Lichens – masters of extraordinary symbiosis with potent pharmaceuticals

Waill A. Elkhateeb, Ghoson M. Daba

Department of Chemistry of Natural and Microbial Products, Pharmaceutical Industries Researches Division, National Research Center, Dokki, Giza, Egypt

Correspondence to Waill A. Elkhateeb, PhD, Department of Chemistry of Natural and Microbial Products, Pharmaceutical Industries Researches Division, National Research Center, El Buhouth Street, Dokki, Giza 12311, Egypt. Tel: (+20)1013241936; fax: (+20) 233 387 758; e-mail: waillahmed@yahoo.com

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Lichens are an excellent example of a symbiotic relationship between members belonging to two unrelated separate kingdoms (fungi and algae), which results in the collection of secondary metabolites. These metabolites can be fungal originated, algal originated, or unique compounds not produced by either fungi or algae individually. Although involved since centuries in traditional folk medicine, lichens have attracted extra attention of scientists owing to the emergence of new diseases, which has required screening for novel compounds capable of curing or supporting currently used compounds. This review highlights the nature, importance, nutritional and pharmaceutical uses, and applications of these enigmatic dual organisms.

Keywords:
lichens, lichens substances, nutrition, pharmaceutical drugs, symbiosis

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Introduction

Lichens are a remarkable example of one of the most important balanced relations in the ecosystem, which is symbiosis. In the case of lichens, this relation defines an association between algae and fungi [1]. This relationship has resulted in the development of a unique organism that is different from its parental individual fungal partner and algal one. Symbiosis fulfils mutual benefit to each member in this relation. One of the simplest exchanged benefits is when the fungal partner derives food from the green algae, whereas the algae partner gets its mineral nutrition and moisture by the help of the fungus [2]. According to the form of the lichens growth, three types were identified, which are crustose, foliose, and fruticose [3,4]. The crustose form is the most simple, and it is noticed on soil, bark, rocks, or wood, whereas foliose and fruticose forms are more complicated, as they show erection or branching [2]. Lichens are capable of growing under different conditions but show sensitivity to many factors such as light, humidity, altitude, and to a greater extent, air quality [5,6]. Uses and applications of lichens are involved in industrial, medicinal, and nutritional fields, and examples are shown in Fig. 1. In this review, the contributions of lichens in traditional medicine have been clarified, and the important metabolites with biological activities originating from lichens are reported. Lastly, some uses and applications of lichens have been described and discussed.

Lichens in ancient medicine

Literatures describing folk medicinal uses of lichens in Europe were started in 1921 [7], whereas the first global review discussing lichen uses was published in 1997 [8]. Numerous genera have been used from decades in North America, such as *Usnea*, *Letharia*, *Xanthoparmelia*, *Ramalina*, *Lobaria* and *Peltigera*, *Cladonia* and *Cladina*, and *Umbilicaria*. On the contrary, *Evernia and Pseudevernia*, *Cetraria*, *Ramalina*, *Lobaria* and *Peltigera*, *Cladonia*, and *Cladina* were commonly used in Europe. Lichens described in traditional medicine of Asian countries included *Usnea*, *Parmotrema* and *Hypotrachyna*, *Cladonia* and *Cladina*, *Thamnolia*, *Ramalina*, *Lobaria* and *Peltigera*, *Umbilicaria*, and *Lethariella*. North African countries also used the genera *Evernia* and *Pseudevernia*, *Xanthoparmelia*, and *Usnea* [9]. As noticed, the genus *Usnea* was commonly used worldwide owing to its medical importance [10]. The genus *Usnea* was identified, and five species in this genus were described in the 18th century under the name lichen, and then they were moved to the genus *Usnea* in 1780 [11]. Nowadays, species under the genus *Usnea* have reached ~350 species [12].

Each lichen genus was used specifically for treating certain disease. *Usnea* sp. is known for its demulcent activities and used to treat mild oral and pharyngeal inflammation. Moreover, *Usnea filipendula* Stirt was previously used for curing cuts and wounds in the former Soviet Union [13]. For stomach diseases, Northern America used *Letharia* [14], whereas

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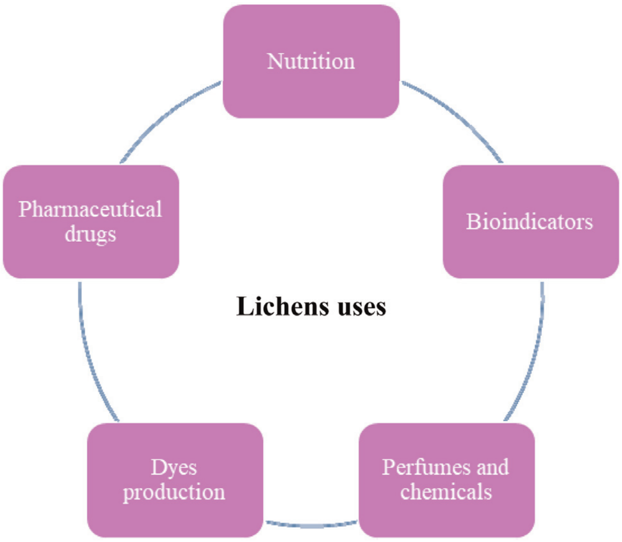
Figure 1



Some pharmaceutical, nutritional, and industrial applications and uses of lichens.

spleen enlargement was cured in Arabian medicine by using *Alectoria usneoides*. Within Spanish folk medicine, the use of lichens in various medical aliments is also documented [14]. Curing and medicinal activities of lichens mainly rely on lichen substances secreted by that specific lichen [15–17].

Lichen substances

Metabolites produced by lichens are the result of responding to various external conditions as a kind of protection against different physical and biological influences. Lichens' metabolites can be classified into two main groups, primary and secondary metabolites [17]. Intracellular metabolites required for the growth and maintenance of cellular function are known as primary metabolites. Such metabolites can be produced by the fungal partner or the algae partner of the lichen, or unique metabolites produced nonspecifically. Amino acids, proteins, polyols, polysaccharides, vitamins, and carotenoids are considered as primary metabolites [18]. Primary metabolites are soluble in water; hence, they can be easily extracted by hot water. The amount of nitrogenous compounds within lichens ranges between 1.6 and 11.4% dry weight of the thallus, whereas carotenoids exist in the range 1.5–24 mg/g dry weight of the thallus. Examples for those carotenoids are β-carotene epoxide, α-cryptoxanthin, lutein, astaxanthin, and mutatoxanthin. Many vitamins are produced by lichens such as ascorbic acid, pantothenic acid, folic acid, nicotinic acid, riboflavin, biotin, thiamine, and α-tocopherol [18]. In contrast to primary metabolites, secondary metabolites are not involved in either growth or reproduction of lichens; therefore, secondary metabolites do not participate in the basic molecular skeleton of the microorganism [17,19,20]. Till now, over one thousand metabolites have been originated and identified from lichens [21]. The majority of these metabolites are unique to lichens, whereas a minority exist in other fungi or higher plants. Moreover, the majority of secondary metabolites are poorly soluble in water; hence, their extraction requires using organic solvents [22]. One characteristic feature of lichens' secondary metabolites is their extreme stability [23]. However, some works have described variability in concentrations of metabolites such as usnic acid and atranorin [24]. The production of secondary compounds is genetically controlled and, in some cases, is dependent on geography and morphology of the species or genus [25]. Histologically, lichens' secondary metabolites are commonly existing in the medulla or to a lesser extent in the cortex. The most usual cortical-located metabolites are atranorin and usnic acid. Moreover, anthraquinones, xanthones, and pulvinic acid derivatives were also reported to be located in the cortex. The expression of lichen metabolites differs among the layers of lichen thallus, and typical cortical metabolites can be distinguished from compounds usually found only in the medulla. The majority of the cortical compounds function as a light filter [26].

Generally, metabolites production, their variation, and concentration are usually taxon specific and depend on many factors, whereas some are synthesized only in permissive physiological stages. Hence, the production of metabolites in axenic cultures can differ significantly from that in nature [18]. For instance, fungal partner (mycobionts) grown without their algal partner (photobionts) produces expected secondary metabolites under certain conditions [27–29] but can also produce different metabolites from those found in symbiosis [30]. In general, different culture conditions are required by every lichen mycobiont to produce specific secondary metabolites. These conditions include specific temperatures, light levels, nutrient medium, pH, the presence of certain sugars or polyols, and stress [29]. According to their chemical structures and biosynthetic origins, lichen secondary metabolites are originated from three chemical pathways: shikimate, acetyl-malonate, and mevalonate [21]. Definitely every metabolite produced by lichens exerts a specific function that assists the lichen itself in one way or another. For example, some phenolic compounds such as melanins are protectors against excessive radiation through ultraviolet B exposure through being accumulated in the thallus [31]. Such compounds exert potent antioxidant activity [32]. Furthermore, many phenolic compounds protect the lichen from being eating by herbivorous animals [33], whereas other secondary metabolites display antimicrobial activities that prevent microbial attacks that may lead to degradation of the thallus [34]. Many lichen-synthesized secondary metabolites are responsible for keeping the equilibrium in the symbiotic relation, whereas others may dissolve rocks for improved attachment of the lichen [35,36].

Lichens' nutritional benefits

Owing to their mild toxicity and difficulty in digestion, people have traditionally conducted different preparation methods to make lichens edible, such as removing secondary compounds and/or hydrolyzing the lichen polysaccharides [32]. This can be accomplished by boiling or steaming which would help to hydrolyze the lichen polysaccharides into digestible forms. Many carbohydrates (polyols) exist in lichens such as adonitol (ribitol), mesoerytritol, glycerol, myo-inositol, D-mannitol, siphulitol, and volemitol; moreover, monosaccharides such as arabinose, D-fructose, D-galactose, D-glucose, D-tagatose, D-xylose had been previously reported [37]. Moreover, oligosaccharides and polysaccharides such as D-mannitol, peltigeroside, sucrose, trehalose, umbilicin, isolichenin, lichenin, and pustulan are also listed. Organic acids such as citric acid, glyceric acid, malic acid, oxalic acid, phospoglyceric acid, and succinic acid are reported from many lichens [38]. On the contrary, some lichen polysaccharides can be extracted in significant yield, such as α-glucans, β-glucans, and galactomannans, which are generally expected to be originated from the fungal partner [37]. The nitrogenous compounds exist in many forms in lichens such as the amines, amino acids, and oligopeptides; examples include ammonia, choline, choline sulfate ester, ethanolamine, methylamine, trimethylamine, alanine, α-aminobutyric acid, arginine, asparagine, aspartic acid, betaine, cystine, phenylalanine, leucine, sarcosine, glutamic acid, glutamine, tryptophan, glycine, isoleucine, tyrosine, lysine, methionine, proline, serine, threonine, valine, and picroroccellin [38]. Carotenoids, chlorophylls, and phycobilins were reported in lichens, and they function as receptors of light energy. Carotenoids have another function as a protective agent that prevents the degradation of chlorophyll by molecular oxygen. The total carotenoid content varies from 23.25 to 123.5 g/g dry weight of the lichen [16]. Furthermore, some sulfur-containing compounds have been reported from lichens such as dimethyl sulfone [38]. Many vitamins and growth factors were also extracted from lichens such as riboflavin, ascorbic acid, niacin, biotin, folic acid, pantothenic acid, thiamine, and vitamin B12 [37].

Lichens as a pollution indicator

To determine environmental contamination quantitatively, some organisms are used as tools in this process. Such organisms are known as biomonitors [39–43]. Owing to the high sensitivity of lichens to different environmental factors, lichens are strong candidates to have a role as bioindicators and/or biomonitors in two methods: (a) mapping all species existing in a specific area (method A), and (b) through individual sampling of lichen species and measuring pollutants accumulating in the thallus, or by transplanting lichens from an uncontaminated area to a contaminated one, and then morphological changes in the lichens thallus were measured (method B) [44–46]. Air pollution owing to industrial pollutants emitted from vehicles and different sources has an influence on diversity and distribution of lichens, which can be used for the Index of Atmospheric Purity. Mapping all species present in a specific area (method A) is a reliable promising method to monitor air pollution [47]. Examples of the most sensitive lichen genera are *Evernia*, *Candelariella*, *Parmelia*, and *Ochrolechia* [48].

Lichens' biological activities and medicinal uses

Natural products are a promising therapeutic alternative to the currently used antimicrobial treatment [49,50]. Lichen-derived products, which are known as lichen substances, and their antibiotic properties are attracting serious attention nowadays, because up to 50% of all discovered lichens have been reported to exert antibiotic properties [8,51]. The study by Burkholder *et al.* [52] was the first pioneered research describing lichens as antibacterial agents. Some of the most frequently reported lichen-derived metabolites with strong antimicrobial activities are usnic acid, vulpinic acid, and evernic acid, which can successfully inhibit growth of many gram-positive bacteria such as *Staphylococcus aureus*, *Bacillus megaterium*, and *Bacillus subtilis*. Nevertheless, such compounds had no effect on the tested gram-negative bacteria (*Escherichia coli* or *Pseudomonas aeruginosa*) [51,53]. The extracts of lichen species *Parmelia sulcata* were reported to contain salazinic acid, which has exhibited antibacterial properties against *Aeromonas hydrophila*, *Bacillus cereus*, *Bacillus subtilis*, *Listeria monocytogenes*, *Proteus vulgaris*, *Yersinia enterocolitica*, *S. aureus*, *Streptococcus faecalis*, *Candida albicans*, and *Candida glabrata* [54]. Diethyl ether, acetone, and ethanol extracts of *Cetraria aculeate* contained protolichesterinic acid with promising antibacterial activity against nine bacteria belonging to gram-positive and gram-negative groups [55]. Most of the antibacterial activities were tested specifically on *Bacillus*, *Pseudomonas*, *E. coli*, *S. aureus*, *Kleibsiella*, *Candida*, *Salmonella*, and *Yersinia* [56–59]. Among the *Bacillus* species, *Bacillus sublitis* was the most sensitive bacterium to lichen metabolites such as atranorin, protolichsterinic acid, salazinic acid, usnic acid, norstictic acid, protoacetraric acid, fumaroprotoacetraric acid, atranol, lecanoric acid, stictic acid, divericatic acids, and zeorin [60–68].

Conclusion

Understanding the importance of lichens, which are existing everywhere and have prestigious contributions in traditional folk medicine all over the world, is currently of great interest. Moreover, a remarkable list of applications are based on lichens, starting from their use as nutrients and animal feed, moving to their use as a source of dyes, their use in many countries as indicators for air quality and changes in climate, as lichens respond to the smallest change in climate or pollution in a way much faster than most other biological options, and finally ending with the pharmaceutical uses of their substances (metabolites). Further studies on lichens and their metabolites are highly required to get optimum benefits from these valuable dual organism.

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Conflicts of interest

There are no conflicts of interest.

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