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Biological Activities and Potential Applications of Lichens

Díaz-Domínguez G[1], Soriano-Santos J[1], Peña-Solis K[2] and Díaz-Godínez G[2]*

[1]Department of Biotechnology, Metropolitan Autonomous University, México

[2]Research Center for Biological Sciences, Autonomous University of Tlaxcala, Mexico

***Corresponding author:** Gerardo Díaz-Godínez, Research Center for Biological Sciences, Autonomous University of Tlaxcala, Tlaxcala, Mexico, Email: diazgdo@hotmail.com

Mini Review

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Abstract

Lichens are complex organisms that are formed by symbiotic associations between fungi and photosynthetic organisms that can be algae or cyanobacteria. Most are terrestrial, although a few species are aquatic. Lichens have been studied for their production of secondary metabolites with biological activity such as antimicrobial, antifungal, antiviral, anticancer, antioxidant, among others; they have also been used in the cosmetics industry, as a source of natural dyes, they have been considered bioindicators and have been useful in some bioremediation processes, in addition, they are a potential source of enzymes. This review mentions some bioactive compounds of lichens as well as their potential uses, emphasizing some of their biological activities.

Keywords: Algae; Biological Activities; Enzymes; Fungi; Lichens

Introduction

Lichens result from the mutualistic symbiotic relationship between fungi (mycobiont, heterotrophic) and algae or cyanobacteria (photobiont, photosynthetic) [1]. The taxonomy of lichens is based on the mycobiont, which in most cases is the one that presents sexual reproduction. Symbiosis involves nutrient exchange, recognition mechanisms and chemical signaling, however, algal cells synthesize carbohydrates through photosynthesis, while the fungus participates in water absorption and protects the alga from adverse environmental conditions, such as extreme temperatures, which is why lichens are very resistant [2]. Due to the presence of a photosynthetic organism, lichens can inhabit substrates practically devoid of organic matter, and when a cyanobacterium is involved in the symbiosis (approximately 10% of lichen species), the partner fungus can also obtain nitrates or ions of ammonium that are processed by cyanobacterium [1,3]. Lichens form a long-lived thallus, which is a multicellular, generally macroscopic structure that generally resembles neither the mycobiont nor the photobiont. The thallus contains more mycobiont cells, however, given the presence of the photobiont, lichens are considered photosynthetic organisms [1]. Lichens grow on different surfaces, including plants and leaf litter, as well as on soil, sand, rock, even on glass, asphalt, etc. Lichens do not have conductive organs or tissues, so they obtain water from the humidity of the environment, mainly from rain and fog. It is worth mentioning that there are a few species that develop in fresh water or tidal marine, since the vast majority are terrestrial [1]. There are thought to be about 15,000–20,000 lichen-forming fungi, of which less than 2% are basidiomycetes and much fewer deuteromycetes, the vast majority being ascomycetes. Lichens play an important role in community ecology and are broadly comparable to other fungal organisms that engage in pathogenic and mutualistic activities [1]. Lichens produce enzymes of biotechnological interest and a great diversity of secondary metabolites to which biological activities have been attributed such as antibiotics, antitumor, antiproliferative, antifungal, cytotoxic effects, antimicrobial, antivirals, antimycobacterial, antiprotozoal, anti-inflammatory, antipyretic, and analgesic, in addition, they have been used as food for humans and animals, many have been used in the production of dyes, alcohol, perfumes, etc. Some civilizations have used these organisms as a medicinal source [4,5].

Biological Activities

The presence of more than 800 lichen metabolites with different uses and properties including biological activities has been reported [6]. Some of them are described below.

Antimicrobial Activity

It has been suggested that the antimicrobial activity of lichens is due to their molecules that inhibit cell wall synthesis, inhibit protein synthesis (translation), disrupt cell membranes, stop metabolic activity and nucleic acid synthesis. Some secondary metabolites are very active against pathogenic microorganisms, such as usnic acid from *Flavoparmelia caperata*, physodic acid from *Hypogymnia physodes*, gyrophoric acid from *Umbilicaria polyphylla*, atranorin from *Physcia aipolia*, protocetraric acid from *Flavoparmelia caperata*, fumarprotocetraric acid from *Cladonia furcata*, stictic acid from *Parmelia conspersa* and lecanoric acid from *Ochrolechia androgyna* [7]. Other lichen compounds with antimicrobial activity are evernic acid, salazinic acid, methyl evernate, obtusatic acid, 20-O-methyl anziaic acid, barbatolic acid, divaricatic acid, among others [8]. It has been suggested that the effect of usnic acid against Gram-positive bacteria is due to its ability to destroy cell membranes, it also inhibits bacterial RNA synthesis or alters DNA replication and is an uncoupler of oxidative phosphorylation [9]. Antimicrobial activity has been determined in extracts of various lichens and in some cases the compounds to which antimicrobial activity has been associated have been isolated, below are some studies where the antimicrobial activity of lichens has been evaluated. In a study, the antimicrobial activity of aqueous methanol and ethanol extracts from the lichens *Xanthoria parietina*, *Physconia* sp., and *Tornabenia atlantica* was evaluated on 11 bacterial species that were *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus cereus*, *Staphylococcus lentus*, *Micrococcus luteus*, *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter aeruginosa* and *Serratia marcescens*. The methanolic extracts of the 3 lichens were more active, mainly against Gram-positive bacteria. It was suggested that the antimicrobial activity was due to usnic acid, diffractaic acid, protocetaric acid, alkaloids and flavonoids [10]. In another investigation, the antimicrobial activity of acetone, methanol, and ethanol extracts of the lichen *Usnea ghattensis* was evaluated on three Gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus faecalis*, and *Bacillus cereus*), and three Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*). The ethanol extract was the most effective against *Bacillus cereus* and *Pseudomonas aeruginosa* and the methanol extract inhibited *Staphylococcus aureus* and *Streptococcus faecalis* [11]. The antimicrobial activity of methanolic extracts of the lichens *Parmotrema reticulatum*, *Heterodermia obscurata*, *Dirinaria consimilis*, *Ramalina pacifica* and *Ramalina hossei* was evaluated. All extracts had effect on three Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus coagulans*) and five Gram-negative bacteria (*Klebsiella pneumoniae*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Ralstonia solanacearum*). The fungus *Colletotrichum capsici* was also inhibited by lichen extracts [12]. The antimicrobial activity of acetone extracts of the lichens *Cladonia furcata*, *Lecanora atra* and *Lecanora muralis* was evaluated on three Gram-positive bacteria (*Bacillus mycoides*, *Bacillus subtilis* and *Staphylococcus aureus*), three Gram-negative bacteria (*Enterobacter cloacae*, *Escherichia coli* and *Klebsiella pneumoniae*) and 10 fungal species (*Aspergillus flavus*, *Aspergillus fumigatus*, *Botrytis cinerea*, *Candida albicans*, *Fusarium oxysporum*, *Mucor mucedo*, *Paecilomyces variotii*, *Penicillium purpurescens*, *Penicillium verrucosum* and *Trichoderma harzianum*). The extracts of *Cladonia furcata* and *Lecanora atra* were effective against all the bacteria and fungi tested, while that of *Lecanora muralis* was mainly effective against bacteria [13]. Acetone extracts of the lichens *Caloplaca pusilla*, *Protoparmeliopsis muralis* and *Xanthoria parietina* were evaluated against the bacteria *Bacillus subtilis*, *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. The extract of *Protoparmeliopsis muralis* strongly inhibited all bacteria [4].

Antioxidant Activity

Antioxidant activity in lichens is mainly attributed to their phenolic compounds content. The compounds methyl orsenillate, orsenillic acid, atranorin and lecanoric acid were extracted with benzene and acetone from the lichen *Parmotrema stuppeum*, which showed moderate antioxidant activity [14]. The depsidones 10-chloropannarin, pannarin and depsides such as divaricatic acid and atranorin from *Erioderma chilense*, *Protousnea malacea*, *Psoroma pallidum* and *Placopsis* sp., showed antioxidant activity [15]. In another study, a high antioxidant activity of secaic acid, usnic acid and salazinic acid isolated from the lichens *Ramalina pacifica*, *Ramalina nervulosa* and *Ramalina celastri* was observed [16]. Physodic acid from the lichens *Pseudevernia furfuracea*, *Evernia prunastri* and *Hypogymnia physodes* was a very effective antioxidant [17]. Atranorin obtained from the lichens *Cladonia rangiferina*, *Cladonia furcata*, *Cladonia pyxidata* showed antioxidant activity [18], and gyrophoric acid from the lichen *Acarospora fuscata* had strong antioxidant activity [19]. In a study, an increase in the antioxidant activity of phenolic compounds in the presence of proteins or carbohydrates was observed, which suggests a synergistic effect of the compounds present in the lichen extract [20].

Anticancer Activity

There are reports on the anticancer activity of lichens, some of them are listed below. Vulpinic acid obtained from *Letharia vulpina* inhibited cell growth in cancer cell lines HepG2, $CaCo_2$, RD, Wehi and Hep2C [21]. Extracts of *Cladonia convoluta*, *Cladonia rangiformis*, *Parmelia caperata*, *Platismatia glauca* and *Ramalina cuspidata* showed activity on malignant neoplasm cell lines cK-562 (chronic myeloid leukemia), U251 (glioblastoma), DU145 (prostate carcinoma) and MCF7 (breast adenocarcinoma) [22]. In a study, it was observed that atranorin, diffractaic acid and divaricatic acid from lichens showed concentration-dependent apoptosis against prostate cancer cells [23]. Acetone extracts of the lichens *Cladonia furcata*, *Lecanora atra* and *Lecanora muralis* showed anticancer activity in the cell lines FemX (human melanoma) and LS174 (human colon carcinoma) [13]. Olivetoric acid and physodic acid isolated from *Pseudevernia furfuracea* and psoromic acid isolated from *Rhizoplaca melanophthalma* showed anti-tumor latency in human U87MG-GBM cell lines and rat cerebral cortex principal cells (PRCC) [24]. Anticancer activity of an extract of *Parmotrema reticulatum* was observed on the cervical cancer cell line of Albino Wistar rats [25]. Atranorin, lichexanthone, and (+)-usnic, diffractaic, divaricatic, perlatolic, psoromic, protocetraric, and norstictic acids isolated from the lichens *Parmotrema dilatatum*, *Usnea subcavata*, *Usnea* sp., *Ramalina* sp., *Cladonia confusa*, *Dirinaria aspera*, and *Parmotrema lichexanthonicum* were effective against UACC-62 and B16-F10 melanoma cells [26]. Depsides (squaric acid, lecanoric acid, atranorin), depsidones (salazinic acid, physodic acid) and caperatic acid were obtained from the lichens *Hyposenomic scalaris*, *Hypogymnia physodes*, *Parmelia sulcata*, *Cladonia uncialis* and *Platismatia glauca*; physodic acid showed strong inhibitory activity against the colorectal cancer cell lines HCT116 and DLD-1 [27]. Among the compounds derived from lichens with anticancer activities are also gyrophoric acid, ramalin, lobarstin, lobaric acid, physciosporin, pinastric acid, olivetolic acid, among others [7,8].

Other Biological Activities

Lichens have been used in many parts of the world as medical remedies, for the treatment of toothaches, sore throats, skin diseases, to heal wounds, headaches, as an antiseptic and bone fractures [28-30]. In the American continent they were used as pastes to cure infections, as well as being a good treatment against diarrhea and indigestion [31]. They have also been used to treat skin rashes, warts, and infected wounds [32,33]. Lichens show allelopathic activity; as they grow slowly, they must protect themselves from plants that can compete against them for the environment in which they develop. They achieve this by leaching lichen substances that inhibit the growth of both lower and higher plants [34]. They also have phagoinhibitory activity, where lichen substances act as inhibitors of mastication by herbivores; they have allergenic activity, due to numerous depsides and usnic acid, in addition, they have photoprotective activity against UV radiation [35]. On the other hand, lichens have shown inhibition of different enzymes, for example, some lichen extracts have shown anti-inflammatory and antinociceptive properties thanks to the inhibition of enzymes related to these processes such as cyclooxygenase and lipoxygenase [36]. They also have inhibitory activity on metabolic enzymes, which represents potential therapeutic applications. Atranorin and various acids produced by lichens have potential applications for the inhibition of enzymes related to polyamine metabolism, such as arginase [37]. Inhibition of xanthine oxidase, which is key in hyperuricemia, and tyrosinase involved in the synthesis of melanin given by lichen extracts were also reported [38]. In a study, eight novel alkylated decalin-type polyketides were isolated from the lichen *Pyrenula* sp., seven polyketides showed inhibitory activities against mammalian DNA polymerases -α and -β [39]. A methanol extract of *Caloplaca biatorina* showed inhibition of xanthine oxidase and aldehyde oxidase [40]. In a methanolic extract of *Everniastrum cirrhatum*, lipase inhibitory activity was observed in a concentration-dependent manner [41]. In another study, ethyl acetate and methanol extracts were obtained from the lichens *Heterodermia leucomelos* and *Ramalina celastri*, which showed inhibitory activity on chicken pancreatic lipases, the methanol extracts were more efficient than the ethyl acetate extracts [42].

Methanolic extracts were obtained from natural thallus and from the *in vitro* culture of the lichens *Graphis guimarana*, *Graphis nakanishiana* and *Graphis schizograpta*, which showed inhibition of tyrosinase and xanthine oxidase [43]. α-Glucosidase inhibitors have potential use in the treatment of diabetes and other carbohydrate-mediated diseases. In this regard, zeorin, methyl β-orcinolcarboxylate and methylorselinate produced by the lichen *Cladonia* sp. showed strong inhibition of α-glucosidase, even superior to acarbose, (a drug to treat type II diabetes mellitus) and the standard (1-deoxynojirimycin) [44]. A methanol extract of *Caloplaca biatorina* showed concentration-dependent inhibition of α-glucosidase [40]. Methanol extract of the lichen *Heterodermia leucomela* showed dose-dependent amylase inhibition [45]. Inhibition by lichen extracts or compounds of other enzymes such as aromatase, cyclooxygenase, trypsin, β-glucuronidase, prolyl endopeptidase, monoamine oxidase, urease, tyrosinase, xanthine oxidase, thioredoxin reductase, topoisomerase, pancreatic elastase, phosphodiesterase, telomerase and acetylcholinesterase has been reported [46]. On the other hand, thanks to the great tolerance of many lichen species to desiccation, radiation and extreme temperatures in hostile environments, these organisms can be considered as bioindicators. Lichens growing on the bark of trees have proven to be air bioindicators, assessing the state of air pollution in a specific area, since lichens show changes in their morphology and/or biological behavior under certain levels of pollution [47]. Lichens are good bioaccumulators of heavy metals (copper, zinc, lead, cadmium, silver, arsenic and manganese) and do not excrete them [48]. It is worth mentioning that lichens have also shown antidiabetic, antiviral, anti-neurodegenerative, anti-genotoxic, insecticidal activities, among others. Since lichens have a great capacity to adapt and survive in diverse ecological environments, they represent a potential source of enzymes for biotechnological use. A study mentions the presence of phenol oxidases, peroxidases and cellulases in lichens [49]. The activity of antioxidant enzymes (superoxide dismutase, catalase, glutathione reductase and glucose-6-phosphate dehydrogenase) were determined in the lichen *Ramalina lacera* in response to rehydration after natural drying [50]. In the thallus of the lichens *Solorina crocea* and *Peltigera aphthosa*, laccase activity was observed, which after separation was determined to be two isoforms of different molecular weight in both cases [51]. In a study, laccase and tyrosinase activity was found in different lichens, those of the order Peltigerales presented both enzymes, and those of the order Lecanorales presented only laccase activity [52]. The lichen *Evernia prunastri* contains a high amount of L-arginine as a reserve of free amino acids from the thallus, this amino acid is hydrolyzed by different isoforms of arginase to produce L-ornithine and urea [53].

Conclusion

Lichens are fascinating and very interesting organisms from a biological and ecological point of view. Given the conditions in which they develop, they are capable of producing many bioactive compounds with potential use in different areas for the benefit of the environment and humans, highlighting the pharmaceutical field, since they have many biological activities, cosmetics, dyes, among others; In addition, their ethnomedicinal value must be taken into account, their application as bioindicators and bioremediators of the environment, as well as their use as food for humans and animals with excellent nutritional value. However, there is still much to discover regarding lichens, their applications and their bioactive properties.

Conflicts of Interest

The authors declare no conflict of interest.

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