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Lichens: a novel and potential source as antimicrobials for human use

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Abstract
The use of lichens in medicine is based on the fact that they contain unique and varied biologically active substances, as antimicrobials. Since they are natural antibiotics, their metabolites exert a wide variety of biological actions including antimycotic, antiviral, anti-inflammatory, analgesic, antipyretic, antiproliferative, and cytotoxic effects, they are considered as potential drugs. They contain a variety of secondary metabolites with strong antioxidant activity. These are substances which have high ability to scavenge toxic free radicals due their phenolic groups. These manifold activities of lichen metabolites have now been recognized, and therefore their therapeutic potential have great impact in pharma industries. The present article discusses the importance of lichens in inhibiting various types of human pathogens in addition to their chemical composition and pharmacological activities.

Keywords: Lichen, antimicrobial, antihelmenthic, phenolic compounds, anthraquinones, dibenzofurans, depsides, depsidones, depsones, triterpenes, gamma lactones and pulvinic acid

INTRODUCTION

Lichens are symbiotic organisms which are composed of fungi and algae [1]. Lichens have been used in various fields, especially as a source of natural drugs in pharmaceutical industry and food supplement. Lichens are effective in the treatment of bronchitis, tuberculosis, and hemorrhoids. Chemical composition of lichens and their biological activities have long been investigated for anti-tumor, anti-viral, anti-herbivore activities. Moreover, pharmaceutical studies were also been carried out for antioxidant and anti-inflammatory activities of aqueous extracts of lichens [2].

Lichens have a varied chemistry and produce many polyketide derived compounds, including some, such as depsides and depsidones. Although lichens have been appreciated in traditional medicines, their value has largely been ignored by the modern pharmaceutical industry because of difficulties in establishing axenic cultures and conditions for rapid growth preclude their routine use in most conventional screening processes. Recently, PCR, genomic library construction and heterologous expression have provided an alternative approach to begin exploring the diversity of polyketide biosynthetic pathways in lichens. The techniques can be expanded to cover other pathway types and be integrated with conventional culture collection-based screening to provide a comprehensive search for novel chemical entities in the lichens [3].

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Chemistry:

The chemistry of about one third of all lichen species has been studied and upto 350 secondary metabolites have been characterised. The chemical structures of approximately 200 of them have been established. They produce extracellular products of relatively low molecular weight crystallized on the hyphal cell walls. Also these chemicals are usually insoluble in water and can be extracted into organic solvents. They amount to between 0.1 and 10% of the dry weight of the thallus, sometimes up to 30% [4].

Lichens produce a wide range of organic compounds that can be divided into two groups, called primary metabolites and secondary metabolites. Primary metabolites are proteins, lipids, carbohydrates, and other organic compounds that are essential to the lichen's metabolism and structure. Some of these metabolites are produced by the lichen's fungal partner and algal or cyanobacterial partners. Secondary metabolites are produced by the fungus alone and secreted onto the surface of hyphae either in amorphous forms or as crystals. If these substances are only found in lichens, then they are called lichen substances [5].

Lichens produce of a diverse array of secondary metabolites which differ in chemical structure and biological activity. These compounds have been used in taxonomic classification of lichen species and as sources of commercial products. The idea of some ecological role of lichen secondary metabolites dates back to the 19th century when these substances were first isolated. Backman (1890) and Zukal (1895) suggested that these substances might be important as chemical defenses to protect the plants against herbivores. Few recent studies have focused on this aspect and the

reports are largely anecdotal. Although several mammalian herbivores such as voles *(Microti-nae)* and squirrels *(Squiridae)* include lichens as a minor component in their diet, only reindeer and caribou use it extensively. Lichens are usually poorly digested by unadapted herbivores, but show relatively high digestibility in reindeer and caribou. This suggest that reindeer and caribou have specialized microorganisms in the rumen capable of handling lichen substances which are absent in other mammalian herbivores.

The secondary chemicals produced by lichens have attracted the attention of investigators for over 100 years, and information about their structure, biogenic origin and phylogenetic significance has accumulated steadily over this period. Lichens synthesize a great variety of secondary metabolites, many of which are unique. Developments in analytical techniques and experimental methods have resulted in the identification of large number lichen substances. Most known lichen substances are usnic acid, phenolic compounds, anthraquinones, dibenzofurans, depsides, depsidones, depsones, triterpenes, gamma lactones and pulvinic acid derivatives and have a multiple biological activity *viz*., antiviral, antibiotic, antitumor, allergenic, plant growth inhibitory and enzyme inhibitory.

The chemical composition and antimicrobial activity of the *Cladia aggregata* was tested, and obtained the chemicals like, barbatic acid, depside, was spectroscopically analyzed and tested against four *Staphylococcus aureus* multi-resistant strains. The structure of barbatic acid was confirmed through NMR and elemental analysis. Biochromatographic assays showed action of this compound, along with other substances contained in organic extracts, suggesting a synergic action, MIC assays placed barbatic acid in the same level of inhibition to other studied lichen substances [6].

Depsides, tridepsides, and tetradepsides consist of two, three, and four hydroxybenzoic acid residues linked by ester groups. These are the most numerous classes of secondary metabolites in lichens. More than one hundred lichen compounds are depsidones, which have an additional ether bond between aromatic rings. Depsidones in lichen are believed to arise by oxidative cyclisation of depsides. It has been found that depsidones are more efficient antioxidants than depsides. Further, a number of depsides have been found to possess important physiological properties. The antioxidant activity of some depsides, such as atranorin (isolated from *Placopsis* sp.) and divaricatic acid (isolated from *Protousnea malacea*), and depsidones, such as pannarin (isolated from *Psoroma pallidum*) and 1-chloropannarin (isolated from *Erioderma chilense*) have been evaluated. The higher efficiency of the depsidones could be related to a larger incorporation into lipidic microdomains. Depsidone and depside compounds such as pannarin, 10-chloropannarin, and sphaerophorin, tested in cell cultures of lymphocytes, were shown to have a higher cytotoxic effect than colchicines.The depsidones salazinic acid, stictic acid, and psoromic acid were the most apoptotic active derivatives among 15 lichen compounds evaluated on primary cultures of rat hepatocytes, screened the antimicrobial properties of acetone, methanol, and aqueous extracts of the lichens *Lasallia pustulata*, *Parmelia sulcata*, *Umbilicaria crustulosa*, and *Umbilicaria cylindrical* [7].

Lichens had to evolve diverse biosynthetic pathways to produce such complex arrays of secondary metabolites. The polyketide biosynthetic pathway appears to be responsible for most of the classes of lichen compounds, whereas pulvinic acids are shikimate derivatives, and the abundance of di- and triterpenoids found in lichens are formed via the mevalonate pathway. There are large numbers of studies reporting the isolation and characterization of individual components of lichen extracts. The ability of certain lichen metabolites to reduce the mutagenicity of chemical mutagens has attracted moderate attention. The depsidones, physodic and physodalic acid prevent the formation of reactive metabolites by blocking the oxidation systems present in the hepatic microsomal fraction. The para-depside gyrophoric and diffractaic acid also inhibited the proliferation of human keratinocyte cells. Ursolic acid inhibited the growth of human epidermoid carcinoma cells by affecting tyrosine kinase activity. The use of ursolic acid for the manufacture of an anticancer agent for suppressing metastasis has been patented. Screening of tissue cultures and thalli of lichens in search of some of the active lichen constituents for inhibition of tumor promoter induced Epstein-Barr virus activation [8]. *Ramalina hossei* contains Usnic acid, sekikaic acid aggregates, tannins and terpenoids and the extracts of this lichen could be used as antifungal against *Aspergillus niger* and *A.fumigatus*. Methanol extracts of *Ramalina pacifica* inhibited both Gram positive and Gram negative bacteria [9].

The antioxidative, antimicrobial and antiproliferative potentials of the methanol extracts of the lichen species *Parmelia sulcata, Flavoparmelia caperata, Evernia prunastri, Hypogymnia physodes* and *Cladonia foliacea* were evaluated. The phenolic and flavonoid content had the antioxidant capacities of the lichen extracts were determined by DPPH radicals scavenging. The highest antimicrobial activity among lichens was demonstrated by *Hypogymnia physodes* and *Cladonia foliacea*. The antiproliferative activity of the lichen extracts was explored on the colon cancer adenocarcinoma cell line further the methanol extracts of *Hypogymnia physodes* and *Cladonia foliacea* showed a better cytotoxic activity. All lichen species showed the ability to induce apoptosis of HCT-116 cells [10].

Antibacterial and antifungal activity of lichen:

Acetone, diethyl ether and ethanol extracts of the lichen *Cetraria aculeata* for their antimicrobial activity have been evaluated. The extracts were found active against *Escherichia coli*, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Proteus*

vulgaris, *Streptococcus faecalis*, *Bacillus cereus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Listeria monocytogenes.* However, no antimicrobial activity against the fungi was detected and it was determined that only protolichesterinic acid was having antimicrobial potential [11].

The lichen extract almost increased by two fold in the presence of the stock solution of the colloidal silver concentrate. Lichen has been shown to possess many antimicrobial as well as antiviral properties. In a related study, it has been reported that out of about fifteen indigenous Nigerian medicinal plants screened for antiviral activity by a vector-based assay technique, only extracts from the lichen *R. farinacea* exhibited potent antiviral activity against HIV-1 and adenovirus type 5. The ointment containing extract of lichen *Ramalina farinaceae* exhibited antimicrobial activities against *Escherichia coli*, *Salmonnella typhi*, *Aspergillus niger* and *Candida albicans* [12].

The aqueous and ethanol extracts prepared from some lichens species were evaluated for antibacterial activity against six standard strains (*Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Klebsiella pneumoniae, Staphylococcus aureus* and *Staphylococcus epidermidis*) and two environmental strains (*Aeromonas*). The aqueous and ethanol extracts showed a variable range of antibacterial activity to both standard strains and environmental strains. Similarly the aqueous extract of *Peltigera polydactyla* and the ethanol extract of the *Ramalina farinacea* exhibited potent antibacterial activities [13].

Antibacterial and antifungal activity of the acetone, methanol and aqueous extracts of the lichen *Lecanora frustulosa* and *Parmeliopsis hyperopta* and their divaricatic acid and zeorin constituents has been screened *in vitro* against the *Bacillus mycoides*, *Bacillus subtilis*, *Staphylococcus aureus*, *Enterobacter cloacae*, *Escerichia coli*, *Klebsiella pneumoniae*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Botrytis cinerea*, *Candida albicans*, *Fusarium oxysporum*, *Mucor mucedo*, *Paecilomyces variotii*, *Penicillium purpurescens*, *Penicillium verrucosum* and *Trichoderma harsianum.* Divaricatic acid and zeorin also showed strong activity against both bacteria and fungi [14]. This would perhaps indicate that the lichens would be used in the treatment of various diseases. In addition, antimicrobial activity of the acetone, diethyl ether and ethanol extracts of the lichen *Cetraria aculeata* tested against different pathogenic bacteria and fungi, it showed only with bacteria but not with fungi. In addition, *Roccella belangeriana* were extracted from different solvents like Acetone, methanol, diethylether, ethanol, ethyl acetate, petroleum ether, chloroform and aqueous extracts and tested against 12 bacterial strains. A maximum antibacterial activity was observed from chloroform extracts against *Enterococci* sp. and minimum activity was observed from ethyl acetate extract against *Klebsiella pneumoniae, Enterococci sp., Salmonella sp. and Shewanella* sp [15].

Hemagglutination and Hemolysis by Lichen Extracts:

Among the 22 species of lichens from 10 different genera possessed a hemagglutinin for one or more of human, sheep, horse, cow, rabbit, guinea pig, and chicken erythrocytes. These were active at very low dilution and were nonspecific. Sheep, horse, and cow erythrocytes were quite insensitive to the agglutinins from lichens. The inactivity of sheep cells indicated that the Forssman antigen was not important in this system. Rabbit and human erythrocytes were most regularly agglutinated, but no specificity for A, B, H, or Rh antigens were found [16].

Antioxidant activity of lichen:

The lichens have the potential to use as antioxidants. Four lichen species *Ramalina peruviana*, *Bulbothrix isidiza*, *Parmotrema tinctorum* and *Cladia aggregata* were extracted with acetone and methanol and evaluated for their antioxidant activity and total phenolic content. The highest radical scavenging activity was shown by acetone extract of *R. peruviana* and the lowest activity was exhibited by methanol extract of *C. aggregata*. Highest antioxidant activity by beta carotene bleaching assay was exhibited by acetone extract of *B. isidiza* followed by acetone extract of *R. peruviana.* This was higher than the antioxidant activity of standard antioxidant a- tocopherol suggesting these lichen species as a source of natural antioxidant. However, highest total phenolic content was shown by acetone extract of *P. tinctorum* than methanol extract of *R. peruviana* [17].

The phytochemical analysis of methanol and chloroform extracts of *Umbilicaria cylindrica* by HPLC-UV method and found that phenolic compound in both extracts was depsidone, salazinic acid in addition to norstictic acid, methyl-*β*-orcinol carboxylate, ethyl haematommate, atranorin, and usnic acid, in different amounts. The lichen extracts showed comparable and strong antioxidant activity, exhibited higher DPPH and hydroxyl radical scavengings, chelating activity, and inhibitory activity towards lipid peroxidation. On characterization of the metabolites of the lichen *Laurera benguelensis* by HPLC, xanthones and anthraquinones was evident in addition to, Lichexanthone, secalonic acid D, norlichexanthon, parietin, emodin, teloschistin and citreorosein. High radical scavenging activity was observed with chloroform extract during antioxidant activity [7]. Further, by HPLC, xanthones and anthroquinones have been characterized from lichen *Laurera benguelensis*. In addition, some of the metabolites were detected from the family Trypetheliaceae for the first time. The preliminary testing of benzene extract and its chloroform and methanol fractions showed weak scavenging activity. However, the chloroform extract showed the highest antioxidant activity [18].

Lichen role in aflatoxin degradation:

Among various aflatoxins, AFB1 the most potent carcinogen [19]. The ingestion on AFB1-contaminated feed is known to cause teratogenicity, immunotoxicity or death in

humans and animals [20]. But, the mechanism of cellular damage caused by Aflatoxin B1 has not fully elucidated [21]. Besides this, the main mechanism in the toxicity of Aflatoxin B1 is the generation of reactive oxygen species and lipid peroxidation [22]. Therefore, Aflatoxin B1 causes sister chromatid exchanges and chromosomal strand breaks as well as forms adducts in human cell and rodent. [23].

Different antioxidant molecules such as ascorbic acid, beta-carotene and tocopherol have been shown to possess anti-carcinogenic and anti-mutagenic properties against AFB1 toxicity. On the other hand, lichens have long been investigated popularly for biological roles; mainly anti-tumor, anti-microbial and anti-oxidant activities. Also, the influence of lichenic substances on DNA binding of AFB1, in mammalian cells, is still under investigation. However, *Dermatocarpon intestiniforme* extracts conferred a protection against AFB1-induced genotoxic and oxidative damage *in vitro.* Further, sister chromatid exchange rates and main antioxidant enzyme activities including superoxide dismutase and catalase in AFB1 and lichen treated human whole blood cultures was studied. It has been demonstrated that dose controlled *D. intestiniforme* lichen diet would play a protective role in the process of AFB1 mutagenesis and/or carcinogenesis [24].

Antifungal and anti helmenthic activities of Lichen

Everniastrum cirrhatum, a foliose lichen that grows luxuriantly in tropical Himalayas, central India and higher altitudes of southern India.The extract of lichen species showed antibacterial activity against Gram positive, Gram negative bacteria. Antifungal activity showed against *Aspergillus niger* and *A. fumigates* and anthelmintic activity showed against, Indian earthworm model. Insecticidal activity was shown against 2nd and 3rd instar larvae of *Aedes aegypti*. At concentration of 5mg/ml and higher, the extract produced marked antithelmintic effect than the reference drug. The extract exhibited potent larvicidal effect. Among larvae, 2nd instar larvae were shown to be more susceptible than 3rd instar larvae. Phytochemical analysis revealed the presence of alkaloids, saponins, tannins and terpenoids. Further, TLC revealed Atranorin, Salazinic acid and Protolichesterinic acid [25].

Antimycobacterial effect of Lichen

Tuberculosis is one of the chronic infectious diseases, one of the major enemies of the humanity from times immemorial. Today, it still remains as one of the most serious medical and social problems. It is responsible for 3 million deaths per year and around 8 million cases of first-recorded disease. The advances in the chemotherapy of tuberculosis in the mid-20th century have recently given way to anxiety over the evolution of drug resistance based on the genetically fixed mutations of *M. tuberculosis*. Moreover, nearly all drugs used for the treatment of tuberculosis possessing different mechanisms of activity in addition to adverse side effects and expensive. Therefore, it is extremely important to search for new, low-toxic substances superior to the available drugs in their activity and efficacy. This primarily concerns the agents possessing activity against *M. tuberculosis* strains with multidrug resistance [26]. The problems of tuberculosis are further worsen the situation with the spread of HIV infection and the increase in prevalence of drug resistance as well as multidrug-resistant strains calls for search of new alternative drugs.

Ethanol extracts of nine lichen species, namely *Everniastrum cirrhatum*, *Flavoparmelia caperata*, *Heterodermia leucomela*, *Lecanora flavidorufa, Leptogium pedicellatum*, *Lobaria isidiosa*, *Rimelia reticulata*, *Phaeophyscia hispidula*, and *Stereocaulon foliolosum*, were evaluated for antimycobacterial properties and was found to be more susceptible to ethanol extract of *F. caperata, H.leucomela, E. cirrhatum, R. reticulata,* and *S. foliolosum*. The extracts prepared from these lichen materials were tested against Mycobacterium tuberculosis showed 90% inhibition [27, 28].

Lichens against *Helicobacter pylori*

Helicobacter pylori is a fastidious, slow-growing bacteria sensitive to changes in pH of the culture media. The fact that the sodium salt of protolichesterinic acid is as inhibitory as the free acid indicates that the activity is not obtained through a lowering of pH. The protolichesterinic acid of lichen found to show antibacterial activity, against *H.pylori* was considerably higher than that exhibited by antibacterial agents such as ampicillin and erythromycin, metronidazole. The traditional use of *Cetraria islandica* (Iceland moss) for relief of gastric and duodenal ulcer and the plant extracts were screened for *in vitro* activity against *H. pylori*. (1)-Protolichesterinic acid, an aliphatic a-methylene-g-lactone, was found to be the active component [29].

Effects of extracts from lichen *Ramalina pacifica* against clinically important diseases

Bactericidal activity of crude extracts from lichen *Ramalina pacifica* were in traditional use for the treatment of respiratory infections, urinary tract infections and pneumonia. The allergenic potential of the aromatic lichen substance atranorin have been investigated using guinea pig maximization test. Sensitivity was induced in 30% of the animals, which corresponds to a moderate allergenic capacity. A modified photoallergy test on the same animals was performed, and irradiation did not found to increase the number of positive reactions, 4 patients with proven contact sensitivity to atranorin, evernic, usnic or physodic acid, were examined with different dilutions [30].

Antibiotic enhancer:

Antimicrobial interactions can be antagonistic, indifferent, additive or synergistic. *Staphylococcus aureus* infection ranging in severity from food poisoning or minor skin infections to severe life - threatening infections. Ampicillin is a member of the group of antibiotics called penicillin otherwise known as B-lactam drugs. Ampicillin is selective inhibitors of bacterial cell wall synthesis and active against growing bacteria. Screening tests with lichens have indicated the frequent occurrence of antimicrobial substances. The best synergistic interactions against *S. aureus* strains in combination with methanol extracts and ampicillin against *S. aureus* strain B, the interaction was synergistic at all the combination ratios used given 100% synergy [31]. Therefore, the combinational therapy would be the next approach in treating seriously debilitated patients who are affected with life threatening *S. aureus* infections.

CONCLUSION

Lichens are symbiotic organisms which are composed of fungi and algae, also contain cyanobacteria. Some species of lichen are medically very important and inhibitory against bacteria and fungi. The secondary metabolites of the lichen are active substances against pathogenic microorganisms. Most known lichen substances are usnic acid, phenolic compounds, anthraquinones, dibenzofurans, depsides, depsidones, depsones, triterpenes, gamma lactones and pulvinic acid derivatives and have a multiple biological activities like antiviral, antibiotic, antitumor, allergenic, plant growth inhibitory and enzyme inhibitory.

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