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MYCORRHIZA AND LICHENS AS TWO MODELS OF FUNGAL SYMBIOSIS

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ABSTRACT

Fungi have evolved many symbioses including different eukaryotes and prokaryotes. Mutualism is one of the symbioses and here both symbionts benefit from the interaction. The most common mutualistic relationships involving fungi are mycorrhiza and lichens. A mycorrhiza is a symbiotic relationship between a roots of a plant and a fungus while lichen associates between a fungus and an algae. Many studies have performed to investigate these symbiotic relationships in depth, however, still have some debates on them, though many taxonomists rely on genetic analyses besides with traditional morphological data. In our study, it highlights the nature, importance, nutritional and pharmaceutical uses, and applications of these mysterious dual between fungi and plant and/or algae.

Keywords: Symbiosis, Lichens, Mycorrhiza, Fungi, Algae, Chemical signaling

INTRODUCTION

Symbiosis defined as the close association between two or more different species that are mutually benefiting from this association (**Delaux, 2017; Šijaković and Perić, 2018; Vega and Biedermann, 2020**). This phenomenon is widespread in nature and has contributed to major changes in the evolution of life on Earth (**Chatterjee, 2016; López-García *et al.* 2017; Turney, 2020**). Symbiosis can serve as a source of evolutionary innovation. Symbioses may be 'obligate', in which case the relationship between the two species is so interdependent, that each of the organisms is unable to survive without the other, or 'facultative', in which the two species involve in a symbiotic partnership through choice, and can survive individually. Obligate symbioses are often evolved over a long period of time, while facultative symbioses may be more modern, behavioral adaptions, given time, facultative symbioses may evolve into obligate symbioses (**Martin and Schwab, 2012; phuong Nguyen, 2019; Nguyen and van Baalen, 2020**). The objective of this review is to show the importance of two interesting fungal symbiosis models namely those occurring in mycorrhizae and lichens. Highlighting such relations can help in understanding such sophisticated models and important compounds produced as a result of these interaction.

MYCORRHIZA AS THE FIRST MODEL OF FUNGAL SYMBIOSIS

Bernhard Frank introduced the term mycorrhizae in 1877, to describe a structure that was 'neither tree root nor fungus alone but resembles the lichen thallus, a union of two different organisms into a single, morphological organ' (**Trappe, 2005**). He had described what we now know as mycorrhizal symbiosis and had correctly identified it as a union of both plant and fungi. However, the first structural account of mycorrhizae was described in 1840 by **Theodor Hartig** to illustrate an intercellular hyphal net and fungal mantle, that we now term the 'Hartig net', although Hartig had not realised fungal origins of these structures (**Trappe, 2005**). The classical description of mycorrhizae is one in which the association is described as 'mutualistic', meaning that both partners benefit with the plant described as providing photosynthetic ally derived carbohydrates in return for nutrition (**Wang *et al.* 2017; Brundrett and Tedersoo, 2018; Ruytinx *et al.* 2020**). However, the association is more complex than this simple description, and it is recognised that there are gradients of association from mutualism to parasitism, even within single species under different environmental conditions or temporal scales (**Smith and Read, 2010**). Furthermore, besides the mycorrhizal partner providing nutrition, it may also benefit the plant partner by conferring some form of protection, such as increased tolerance to biotic and abiotic stress (**Lenoir *et al.* 2016**). Mycorrhizae may be subdivided into four main categories and these include: arbuscular mycorrhiza (AM), ectomycorrhiza (EcM), ericoid mycorrhiza (ErM) and orchid mycorrhiza (OrM) (**Soudzilovskaia *et al.* 2019; Tedersoo and Bahram, 2019; Karliński, 2020**). These subcategories are discussed as follows along with the evolutionary origins of this association.

Ectomycorrhiza are characterised, by the development of both a Hartig net and a mantel. The Hartig net is the primary site of nutrient, water and carbohydrate exchange between symbionts and consists of a network of highly branched intercellular hyphae, clustered between epidermal and cortical cells of the plant partner's root system. By contrast, the mantel exists external to the root as a dense, and often protective, hyphal sheath (**Smith and Read, 2010**). Ectomycorrhiza occur on every continent excluding Antarctica and the lifestyle occurs in at least 162 fungal genera and possibly as many as 249, with ectomycorrhiza having arisen around 66 times (**Tedersoo *et al.* 2010**). In total, 2% of angiosperms form ectomycorrhiza, representing around 5,600 species with around 285 Gymnosperm species also forming ectomycorrhiza (**Brundrett, 2009; Brundrett and Tedersoo, 2018**). Although ectomycorrhiza occur in far fewer plants than, for example, arbuscular mycorrhiza, they command much attention. Globally, many important tree species such as eucalypts and pines that are used in commercial forestry are obligate ectomycorrhiza trees and Ectomycorrhiza are essential for those commercial important tree establishment and growth (**Ge *et al.* 2017; Becquer *et al.* 2019**). Furthermore, unlike AM, ErM and OrM, most ectomycorrhiza could reproduce sexually and form macroscopic fruiting bodies (Fig 1.). These sporocarps are amongst some of the most highly revered and sought after of all edible fungi, including the hypogenous ascomycetes known as truffles (*Tuber* spp.) (**Thomas *et al.* 2019**) and many epigeous basidiomycetes, such as chanterelles (*Cantharellus* spp.), penny buns (*Boletus edulis*) and saffron milk caps (*Lactarius deliciosus*) (**Zambonelli and Bonito, 2013**). Many of these species have a high socioeconomic importance and consequently ectomycorrhiza are the most widely studied of all mycorrhizal fungi (**Martínez-Ibarra *et al.* 2019; Sourzat, 2020**).

Arbuscular mycorrhiza are the most widespread of all mycorrhiza, occurring with over 80% of terrestrial plant species (**Smith and Read, 2010**) and are defined by the formation of highly branched structures within plant root cortex cells, known as arbuscules (**Wipf *et al.* 2019**). These structures, with a large surface area, facilitate the exchange of carbon, water and nutrients with their plant partner (**Walder and van der Heijden, 2015; Luginbuehl and Oldroyd, 2017;**

Konečný *et al.* 2019). Occurring in both vascular plants and bryophytes, the environmental tolerance of arbuscular mycorrhiza are, in general, higher than ectomycorrhiza with the former occurring in a wide range of habitat types from desert to saturated and sodic ground (**Bernardo *et al.* 2019; Bahadur *et al.* 2019; Wang *et al.* 2019; Lee *et al.* 2020**). Consequently, arbuscular mycorrhiza have been found on every continent, including some Antarctic islands (**Barbosa *et al.* 2017**). The establishment of arbuscular mycorrhiza requires a signalling cascade and this begins with plant-derived strigolactones being perceived by the arbuscular mycorrhiza fungi, which in turn produces chitooligosaccharides and lipochitooligosaccharides (**Feng *et al.* 2019; Pons *et al.* 2020**). The latter two compounds appear to function as fungal signalling molecules to the plant (**Luginbuehl and Oldroyd, 2017**) and from this point the arbuscular mycorrhiza association is developed. Unlike many ectomycorrhiza species that form large epigeous sporocarps, arbuscular mycorrhiza are largely hypogeous and the dispersal of propagules presents some challenges. Soil disturbance is likely to be a primary mode of arbuscular mycorrhiza fungal propagule liberation (spores, hyphae and colonized root fragments) for subsequent movement by vectors including wind (**Chaudhary *et al.* 2020**) and animal (**Stephens and Rowe, 2020**). However, there is much we don't know about arbuscular mycorrhiza spore dispersal and the influence on fungi community structure at a range of different spatio-temporal scales. Furthermore, despite the ubiquity of arbuscular mycorrhiza, by 2013 only 250 species had been described (**Öpik *et al.* 2013**) and this one example serves to highlight how much more research is needed into mycorrhizal fungi in general.

Ericoid mycorrhiza occur exclusively with Ericales (Ericaceae and Diapensiaceae) and ericoid mycorrhiza plants are found on every continent, with the exception of Antarctica (**Leopold *et al.* 2020**). Despite the seemingly broad geographic distribution, there are many areas in which they are largely absent such as Neotropical and African lowland rainforests and whilst much is known about the biogeography of Ericoid mycorrhiza plants we have very limited knowledge about the diversity and distribution of ericoid mycorrhiza fungi (**Kohout, 2017**). Ericoid mycorrhiza are endophytes and, are structurally characterized by the formation of coils within the epidermal cells of the fine root hairs of a plant host, with the formation of a loose external hyphal network. These intracellular coils are different to the arbuscules formed by arbuscular mycorrhiza, however, they are also the sites of nutrient/carbohydrate exchange and may be densely clustered or loosely arranged. Often occurring in nutrient poor soils, with complex forms of organic matter, ErM seem to specialize in environments with considerable climatic and edaphic stresses (**Cairney and Meharg, 2003**). For example, ericoid mycorrhiza are able to develop resistance to toxic metals such as lead, and may therefore develop the ability to colonize similarly polluted soils. Moreover, it may be the very physiological attributes that have evolved to facilitate the survival of ErM in naturally high-stress environments that may confer resistances to metals which have similar modes of toxicity, thereby enabling survival in heavily polluted soils (**Coninx *et al.* 2017; Herrera *et al.* 2018**). **Cairney and Meharg, (2003**) revealed that such adaptations may include enzymes that are resistant to inactivation by metal binding, the ability of membranes to withstand attack from oxygen radicals, and the production of proteins with the ability to detoxify potentially toxic metals. Whereas arbuscular mycorrhiza and ectomycorrhiza are important for many of our food and timber crops, the direct economic relevance of ericoid mycorrhiza appears to be less. However, ericoid mycorrhiza inoculation may be beneficial in the fruit crops of cranberries and blueberries (**Scagel, 2005**).

Orchid mycorrhizas associate exclusively with Orchidaceae, which represents the world's biggest family in plant kingdom (**Xing *et al.* 2017; Gao *et al.* 2020**). The small size of orchid seed, with few food reserves, leads to a dependence on OrM for germination and early seedling development (**Smith and Read, 2010**). At initiation, the fungal hyphae penetrate cortical cells and form complex coiled or branched structures, called pelotons, as the primary site of nutrient/carbohydrate exchange. At maturity, although most orchids are photosynthetically active, there are around 100 species that are achlorophyllous and are therefore dependant on their fungal partners for the whole of their lifecycle. These species are known as myco-heterotrophs (**Leake, 2005**). The lifecycle of orchid mycorrhizas is further complicated by the growing body of evidence showing that both photosynthetic and myco-heterotrophic orchids may indirectly derive carbon from neighbouring trees (**Dearnaley, 2007**). In one study of the orchid species *Epipactis microphylla*, 78% of root samples were found to be colonized by ectomycorrhiza from the genus *Tuber*. Under microscope, it was observed that these ectomycorrhiza species were forming OrM-like mycorrhizae complete with pelotons and with some colonizing surrounding trees also (**Selosse *et al.* 2004**). Orchid mycorrhizas are one of the least studied of all the mycorrhizae classifications and clearly there is more work to be done in the future. The economic importance of orchid mycorrhizas may not be immediately obvious, but vanilla is an orchid-derived crop and a global trade in horticultural orchids is well established. For example, in 2012, the value of globally traded orchid cut flower stems was US$ 504 million (**De, 2015**).

Mycorrhizal fungi are clearly ubiquitous and of great importance for life on earth. However, they may also be one of the oldest symbiotic associations that we have evidence for. Fossilized evidence of plant spores suggests an appearance of land plants *c.* 470 million years ago, within the Ordovician period, and these first arrivals were likely dominated by non-vascular land plants growing in damp environments and on continental surfaces (**Rubinstein *et al.* 2010**). Incredibly, the first fossil evidence for fungi considerably predates this. Microfossils from estuarine environments, dated to1–0.9-billion years old have been located in Canada and assigned to the species *Ourasphaira giraldae* (**Loron *et al.* 2019**). It is possible that terrestrial fungi may have predated terrestrial plants but the first evidence for mycorrhizae also appears in the Ordovician period, around 460 million years ago with the appearance of Glomales-like fungi. This raises the intriguing prospect that mycorrhizae may have had a pivotal role in the colonisation of land by plants and have been integral in their evolutionary history.

Figure 1 An example of large epigeous sporocarps formed by ectomycorrhiza. The edible fungi species *Leccinum versipelle* found growing in September 2020 with *Betula pendula* in Scotland, UK. Photographs taken by Dr. P W Thomas.

LICHENS AS THE SECOND MODEL OF FUNGAL SYMBIOSIS

Lichens are unique structures formed by an association between fungi and algae or cyanobacteria, by developing a unique morphological form that is separate from either component organism (**Elkhateeb and Daba, 2019; Elkhateeb *et al.* 2020**). In this often-mutualistic relationship, the fungus and the algae are referred as mycobiont and the phycobiont (**Sharma and Mohammad, 2020**) respectively. The mycobiont component most commonly belongs to the Ascomycetes, however, some may be Basidiomycetes and may even form mushroom-like spore bearing structures. The Phycobiont component belongs to the divisions Chlorophyta and Cyanophyta (**Shukla *et al.* 2010; Daba *et al.* 2019; Elkhateeb and Daba, 2020**). Lichens can grow on a range of surfaces from rocks to existing as epiphytes on trees or leaves (Fabian *et al.* 2005). The majority of described lichens are terrestrial, although a few are marine and have the ability to adapt to water and saline stress. Other lichens may adapt to other stressors, like extreme temperature and air pollutants (**Nash, 2008**). Interactions between the symbiotic partners explain this spectacular success of lichens in unusual environments (**Bačkor and Fahselt, 2008**). The vegetative component of lichen is called the thallus and this can be subdivided into four main categories. Foliose: A leaf-like thallus, attached to the substrate at various points. Crustose: A thallus which is flattened against the substrate and its lower surface is entirely attached. Fruticose: the thallus is mainly composed of pendulous or, less commonly, upright branches and is attached at a single point. Squamulose: In which the thallus begins like a foliose lichen, but subsequently develops erect branches named podetia (**Clair *et al.* 2002; Solhaug *et al.* 2009; Nayaka, S. 2014; Monge-Najera J. 2019**).

Lichens are an excellent example of a symbiotic relationship between members belonging to two different separated kingdoms fungi and algae, which results in the production of secondary metabolites (**Goga *et al.* 2020; Elkhateeb and Daba, 2020**). Biological valuation of secondary metabolites from lichens showed that they were produced as a defence compounds to protect themselves against microbes and other predators. Lichens are known to produce aliphatic and aromatic compounds of low molecular weight (**Ahmed *et al.* 2017**). Furthermore, lichens are a rich source of biologically active compounds and theses are significantly understudied. These metabolites can be fungal created and/or algal

created, and some compounds are not produced by either fungi or algae individually. Lichens have a rich history of use in traditional medicine and also have attracted modern-day attention of researchers screening for novel compounds capable of curing several target diseases, as well as supporting currently used compounds (**Malhotra *et al.* 2008; Podterob AP. 2008; Molnár K, Farkas E. 2010; Mitrović *et al.* 2011; Ranković, 2015; Crawford, 2019**).
The ideal environment for growing lichens are very cold and dry conditions. However, lichens can survive high temperatures, drought, inundation, salinity, high concentrations of air pollutants, continuous light and nutrient-poor and highly nitrified environments (**Joel and Martin, 2005; Hawksworth, 2015; Ahmed *et al.* 2017; Elkhateeb and Daba, 2019; 2020; Elkhateeb *et al.* 2020**). These extreme conditions encourage the elaboration of lichen substances. Lichens have been evaluated with three layers and each layer has its own specificity. These are surface layer (upper cortex, mycobiont only present in this layer), algal layer (the symbiotic partner algae is present), and medullar layer (**Knut *et al.* 2009**).

LICHENS SIGN OF SYMBIOTIC ASSOCIATION

Lichen fungi govern to the mycobiont and algae or cyanobacteria belongs to the photobionts communities which execute part of photosynthesis in symbiotic relationship. Ascomycetes (98%) have been identified as dominant fungi in lichens over basidiomycetes (0.3%) (**DePriest, 2004**). Basidiomycetes were discovered in 52 lichen genera sourced from various areas around the globe, basidiomycetes were especially common in lichens from the *Parmeliaceae* (**Spribille *et al.* 2016**). Cyanobacterial photobionts additionally get from different genera, three of the most widely recognized being *Nostoc*, *Scytonema*, and the recently described *Rhizonema* (**Lücking *et al.* 2009**). Lichen secondary metabolites are produced by fungi and comparatively low molecular weight chemical substances (**Türk *et al.* 2006**). The lichen has different functional layers and each functional layer accumulates specific secondary metabolites such as upper cortex which is mycobiont layer (accumulates atranorin, parietin, usnic acid, fungal melanins), medullary layer (accumulates physodic acid, physodalic acid, protocetraric acid), and an algal layer which is having photobionts. The cell wall of the photobionts is more permeable and some of the carbohydrates are synthesised via photosynthesis and become available to the fungi. Symbiosis can be existed with either single or two photosynthetic partners. For instance, *Cephalodiate* species contains two photosynthetic partners such as green alga and cyanobacteria in which green alga act as primary photobionts (**Bhattacharyya *et al.* 2016**).

CHEMICAL SIGNALING IN SYMBIOSIS

Cooperation's between the mycobiont and photobionts are basic for lichen interaction and these connections start before the mycobiont and photobionts to reach one another. After finding a suitable photobionts for survival, lichen fungi can be reproduced by releasing of isolated spores, (**Eaton *et al.* 2018**). The mechanism of interactions is recognised as mycobiont hyphae closely contact and start covering the photobionts cells (**Lauterwein *et al.* 1995**). This kind of close proximity and contact causes alteration in gene expression of photobionts and mycobiont and the mycobiont starts growing in the direction of photobionts (**Weckessera *et al.* 2007**). The most popular perception for the establishment of the fungi and algae symbiosis is, mycobiont releases lectins which enhance attraction and binding capacities to each other (**Cardarelli *et al.* 1997**). Lectins are sugar binding proteins and can make interactions to the external environment and between cells. For instance, *Peltigera canina* releases lectins and act as a chemo attractant to *nostoc* cells. The lectin concept has been proved by observing the up regulation of lectin genes in presence of photobionts (**Ernst-Russell *et al.* 1999**) and eventually plays a key role in selecting suitable photobionts partner in symbiotic relation. It has been proposed that one symbiotic likely controls the development of the other, with a dominance of proof demonstrating it is the mycobiont that controls development of the photobionts. The lichen chemical substances such as usnic acid, vulpinic acid and lichen extract harness the cell division of photobionts (**Correche *et al.* 2004**).

LICHENS SECONDARY METABOLITES

Lichen substances accumulations vary based on many factors including geographic location, microhabitat conditions and altitude. For instance, *Lecanora rupicola* is found in both the northern and southern hemispheres but the presences of xanthones is more prevalent in its Mediterranean range (**Elkhateeb and Daba, 2020; Elkhateeb *et al.* 2020**). Interestingly, lichen substances are completely different to those produced by the symbionts grown in isolation. This can be seen clearly in the case of *Lecanora dispersa*, which produces a large quantity of 2, 7-dichlorolichexanthone. However, when the fungi are cultured in the absence of algae, pannarin and depsidones are found to accumulate more than 2, 7-dichlorolichexanthone (**Kon *et al.* 1997**).
Polysaccharides derived from lichens are reported to have many biological activities, such as antitumor, antiviral, and immunostimulatory properties (**El-Garawani *et al.* 2020**). Depsidones and fatty acids are found to accumulate in *Parmelia stygia* (**Mischenko *et al.* 1984**). *Cladonia foliacea, Dermatocarpon miniatum, Neofuscella pulla, Everinia divaricata* and *Evernia prunastri* lichens are reported to exhibit antioxidant and antimicrobial properties (**Aslan *et al.* 2006**). Carotenoids have also been extracted from the genera of *Cladonia, Lobaria, Stereocaulon, Nephroma* and *Sticta* (**Czeczuga *et al.* 1988**). Depsidones are considered to be more powerful antioxidants than depsides. The reason behind the biological activities of depsidones is due to incorporation into lipidic microdomains. Rigid polycyclic ring of depsidones have great potential against integrase of HIV- 1 (**Neamati *et al.* 1997**).

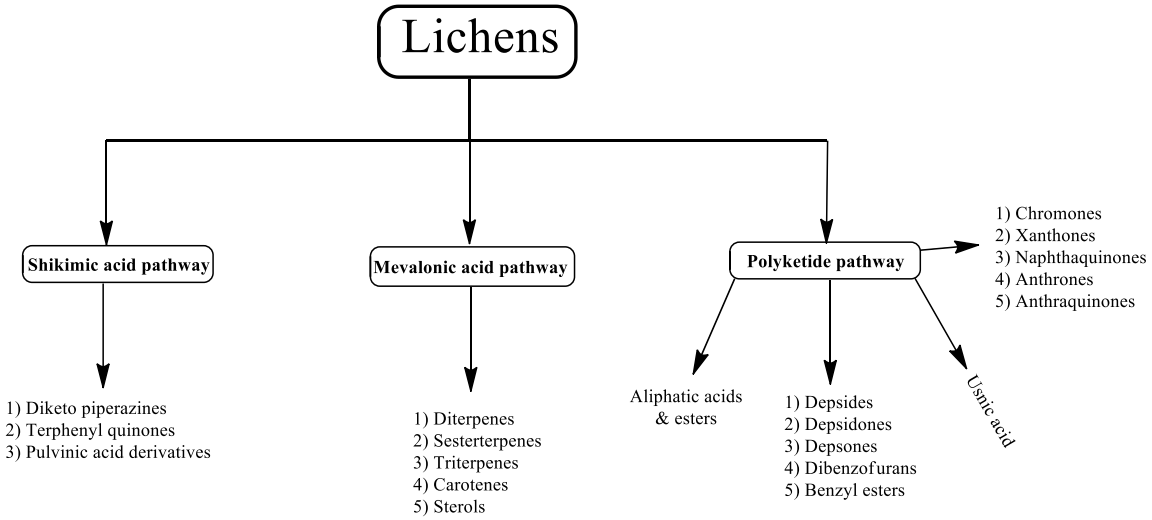

Figure 2 Schematic representation of Lichens carbon metabolism for the biosynthesis of major class

Lichens have a rich history of use by humans and this includes as a component of folk medicines, dyes and as perfumes (**Kristiina *et al.* 2005**). Historically, different genera of lichens have been used in the treatment of many of diseases. *Evernia, Peltigera, Parmelia, Cladonia, Rocella* and *Pertusaria* have been identified, based on their specific bio-activity, to have therapeutic potential in the treatment of epilepsy, diarrhoea, infections, convulsions and fever (**Kumar *et al.* 1996**). The foliose lichen of *Peltigera caninna* is used for the treatment of liver ailments and its effectivity can be explained due to the presence of a high methionine content (**Subramanian and Ramakrishnan, 1964**). Historically, the Perso-Arabic traditional medicine system known as "Unani" or "Yunani" also detailed the potential of lichens in curing various diseases such as inflammation, vomiting, stomach disorder, pain in liver, vesicular calculus, amenorrhea and treatment of wounds (**Kirtikar and Basu, 1984**). There are three major metabolic pathways such as 1) polymelanoate, 2) shikimic acid and 3) mevalonic acid pathways (**Joel and Martin, 2005**). Polymalonate pathway: Secondary metabolites of lichens synthesised from this pathway are unique class of functional groups such as depsides, and depsidones (**Chialvo *et al.* 2018; Ranković and Kosanić, 2021**). Depsides are esters of phenyl carboxylic acids

with a phenyl benzoate skeleton, while depsidones are synthesised from depsides by insertion of oxygen linkage between two phenyl rings. This can be accomplished only when consolidation of fungi and algae woven together. Shikimic acid pathway: This pathway embodies the synthesis of biologically potential functional groups such as pulvinic acid and terphenylquinone. These lichen substances are achieved through the articulation of two phenylpyruvate units. Stictaceae family of lichens are being major source for these molecules. Mevalonic acid pathway: Secondary metabolites are synthesised via the mevalonic acid pathway are mainly terpenes. Diterpenes are identified in little number, up to now Nephrene and 16a-Hydroxycuarene have been recognized from lichens. Triterpene are identified in more number, comparing to diterpenes for instance twenty different functional groups of triterpene have been identified. Zeroin is being major triterpene which is present in different lichens. These are the main concerns in developing the diversity of secondary metabolites in lichens. Lichen bioactive principles are largely obtained through the polyketide pathway while rest of the lichen substances are formed from the shikimic and mevalonic acid pathway (**Joel and Martin, 2005**) (Figure 2). **Rezanka *et al***, (2003) have identified xanthone glucosides and **Torres *et al***. (2004) from *Collema cristatum* have identified mycosporine collemin A. Some of the important lichen metabolites isolated from different lichen species have been depicted in figure 3.

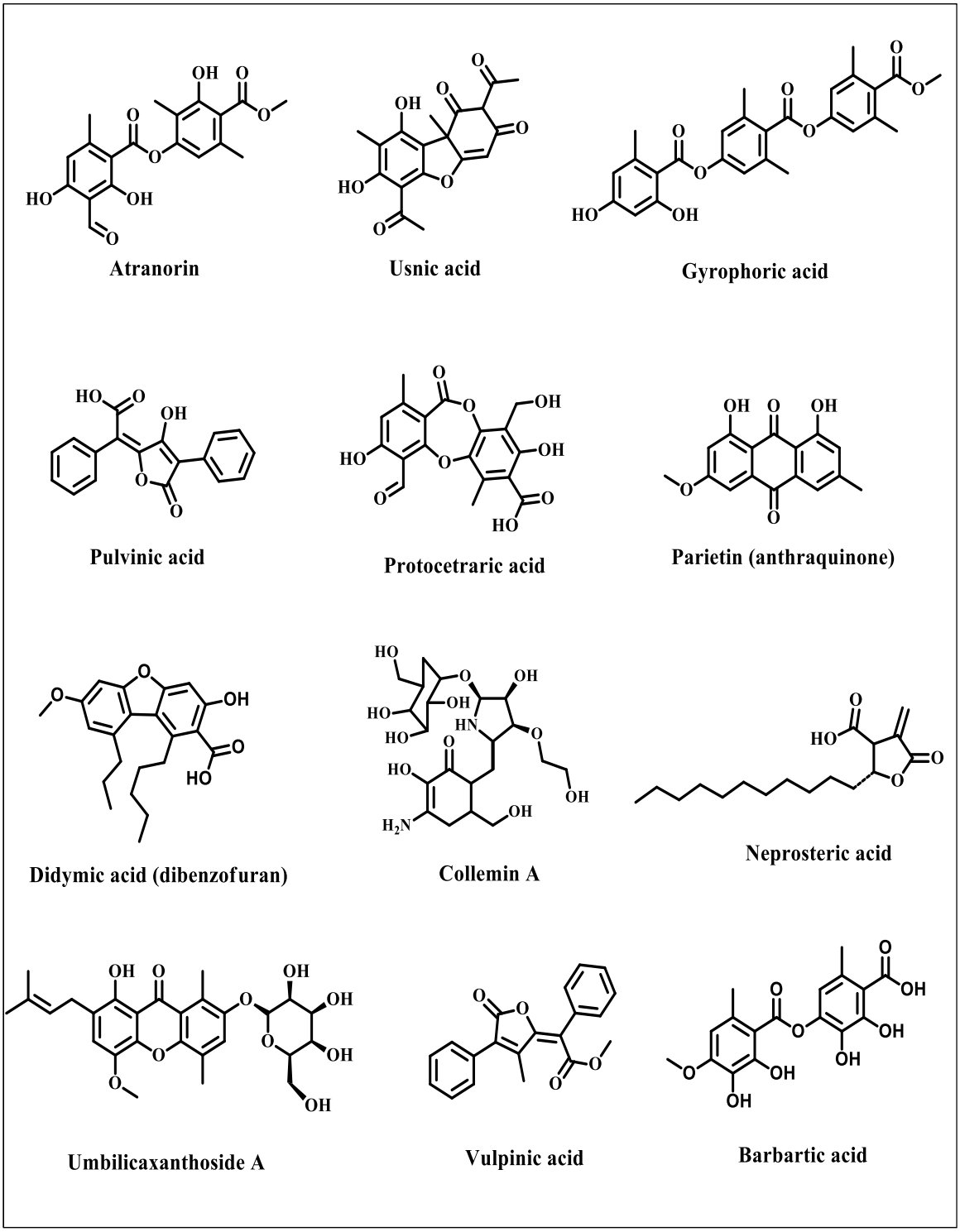

Figure 3 Important secondary metabolites of lichen species

IMPORTANCE OF LICHEN SUBSTANCES

Most of the lichen secondary metabolites exhibit significant biological activities. For instance, Usnic acid exhibits several biological properties such as antimicrobial, larvicidal, anticancer, and UV absorption etc. (**Ahmed *et al.* 2017; Elkhateeb and Daba, 2019; Elkhateeb and Daba, 2020; Elkhateeb *et al.* 2020**).

Antibiotic activity

Screening of lichen extracts and isolation of bioactive molecules started in 1950, against mycobacterium and gram positive bacteria. In addition to these biological activities, extracts of lichens and their isolated molecules have also been evaluated against gram positive and negative bacteria and yeasts as well (**Bhattacharyya *et al.* 2016**). Usnic acid has significant biological profile against pathogenic gram +ve organisms and anaerobic bacteria (**Türk *et al.* 2006**). In addition, usnic acid has also been used in topical preparations, toothpastes and mouth washes. Lichen compounds significantly inhibit bacterial growth at lower concentration, while comparing with other antibiotics (**Bhattacharyya *et al.* 2016**).

ANTITUMOUR AND ANTIMUTAGENIC ACTIVITY

Lichen extracts and their substance have been investigated for antitumor and antimutagenic activities (**El-Garawani *et al.* 2019; 2020**). Usnic acid is class of dibenzofuran functional group and it has multiple biological activities. It shows antitumor activity against Lewis Lung carcinoma and P388 leukaemia through the mechanism of mitosis inhibition and apoptotic induction (**Galanty *et al.* 2019; Macedo *et al.* 2020**). Interestingly, depside and depsidone series, for example 1^1-chloropannarin and sphaerophorin have shown higher cytotoxicity than colchicine against cell cultures of lymphocytes. (**Correche *et al.* 2004**).

ANTIOXIDANT ACTIVITY

Free radicals play an essential key role in biochemical process in the cell. They present as hydroxyl radicals, superoxide anions, and hydrogen peroxides and nitric oxides in cells (**Prescott and Bottle, 2017; Żukowski *et al.* 2018; Sharma *et al.* 2018**). These reactive oxygen species binds to nucleic acids, proteins, unsaturated fatty acids adversely affect their structure, in addition chronic diseases, such as Alzheimer's disease, atherosclerosis, emphysema, hemochromatosis, many forms of cancer (for instance, melanoma), Parkinson's disease, may be related to free radicals. Free radicals also obtained through the mechanism of oxidative stress. The oxidative stress is also exhibited in lichen thalli, and bioactive principles were derived to protect against radicals derived by UV light (**Ahmed *et al.* 2017**).

Lichens secondary metabolites having strong antioxidant properties and act as scavengers for free radicals. Depsides; atranorin and divaricatic acid, depsidones; pannarin and 1'-chloropannarin, exhibited the antioxidant activities. Moreover, lichens growing in Antarctica could get affected by low temperature, darkness, drought, and high UV- B and solar irradiation conditions. These conditions provoke for the development of secondary metabolites which are sustainable to oxidative stress (**Heng Luo *et al.* 2009**).

ANTIMICROBIAL ACTIVITY

Lichen substances are derived for defence against most of the pathogens in nature. There are several interesting examples found reported in literature. Atranorin (isolated from *Physcia aipolia*), fumarprotocetraric acid (*Cladonia furcata*), gyrophoric acid (*Umbilicaria polyphylla*), lecanoric acid (*Ochrolechia androgyna*), physodic acid (*Hypogymnia physodes*), protocetraric acid [*Flavoparmelia caperata* (as *Parmelia caperata*)], stictic acid [*Xanthoparmelia conspersa* (as *Parmelia conspersa*)] and usnic acid (*Flavoparmelia caperata*) exhibited potential antimicrobial effects against six types of bacteria and ten types of fungi, including human, animal, plant pathogens, mycotoxin producers and food-spoilage organisms (**Branislav and Marijana, 2008**). Usnic acid was found to be a good antimicrobial agent when compared to streptomycin (**Moura *et al.* 2017**). The depsidone molecules of physodic acid and stictic acid were identified as the weakest. The lichen, *Protousnea poeppigii* extracts (DCM, MeOH) showed potential activity against fungal pathogens such as *Microsporum gypseum*, *Trichophyton rubrum* and *T. mentagrophytes*. Also these extracts showed higher activities against *Candida albicans*, *C. tropicalis*, *Saccharomyces cerevisiae* and *Aspergillus niger*, *A. fumigatus* and *A. flavus* (**Guillermo *et al.* 2008; Babita *et al.* 2008; Shukla *et al.* 2010**). The secondary metabolites of lichen and their biological activities have been given in table 1.

Table 1 The secondary metabolites of lichen species and their biological activities

No.	Lichen species	Isolated molecules	Bioactivity	References
1	*Cladonia* spp.	Usnic acid and other lichen acids	Antibiotic	**Moura *et al.* 2017**
2	*Cladonia arbuscula*	(+)-usnic acid	Antimycobacterial activity	**Noël *et al.* 2020**
3	*Cladonia leptoclada*	(–) usnic acid	Anti-tumour	**Kumar *et al.* 2019**
4	*Pseudocyphellaria glabra* *Pseudocyphellaria homoeophylla*	Usnic acid	Antiviral, antimicrobial and Cytotoxic	**Odimegwu *et al.* 2019; Bhattacharjya *et al.* 2020**
5	*Lecanora hybocarpa*	Naphthazarin dimer, substituted pentacyclic hybocarpone	Cytotoxic	**Sadegh Vishkaei *et al.* 2016**
6	*Lobaria pulmonaria*	Depsidones and melanins	Pigments for light screening	**Goncu *et al.* 2020**
7	*Erioderma chilense*	Depsidones 1-chloropannarin & pannarin	Antioxidant	**Bhattacharyya *et al.* 2016**
8	*Alectoria ochroleuca*	Vulpinic and (–) usnic acid	Antifungal	**Gylfason, 2019**
9	*Cetraria islandica*	Fumaroprotocetraric and protocetraric acid.	HIV-1 reverse transcriptase inhibitor	**Freysdottir *et al.* 2008**
10	*Evernia prunastrii*	Orsellic acid, orcinol, orcinol monomethyl ether, usnic acid, everninic acid, methyl evernate, evernyl 3,5-dimethoxy toluene, ethyl evernate, evernic acid and atranorin.	Perfumes production	**Calchera *et al.* 2019**
11	*Flavoparmelia caperata*	Polysaccharide (PC 2)	Enhancing long term potentiation	**Hirano *et al.* 2003**
12	*Hypotrachyna revolute*	80-methylmenegazziaic acid	Antioxidant	**Fernández-Moriano *et al.* 2016**
13	*Lethariella canariensis*	Atranol, chloroatranol, methyl β-orsellinate, methyl hematommate, ethyl hematommate.	Antioxidant, phytotoxic	**Marante *et al.* 2003**
14	*Parmelia stygia*	Fumaroprotocetraric acid depsidones	Smooth muscle relaxant	**Mischenko *et al.* 1984**
15	*Protousnea poeppigii*	Isodivaricatic acid, 5-propylresorcinol, divaricatic-acid, usnic acid	Antiprotozoal, antifungal	**Schmeda-Hirschmann *et al.* 2008**
16	*Pseudevemia furfuracea*	Physodic acid, chloro-atranorin, atranorin, and olivetoric acid	Antimicrobial	**Türk *et al.* 2006**
17	*Protousnea* spp.	Resorcinol derivative	Tyrosinase inhibition	**Kinoshista *et al.* 1994**

18	*Pseudoevernia furfuracea*	D-Usnic acid, evernic acid and atranorin	Anti-Allergy	**Sarikurkcu *et al.* 2016**
19	*Thamnolia subuliformis*	Rhamnopyranosyl galactofuranan	Immunilogically active	**Olafsdottir *et al.* 2003**
20	*Ramalina farinacea*	(+)-Usnic Acid, Norstictic Acid, and Protocetraric Acid	Antimicrobial	**Tay *et al.* 2004**
21	*Stereocaulon alpinum*	Lobaric acid	Inhibit 5-lipoxygenase from porcine leukocytes	**Ingolfsdottir *et al.* 1997**
22	*Stereocaulon ramulosum*	Methyl haematommate	Antifungal	**Hickey *et al.* 1990**
23	*Caloplaca species*	Anthraquinone	Broad-spectrum antimicrobial	**Manojlovic *et al.* 2005**
24	*Xanthoria parietina Thelotrematateaceae*	Parietin	UV-protecting agent	**Wolseley *et al.* 2009**
25	*Umblicaria Antarctica*	Gyrophoric acid, lecanoric acid, and methyl orsellinate	PTP1B Inhibition	**Shukla *et al.* 2010**
26	*Usnea campestris*	Usnic acid	Antimicrobial	**Yousuf and Choudhary, 2014**
27	*Usnea diffracta*	Diffractaic acid usnic acid	Analgesic & antipyretic	**Okuyama *et al.* 1995**
28	*Usnea diffracta*	Diffractaic acid & usnic acid	Anti-inflammatory	**Xu *et al.* 2018**
29	*Usnea diffracta*	Decarboxy stenosporic acid	Antibacterial activity against *Staphyrococcus aurens*	**Okuyama *et al.* 1995**
30	*Usnea longissima*	Usnic acid, depside	Inhibit photosystem II	**Takahagi *et al.* 2008**
31	*Usnea longissima*	Usnic acid	Inhibit plant growth	**Siddiqi *et al.* 2018**
32	*Usnea longissima*	Lichesterinic, evernic acid, and (+)- usnic	Inhibit Epstein-Barr virus	**Yamamoto *et al.* 1995**
33	*Usnea misaminensis*	Usnic acid	Relaxant of smooth muscle	**Rawat *et al.* 2006**
34	Cladonia furcata, Umbilicaria polyphylla, Hypogymnia physodes.	Fumarprotocetraric acid, physodic acid, gyrophoric acid.	Antimicrobial activity	**Ranković *et al.* 2009**
35	*Parmotrema dilatatum, Parmotrema tinctorum, Pseudoparmelia sphaerospora*.	usnic acid, orsellinic acid esters, salazinic acid	Anti *Mycobacterium tuberculosis*	**Honda *et al.* 2010**
36	*Cladonia gracilis, Ramalina dendriscoides, Usnea baileyi, Stereocaulon massartianum.*	Usnic acid, barbatic acid, norstictic acid, stictic acid, salazinic acid, galbinic acid, and diffractaic acid	Antibacterial activity against *Bacillus subtilis Staphyrococcus aurens Escherichia coli Pseudomonas aeruginosa*	**Santiago *et al.* 2010**
37	*Cladia aggregate*	Barbatic acid	Inhibits the growth of *Staphyrococcus aurens*	**Martins *et al.* 2010**
38	*Ramalina terebrata*	Usnic acid, Usimine A, Usimine B, Usimine C	Inhibits the growth of *Bacillus subtilis Staphyrococcus aurens Escherichia coli Pseudomonas aeruginosa*	**Paudel *et al.* 2010**
39	*Evernia divaricate*	Divaricatinic acid, 2-O-Methylnordivaricatic acid, divaric acid, 2,4-di-Omethyldivaric acid	Antibacterial activity *Bacillus subtilis Staphyrococcus aurens Pseudomonas aeruginosa*	**Yuan *et al.* 2010**
40	*Hypogymnia physodes*	Physodic acid	Active against *Bacillus mycoides*	**Ranković *et al.* 2008**
41	*Parmelia caperata*	Usnic acid	Active against *Bacillus subtilis*	**Ranković *et al.* 2008**
42	*Physcia aipolia*	Atranorin	Active against *Enterobacter cloacae*	**Ranković *et al.* 2008**
43	*Umbilicaria polyphylla*	Gyrophoric acid	Active against *Escherichia coli Klebsiella Pneumoniae Staphylococcus aureus*	**Ranković *et al.* 2008**
46	*Cetraria islandica*	(+)-protolichesterinic acid	Active against *Staphylococcus aureus*	**Ingolfsdottir *et al.* 1997**
47	*Cladonia stellaris*	(-)-Usnic acid		**Elo *et al.* 2007**
48	*Letharia vulpine*	Vulpinic acid		**Shrestha *et al.* 2016**
49	*Alectoria sarmentosa*	(-)-usnic acid, physodic acid, alectosarmentin, and 8^1-O-ethyl palectoronic acid	Active against *Staphylococcus aureus* and *Mycobacterium semgmatis*	**Gollapudi *et al.* 1994**
50	*Lobaria kurokawae*	Retigeric acid A (RA) Retigeric acid B (RB)	Both RA & RB shown cytotoxic activity against DU145, MCF-7, RWPE1, Human hTERT-RPE1, Human osteosarcoma	**Liu *et al.* 2010**

			U2OS and Saos2	
51	*Pseudevernia furfuracea*	Olivetoric acid	Antiangiogenic activity	**Koparal *et al.* 2010**
52	*Xanthoparmelia somloensis*	(+) usnic acid	Gyrophoric acid usnic acid exhibited wound healing activity on HaCaT cells	**Kanigowski *et al.* 2016**
53	*Lasallia pustulata*	Gyrophoric acid		**Doherty *et al.* 2014**
54	*Cornicularia epiphorella*	Epiphorellic acid-1	Both molecules exhibited apoptotic activity	**Basnet *et al.* 2018**
55	*Sphaerophorus globosus*	Sphaerophorin		**Russo *et al.* 2008**

CONCLUSION

Importance of mycorrhiza and lichens, which are existing everywhere and have admired contributions in traditional medicine all over the world, is currently of great interest. Moreover, a remarkable list of applications are based on mycorrhiza and lichens, starting from their use as nutrients and animal feed, moving to their use as a source of dyes, and use in many countries as indicators for air quality and changes in climate, and finally with the pharmaceutical uses of their substances (secondary metabolites). Further studies on mycorrhiza and lichens on their metabolites are highly required to get optimum benefits from these valuable symbiosis between fungi and algae and plant

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