RESEARCH ARTICLE

Lichens: A myriad hue of Bioresources with medicinal properties

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ABSTRACT

Lichens form an ideal model to study its bioactive metabolites. A symbiotic association between fungus and a chlorophyll containing partner; the green algae or cyanobacteria, and sometimes both together form lichens. Lichens are important species for several reasons. The unique and biologically active substances present in the lichen thalli contribute to several important medicinal values of lichens like antiviral, antibacterial, antifungal, antioxidant, cytotoxic effect and many more. All these manifold activities of lichen metabolites represent the therapeutic potential of lichens that has a great impact in Pharma industries. The present article is a review on the importance of lichens in contributing towards valuable resources emphasising on its medicinal properties.

Keywords: Lichens, Biomonitors, Medicinal properties, Therapeutic potential.

INTRODUCTION

Lichens, the symbiosis between a fungal and algal partner, are found all around the world. They grow in the residual areas of any extremities where life can survive, which may be harsh for any other organisms to exist. The usual habitats of lichens are bare rock, sand, soil, dead wood, living bark and rusty materials surviving extreme conditions of temperature. The adaptations and survival factor in such environments has led lichens giving rise to a large number of unique secondary metabolites. Over 20000 species of lichens are known worldwide. While the ethnic uses of lichens and the pharmaceutical potential of their secondary metabolites have been recognized, the knowledge regarding a large number of lichen substances still remains a mystery. The area of bioactivity research towards focussing lichen derivatives as drug targets and its screening needs an emphasis. An updated overview on the knowledge of secondary metabolites from lichens can highlight their potentials for pharmaceuticals as well as other applications. This review focuses on the lichen medicinal values emphasising on its bioactive potentials. There is a need for expanding research in this area of study exploring the unique compounds of lichens which are promising reservoirs with high medicinal values.

Lichen habitat and distribution

Lichens colonize some of the most inhospitable habitats on earth. Lichens are known to pioneer different types of hostile environments from extreme temperatures to desiccated colonisations. Very old environments as well as arid and semi-arid regions like cryptogamic soil crusts are also conditions favouring lichen habitat. Fog, dew or high air humidity ensures survival in dry areas (Beckett et al., 2008). Lichens are also reported to grow in desert regions due to its capability to become hydrated without being in contact to any liquid or water (Printzen et al., 2012). This suggests that lichens are slow-growing as well as long-living host organisms. The favourable environments for lichen habitat are considered to be microsites which are rocks, barren soil, man-made substrates and epiphytic life-styles. Around 8% of the earth land surface is covered by lichens (Ahmadjian, 1995). Lichen flora is approximately estimated to cover 18500 species worldwide (Feuerer & Hawksworth, 2007).

Growth forms

Major ecological groups of lichens include:

- Epiphytic lichens which are i) corticolous found on the bark, ii) lignicolous found on wood and iii) folicolous found on leaves
- Terricolous lichens found on ground (soil)
- Muscicolous found on moss
- Saxicolous found on rocks.

Lichens have a variety of different growth forms which are

- Crustose (or Crustaceous) lichens: These types of lichens encrust and spread over and into the surface of their habitat which cannot be removed from the surface without crumbling away.
- Foliose lichens: Leaf like lobes spreads over the surfaces which are attached by root-like threads and can be removed with the help of a knife.
- Fruticose lichens: Shrubby forms with many branches and they can be removed from the surface by hand.

Other intermediate categories include:

- Leprose lichens: The surface of the lichen is powdery or granular. There is no prominent thallus and hence strongly attached with the substratum.
- Placodioid lichens: The thallus of the lichen is closely attached to the substratum at centrally and free at the margin as it lacks rhizines.
- Squamulose lichens: This form of lichen is neither a crustose nor foliose type but an intermediate form. Minute lobes are present on the dorsiventral surface of the lichen with either presence or absence of rhizines.

Lichen metabolites

Being one of the slowest growing symbiotic associations, lichens occupy low-resource habitats and thereby produce certain defence chemicals to survive in the harsh environments. These chemicals are the reservoirs of lichens; the secondary metabolites that render chemical defence and protection against various microbes, animal predators and plants, to avoid environmental stress with respect to UV damage, desiccation and also for the physiological regulation of metabolism (Huneck & Yoshimura, 1996). The lichen compounds exhibit significant biological activities (Huneck, 1999). Lichens and their metabolites have a manifold activity exhibiting antiviral, antibacterial, antifungal, antibiotic, antitumor, allergenic, plant growth inhibitory, antiherbivore, antioxidant and enzyme inhibitory activities (Karagoz et al., 2009) (Ramya & Thirunalasundari, 2013). Hence, potential value of these metabolites for medicinal purposes is generating an increasing interest in research areas.

More than a thousand primary and secondary metabolites with identified structures have been identified in lichens (Molnár and Farkas, 2010). Primary metabolites are proteins, lipids, carbohydrates, and other organic compounds that are essential to the lichen's metabolism and structure which are produced by lichen's fungal partner and algal or cyanobacterial partners. Primary lichen substances are intracellularly synthesised. These metabolites are independently synthesised by both the symbionts having structural functions and play essential roles in cellular metabolism. Chitin, lichenin, isolichenin, hemicellulose, pectins, disaccharides, polyalcohols, amino acids, enzymes, and pigments like algal chromophores: chlorophyll and, β-carotenes, xanthophylls, etc., are some of the primary metabolites reported in lichens (Podterob, 2008).

Several studies have confirmed that the secondary metabolites are exclusively from fungal origin (Culberson & Armaleo, 1992; Hamada et al., 1996; Stocker-Wörgötter & Elix, 2002). It has been reported by several studies that the metabolic interaction between the fungal and its algal partner is the main reason for the production of these secondary chemicals (Molina et al, 2003). Generally, the lichen secondary compounds are categorised as depsides, depsidones, dibenzofurans and pulvinic acid derivatives having low molecular weight (Turk et al., 2003), which are produced by the fungus alone and secreted onto the surface of hyphae either in amorphous forms or as crystals (Elix, 1996). These substances are stress compounds or organic substances produced under extreme conditions. Phytochemical analysis of lichens has portrayed the presence of flavanoids, saponins, alkaloids, tannins, phlobotannins, steroids and glycosides (Ramya & Thirunalasundari, 2014).

These secondary metabolites which are called 'the lichen substances' have evolved through various transformations leading to important biosynthetic pathways and thereby producing a complex arrays of compounds. Most classes of the lichen metabolites are from the acetyl-polymalonyl pathway. Pulvinic acids and terphenyl-quinones belong to shikimic acid derivatives while mevalonate pathway accounts for the wealth of di- and triterpenoids as well as steroids found in lichens (Elix et al, 2008). Though a large number of research works have reported the isolation and structural characterization of individual lichen compounds, lacunae in studying the lichen metabolites as strong therapeutics still persist.

Medicinal value of Lichens

In the thrust to discover various drug therapies, natural products are taking a central place. Though several thousand compounds have been identified and purified from various natural sources including plants, microorganisms, fungi etc. to treat various diseases, there are many more untapped reservoirs having enormous medicinal properties and lichens being one among them. Also due to the increase in multi drug-resistance among pathogens, there is a growing demand for novel bioactive compounds. In the present scenario of life style, usage of synthetic drugs continuously has developed resistance characteristics. Hence, a need to find new promising molecules of natural origin in the control and prevention of various human, animal and plant diseases persists. Also due to long-term usage of the synthetic drugs, numerous side effects are being identified apart from resistance. In search of new bioactive molecules of natural origin, lichens are one among the promising resources which can be unravelled for its unique metabolites and has been the subject of many research teams. Lichen secondary metabolites are considered as potential resources as these compounds function as chemical defence against biotic and abiotic stressed conditions (Balaji & Hariharan, 2007). The name "Lichen" itself indicates the medicinal importance of the species which can be traced back to the Greek word, "Leprous" used for treating diseases (Llano, 1944). Lichen substances are unique to lichen symbiosis which helps the organism to survive in extreme environmental conditions. Almost majority group of lichens have been reported to contain antibiotic property (Sharnoff, 1997). Among them, the best compound that has been demonstrated to have a wide spectrum of antibiotic activity is Usnic acid (Rowe et al. 1991). A great diversity of biological effects are exhibited by lichen metabolites like antiviral, antibacterial, antibiotic, antiinflammatory, analgesic, antipyretic, antiproliferative and cytotoxic activities (Boustie & Grube, 2005).

Research today is focusing towards break through discovery of newer therapies and compounds for better treatment of diseases without any side effects. In this effort, hunt for compounds from natural products especially in the treatment of cancer have been developed and commercialized. However, the challenge continues towards a search for improved cytotoxic agents as anti-cancer drugs. Lichens are one among the bio-resources that has many untapped metabolites which can contribute to modern day medicine.

A brief summary on the importance of the anticancerous property of the lichens based on recent articles is given in Table 1.

Lichens as traditional medicine

Various species of lichen forming fungi have wide geographical distributions which are used in the traditional system of medicine. Lichens are being used as traditional medicines across the world. Applications of lichens emphasising on the importance of its medicinal values can be linked with folklore. For centuries, lichens have been used as ingredients in folk medicine. Also, lichens+ have been used among many cultures to treat variety of ailments as part of their traditional medicines (Dayan & Romagni, 2001).

Table 1 : Summary on the importance of the anticancerous property of the lichens

Name of the lichen	Lichen metabolite	Medicinal property reported	Reference
Pseudevernia furfuracea (L.)	Olivetoric and physodic acid	Has cytotoxic and oxidative effects on cultured human amnion fibroblasts	Emsen et al. (2017)
-	Usnic acid and atranorin	Strong inhibitory effects on cancer cell proliferation and migration. Anti-invasive effects on human prostate and melanoma cancer cells	Galanty et al. (2017)
-	Physodic acid	Induces ROS production and apoptosis in melanoma cells.	Cardile et al. (2017)
Evernia prunastri *Usnea ghattensis*	Evernic and usnic acids	The metabolites have been reported as protective against redox impairment mediated cytotoxicity	Fernández-Moriano et al. (2017)
Hypogymnia physodes	Physodic acid	Cytotoxic activity observed against breast cancer cell lines : MDA-MB-231, MCF-7, T-47D	Studzińska-Sroka et al. (2016)
Cetraria islandica	Fumarprotocetraric acid	Neuroprotective activity against hydrogen peroxide-induced oxidative stress model in astrocytes. Cytotoxic potential against human HepG2 and MCF-7 cell lines.	Fernández-Moriano et al. (2015)
Vulpicida Canadensis	Usnic, pinastric and vulpinic acids		
Ramalina fraxinea and Ramalina fastigiata	Evernic acid, obtusatic acid, sekikaic acid atranorin, protocetraric acid and usnic acid	All the samples exhibited strong anticancer activity against human epithelial carcinoma (HeLa), human lung carcinoma (A549) and human colon carcinoma (LS174) cells	Ristic et al. (2016)
Usnea barbata	Usnic acid	Anticancer and antioxidant activity	Zugic et al. (2016)
Usnea strigosa (Ach.)	Norstictic acid	Inhibits breast cancer cell proliferation, migration, invasion	Ebrahim et al. (2016)
Pseudevernia furfuracea	Olivetoric acid (OLA) and physodic acid (PHA)	*In-vitro* antitumor activities on glioblastoma cells	Emsen et al. (2016)
Rhizoplaca melanophthalma	Psoromic acid	*In-vitro* antitumor activities on glioblastoma cells	Emsen et al. (2016)
Xanthoparmelia chlorochroa	Usnic, salazinic, constictic, and norstictic acids	Anticancerous activity against against Burkitt's lymphoma (Raji) cells. Extracts from both lichens decreased proliferation, accumulated cells at the G0 /G1 stage, and caused apoptosis in a dose-dependent manner. Both lichen extracts also caused upregulation of p53.	Shrestha et al. (2015)
Tuckermannopsis ciliaris	Protolichesterinic acid		
Parmelia sulcata	Not mentioned	Reports caspase-independent apoptotic cell death at lower doses and genotoxic at higher doses	Ari et al. (2015)
Parmotrema reticulatum	Catechin, purpurin, tannic acid and reserpine	An antioxidant extract induces cell cycle arrest and apoptosis in MCF-7. Both anticancerus and antioxidant acivity reported	Ghate et al. (2013)
-	Usnic acid	Cell cycle arrest and cell death via mitochondrial membrane. Induction of apoptosis in human lung carcinoma cells.	Singh et al. (2013)
Parmelia caperata	Protocetraric and usnic acids	Strong antioxidant, antimicrobial, and anticancer effects	Manojlović et al. (2012)
P. saxatilis and P. Sulcata	Salazinic acid		

Xanthoria parietina	Parietin	Cytotoxicity against Human ovarian carcinoma A2780, Human breast adenocarcinoma MCF-7, Human colon adenocarcinoma HT-29, Human promyelocytic Leukemia, Human T cells lymphocyte leukemia, Jurkat Human cervix adenocarcinoma, Human breast adenocarcinoma, Human colon carcinoma	Backorová et al. (2011)
Umbilicaria Hirsuta	Gyrophoric acid		
Cladonia Arbuscula	Usnic acid	Effective inhibitors of DNA synthesis against Breast cancer cell line - T47D and Pancreatic cancer cell line Capan-2	Einarsdóttir et al., (2010)
AlectoriaOchroleuca	Usnic acid		

Knowledge of these medicinal uses is available to us because of the contributions of traditional knowledge holders among various cultures. The medicinal use of lichens can be traced back to the 18th dynasty (1700-1800 BC) where the species of *Evernia* and *Parmeliaceae* was first used as a drug (Launert, 1981). Lichens in traditional medicine are most commonly used for treating wounds, skin disorders, respiratory and digestive issues, obstetric and gynaecologic concerns (Crawford, 2007)

Medicinal uses of lichens are reported among the cultures in Africa, Europe, Asia, North America, and South America. The lichen genera that were reported to be used in traditional medicine are *Usnia, Evernia, Letharia, Parmotrema, Everniastrum, Xanthoparmelia, Cladonia, Cladina, Ramalina, Lobaria, Peltigera* and *Umbilicaria* (Crawford, 2007). The medicinal properties of the lichen species changes based on the substrate of its growth which imbibes the medicinal properties.

Lichens as Biomonitors

Bioindicators or Biomonitors are organisms that react to environmental pollution with their life functions providing quantitative information about the environment surrounding them. Lichens are amongst the most sensitive organisms to environmental changes at the ecosystem level playing a beneficial role complementary to chemico-physical monitoring methods and thereby can be used as biomonitoring systems. Some lichens absorb many toxic substances like sulphur dioxide, fluorides and heavy metals from the atmosphere. They readily accumulate pollutants in their thallus like heavy metals and other components from the ambient air through their entire surface (Conti et al., 2001). Accumulated pollutants have shown a close correlation with the atmospheric levels of the pollutants and have proved the lichen's capability as an effective biomonitor (Godinho et al., 2008). This highlights the ecological importance of lichen species. It is observed that crustose lichens are highly resistant to air pollution than fruticose lichens which justifies its presence in majority of the polluted land surfaces.

Lichen genomics

With the advent of the genomic era, lichenology also steps ahead towards a focus on the molecular mechanics of lichenization. The importance of culturing lichen mycobionts and photobionts has led to the investigation of fungal genome sequencing. Genomics has paved way to explore the impossible aspects of lichen genomes. Metagenomic analysis using taxon-specific primers is of great help in identifying the symbiotic partners and the biosynthetic pathways associated with the metabolites of lichens (Annette Kampa et al., 2013). Hence, the introduction of new technologies has bypassed many of the difficulties in identifying the structural small molecules that was previously difficult.

Molecular research on lichen symbiosis has been conducted within a phylogenetic context aiming to establish an evolutionary framework, and also to gain information on symbiont specificity (De Priest, 2004). Hence, with the advent of modern techniques, strategy based on bioinformatic prediction, genomic techniques and advanced analytics can help to characterize the molecules present in lichens taking it a step forward as druggable molecules.

Future scope of Lichenology

Though industrial production of lichen metabolites is yet to progress, approaches towards axenic cultivation of the lichen mycobionts have been successfully performed to analyse the secondary metabolites produced by the lichen forming fungi (Stocker-Wörgötter, 2008). This has given hope in identifying novel molecules that can be of pharmaceutical importance. Lichens grow very slowly and hence the optimization of its culturing conditions in the laboratory towards obtaining abundant biomass production is a challenging task (Behera et al., 2009). Once this can be solved, access to lichen-derived substances for possible applications in pharmaceutical research can surely be a break through phenomenon

CONCLUSION

Lichens are an untapped source of biological activities of industrial importance. Their potential is yet to be fully discovered and utilized. Lichen-derived bioactive compounds hold great promise for biopharmaceutical applications towards development of new formulations or technologies for the benefit of human life. Although thousands of secondary metabolites have been identified in lichens, unravelling new lichenoric compounds will be a continual process in further exploration of the mysteric species - The Lichens.

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