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LICHEN AS A FUTURE SOURCE FOR NEW ANTIFUNGALS

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ABSTRACT

Lichen species are extremely environmentally adaptive and can be found in the arctic or thermal vents, on rocks, non fertile soils, as well as on various plants and organisms. Among those strategies, the production of secondary metabolites protrudes. Secondary metabolites are chemical compounds synthesized by plants to accomplish specific functions related with plant protection and species survival, so the presence of lichens make it a potential source of phytochemicals with antifungal activity of plant and human importance. The present review compiles recent information of research related to different types of secondary metabolites (glycosides, phenolic compounds, alkaloids and terpenes) present in species of the lichens and that have demonstrated some type of activity against fungi, including *in vitro* and *in vivo* studies, as well as their structure-activity relationship and action mechanisms.

INTRODUCTION

Lichens are a symbiotic association between a fungal partner, the mycobiont, and a photosynthetic partner, the photobiont. Usually, 95% of its body, named thallus is composed of the lichenized fungi, whose hyphae envelop the photobiont population (Hale, 1974). In most lichens, the mycobiont is an *Ascomycota* or in a minority of cases, a *Basidiomycota*. About 20% of all known fungal species are lichenized (Begon et al. 2006). The lichenization is a highly advantageous process for the fungal partner, and happens several times in different moments and diverse taxonomic groups in the evolutionary history of the kingdom, Fungi. Globally, there are estimated to be approximately 13,500 lichen species. Lichens have a history of medicinal use and Beneficial claims have been correlated, to some extent, with their polysaccharide contents. The unique biochemical compounds produced by lichens have made them useful for people in traditional cultures as a food source, for dyes, fragrances and as medicines (Galun, 1988). Lichens grow on all continents and species distribution is influenced by a range of variables, including both climate and aspect. It is estimated that lichens are the dominant vegetation on 8% of the earth's terrestrial surface. Hence, lichens are a part of many food webs; including humans, vertebrates, and invertebrates. Lichens are used as a regular food source in Africa, America, Asia and Europe, and occasionally as a delicacy or a desert. Even though some lichens are thought to be amongst the oldest living organisms on Earth, as a general rule they are less familiar than vascular plants and are frequently grouped with fungi or with mosses in many studies (Richardson, 1988; Richardson, 1991; Shukla et al., 2010).

More recently, research has expanded to include secondary metabolites produced by lichens (Shrestha and Clair, 2013). Lichens have been historically used as dyes, perfumes, and home remedies in folk medicine (Shukla et al., 2010; Zambare and Christopher, 2012). The 'Indian Medicinal Plant'(1984) describes the medicinal properties of lichens used for the treatment of blood and heart diseases, leprosy, bronchitis, bleeding pile, asthma, inflammation, liver, and stomach diseases. The lichen species are extremely environmentally adaptive and can be found in the arctic or thermal vents, on rocks, non fertile soils, as well as on various plants and organisms (Seymour et al., 2005). The presence of secondary metabolites in plants makes them natural sources of remedies, used as natural medicines by local population in diseases treatment including fungal, bacterial and viral infections (Dandapat and Paul, 2019**).** Fungi comprise a major part of biodiversity, from around 100,000 known fungal species, more than 400 species are known as animal and plant pathogens (Garrido et al., 2010). Worldwide occurrence of fungal infections, has been dramatically increased in the last 20 years, due to a continuous increase mainly among immunocompromised hosts, they produce serious invasive mycoses in individuals submitted to organ transplants, cancer, and diabetes mellitus (Scorzoni et al., 2007; Razzaghi and Rai, 2013). Superficial mycoses are among the most frequent forms of human infections (those involving the skin and mucosal surfaces) not only in immunocompromised host, but also in healthy individuals, being estimated to affect more than 20-25% of the world's population (Vena et al., 2012 ;Razzaghi and Rai, 2013). Dermatophytes are the most common cause of skin infections and they can achieve this due to virulence factors such as their ability to adhere and invade keratinized tissues (Rodríguez and Santa, 2012). New data indicate that relative proportions of organisms causing nosocomial bloodstream infections have changed over the last decade, with *Candida* species now firmly established as one of the most frequent agents. *Candida albicans* is part of human flora but under some circumstances in susceptible individuals it can cause systemic and superficial infections (Rodríguez and Santa, 2012), while systimatic fungal infections (is mainly due to the increasing number of immunocompromised individuals with altered immune function including primary immune deficiency, cancer chemotherapy, HIV/AIDS, hematologic and solid organ transplantation, prematurity, and immune-modulatory medications (Brown et al., 2012; Lass, 2017). Invasive aspergillosis, an infection caused by fungi of the Aspergillus taxon, remains a significant threat, particularly in immunosuppressed patients (Kullberg and Oude, 2002). The most prevalent Aspergillus species are A. fumigatus, A. flavus, A. terreus, and A. niger (Sugui et al., 2014). Aspergillus spp. has the capacity to cause a broad range of clinical diseases, from mild and superficial infections, to life-threatening and invasive illnesses with more than 80% mortality rate (Mayr and Lass, 2011). Pulmonary aspergillosis is considered the most prevalent manifestation of invasive aspergillosis (Erjavec et al., 2009). Nowadays antifungal drugs are essentially limited to three chemical classes: polyenes (amphotericin B), azole drugs (imidazoles, fluconazole, itraconazole, voriconazole and posaconazole) and echinocandins (Maertens, 2004; Patterson et al., 2016); isavuconazole has been described as a new extended-spectrum triazole (Miceli and Kauffman, 2015; Garcia et al., 2017). These agents display several limitations that can lead to complications; for example, amphotericin B was during nearly 30 years the only drug, and it is one of the few drugs that kill fungal cells, but can cause significant nephrotoxicity in patients (Razzaghi and Rai, 2013), with a rapid development of fungal resistance (specially to azoles and to flucytosine), drug-drug interactions, fungistatic but not fungicidal mode of action. Thus, there is an urgent need for developing new antifungals with a broad spectrum and with fewer dose-limiting side effects (Graybill, 1996; Maertens and Boogaerts, 2000). On the other hand, plants can experience fungal infections too. Fungal plant pathogens comprise an important group of microorganisms that causes significant economic losses in agriculture around the world, such as they can infect any tissue at any stage of plant growth (Garrido et al., 2010). Plant diseases control depends upon the application of chemical fungicides, despite their potentially toxic effects on non-target organisms and the environment (Santos et al., 2008; Ferrer et al., 2009). Although effective, their extensive use for several decades has disrupted biological control by natural enemies and has led to new pathogen strains that are resistant to fungicides (Fernandez et al., 2006). Despite the huge amount of information about fungal plant pathogens, there is a limited commercial fungicide developed from a new knowledge approach. The absence of fungicides that can act in more than one site of action is a direct consequence of fungal resistance, which is common among currently used agrochemicals (Brent and Hollomon, 1995; Arango et al., 2004). The aim of this review is to present the state of art of antifungal activity of secondary metabolites present in lichens since, to our knowledge, there is not condensed information on this topic.

1.1. Production of secondary metabolites in Lichens:

Natural products-based medications have a very long history. Even today, people are making use of plant resources for the preparation of medicines to improve health conditions, mainly because of their efficacy and safety. A rich biodiversity of plants in nature is one among the major sources of natural medicines to treat and prevent diseases, and plant-based products are widely employed in many traditional medications by indigenous people around the world. According to the World Health Organization report, nearly 60% of the world's population relies on traditional medicinal practices and herb-based medicines to meet their health needs (Pereira et al., 2020).

Lichens are a known source of over 1,000 unique secondary metabolites (Bačkorová et al., 2012), which are produced by the fungus and secreted onto the hyphae surface. The multitude of compounds present in lichens provides us with the opportunity to discover new therapeutic agents. However, only a limited number of these metabolites have been screened for their bioactivities have been proposed (Table 1) (Bézivin et al., 2004; Suh et al., 2017). Lichenochemicals include but are not limited to chemical families, such as flavonoids (Calcott et al., 2018) and terpenoids (Zhang et al., 2016), tridepsides (Manojlović et al., 2012; Bačkorová et al., 2012; Kosanić et al., 2014), orsinol tridepsides, orcinol tetradepsides, aphthosin (Cardile et al., 2017), and phenolic compounds (Nguyen et al., 2017). For example, lichen compounds reported for Umbilicaria species include compounds with different aromatic, aliphatic and cyclic structures, such as lecanoric acid, gyrophoric acid, umbilicaric acid, and norstictic acid (Feige and Lumbsch, 1993), parietin (Plsíkova et al., 2014), myristic acid, palmitic acid, palmitoleic acid, stearic acid, oleic acid, linoleic acid and linolenic acid (Galindo et al., 2016). Histologically, lichen secondary metabolites are deposited in either the cortex or, more commonly, the medulla. The most usual cortical compounds are usnic acid and atranorin, but anthraquinones, pulvinic acid derivates, and xanthones may also occur here (Marques, 2013). Secondary metabolites are not absolutely essential for the survival and growth of lichens (Bentley 1999), and the functions of these compounds in the lichen symbioses are still poorly understood (Hager et al. 2008). However, it is important that they may help to protect the thalli against herbivores, pathogens, competitors, and external abiotic factors, such as high UV irradiation. Also, lichens have impact interactions with their environment.

1.2. Antifungal activity of Lichens:

There are many studies on the antifungal activity of lichen secondary metabolites. For example, atranorin (from Physcia aipolia), fumarprotocetraric acid (from Cladonia furcata), gyrophoric acid (from Umbilicaria polyphylla), lecanoric acid (from Ochrolechia androgyna), physodic acid (from Hypogymnia physodes), protocetraric acid (from Flavoparmelia caperata), stictic acid (from Xanthoparmelia conspersa), usnic acid (from Flavoparmelia caperata), obtusatic acid (from

Ramalina fraxinea), methyl evernate (from R. fastigiata), O-methyl anziaic acid (from Melanelia fuliginosa), divaricatic acid (from Evernia mesomorpha), and parietin (from Xanthoria parietina) showed relatively strong antimicrobial effects against numerous fungi, among which were human pathogens (Ranković et al. 2008; Basile et al. 2015; Ristić et al. 2016a, b). The lichen extract almost increased by twofold in the presence of the stock solution of the colloidal silver concentrate. The ointment containing extract of lichen Ramalina farinacea exhibited antimicrobial activities against Aspergillus niger and Candida albicans (Ofokansi and Esimone 2005). Ranković et al. (2007) tested aqueous, acetone and methanol extracts of Cladonia furcata, Parmelia caperata, Parmelia pertusa, Hypogymnia physodes, Umbilicaria polyphylla, Lasallia pustulata, Parmelia sulcata, Umbilicaria crustulosa and Umbilicaria cylindrica from Serbia on ten species of fungi. The strongest activity was observed with methanol extracts of Parmelia pertusa and Parmelia sulcata and the weakest activity was manifested by Parmelia caperata and Umbilicaria cylindrica. Aqueous extracts of all tested lichen species were inactive.

Table 1 Biological activity of compounds from some lichens

Compound	**Lichen**	**Biological Activities**
Atranorin	*Hypogymnia tubulosa*	Antimicrobial, antioxidant,
Usnic acid	*Usnea sp.*	antioxidant, antibacterial, antifungal
Evernic acid	*Evernia prunastri*	Antifungal, antibacterial, antioxidant,
Ramalin	*Ramalina terebrata*	Antioxidant, antimicrobial
Thamnolic acid	*Thamnolia vermicularis*	Antibacterial, antifungal
Umbilicaric acid	*Umbilicaria hoffm*	antimicrobial

Extracts of Andean lichens Protousnea poeppigii and Usnea florida demonstrated antimicrobial activity against the pathogenic fungi Microsporum gypseum, Trichophyton mentagrophytes and T. rubrum (Paudel et al. 2008). According to Schmeda-Hirschmann et al. (2008), dichloromethane and methanol extracts of Protousnea poeppigii had strong antifungal effects against the fungal pathogens Microsporum gypseum, Trichophyton mentagrophytes and T. rubrum. The extracts were also active against the yeasts Candida albicans, C. tropicalis, Saccharomyces cerevisiae and the filamentous fungi Aspergillus niger, A. flavus and A. fumigatus, but with much higher strength. In addition, antibacterial and antifungal activity of the acetone, methanol and aqueous extracts of the lichen Lecanora frustulosa and Parmeliopsis hyperopta has been screened in vitro against Aspergillus flavus, Aspergillus fumigatus, Botrytis cinerea, Candida albicans, Fusarium oxysporum, Mucor mucedo, Paecilomyces variotii, Penicillium purpurescens, Penicillium verrucosum and Trichoderma harsianum. Tested lichen species also showed strong activity against fungi (Kosanić et al. 2010). Candida albicans was the most sensitive fungal species examined. Mitrović et al. (2011) studied antifungal activity of methanol extracts of five lichen species (Flavoparmelia caperata, Evernia prunastri, Hypogymnia physodes and Cladonia foliacea). The antimicrobial activity was estimated by determination of the minimal inhibitory concentration by the broth microdilution method against ten species of fungi. Extract of Cladonia furcata was the most active antfungal agent with minimum inhibitory concentration values ranging from 0.78 to 25 mg/mL, while the lowest activity showed. Lecanora muralis. In similar research, antifungal activity of hexane, ethyl acetate and methanol extracts of Parmelia reticulata was evaluated against soil-borne pathogenic fungi, namely, Sclerotium rolfsii, Rhizoctonia solani, R. bataticola, Fusarium udum, Pythium aphanidermatum and P. debaryanum by Goel et al. (2011). Maximum antifungal activity was exhibited by hexane and ethyl acetate extracts against most of the test pathogens. *In vitro* antifungal activity of acetone, methanol and chloroform extracts of Parmotrema tinctorum was investigated against ten plant pathogenic fungi viz. Aspergillus niger, A. flavus, A. fumigatus, Alternaria alternata, Fusarium oxysporum, F. solani, F. roseum, Ustilago sp., Albugo candida and Penicillium citrinum, with reference to commercially available synthetic antifungal drug ketoconazole (positive control) using disk diffusion assay (Tiwari et al. 2011). Methanol extract was most effective against all investigated fungi followed by acetone and chloroform extract. Principal component analysis (PCA) concluded that though ketoconazole was effective against five of the investigated fungi, the extracts of Parmotrema tinctorum were more effective against rest of the five broad-spectrum plant pathogenic fungi (A. fumigatus, F. solani, F. roseum, P. citrinum and Ustilago spp.). In the study described by Ranković et al. (2012), acetone lichen extracts obtained from Usnea barbata showed a moderate antifungal activity. It inhibited the microorganisms tested at concentrations from 0.125 to 12.5 mg/mL. The acetone extract from T. candida inhibited all the tested microorganisms, but at higher concentrations. In related research, Evernia prunastri and Pseudoevernia furfuracea lichens were screened for their antimicrobial effects by Kosanić et al. (2013) who found varying antimicrobial success in inhibition of fungi and Pseudoevernia furfuracea was found to be the most effective. Kosanić et al. (2014a) were extracted with acetone the three Cladonia species (C. furcata, C. rangiferina and C. pyxidata) in order to investigate their antimicrobial effect. As test organisms in this study were used Aspergillus flavus, A.fumigatus, Candida albicans, Penicillium purpurescens and P. verrucosum. They obtained results showed that extracts from C. furcata and C. rangiferina showed similar antifungal activity. They inhibited the microorganisms tested at concentrations from 0.78 to 25 mg/mL, while extracts from C. pyxidata inhibited all the tested microorganisms, but at higher concentrations. Lecanora muralis, Parmelia saxatilis, Parmeliopsis ambigua, Umbilicaria crustulosa and Umbilicaria polyphylla were tested for their antibacterial and antifungal activity (Kosanić et al. 2014b). The antimicrobial activity was estimated by determination of the minimal inhibitory concentration by the broth microdilution method against six species of bacteria and ten species of fungi, and it has been found that of the lichens tested Umbilicaria polyphylla had largest antimicrobial activity with minimum inhibitory concentration values ranging from 0.78 to 1.56 mg/mL. Sariozlu et al. (2016) investigated antibacterial, antifungal activity and MIC values of the acetone, methanol and chloroform extracts of the lichen Bryoria capillaris against yeasts and filamentous fungi using disk diffusion method. The obtained results were shown that the tested extracts have considerable antimicrobial effect to tested pathogenic microorganism.

Two Ramalina lichens were explored for their antimicrobial effect by Ristić et al. (2016a) against five species of bacteria and 10 species of fungi. This extract exhibited no inhibition of growth against fungal strain A. flavus as well. Acetone extract of lichen species R. fastigiata showed significant antimicrobial properties. Dixit et al. (2018) evaluated the antimicrobial and antifungal properties of ichen extract (Usnea sp. and Parmotrema sp.) against some fungal species. In this study, the lichen was extracted in acetone and methanol. The fungal isolates used in this study were Aspergillus niger, A. flavus, Candida sp. and Tricophyton sp. Conventional antifungal drugs cause serious mammalian cytotoxicity, partly through the intracellular production of reactive oxygen species (ROS), and because of fungi are eukaryotic organisms that share diverse metabolic profiles with animal and plant cells; therefore, several antifungal agents discovered to be potentially active against pathogenic fungi have failed to survive during testing process because the fungicide target site is found in another organism, causing toxicity. With the rapid emergence of fungal resistance, a strong demand for antifungal agents with a new mode of action has arisen. One of the modern pathogenic fungi research challenges, is to find out new modes of action that provide improved fungicide activity against health important target, combined with the protection of environmental and public safety (Takimoto et al., 1999; Manzano et al., 2008). Antifungal compounds not only serve as drugs or templates for drugs, in many cases, they lead to the discovery and better understanding of targets and pathways involved in the disease process (Brahmachari, 2011). Even though individual antifungal compounds from lichens have not been studied, some secondary metabolites from other sources had been identified and their mechanisms of action have been proposed (Table 2). Phenolic compounds have been shown to inhibit enzymes by reacting with the sulfhydryl groups of amino acids (Cowan, 1999). Quinones, flavones, flavonoids, tannins and flavonols form complexes with the nucleophilic amino acids of proteins which leads to their inactivation. Flavones are phenolic structures containing one carbonyl group. The possible mechanism of action of flavones and flavonoids is hampered by conflicting findings. Flavonoids lacking hydroxyl groups on their β-rings are more active against microorganisms than are those with the two OH groups; this finding supports the idea that their microbial target is the membrane. However, several authors have also found the opposite effect, the more hydroxylation, the greater the antimicrobial activity. The latter finding reflects the similar result for simple phenolics. It is safe to say that there is no clear predictability for the degree of hydroxylation and toxicity to microorganisms. Quinones are known to complex irreversibly with nucleophilic amino acids in proteins, often leading to inactivation of the protein and loss of function. For that reason, the potential range of quinone antimicrobial effects is great. Probable targets in the microbial cell are surface-exposed adhesins, cell wall polypeptides, and membrane-bound enzymes. Quinones may also render substrates unavailable to the microorganism. As with all plant-derived antimicrobials, the possible toxic effects of quinones must be thoroughly examined (Cowan, 1999; Montes, 2009). It has been shown that phenolic alcohols (thymol, carvacrol, eugenol) are the strongest inhibitors of enzymatic processes. This is attributed to its lipophilic characteristic and its free OH groups (Cowan, 1999; Chahdoura et al., 2016). Many phytopathogenic (except for biotrophic) fungi secrete hydrolytic enzymes that diffuse into host cells prior to the advance of microorganisms, which can be inhibited by free radicals of oxidized phenols that function as nonspecific inhibitors; such as tannins, cyanidin, delphinidin and malvidin anthocyanindins (Cowan, 1999; Montes, 2009). Highly aromatic planar quaternary alkaloids such as berberine and harmane action mechanism are attributed to their ability to intercalate with DNA (Cowan, 1999).

Table 2 Cellular targets of secondary metabolites:

Antifungal compounds	**Cellular targets**
Phenolic compounds: -Phenolic alcohols	- Cell membrane or cell wall union through hydrogen bonds
Alkaloids	- Intercalate with DNA
Terpenes	- Damage to biomembranes
Saponins	- Disintegration of the membrane

2. CONCLUSION

Lichens can be considered an important source of bioactive substances with antifungal activity and excellent candidates for the development and formulation of new generation antifungal agents with fewer side effects, a broader action spectrum and lower cost than the current ones. More research needs to be developed to identify the bioactive components and evaluate their future applications.

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