Biological activities of secondary lichen metabolites

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Abstract

Lichens produce a great variety of secondary metabolites and most of them are unique. These chemically diverse lichen substances accumulate on the outer surfaces of the hyphae. They have several biological activities, including photoprotection against intense radiation, as well as allelochemical, antiviral, antitumor, antibacterial, antiherbivore, antioxidant, antipyretic, and analgesic action. These compounds are also important factors in metal homeostasis and pollution tolerance of lichen thalli.

Introduction

Our paper based on a detailed review (MOLNÁR and FARKAS 2010), and the complete list of references is shown in that paper.

Lichens produce a great number of various secondary metabolites, and most of them occur exclusively in these symbiotic organisms. They are produced by the mycobiont (ELIX 1996), and accumulate as extracellular tiny crystals on the outer surfaces of the hyphae. Approximately 1050 secondary compounds have been identified to date (STOCKER-WÖRGÖTTER 2008). Lichen products are restricted to specific areas of the thallus (FEIGE and LUMBSCH 1995, NYBAKKEN and GAUSLAA 2007), which correlate with the different functions of lichen metabolites. HYVÄRINEN et al. (2000) reported that the concentrations of secondary compounds in some lichen species are higher in reproductive structures than in the vegetative parts of the thallus. This pattern is concordant with the optimal defense theory, which states that the structures most important for fitness should be chemically better defended. The distribution patterns of secondary metabolites are usually taxon specific, and therefore have been widely used in lichen taxonomy and systematics (e.g., CULBERSON 1969, HAWKSWORTH 1976, NYLANDER 1866). Lichen substances are classified by CULBERSON and ELIX (1989) according to their biosynthetic origins and chemical structural features. Most secondary lichen metabolites are derived from the acetyl-polymalonyl pathway, while others originate from the mevalonic acid and shikimic acid pathways (Figure 1).

Due to experimental techniques, our knowledge of the biological activities (Figure 2) of these extracellular products has increased significantly in the last decades, and it was recently reviewed by the present authors (MOLNÁR and FARKAS 2010).

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Figure 1. Biosynthetic pathways of lichen secondary metabolites [modified from ELIX and STOCKER-WÖRGÖTTER (2008)].

Figure 2. Lichen substances have several biological activities.
Antioxidant activity

Free radicals play an important role in many chemical processes in the cells, but they are also associated with unwanted side effects, causing cell damage. Since synthetic antioxidants are often carcinogenic, finding natural substitutes is of great interest. Lichens have been found to contain a variety of secondary lichen substances, which are strong antioxidant compounds. According to LUO et al. (2009), the extreme conditions in Antarctica increase oxidative stress, consequently, Antarctic lichens contain larger amounts of antioxidant substances and have higher antioxidant activity than tropical or temperate lichens. AMO de PAZ et al. (2010) reported that methanol extracts of *Xanthoparmelia camtschadalis* and *X. conspersa* (Figure 3.), as well as their isolated lichen compounds (salazinic acid, stictic acid, and usnic acid) protected human astrocytes from hydrogen peroxide-induced damage. Astrocytes are the first line of defense in the brain against neurotoxicity of reactive oxygen species (ROS), thus salazinic acid, stictic acid, and usnic acid could act as antioxidant agents in those neurodegenerative disorders associated with oxidative damage (e.g., Alzheimer’s disease and Parkinson’s disease).

![Figure 3. Xanthoparmelia conspersa contains the β-orcinol depsidone stictic acid as major lichen compound in the medulla. This antioxidant lichen substance plays an important role in the protection against oxidative stress.](image)

Effect on metal homeostasis and pollution tolerance

Lichen secondary metabolites are sensitive to heavy metal accumulation and might play a general role in metal homeostasis and pollution tolerance. According to BIALONSKA and DAYAN (2005) the levels of atranorin, physodic acid and hydroxyphysodic acid significantly decreased in thalli of *Hypogymnia physodes* transplanted to the vicinity of a chemical plant producing chromium, phosphorous and sulfur compounds. In contrast, the level of physodalic acid increased significantly, suggesting that this compound might be effective against pollution stress. Usnic acid and divaricatic acid were both found to significantly increase the intracellular uptake of Cu$^{2+}$ in *Evernia mesomorpha* and in *Ramalina menziesii* (usnic acid only) (HAUCK et al. 2009), but intracellular uptake of Mn$^{2+}$ was reduced. The influence of the compounds facilitate the survival of the two lichen species.
Photoprotection

Lichens use a number of strategies to protect the light-sensitive algal symbionts against high levels of light and the damaging effects of UV radiation, e.g., light screening and UV-B protection by lichen compounds. The light-screening theory was formulated by ERTL (1951), who found that cortical lichen compounds increase the opacity of the upper cortex, and thus decrease high incident irradiance reaching the algal layer. Light screening cortical pigments (such as parietin, usnic acid, vulpinic acid) regulate solar irradiance reaching the algal layer (GALLOWAY 1993, SOLHAUG and GAUSLA 1996, see also FARKAS 2007) by absorbing much of the incident light and thus protecting the photosynthetic partner against intense radiation (RAO and LEBLANC 1965) (Figure 4). UV-B inhibits photosynthesis and damages DNA. Several lichen secondary metabolites (including atranorin, calycin, pinastric acid, rhizocarpic acid, usnic acid, vulpinic acid) have strong UV absorption abilities and might function as filters for excessive UV-B irradiation (RUNDEL 1978, SOLHAUG and GAUSLA 1996).

Allelopathy

Lichen secondary metabolites can function as allelopathic agents, i.e., they may affect the development and growth of neighboring lichens, fungi, mosses and vascular plants, as well as microorganisms (LAWREY 1995, MACÍAS et al. 2007, ROMAGNI et al. 2004, RUNDEL 1978). Competition occurs between lichen thalli for space and light on a variety of substrates, and plays important roles in determining the structure of lichen communities and the distribution of individual species (ARMSTRONG and WELCH 2007). Lichen secondary chemistry might play a role in this competition (ARMSTRONG and WELCH 2007).

Antimicrobial activity

Atranorin, fumarprotocetraric acid, gyrophoric acid, lecanoric acid, physodic acid protocetraric acid, stictic acid and usnic acid showed relatively strong antimicrobial effects against six bacteria and ten fungi, among which were human, animal and plant pathogens, mycotoxin-producers and food-spoilage organisms (RANKOVIĆ and MiŠIĆ 2008). Since
microorganisms have developed resistance to many antibiotics, pharmacologists need to pursue new sources for antimicrobial agents. All these results suggest that lichens and their metabolites yield significant new bioactive substances for the treatment of various diseases caused by microorganisms.

**Antiherbivore activity**

Lichens are grazed by herbivores, *e.g.*, insects, mites, snails, slugs. However, herbivory on lichens seems to be rare, presumably due to their low nutritional quality, specific structural features and the production of defense compounds (Nimis and Skert 2006, Pöyykö et al. 2005). It is known that natural plant-derived products have a less detrimental impact on the environment than synthetic chemicals, and thus lichen substances could be good candidates for new pesticides (Dayan and Romagni 2001).

**Cytotoxic, antitumor, and antiviral activity**

Many lichen secondary metabolites exhibit cytotoxic and antiviral properties and could be potential sources of pharmaceutically useful chemicals. Human Papilloma Virus can cause cervical cancer. Due to clinical experiments, the adjuvant treatment with usnic acid and zinc sulphate after radiosurgery promotes reepithelization and reduces recurrence (Scirpa et al. 1999). Usnic acid decreases proliferation of human breast cancer cells and human lung cancer cells without any DNA damage (Mayer et al. 2005), accordingly, it may represent a novel source for a natural non-genotoxic anticancer drug (chemotherapeutic agent).

**Allergy to lichen substances**

Lichen substances can be contact allergens (*e.g.*, atranorin, lobaric acid, stictic acid). They can cause occupational allergic contact dermatitis in forestry and horticultural workers (“woodcutter’s eczema”), as well as cause non-occupational allergic dermatitis during all kinds of outdoor activities, such as cutting firewood, hunting, and using cosmetics (perfumes, after-shave lotions, sunscreen products) that contain lichen metabolites (Aalto-Korte et al. 2005). Various skin and respiratory symptoms have been observed, such as erythema, itching, scaling, contact urticaria, rhinitis, and asthma (Aalto-Korte et al. 2005, Mitchell and Champion 1965).

**Candidates for antipyretic and analgesic drugs**

Some lichen substances have been shown to relieve pain effectively or reduce fever and inflammation in various mammals, and it is reasonable to assume that these compounds also could be effective in humans. Vijayakumar et al. (2000) reported that usnic acid, isolated from *Roccella montagnei*, showed significant anti-inflammatory activity in rats. Diffractaic and usnic acids have an analgesic effect in mice in vitro (Okuyama et al. 1995), and usnic acid also is an antipyretic.

**Conclusions**

More than 1000 secondary products have been identified to date in lichens, and new compounds will certainly be found from poorly studied or newly discovered lichens, especially from the under-collected tropics. Furthermore, development in analitical
techniques will result in the more complete knowledge of the biological activities of lichen secondary substances, as well as their role in lichen symbiosis.

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References

References not listed here can be found in MOLNÁR and FARKAS (2010).


