MTT method *In-vivo*- using Albino wistar rats	2014

ENZYME INHIBITORY ACTIVITY

Lichen acids mainly atranorin, evernic, physodic and usnic acids are powerful inhibitor of some metabolicenzymes. Some lichen extracts and chemicals have also been shown to inhibitlipoxygenase. It is possible that the inhibition of prostaglandin biosynthesis and the inhibition of leukotriene B4 biosynthesis are related to some lichen compounds' anti-inflammatory, analgesic, and antipyretic properties, as well as their local anaesthetic effect[99].

Tyrosinase and xanthine oxidase inhibition by extracts of natural or cultured lichen tissuewas found to be superior to the assay standards in some cases. Tyrosinase is involved in thebiosynthesis of melanin. Tyrosinase is a crucial enzyme in mammalian cells to prevent overproductionof the melanin pigment. Melanin has the ability to neutralise reactive oxygen species (ROS) in animalskin as well as absorb UV radiation to protect the skin. As a result, it is employed in the healthcare and cosmetics. Therefore, it is necessary to suppress the production of excess tyrosinase enzyme[100]. Some lichens have the ability to stop tyrosinase from doing its job. Tyrosinase inhibitory action was demonstrated to occur significantly in lichens including *Graphisas samensis, Graphina multistriata, Graphis Phaeographop sisindica*, and *Graphis nakanishiana. Usnea longissima* and *Umbilicaria esculenta* are two edible and therapeutic lichens that have been reported to have tyrosinase inhibition properties[101].

Table 6: Enzyme inhibitory activity of lichen secondary metabolites

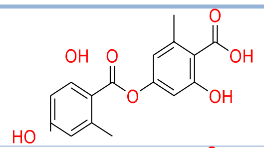
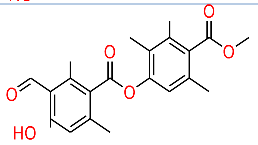
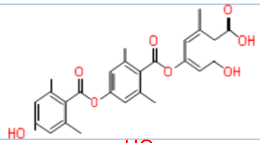
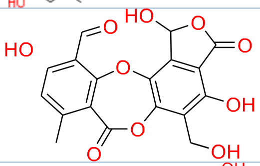
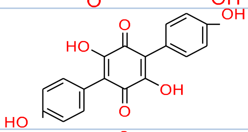
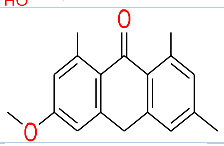
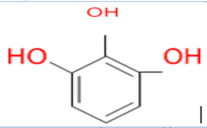
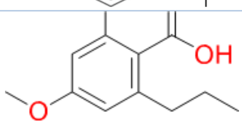
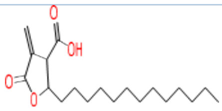
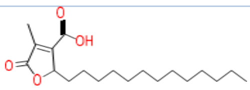
Lichen name	Bioactive molecule	*In-vitro* and *In-vivo* anticancer method	Year of report
Caloplaca biatorina	Atranorin	*In-vitro*- microculturetetrazolam test (MTT) *In-vivo*- using male BALB/c mice	2010
Physcia aipolia	Salazinic acid	*In-vitro*- MTT method *In-vivo*- using Albino wistar rats.	2014
Flavoparmelia caperata	Usnic acid	*In-vitro*- MTT method *In-vivo*- using Swiss albino mice	2015

CONCLUSION

The review has offered significant information on the origin, variations, uses, and applications of lichen-produced secondary metabolites. These secondary metabolites have a wide range of uses in medicine, therapy, food, fragrance, and coloring industries. Lichens have become increasingly important in addressing environmental issues caused by air pollution and global warming, as they possess environmentally friendly properties that can help mitigate these problems. Therefore, it is our responsibility to preserve and protect the invaluable lichen species to maintain the balance ofnature. Lichens not only serve as a significant component of the natural world but can also be utilized as a food source for humans with proper preparation. They play a crucial role in the preservation and distribution of nutrients, such as carbon, nitrogen, trace elements, soil composition, and rock weathering, on a global scale. Lichens have the ability to absorb a wide range of chemical substances

from their environment, making them potential sources of various compounds. Some lichen species, such as *Cetraria nivalis*, *Cetraria islandica*, and *Cladonia arbuscula*, have been found to have high invitro digestibility, making them suitable for consumption by humans. Additionally, the review highlights that lichen bioprospecting research has focused on species with a higher likelihood of containing valuable medicinal compounds. To developing new culture media to enhance thegrowth of photobiont and mycobiont in-vitro may result in increased biomass production of medicinally important secondary metabolites. Cultured lichens can serve as a sustainable source for the production of these compounds, ensuring a more consistent and reliable supply for future research and development. Overall, lichens hold great potential in medicinal fields, and their preservation and sustainable utilization are crucial for both environmental and human well-being. Further exploration and research in lichen bioprospecting can lead to the discovery of novel compounds and applications that may contribute to the advancement of pharmaceutical applications.

Table 7: Structure and uses

Name	Structure	Source and uses	Molecular formula	Molecular weight	Year	Reference
Lecanoric Acid		*Dimelaena oreina*, *Umbilicaria angulate*. Used as antibacterial and antifungal	$C_{16}H_{14}O_{7}$	318.281 g/mol	1996	23
Atranorin		Candelaria, concolor, elatina. Used as Analgesic, Anti-inflammatory, Antibacterial, Antifungal, Cytotoxic, Anti-oxidant, Anti-viral and immunomodulatory properties	$C_{19}H_{18}O_{8}$	374.345 g/mol	1997	32
Gyrophoric Acid		*Dimelaena oreina*, *Umbilicaria angulate*. Used as Anti-cancer.	$C_{24}H_{20}O_{10}$	468.4 g/mol	1999	34
Salazinic Acid		*Hypotrachyna cirrhata*, *Ramalina siliquosa* and *Cetrelia cetrarioides*. Used as Anti- oxidant and Photo protectant.	$C_{18}H_{12}O_{10}$	388.3g/mol	1999	41
Atromentin		*Hydnellum diabolus*, *Omphalotus subilludens* Used as Anti- bacterial, Anti-coagulant and smooth muscle stimulant.	$C_{18}H_{12}O_{6}$	324.28 g/mol	2003	46
Physcion		*Rumex dentatus, Ageratina altissima*. Used as laxative, Hepatoprotective, anti- inflammatory, anti-microbial and anti-proliferative effects.	$C_{16}H_{12}O_{5}$	284.26 g/mol	2005	51
Pyrogallol		*Gunnera perpensa*, Nigella. Used as cytotoxicand antioxidant.	$C_{6}H_{3}OH$	126.11 g/mol	2011	81
Divaricatinic acid		*Parmotrema tinctorum, Evernia divaricate, Evernia esorediosa* and another organism. Used as anti-oxidant and anti-cancer.	$C_{11}H_{14}O_{4}$	210.226g/ mol	2014	95
(+)- Protoli chesterinic acid		Found in Rhizoplaca, *Cetraria aculeata*. Used as anti-bacterial, anti-microbial.	$C_{19}H_{32}O_{4}$	324.5g/mol	2015	98
(+)- Lichesterinic Acid		Found in Rhizoplaca and *Cetraris aculeata*. Used as anti-fungal and anti-bacterial activity.	$C_{19}H_{32}O_{4}$	324.5g/mol	2017	101

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Ascaso, C, and Wierzchos, J. Structural aspects of the lichen-rock interface using backscattered electron imaging. Botanica Acta.1994; 107(2): 251- 256.

2. Bézivin C, Tomasi, S, Lohézic-Le Dévéhat, F, and Boustie J. Cytotoxic activity of some lichen extracts on murine and human cancer cell lines Phytomed. 2003;10(6):499-503.

3. Burkholder, P.R, Evans, A.W, and et al. Antibiotic Activity of Lichens. Proceedings on National Academic Science. USA.1944; 30(9): 250-255.

4. Carcia-Rowe J, Saiz-Jimenez, C. Lichens, and bryophytes as agents of deterioration of building materials in Spanish cathedrals. Int Biodeterior. 1991; 28(4): 151–163.

5. Cardarelli M, Serino G, and et al. Antimitotic effects of usnic acid on different biological systems.Cell Mol Life Sci. 1997; 53(7): 667–672.

6. Fournet, A, Ferreira, M.E, and et al. Photoprotector capacity of lichen. Comp Biochem Physiol Pharmacol Toxicol Endocrinol.1997; 116(5): 51–54.

7. Grice, H C. Safety Evaluation of butylated Hydroxytoluene (BHT) in the Liver, Lung and Gastrointestinal Tract. Food Chem. Toxicol. 1986;24(1): 1127–1130.

8. Grynkiewicz M, Polkowska, Z,and Namiesnik, J. Determination of polycyclic aromatic hydrocarbons in bulk precipitation and runoff waters in an urban region (Poland). Atmos. Environ. 2002; 36(4): 361- 369.

9. Gülçin, I, Oktay, M, Küfrevioğlu, O.I. and Aslan, A. Determination of antioxidant activity of lichen *Cetraria islandica* (L). Ach. J Ethnopharmacol.2002; 79(3): 325-9.

10. Gauslaa Y. Rain dew and humid air as drivers of morphology function and spatial distribution in epiphytic lichens. The Lichenologist 2014; 46(6): 1-16.

11. Benítez Á, Prieto M, González Y, Aragón G. Effects of tropical montane forest disturbance on*Epiphytic macrolichens*. Science of the Total Environment 2012; 441(4): 169- 75.

12. Bates ST, Cropsey GW, Caporaso JG, Knight R, Fierer N. Bacterial communities associated withthe lichen symbiosis. Appl Environ Microbiol 2011; 77(5): 1309-14.

13. Kappen L, Some aspects of the great success of lichens in Antarctica. Antarctic Science 2000;12(2): 314-24.

14. Schlensog M, Pannewitz S, Green T, Schroeter B. Metabolic recovery of continental antarcticcryptogams after winter. Polar biology 2004; 27(3): 399-408.

15. Kappen L, Schroeter B, Scheidegger C, Sommerkorn M, Hestmark G. Cold resistance andmetabolic activity of lichens below 0°C. Advances in Space Research 1996; 18(1): 119-28.

16. Richardson DH. Reflections on lichenology achievements over the last 40 years and challengesfor the future. Canadian Journal of Botany. 2002; 80(7): 101-113.

17. Parasyri A, Papazi A, Stamatis N et al. Lichen as MicroEcosystem Extremophilic Behavior with Astrobiotechnological Applications. Astrobiology 2018; 18(3): 1528-42.

18. Robinson SA, Wasley J, Tobin AK. Living on the edge– plants and global change in continental and maritime Antarctica. Global Change Biology. 2003; 9(4): 1681-717.

19. Neamati N, Hong, H, Mazumder A, Wang S, and et al. Depsides and depsidones as inhibitors ofHIV-1 integrase: discovery of novel inhibitors through 3D database searching. J. Med. Chem.1997; 40(5): 942–951.

20. Pawlik-Skowron´ ska, B, Wójciak H, and Skowron´ ski T. Polynuclear aromatic hydrocarbons, phenols, and trace metals in selected soil profiles and plant bioindicators in the Holy Cross Mountains. Pol. J. Ecol.2007; 56(8): 195–207.

21. Kinghorn, A.D, Pezzuto, J.M, and etal. Mechanistic evaluation of new plant-derived compoundsthat inhibit HIV-1 reverse transcriptase. J. Natural Prod. (Lloydia). 1995;58(6): 1024–1031.

22. Periera E.C, Nascimento, S.C. Analysis of *Usnea fasciata* crude extracts with antineoplastic activity. Tokai J. Exp. Clin. Med. 1994 ;19(5): 47–52.

23. Proksa B, and Proksova, A. Lichens metabolites. Usnic acid and its biological activity. Farm. Obz. 1999;68(4):139–143.

24. Richardson, D.H.S. Medicinal and other Economic aspects of lichens, in CRC handbook of lichenology, Galun, M., (Ed.) CRC press, Boca Raton, FL. 1988;1(1): 93-108.

25. Sarret G, Manceau A, and et al. Molecular mechanisms of Pb and Zn hyperaccumulation and tolerance in lichens. Environ. Sci. Technol. 1998;32(4): 3325– 3330.

26. Shahidi Fand Wanasundara. P.K.J.P.D. Phenolic antioxidants. Sci. Nutr. 1992;32(4): 67–103.

27. Lucking, R Hodkinson, B.P, Leavitt, S.D. The classification of lichenized fungi in the Ascomycota and Basidiomycota-Approaching one thousand genera. Bryologist 2016; 119(8): 361– 416.

28. Grube, M. Cernava, T, Soh and et al. Exploring functional contexts of symbiotic sustain within lichen-associated bacteria by comparative omics. ISME J. 2015; 9(2): 412–424.

29. Spribille, T. Tuovinen, and et al. Basidiomycete yeasts in the cortex of ascomycete macrolichens.Stabentheiner, E. Toome Science 2016; 353(6): 488–492.

30. Muggia, L. Kopun, T. Grube, M. Effects of Growth Media on the Diversity of Culturable Fungi from Lichens. Molecules 2017; 22(8): 824-828.

31. Ahmadjian, V. The lichen photobiont—What can it tell us about lichen systematics. Bryologist 1993; 96(2):310–313.

32. Ascaso, C. and Wierzchos, J. Structural aspects of the lichen-rock interface using backscattered electron imaging. Botanica Acta.1994; 107(4):251- 256.

33. Bézivin C, Tomasi, Cytotoxic activity of some lichen extracts on murine and human cancer cell lines. Phytomed.2003; 10(6):499-503.

34. Burkholder, P.R. Evans, A.W. McVeigh, I. and Thornton, H.K. Antibiotic Activity of Lichens. Proceedings on National Academic Science, USA,1944; 30(9): 250-255.

35. Carcia-Rowe, J. Saiz-Jimenez, C. Lichens and bryophytes as agents of deterioration of building materials in Spanish cathedrals. Int. Biodeterior. 1991;28(3): 151–163.

36. Cardarelli M., Serino, G. and et al Antimitotic effects of usnic acid on different biological systems.Cell. Mol. Life Sci.1997; 53(6): 667–672.

37. Fournet, A. Ferreira and et al. Photoprotector capacity of lichen. Comp. Biochem. Physiol. Pharmacol. Toxicol. Endocrinol. 1997;116(5): 51–54.

38. Grice H.C. Safety Evaluation of Bbutylated Hydroxytoluene (BHT) in the Liver. Lung and Gastrointestinal Tract. Food Chem. Toxicol. 1986; 24(1): 1127–1130.

39. Grynkiewicz M, Polkowska, Z, and et al. Determination of polycyclic aromatic hydrocarbons in bulk precipitation and runoff waters in an urban region (Poland). Atmos. Environ.1984; 36(1): 361- 369.

40. Gülçin, I, Oktay, M., Küfrevioğlu and et al. Determination of antioxidant activity of lichen *Cetraria islandica* (L). Ach. J Ethnopharmacol. 2002; 79(3): 325-9.

41. Ogmundsdottir H M, Zoega G M, and et al. Pharmacol. 1998; 50(1); 107– 115.

42. Haawthorne S.B, Grabanski, C.B and et al. Comparisons of Soxhlet extraction, pressurized liquidextraction, supercritical fluid extraction and subcritical water extraction for environmental solids: recovery, selectivity and effects on sample matrix. Chromatogr. A. 2000; 892(50: 421-433.

43. Hidalgo M.E, Gonzales I, and et al. Boldine as a sunscreen. Cosmetic Toiletries.1998;113(4): 59–66.

44. Hidalgo M.E, Fernandez E, Quilhot, W. and Lissi, E. 1994. Antioxidant capacity of depsides anddepsidones. Phytochem.1994; 37(7): 1585–1587.

45. Huneck S. The significance of lichens and their metabolites. Naturwissenschaften. 1994;86(50):559–570.

46. Ingolfsdottir K, Hjalmarsdottir MA, Guojonsdottir, G.A, Brynjolfsdottir, A, Sigurdsson, A. and Steingrimsson, O. In vitro susceptibility of Helicobacter pylori to protolichesterinic acid from *Cetraria is landica*. Antimicrob. Agents Chemotherapy.1997; 41(6): 215- 217.

47. Jang Y.Y, Song, J.H, Shin, Y.K, Han, E.S. and Lee, C.S. Protective effect of boldine on oxidativemitochondrial damage in streptozotocin-induced diabetic rats. Pharmacol. Res.2000; 42(8): 361–371.

48. Joneson, S. and Lutzoni, F. Revisiting compatibility and thigmotropism in the lichen symbiosis. Symbiosis.2009; 47(8): 109–115.

49. Kipopoulou A.M, Ma˜noli, E. and Samara, C. Bioconcentration of Polycyclic Aromatic Hydrocarbons (PAHs) in vegetables grown in an industrial area. Environ. Poll.1999; 106(5): 369-380.

50. Kłos Andrzej, Rajfur Małgorzata, and et al . Heavy metal sorption in the lichen cation active layer.Bioelectrochem.2007; 71(1): 60- 65.

51. Kumar K.C. and Muller, K. Lichen metabolites. J. Nat. Prod.1999; 62(8): 821–823.

52. Lal, B. and Upreti, D.K. Ethnobotanically notes on three Indian lichens. Lichenologist.1995; 27(4): 77–79.

53. Larson, D.W. The absorption and release of water by lichens. In: Peveling, E. Ed., Progress and Problems in Lichenology in the Eighties. *Bibliothca lichenologica* Cramer, Berlin, 1987;25(7):351– 360.

54. Lawrey, J.D. Biological role of lichen. Bacillus subtilis, Proteus vulgaris, Aeromonassubstances. J. Bryol. 1986;89(2): 111-122.

55. Lawrey, J.D. Lichen secondary compounds: evidence for a correspondence betweenantiherbivore and antimicrobial function. J. Bryol. 1989;92(2): 326-328.

56. Neamati, N, Hong, and et al. Depsides and depsidones as inhibitors of HIV-1 integrase: discovery of novel inhibitors through 3D database searching. J. Med. Chem. 1997;40(9): 942–95.

57. Pawlik-Skowron´ ska, B, Wójciak, H. and Skowron´ ski, T. Polynuclear aromatic hydrocarbons,phenols, and trace metals in selected soil profiles and plant bioindicators in the Holy Cross Mountains. Pol. J. Ecol.2008; 56(5):195–207.

58. Pengsuparp, T, Cai, L,and et al. Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. J. Natural Prod. (Lloydia). 1995;58(5): 1024–1031.

59. Proksa B. and Proksova, A. Lichens metabolites. Usnic acid and its biological activity. Farm. Obz.1999; 68(3): 139–143.

60. Richardson, D.H.S. Medicinal and other Economic aspects of lichens, in CRC handbook oflichenology, Galun, M., (Ed.) CRC press, Boca Raton, FL. 1988;1(6): 93-108.

61. Yang Y, Bhosle SR, Yu YH et al. Tumidulin, a Lichen Secondary Metabolite, Decreases theStemness Potential of Colorectal Cancer Cells. Molecules 2018; 23(2): 2968.

62. Nguyen HX, Nguyen NT, Nguyen MHK et al. Tyrosinase inhibitory activity of flavonoids fromArtocarpus hetero-phyllous. Chemistry Central Journal 2016; 10(4): 1-6.

63. Fazio AT, Adler MT, Bertoni MD, Sepúlveda CS, Da-monte EB, Maier MS et al. Lichensecondary metabolites from the cultured lichen mycobionts of *Teloschistes chrysoph-thalmus* and *Ramalina celastri* and their antiviral activities. Zeitschrift für Naturforschung C 2007; 62(3): 543-9.

64. Oh JM, Kim YJ, Gang H-S, Han J, Ha H-H, Kim H et al. antimicrobial activity of divaricatic acid isolated from the lichen Evernia mesomorpha against Methicillin-Resistant *Staphylococcus aureus*. Molecules 2018; 23(2): 3068.

65. Ganesan A, Mahesh A, Sundararaj JP, Mani K, Ponnusamy P et al. Antihyperglycemic and anti- oxidant activity of various fraction of *Parmotrema hababianum* in streptozotocin-induced diabetic rat. Bangladesh Journal of Pharmacology 2016; 11(1): 935-9.

66. Goga M, Antreich SJ, Ba kor M, Weckwerth W, Lang I et al. Lichen secondary metabolites affect growth of Physcom-itrella patens by allelopathy. Protoplasma 2017; 254(3): 1307-15.

67. Shukla I, Azmi L, Gupta SS, Upreti DK, Rao CV et al. Amelioration of anti-hepatotoxic effect by *Lichen rangiferinus* against alcohol induced liver damage in rats. Journal of Ayurveda andintegrative medicine 2019; 10(4): 171-7.

68. Padhi S, Masi M, Panda SK et al. Antimicrobial secondary metabolites of an endolichenic *Aspergillus niger* isolated from lichen thallus of *Parmotrema ravum*. Natural product research 2019;13(1): 1-8.

69. Maurya IK, Singh S, Tewari R, Tripathi M, Upadhyay S, Joshi Y et al. antimicrobial activity of Bulbothrix setschwanen-sis (Zahlbr.) Hale lichen by cell wall disruption of *Staphy-lococcus aureus* and *Cryptococcus neoformans*. Microbial pathogenesis 2018; 115(2): 12-8.

70. Dailey R. N, Montgomery D. L, Ingram J. T, Siemion R, Vasquez M, and Raisbeck M. F et al. Toxicity of the lichen secondary metabolite (+)-usnic acid in domestic sheep. Vet. Pathol.2008; 45(3):19 – 25.

71. Esimone C. O, Grunwald T, Nworu C. S, Kuate S, Proksch P, and Überla K et al. Broad-spectrumantiviral fractions from the lichen *Ramalina farinacea* (L.) Ach. Chemotherapy2009; 55(2):119 – 126.

72. Halama P. and Van Haluwin C, Antifungal activ-ity of lichen extracts and lichenic acids. BioControl2004; 49(2): 95 – 107.

73. Hauck M, et al. Metal homeostasis in Hypogymniaphysodes is controlled by lichen substances. Environ. Pollut. 2008;153(2):304 – 308.

74. Hauck M, Willenbruch K, and Leuschner C et al. Lichen substances prevent lichens from nutrient deficiency. J. Chem. Ecol.2009; 35, 71 – 73.

75. Rankovic´ B. and Mišic´ M. Antifungal activity of extracts of the lichens Alectoria sarmentosa and *Cladonia rangiferina*. Mikol. Fitopatol.2007; 41(3):276 – 281.

76. Rankovic´ B. and Mišic´ M. The antimicrobial activity of the lichen substances of the lichens *Cladonia furcata, Ochrolechia androgyna, Parmelia caperata* and *Parmelia conspersa*. Biotechnol. Biotechnol. 2008; 22(2): 1013 – 1016.

77. Rankovic´ B, Mišic´ M, Sukdolak S et al. The antimicrobial activity of substances derived from the lichens Physcia aipolia, *Umbilicaria polyphylla, Parmelia caperata* and *Hypogymnia physodes*. World J. Microbiol. Biotechnol.2008 ;24(1): 1239 – 1242.

78. Schmeda-Hirschmann G, Tapia A, Lima B, Pertino M, Sortino M, Zacchino S, Rojas De Arias A, Feresin G. E et al. A new antifungal and antiprotozoal depside from the Andean lichen *Protousnea poeppigii*. Phytother. 2008. 22(2) 349 – 355.

79. Whiton J. C. and Lawrey J. D. Inhibition of *Cladonia cristatella* and *Sordaria fimicola* ascospore germination by lichen acids. 1982;85(3): 222 – 226.

80. Whiton J. C. and Lawrey J. D. Inhibition of crustose lichen spore germination by lichen acids. Bry-ologist,1984; 87(3): 42 – 43.

81. Halama P. and Van Haluwin C, Antifungal activity of lichen extracts and lichenic acids. BioControl 2004; 49(5): 95 – 107.

82. Rankovic´ B. and Mišic´ M. Antifungal activity of extracts of the

lichens *Alectoria sarmentosa* and *Cladonia rangiferina*. Mikol. 2007; 41(1): 276 – 281.

83. Plaza C, Salazar C, Plaza R. In vitro analysis of antibacte-rial and antifungal potential of lichen species of *Everniastrum cf vexans, Parmotrema blanquetianum, Parmotrema reticulatum* and *Peltigera laciniata*. MOJ Drug des Develop Ther 2018; 2(2): 126-35.

84. Resende DI, Pereira-Terra P, Inácio ÂS et al. Lichen xanthones as models for new antifungal agents. Molecules 2018; 23(1): 2617.

85. Yu X, Guo Q, Su G et al. Usnic acid derivatives with cytotoxic and antifungal activities from thelichen *Usnea longissima*. Journal of natural products 2016; 79(5): 1373-80.

86. Siddiqi KS, Rashid M, Rahman A, Husen A, Rehman S. Biogenic fabrication and characterization of silver nano-particles using aqueous-ethanolic extract of lichen (*Usnea longissima*) and their antimicrobial activity. Biomater Res. 2018; 22(2): 2-56.

87. Kalinowska, K, Gwozdz HA, Niezgoda PE, Roznicowanie Dermatofitōw z Rodzaju,et al.Trichophyton. Micol Lek 2009; 16(9): 171-177.

88. Kalinowska K, Gwozdz HA, Niezgoda PE, Rōznicowanie dermatofitōw z rodzaju, et al. Microsporum oraz Epidermophyton. Mikol Lek 2010; 17(5): 47-52.

89. Furmanek L, Czarnota P, Seaward MR, et al. A Review of the Potential of Fusarium Lichen Substances as Antifungal Agents: The Effects of Extracts and Lichen Secondary Metabolites on Fungi. Archives of Microbiology 2022;204(8): 523.

90. Tekiela A, Furmanek L, Andrusiewicz M, Bara G, Seaward MR, et al. Can Lichen Secondary Compounds Impact upon the Pathogenic Soil Fungi Fusarium Oxysporum and F. Avenaceum. Folia Cryptogamica 2021;58 (2):165-181.

91. Damonte EB, Coto CE. Treatment of arenavirus infections: from basic studies to the challenge of antiviral therapy. Adv Virus Res 2002; 58(2): 125-55.

92. Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. Emerging infectious diseases 2002; 8(5): 225-230.

93. Baraona E, Lieber CS et al. Effects of ethanol on lipid metabolism. Journal of lipid research 1979; 20(1): 289-315.

94. Scirpa P, Scambia G, Masciullo V et al. A zinc sulfate and usnic acid preparation used as post- surgical adjuvant therapy in genital lesions by Human Papillomavirus. Minerva Ginecol 1999; 51(2):255-60.

95. Ingólfsdóttir K, Kook Lee S, Bhat KP et al. Evaluation of selected lichens from Iceland for cancer chemopreventive and cytotoxic activity. Pharmaceutical biology 2000; 38(3): 313-317.

96. Zeytinoglu H, Incesu Z, Tuylu BA, Turk A, Barutca B. Determination of genotoxic, antigenotoxicand cytotoxic potential of the extract from lichen *Cetraria aculeata* (Schreb.) Fr. in vitro. PhytotherapyResearch 2008; 22(2): 118-23.

97. Legaz ME and Vicente C Endogenous inactivators of arginase, l-arginine decarboxylase and agmatine amidino hydrolase in Evernia prunastri thallus. Plant Physiology 1983;71(1):300 – 302.

98. Legaz ME, Vicente C, Pedrosa MM, et al. Binding of lichenphenolics to purified secrete1d arginase from the lichenEvernia prunastri. Journal of Biochemistry and MolecularBiology 2001; 34(2):194 – 200.

99. Ingo´lfsdo´ttir K, Bloomfield SF, Hylands PJ, et al. In vitro evaluation of the antimicrobial activityof lichen metabolites as potential preservatives. Antimicrobial Agents and Chemotherapy 1985; 28(2):289 –292.

100. Ingo´lfsdo´ttir K, Breu W, Huneck S, Gudjonsdottir GA, Wagner H, et al. In vitro inhibition of5-lipoxygenase by protolichesterinic acid from *Cetraria islandica*. Phytomedicine 1994;1(2):187 – 191.

101. Ingo´lfsdo´ttir K, Hja´lmarsdo´ttir MA, Guðjo´nsdo´ttir GA, Brynjolfs-do´ttir A, Sigurðsson A, Steingrı´msson O et al. In vitro susceptibility of Helicobacter pylori to protolichesterinic acid from *Cetraria islandica*. Antimicrobial Agents andChemotherapy1997; 41(2): 215 – 217.

102. Dailey R. N, Montgomery D. L, Ingram J. T, Siemion R, Vasquez M, and Raisbeck M. F. Toxicity of the lichen secondary metabolite (+)-usnic acid in domestic sheep. Vet. Pathol.2008; 45(3):19–25.

For any questions related to this article, please reach us at: globalresearchonline@rediffmail.com
New manuscripts for publication can be submitted at: submit@globalresearchonline.net and submit_ijpsrr@rediffmail.com