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REVIEW ARTICLE

Antioxidant potential of lichen species and their secondary metabolites. A systematic review

Carlos Fernández-Moriano[1], María Pilar Gómez-Serranillos[1], and Ana Crespo[2]

[1]Department of Pharmacology and [2]Department of Plant Biology II, Faculty of Pharmacy, Universidad Complutense Madrid, Madrid, Spain

Abstract

Context: Pharmacological interest of lichens lies in their capacity to produce bioactive secondary metabolites, being most of them phenolic compounds with reactive hydroxyl groups that confer antioxidant potential through various mechanisms. Increasing incidence and impact of oxidative stress-related diseases (i.e., neurodegenerative disorders) has encouraged the search of new pharmacological strategies to face them. Lichens appear to be a promising source of phenolic compounds in the discovery of natural products exerting antioxidant activity.

Objective: The present review thoroughly discusses the available knowledge on antioxidant properties of lichens, including both *in vitro* and *in vivo* studies and the parameters assessed so far on lichen constituents.

Methods: Literature survey was performed by using as main databases PubMed, Google Scholar, Scopus, Science Direct, and Recent Literature on Lichens. We reviewed 98 highlighted research articles without date restriction.

Results: Current report collects data related to antioxidant activities of more than 75 lichen species (from 18 botanical families) and 65 isolated metabolites. Much information comes from *in vitro* investigations, such as chemical assays evaluating radical scavenging properties, lipid peroxidation inhibition, and reducing power of lichen species and compounds; similarly, research on cellular substrates and animal models generally measures antioxidant enzymes levels and other antioxidant markers, such as glutathione levels or tissue peroxidation.

Conclusion: Since consistent evidence demonstrated the contribution of oxidative stress on the development and progression of several human diseases, reviewed data suggest that some lichen compounds are worthy of further investigation and better understanding of their antioxidant and neuroprotective potentials.

Keywords

Antioxidants, neurodegenerative diseases, lichens, oxidative stress, scavenging properties

History

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Introduction

A lichen is a stable, ecologically obligate, self-supporting mutualism between an exhabitant fungus (the mycobiont) and one or more extracellularly located inhabitants, which can be either unicellular or filamentous photoautotrophic partners (the photobiont: alga or cyanobacterium) (Hawksworth & Honegger, 1994). Lichens have been used with medicinal purposes since the ancient times. For instance, *Usnea barbata* (L.) Weber ex F.H. Wigg (Parmeliaceae) and other *Usnea* species were used to treat hair-related diseases, *Lobaria pulmonaria* (L.) Hoffm. (Lobariaceae) and *Parmelia sulcata* Taylor (Parmeliaceae) for pulmonary and cranial diseases, respectively, yellow-orange colored *Xanthoria parietina* (L.) Th. Fr. (Teloschistaceae) for jaundice, *Peltigera aphthosa* (L.) Willd. (Peltigeraceae) for aphta, *Parmelia saxatilis* (L.) Ach. (Parmeliaceae) for epilepsy, etc. (Brodo et al., 2001; Malhotra et al., 2008).

Pharmaceutical importance of lichens lies in their capacity to produce a great variety of secondary metabolites, many of which only appear in these lichenised fungi. Phenolic compounds are the most relevant secondary metabolites of lichen samples, and the best studied metabolites can be principally classified as depsides, depsidones, dibenzofurans, and pulvinic acid derivatives (Huneck, 1999). Chemical structures of some representative compounds of each group are shown in Figure 1. Systematic study of pharmacological properties of lichen compounds has recently started and they have attracted much attention in recent investigations because of their antiviral, antibiotic, antitumor, allergenic, and plant growth inhibitory activities (Dias & Urban, 2009; Einarsdóttir et al., 2010; Esimone et al., 2007; Honda & Vilegas, 1999; Nishitoba et al., 1987).

In the last years, there is an increasing interest in new bioactive natural products for the prevention and treatment of various human diseases, with remarkable attention to neurodegenerative diseases and compounds exerting

Correspondence: M. Pilar Gómez-Serranillos, Department of Pharmacology, Faculty of Pharmacy, University Complutense Madrid, Plaza de Ramón y Cajal s/n 28040, Madrid, Spain. Tel: +34 913941767. Fax: +34 913941624. E-mail: pserra@ucm.es

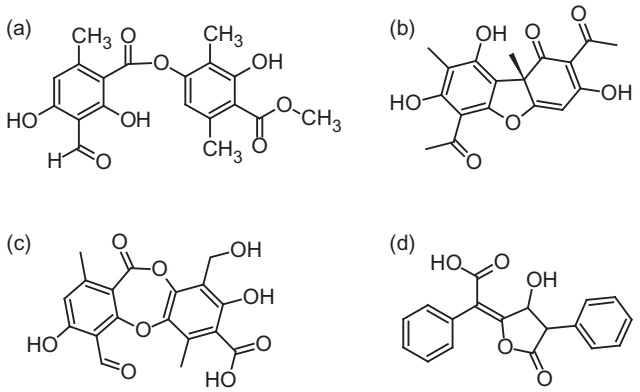

Figure 1. Chemical structures of depside atranorin (a), dibezofuran usnic acid (b), depsidone protocetraric acid (c), and pulvinic acid (d).

neuroprotective potential and oxidative stress reversion (Gonzalez-Burgos et al., 2013; Wang et al., 2013). This is due to the fact that compounds of natural origin normally have beneficial effects on the human organism with lower incidence of unwanted effects. Regarding this point, lichens are the subject of many research teams (Karakus et al., 2009; Kosanić et al., 2012b).

The present review aims to summarize and discuss the available information about the antioxidant properties of lichens and their isolated secondary metabolites in order to facilitate and guide future research on these natural products.

Oxidative stress

Free radicals (including reactive oxygen species, such as the hydroxyl radical, superoxide anion, hydrogen peroxide, and reactive nitrogen species, such as nitric oxide) play important roles in many chemical processes of the cells under physiological conditions, but they are also associated with pathology and cell damage. Oxidative stress is defined as an imbalance between biochemical processes leading to the production of reactive oxygen species (ROS) and those responsible for the removal of ROS, the antioxidant cascade. In that situation, free radicals will be able attack nucleic acids and proteins, as well as unsaturated fatty acids in the cell membrane; several human chronic diseases (such as neurodegenerative diseases) are related to this problem (Molnár & Farkas, 2010; Sayre et al., 2008).

On the contrary, antioxidant agents inhibit and prevent those ROS that can cause degenerative diseases. Since many synthetic antioxidants have shown toxic and/or mutagenic effects (Grice, 1986; Wichi, 1988), the scientific attention shifted towards the discovery of naturally occurring antioxidants. With this regard, numerous plant constituents have been shown to exert antioxidant activity, being flavonoids and other phenolic compounds such as hydroxycinnamic derivatives, catechins, theaflavins, curcumins and terpenoids remarkable among them (Gonzalez-Burgos et al., 2012; Sundararajan et al., 2006). They are mostly phenolic compounds containing reactive hydroxyl groups and their antioxidant properties might be based on their ability to scavenge ROS, chelate metal ions (i.e., iron and copper), stabilize unpaired electrons, and modulate the endogenous enzymatic and non-enzymatic antioxidant defense systems.

There is unquestionable evidence for some participation of oxidative stress in all neurodegenerative diseases (such Alzheimer's, Parkinson's and Huntington's diseases or amyotrophic lateral sclerosis among them). It therefore suggests possibilities of intervention into etiology or disease progression through individual or combined use of antioxidants capable to enhance endogenous enzymatic or non-enzymatic defense processes (Sayre et al., 2008). Thus, since natural antioxidants are preferred over synthetic ones and there is solid basis in thinking of a potential neuroprotective activity for phenolic compounds, investigation of the antioxidant potential of lichen metabolites becomes an interesting strategy for the prevention or treatment of various oxidative stress-related diseases.

Detailed mechanisms and pathways involved in the antioxidant activity of lichens still need further investigation. But classification of these issues known so far could help to understand the pharmacology of lichens secondary metabolites, and their possibilities in the treatment of neurodegenerative disorders, thus promoting the development of neuroprotective natural products.

Literature search

Current report is intended to discuss past and current research on antioxidant properties of lichens and their secondary metabolites. With this aim, an extensive review of scientific literature was carried out by considering all highlighted research articles and other reviews on the issue, without date or language restriction. Five main databases (PubMed, Google Scholar, Scopus, Science Direct, and Recent Literature on Lichens) were used as information sources through the inclusion of the search terms ''lichens'', ''lichen metabolites'', ''antioxidant activities'', ''oxidative stress'', and their combinations. As a result, a total of 98 bibliographic references are included in the present work.

Antioxidant properties of lichens

Some lichen extracts and metabolites have already been reported for antioxidant properties due to their phenolic content; for instance, the antioxidant activities of some depsides and depsidones isolated from several lichen species have been demonstrated (de Paz et al., 2010; Hidalgo et al., 1994; Jayaprakasha & Rao, 2000), as well as the *in vitro* properties of some lichen extracts (Gülçin et al., 2002; Stojanović et al., 2010). Even so, both studies on intracellular ROS modulation by lichen metabolites/extracts and their *in vivo* effects have been recently started.

Table 1 actually includes the antioxidant activity as revealed by *in vitro* assays of more than 75 species divided into 18 botanical families, among which Parmeliaceae family is the best studied, as it is one of the most rife and widespread. Some of the reflected studies are macrostudies in which authors evaluated the same antioxidant parameter in numerous species. Similarly, in Table 2, we gather all available data related to *in vitro* antioxidant activity of isolated lichen metabolites, referring to more than 65 compounds. In general, antioxidant activity has been mainly evaluated based on some

Table 1. Antioxidant activities of lichen extracts.

Lichen species	Solvent	LP inhibition (IC_{50} or %INH)	DPPH (IC_{50} or %INH)	SO^{-} RSA (IC_{50} or %INH)	Reducing power (A_{700} or IC_{50})	Phenolic/flavonoid content	Isolated compounds/ composition	Reference
Arthoniaceae Reichenb. ex Reichenb.								
Arthothelium awastii Patw. & Makhija	ME	2.1–68.4% 15.7 µg/ml	2.6–68.4% 13.2 µg/ml	Not studied (NS)	NS	Different content depending on lichen culture conditions	NS	Verma et al. (2008b)
Catillariaceae Hafellner.								
Toninia candida (Weber) Th.Fr.	ChE, ME, PE	ChE: 41.7 µg/ml ME: 46.5 µg/ml PE: 21.5 µg/ml	ChE :48.9 µg/ml ME: 51.5 µg/ml PE: 50.1 µg/ml	NS	ChE: 56. 7 µg/ml ME: 78.5 µg/ml PE: 51.5 µg/ml	ChE: 45.2 mg GA/g ME: 76.3 mg GA/g PE: 42.9 mg GA/g	Nortistic acid, stictic acid, usnic acid, protocetraric acid, atranorin	Manojlovic et al. (2012b)
	AcE	NS	115.8 µg/ml	221.5 µg/ml	0.055 (500 µg/ml)	49.8 µg PE/mg	Norstictic acid, stictic acid, protocetraricacid, usnic acid, atranorin	Ranković et al. (2012)
Cladoniaceae Zenker.								
Cladonia amaurocraea (Flörke) Schaerer	AcE, DmE, EE, ME	AcE: 80.3% DmE, EE, ME: numeric value not reported (NVNR)	NVNR	NS	NS	AcE: 0.018 mg/g DmE: 0.016 mg/g EE: 0.005 mg/g ME: 0.174 mg/g	Atranorin, usnic acid	Singh et al. (2011)
Cladonia clathrata Ahti & L. Xavier	EE 70%	NS	50.2% 69.3 µg/ml	NS	NS	371.8 mg GA/g	NS	Silva et al. (2010)
Cladonia digitata (L.) Hoffm.	ME	9.8 %	NS	NS	0.085	13.7 mg GA/g	NS	Ranković et al. (2010b)
Cladonia fimbriata (L.) Fr.	ME	20.4%	NS	NS	0.114	26.4 mg GA/g	NS	Ranković et al. (2010b)
Cladonia foliacea (Huds.) Willd.	ME	NS	>1000 µg/ml	NS	NS	78.1 mg GA/g (28.2 mg Rutin/g)	NS	Mitrovic et al. (2011)
Cladonia furcata (Hudson) Schrad.	AcE, ME	NVNR	AcE: 471.3 µg/ml ME: >1000 µg/ml	NVNR ME > AcE	NVNR AcE > ME	NS	NS	Luo et al. (2009)
	AcE, ME, WE	NS	NVNR ME > AcE > WE	NVNR ME > AcE > WE	NVNR ME > AcE > WE	AcE: 12.1 µg PE ME: 52.7 µg PE WE: 5.8 µg PE	NS	Kosanic et al. (2011)
	AcE	NS	44.8%	23.9%	0.051	12.9 µg PE/mg (10.6 µg RE/mg)	NS	Ranković et al. (2011)
Cladonia mediterranea P.A.Duvign. & Abbayes	AcE, DmE, EE, ME	AcE: 73.7% DmE, EE, ME: NVNR	NVNR	NS	NS	AcE: 0.006 mg/g DmE: 0.001 mg/g EE: 0.008 mg/g ME: 0.009 mg/g	Usnic acid	Singh et al. (2011)
Cladonia rangiformis Hoffm	ChE, ME, WE	ChE: 48.3% ME: 1.6% WE: −11.5%	NS	NS	ChE: 0.083 ME: 0.115 WE: 0.034	ChE: 0.048 µg GA/ml ME: 0.010 µg GA/ml WE: 0.004 µg GA/ml	NS	Yücel et al. (2007)
Graphidaceae Dumort.								
Graphis guimarana Vain.	ME 10%	NS	NS	19.7–23.2 µg/ml	NS	NS	NS	Behera et al. (2006a)
Graphis nakanishiana Patw. & C.R. Kulk.	ME 10%	NS	NS	11.2–14.2 µg/ml	NS	NS	NS	Behera et al. (2006a)
Graphis schizograpta Müll. Arg.	ME 10%	NS	NS	12.3–25.6 µg/ml	NS	NS	NS	Behera et al. (2006a)
Icmadophilaceae Triebel								
Thamnolia vermicularis (Sw.) Schaer.	ME	2 mg/ml: 67.0%	2 mg/ml: 72.0% 0.2 mg/ml: 36.0%	NVNR	NVNR	NS	NS	Luo et al. (2006)
Lecanoraceae Körb.								
Lecanora atra (Hudson) Ach.	AcE, ME, WE	NS	AcE: 94.7% ME: 93.3% WE: 93.2%	AcE: 84.5% ME, WE: NVNR	NVNR	AcE: 73.0 µg PE ME: 71.0 µg PE WE: 69.8 µg PE (AcE: 54.8 µg RE	NS	Kosanić and Ranković (2011)

(*continued*)

Table 1. Continued

Lichen species	Solvent	LP inhibition (IC_{50} or %INH)	DPPH (IC_{50} or %INH)	SO^{-} RSA (IC_{50} or %INH)	Reducing power (A_{700} or IC_{50})	Phenolic/flavonoid content	Isolated compounds/ composition	Reference
						ME: 53.7 µg RE WE: 52.6 µg RE)		
	AcE	NS	94.7%	84.5%	0.109	73.0 µg PE/mg (54.8 µg RE/mg)	NS	Ranković et al. (2011)
Lecanora muralis (Schreber) Rabenh.	AcE	NS	52.3%	33.6%	0.061	43.2 µg PE/mg (34.6 µg RE/mg)	NS	Ranković et al. (2011)
Lobariaceae Chevall.								
Lobaria pulmonaria (L.) Hoffm.	ME, WE	ME: 87.5% WE: −17.1%	NS	NS	ME: 0.417 WE: 0.233	ME: 87.9 mg GA/g WE: 39.2 mg GA/g	NS	Odabasoglu et al. (2004)
Nephromataceae Wetm. ex J. C. David & D. Hawksw.								
Nephroma parile (Ach.) Ach.	ME	3.6%	NS	NS	0.098	6.2 mg GA/g	NS	Ranković et al. (2010a)
Ochrolechiaceae R. C. Harris ex Lumbsch & I. Schmitt								
Ochrolechia parella (L.) A.Massal.	ME	8.5%	NS	NS	0.077	5.6 mg GA/g	NS	Ranković et al. (2010b)
Ochrolechia tartarea (L.) A. Massal.	ME	26.6%	NS	NS	0.202	29.4 mg GA/g	NS	Ranković et al. (2010a)
Parmeliaceae Zenker								
Bryoria fusfescens (Gyeln.) Brodo & D. Hawksw	ME, WE	ME: 12.6% WE: 18.4%	NS	NS	ME: 0.215 WE: 0.201	ME: 48.6 mg GA/g WE: 30.3 mg GA/g	NS	Odabasoglu et al. (2005)
Cetraria aculeata (Schreber) Fr.	AcE, ME	NVNR	AcE: >1000 µg/ml ME: >1000 µg/ml	NVNR AcE > ME	NVNR AcE > ME	NS	NS	Luo et al. (2009)
Cetraria fastigiata (Nyl.) Kärnefelt	AcE, DmE, EE, ME	AcE: 80.3% DmE, EE, ME: NVNR	NVNR	NS	NS	AcE: 0.019 mg/g DmE: 0.048 mg/g EE: 0.009 mg/g ME: 0.050 mg/g	Lichensterinic acid	Singh et al. (2011)
Cetraria islandica (L.) Ach.	WE	50 µg: 96.0% 100 µg: 99.0% 200 µg: 100.0% 500 µg: 100.0%	NVNR	NVNR	NVNR	0.039 µg PE/mg	NS	Gülçin et al. (2002)
	AcE, ME, WE	NS	NVNR	NVNR	NVNR	AcE: 25.0 µg PE ME: 38.0 µg PE WE: 18.2 µg PE (AcE: 7.7 µg RE, ME: 25.8 µg RE, WE: 1.4 µg RE)	NS	Kosanić and Ranković (2011)
Cetraria pinastri (Scop.) Gray	ME	48.8%	NS	NS	0.188	32.9 mg GA/g	NS	Ranković et al. (2010b)
Evernia prunastri (L.) Ach.	BE, DE, EE, ME	Crude wax: weak activity DE: activity EE: activity ME: activity	NS	NS	NS	NS	NS	Racine et al. (1980)
	ME	NS	727.7 µg/ml	NS	35.5 µg AA/g 0.6 µg T/g	18.2 µg GA/mg	NS	Stojanovic et al. (2010)
	ME	NS	>1000 µg/ml	NS	NS	80.7 mg GA/g (27.46 mg rutin/g)	NS	Mitrović et al. (2011)
	AcE	NS	663.1 µg/ml	1033.6 µg/ml	500 µg/ml: 0.029	34.1 µg PE/mg	Evernic acid, physodic acid, usnic acid, atranorin, chloroatranorin	Kosanić et al. (2013)
Flavocetraria nivalis (L.) Kärnefelt & A. Thell	AcE, DmE, EE, ME	NVNR	NVNR	NS	NS	AcE: 0.013 mg/g DmE: 0.012 mg/g	Usnic acid	Singh et al. (2011)

						EE: 0.007 mg/g ME: 0.162 mg/g		
Flavoparmelia caperata (L.) Hale	ME	NS	347.2 µg/ml	NS	21.6 µg AA/g 19.3 µg T/g	11.9 µg GA/mg	NS	Stojanović et al. (2010)
	ME	NS	549.0 µg/ml	NS	NS	90.8 mg GA/g (33.6 mg rutin/g)	NS	Mitrović et al. (2011)
Hypogymnia physodes (L.) Nyl.	ME	NS	79.7 µg/ml	NS	96.9 µg AA/g 25.3 µg T/g	17.5 µg GA/mg	NS	Stojanović et al. (2010)
	ME	NS	45.6 µg/ml	NS	NS	141.6 mg GA/g (20.1 mg rutin/g)	NS	Mitrović et al. (2011)
	AcE, ME, WE	NS	AcE: 60.2% ME: 73.2% WE: 30.9%	NVNR ME > AcE > WE	NVNR ME > AcE > WE	AcE: 30.1 µg PE ME: 86.8 µg PE WE: 6.3 µg PE	NS	Kosanić et al. (2011)
Lethariella cashmeriana Krog	Hot WE	NS	NS	NS	Activity: 35.4	NS	Chlororubrocashmeriquinone Rubrocashmeriquinone	Kinoshita et al. (2010)
Lethariella sernanderi (Most.) Obermayer	Hot WE	NS	NS	NS	Activity: 163.9	NS	Canarione Rubrocashmeriquinone Chlororubrocashmeriquinone	Kinoshita et al. (2010)
Lethariella sinensis J.C.Wei & Y.M.Jiang	Hot WE	NS	NS	NS	Activity: 23.8	NS	7-Chlorocanarione Rubrocashmeriquinone Chlororubrocashmeriquinone	Kinoshita et al. (2010)
Parmelia caperata (L.) Ach.	AcE, ME, WE	NS	NVNR AcE > ME > WE	NVNR AcE > ME > WE	NVNR AcE > ME > WE	AcE: 40.4 µg PE ME: 15.3 µg PE WE: 14.9 µg PE	NS	Kosanić et al. (2011)
	AcE	NS	46.4%	61.5%	0.057	40.4 µg PE/mg (15.3 µg RE/mg)	NS	Kosanić et al. (2012a)
Parmelia centrifuga (L.) Ach.	ME	54.2%	NS	NS	0.375	49.8 mg GA/g	NS	Ranković et al. (2010a)
Parmelia crinita Ach.	ME	16.0%	NS	NS	0.172	12.8 mg GA/g	NS	Ranković et al. (2010b)
Parmelia pertusa Schaerer	AcE, ME, WE	NS	NVNR	NVNR Weak activity	NVNR Weak activity	AcE: 18.2 µg PE ME: 34.6 µg PE WE: 12.0 µg PE (AcE: 6.6 µg RE, ME: 18.2 µg RE, WE: 5.3 µg RE)	NS	Kosanić and Rankovic (2011)
Parmelia saxatilis (L.) Ach.	ME	25.0%	No activity	NS	NS	1.0% (w/w)	NS	Gülluce et al. (2006)
	ME, WE	Ferric thiocyanate method WE: 86.1% ME: 94.8% TBA test WE > ME	WE: 19.8% ME: 63.6%	WE: 83.0% ME: 80.0%	ME > WE	WE: 24.3 mg PE/mg ME: 55.1 mg PE/mg	Atranorin, chloroatranorin, salazinic acid	özen and Kinalioglu (2008)
	AcE	NS	55.3%	35.3%	0.066	40.6 µg PE/mg (20.6 µg RE/mg)	NS	Kosanić et al. (2012a)
Parmelia sulcata Taylor	ME	NS	493.6 µg/ml	NS	25.3 µg AA/g 41.9 µg T/g	7.9 µg GA/g	NS	Stojanović et al. (2010)
	ME	NS	584.2 µg/ml	NS	NS	88.3 mg GA/g (44.9 mg rutin/g)	NS	Mitrović et al. (2011)
	AcE, ME, WE	NS	NVNR AcE > ME > WE	NVNR AcE > ME > WE	NVNR AcE > ME > WE	AcE: 38.2 µg PE ME: 25.1 µg PE WE: 9.6 µg PE	NS	Kosanić et al. (2011)
	AcE	NS	38.8%	33.8%	0.034	18.2 µg PE/mg (6.6 µg RE/mg)	NS	Kosanić et al. (2012a)
Parmotrema pseudotinctorum (Abbayes) Hale	ME	NS	500 µg/ml: 90.7% + honey: 81.5%	NS	NS	NS	Atranorin, lecanoric acid	Prashith Kekuda et al. (2009)
	ME	NS	62.1–89.4%	NS	0.265–0.776	NS	Atranorin, lecanoric acid	Praveen Kumar et al. (2010)
Parmotrema stuppeum (Taylor) Hale	BE, AcE	BE: 30.0–65.0% AcE: 35.0–68.0%	NS	NS	NS	NS	Methyl orsellinate, orselinic acid, atranorin, lecanoric acid	Jayaprakasha and Rao (2000)
	ME			NS	NS		NDR	Verma et al. (2008b)

(*continued*)

Table 1. Continued

Lichen species	Solvent	LP inhibition (IC_{50} or %INH)	DPPH (IC_{50} or %INH)	$SO^{\cdot-}$ RSA (IC_{50} or %INH)	Reducing power (A_{700} or IC_{50})	Phenolic/flavonoid content	Isolated compounds/ composition	Reference
Parmotrema tinctorum (Delise ex Nyl.) Hale		3.6–71.3% 11.5 µg/ml	1.1–57.2% 13.6 µg/ml			Depends on lichen culture conditions		
Platismatia glauca (L.) Culb. & C. Culb.	ME	27.0%	No activity	NS	NS	1.1 % (w/w)	NS	Güllüce et al. (2006)
Pseudoevernia furfuracea (L.) Zopf	ME, WE	ME: 26.4% WE: 48.2%	NS	NS	ME: 0.229 WE: 0.229	ME: 75.1 mg GA/g WE: 61.7 mg GA/g	NS	Odabasoglu et al. (2005)
	AcE, ME, WE	NS	AcE: 87.3% ME: 57.9% WE: 33.9%	NVNR	NVNR	AcE: 76.4 µg PE ME: 37.0 µg PE WE: 18.7 µg PE (AcE: 37.6 µg RE, ME: 21.0 µg RE, WE: 1.8 µg RE)	NS	Kosanić et al. (2011)
	BuE, DcmE, EaE, ME	BuE: No activity DcmE: 17.8% EaE: 23.8% ME: 17.2%	TLC spray	NS	NS	NS	Atraric acid, metil hematommate, methyl chlorohematommate	Güvenç et al. (2012)
Pseudoevernia furfuracea (L.) Zopf	AcE	NS	401.7 µg/ml	632.0 µg/ml	500 µg/ml: 0.058	76.4 µg PE/mg	Physodic acid, physodalic acid, atranorin, chloroatranorin, 3-hydroxiphysodic	Kosanić et al. (2013)
Pseudophebe pubescens (L.) M. Choisy	AcE, DmE, EE, ME	AcE: 82.4% DmE, EE, ME: NVNR	AcE: 51.8% DmE, EE, ME: NVNR	NS	NS	AcE: 0.017 mg/g DmE: 0.012 mg/g EE: 0.001 mg/g ME: 0.027 mg/g	Atranorin	Singh et al. (2011)
	AcE, ME	NVNR	AcE:>1000 µg/ml ME: >1000 µg/ml	NVNR ME > AcE	NVNR AcE > ME	NS	NS	Luo et al. (2009)
Usnea antarctica Du Rietz	AcE, ME	NVNR	AcE: 445.7 µg/ml ME: >1000 µg/ml	NVNR AcE = ME	NVNR AcE > ME	NS	NS	Luo et al. (2009)
Usnea aurantiacoatra (Jacq.) Bory	AcE, ME	NVNR	AcE: 642.6 µg/ml ME: 791.3 µg/ml	NVNR AcE = ME	NVNR AcE > ME	NS	NS	Luo et al. (2009)
Usnea barbata Motyka	AcE	NS	667.9 µg/ml	979.3 µg/ml	500 µg/ml: 0.019	31.3 µg PE/mg	Norstictic acid, usnic acid, atranorin, chloroatranorin	Ranković et al. (2012)
Usnea complanata (Müller Arg.) Motyka	WE, EE, EaE, ME	WE: 132.4 µg/ml EE: 125.0 µg/ml EaE: 157.9 µg/ml ME: 74.6 µg/ml	WE: 25.0 µg/ml EaE: 25.0 µg/ml EE: 22.9 µg/ml ME: 80.0 µg/ml	NS	NS	TLC technique	Usnic acid, psoromic acid	Behera et al. (2012)
Usnea florida (L.) Weber ex F.H.Wigg.	AcE, ME	ME: 15.0% WE: 13.4%	NS	NS	ME: 0.069 WE: 0.083	ME: 10.5 mg GA/g WE: 10.4 mg GA/g	NS	Odabasoglu et al. (2004)
Usnea ghattensis G. Awasthi	AcE, DmE, ME, PE	AcE: 55.0% DmE: 17.0% ME: 87.0% PE: 38.0%	AcE: 31.0% DmE: 11.0% ME: 73.0% PE: 43.0%	AcE: 18.0% DmE: 7.0% ME: 56.0% PE: 27.0%	NS	AcE: 14.0 mg/g DmE: 12.0 mg/g ME: 35.0 mg/g PE: 9.0 mg/g	NS	Behera et al. (2005a)
	ME	2–20 mg/ml: 3.8–73.3%	NVNR	20 mg/ml: 30.0%	NVNR	13.0 µg PE/mg	NS	Behera et al. (2006c)
	ME	67.0%	89.6%	89%	NS	NS	Usnic acid, nortistic acid	Verma et al. (2008a)
Usnea longissima Ach.	ME, WE	ME: 82.4% WE: 25.6%	NS	NS	ME: 0.178 WE: 0.100	ME: 38.6 mg GA/g WE: 18.3 mg GA/g	NS	Odabasoglu et al. (2004)
	ME	6 mg/ml: 97.3%	6 mg/ml: 1.0 mg/ml	NS	NS	2.62%	NS	Kim and Cho (2007)
Peltigeraceae Dumort.								
Peltigera rufescens (Weiss) Humb.	ME, WE	ME: 74.0% WE: 26.4%	NS	NS	ME: 0.542 WE: 0.218	ME: 66.4 mg GA/g WE: 38.1 mg GA/g	NS	Odabasoglu et al. (2005)
Physciaceae Zahlbr.								
Anaptychia ciliaris (L.) Körb.	ME	22.6%	NS	NS	0.195	27.6 mg GA/g	NS	Ranković et al. (2010a)
Heterodermia podocarpa (Bel.) D. D. Awasthi	ME	3.4–52.7% 12.7 µg/ml	1.6–53.7% 18.4 µg/ml	NS	NS	Different contents depending on lichen culture conditions	NDR	Verma et al. (2008b)

Physcia caesia (Hoffm.) Fürnr.	AcE, DmE, EE, ME	NVNR	NVNR	NS	NS	AcE: 0.065 mg/g EE: 0.015 mg/g ME: 0.128 mg/g DmE: 0.016 mg/g	Atranorin, zeorin	Singh et al. (2011)
Ramalinaceae C. Agardh								
Ramalina conduplicans Vain.	ME	NS	58.2–85.4%	NS	NS	NS	Usnic acid, salazinic acid, sekikaic acid	Vinayaka et al. (2009)
Ramalina hossei Vain.	ME	NS	500 µg/ml: 89.8% + honey: 86.6%	NS	NS	NS	Usnic acid, sekikaic acid	Prashith Kekuda et al. (2009)
Ramalina pollinaria (Westr.) Ach.	ME	26.0%	No activity	NS	NS	1.0 % (w/w)	NS	Güllüce et al. (2006)
Ramalina polymorpha (Lilj.) Ach.	ME	19.0%	No activity	NS	NS	0.8 % (w/w)	NS	GüllGüllüce et al. (2006)
Ramalina terebrata Hook. F. & Taylor	ME-WE (90/10)	NS	TLC spray 2–3 antioxidant active spots	NS	NS	NVNR	NS	Bhattarai et al. (2008)
	ME-WE (90/10)	NS	302.4 µg/ml	NS	NS	NS	NS	Paudel et al. (2008)
Sphaerophoraceae Fr.								
Sphaerophorus globosus (Huds.) Vain.	AcE, ME	NVNR	AcE: >1000 µg/ml ME: >1000 µg/ml	NVNR AcE > ME	NVNR AcE = ME	NS	NS	Luo et al. (2009)
Stereocaulaceae Chevall.								
Stereocaulon alpinum Laurer ex Funck	ME-WE (90/10)	NS	TLC spray 2–4 antioxidant active spots	NS	NS	NVNR	NS	Bhattarai et al. (2008)
	ME-WE (90/10)	NS	409.3 µg/ml	NS	NS	NS	NS	Paudel et al. (2008)
	AcE, ME	NVNR	AcE: >1000 µg/ml ME: >1000 µg/ml	NVNR AcE > ME	NVNR AcE > ME	NS	NS	Luo et al. (2009)
Teloschistaceae Zahlbr.								
Calopaca regalis (Vain.) Zahlbr.	ME-WE (90/10)	NS	TLC spray 2–3 antioxidant active spots	NS	NS	NVNR	NS	Bhattarai et al. (2008)
	ME-WE (90/10)	NS	251.7 µg/ml	NS	NS	NS	NS	Paudel et al. (2008)
Fulgensia fulgens (Sw.) Elenkin	ME	21.6%	NS	NS	0.136	12.4 mg GA/g	NS	Ranković et al. (2010b)
Xanthoria elegans (Link) Th. Fr.	AcE, DmE, EE, ME	NVNR	NVNR	NS	NS	AcE: 0.008 mg/g EE: 0.003 mg/g ME: 0.151 mg/g DmE: 0.036 mg/g	Xhantorina	Singh et al. (2011)
Trypetheliaceae Zenker								
Laurera benguelensis Zahlbr.	ChE and benzene (BF) and methanol fractions (MF)	NS	ChE: 432.0 mg/ml BF: 645.8 mg/ml MF: 758.0 mg/ml	NS	NS	NS	Lichexanthone, secalonic acid D, norlichexanthon, parietin, emodin, teloschistin and citreorosein	Manojlovic et al. (2010)
Umbilicariaceae Chevall.								
Lasallia pustulata (L.) Mérat	AcE, ME, WE	NS	AcE: 90.9% ME: 69.9% WE: 65.1%	AcE: 67.4% ME, WE: NVNR	NVNR AcE > ME > WE	AcE: 84.3 µg PE ME: 49.6 µg PE WE: 23.9 µg PE	NS	Kosanić et al. (2011)
Umbilicaria Antarctica Frey & Lamb	AcE, ME	NVNR	AcE: 121.3 µg/ml ME: >1000 µg/ml	AcE: 91.1% ME: NVNR	NVNR AcE > ME	NS	Lecanoric acid	Luo et al. (2009)
Umbilicaria aprina var. halei Nyl.	ME	NS	5 mg/ml: 34.6%	NS	NS	40.6 mg GA/g	Lecanoric acid	Buçukoglu et al. (2012)
Umbilicaria crustulosa (Ach.) Lamy	AcE	NS	60.1%	Moderate 42.0%	Low 0.050	39.6 µg PE/mg (28.1 µg RE/mg)	NS	Kosani ć et al. (2012b)
Umbilicaria cylindrica (L) Delise ex Duby	AcE, ME, WE	NS	NVNR	NVNR	NVNR	AcE: 19.1 µg PE ME: 42.5 µg PE WE: 19.1 µg PE	NS	Kosani ć and Rankovic (2011)

(*continued*)

Table 1. Continued

Lichen species	Solvent	LP inhibition (IC_{50} or %INH)	DPPH (IC_{50} or %INH)	$SO^{\cdot-}$ RSA (IC_{50} or %INH)	Reducing power (A_{700} or IC_{50})	Phenolic/flavonoid content	Isolated compounds/ composition	Reference
						(AcE: 12.9 µg RE, ME: 19.1 µg RE, WE: 11.1 µg RE)		
	ME	NS	21.1% (5 mg/ml)	NS	NS	0.9 mg GA/g	NS	Buçukoglu et al. (2012)
	AcE	NS	39.4%	Moderate 33.9%	Low 0.035	19.1 µg PE/mg (12.9 µg RE/mg)	NS	Kosani ć et al. (2012b)
	ChE, ME	ChE: 29.3 µg/ml ME: 35.4 µg/ml	ChE: 31.3 µg/ml ME: 34.4 µg/ml	NS	NS	ME: 79.2 mg GA/g ChE: 71.3 mg GA/g	Salazinic acid, norstictic acid, methyl-β-orcinol carboxylate, ethyl haematommate, usnic acid, atranorin	Manojlovi ć et al. (2012b)
Umbilicaria esculenta (Miyoshi) Minks	ME	6 mg/ml: 92.1%	6 mg/ml: 1.3 mg/ml	NS	NS	1.5%	NS	Kim and Cho (2007)
Umbilicaria decussata (Vill.) Zahlbr.	ME	NS	5 mg/ml: 23.4%	NS	NS	3.3 mg GA/g	NS	Buçukoglu et al. (2012)
Umbilicaria hyperborea (Ach.) Hoffm.	AcE, DE, EE, ME	NVNR	NVNR	NS	NS	AcE: 0.001 mg/g DmE: 0.029 mg/g EE: 0.001 mg/g ME: 0.046 mg/g	Gyrophoric acid	Singh et al. (2011)
Umbilicaria leiocarpa DC.	ME	NS	5 mg/ml: 32.8%	NS	NS	35.9 mg GA/g	NS	Buçukoglu et al. (2012)
Umbilicaria nylanderiana (Zahlbr.) H. Magn.	ME	53.0%	400.2 µg/ml	NS	NS	3.0 % (w/w)	NS	Güllüce et al. (2006)
	ME	NS	5 mg/ml: 32.9%	NS	NS	48.3 mg GA/g	Umbilicaric acid	Buçukoglu et al. (2012)
Umbilicaria polyphylla (L.) Baumg.	AcE	NS	72.8%	Moderate 55.4%	Low 0.065	47.0 µg PE/mg (30.3 µg RE/mg)	NS	Kosanić et al. (2012b)
Umbilicaria virginis Schaerer	ME	NS	5 mg/ml: 20.3%	NS	NS	15.3 mg GA/g	Gyrophoric acid	Buçukoglu et al. (2012)
Verrucariaceae Zenker								
Dermatcarpon intestiniformis (Körber) Hasse	ME, WE	ME: 5.3% WE: 9.5%	NS	NS	ME: 0.119 WE: 0.131	ME: 18.6 mg GA/g WE: 9.2 mg GA/g	NS	Odabasoglu et al. (2005)
Some macrostudies:								
Macrostudy of 46 lichen species Highest activities: - *Sticta nylanderiana* Zahlbr. (S.n.) - *Peltigera praetextata* (Flörke ex Sommerf.) Zopf (P.p.)	ME	S.n.: 85.5% P.p.: 85.4%	S.n.: 90.4% P.p.: 87.8%	NS	S.n.: 1.5 P.p.: 1.0	S.n.: 156.1 µg CE/mg P.p.: 109.3 µg CE/mg	*Sticta nylanderiana*: lecanoric acid	Luo et al. (2010)
Macrostudy of 77 lichen species (*Graphidaceae sp.*)	DmE, ME	NS	NS	Screening of 77 extracts by two methods. Highest $SO^{\cdot-}$ RSA (>50%): *Graphina multistriata* *Graphina salacinilabiata* *Graphis assamensis* *Graphis guimarana* *Graphis sikkimensis*	NS	NS	NS	Behera et al. (2003)

Macrostudy of 85 lichen species	EE	NS	Screening of 99 extracts. Highest DPPH scavenging activities: *Hypogymnia vittata* *Peltigera aphthosa* *Nephromopsis ornata* *Pseudevernia furfuraceae* *Cladonia vulcani* *Peltigera elizobethae*	NS	NS	*Peltigera aphthosa*: solorinine	Hara et al. (2011)

NS, not studied; NVNR, numeric value not reported; LP, lipoperoxidation; %INH, percentage of inhibition; SO^{-} RSA, superoxide radical scavenging activity; GA, gallic acid; PE, pyrocatechol equivalent; RE, rutin equivalent; AA, ascorbic acid; T, tocopherol; TBA, thiobarbituric acid; CE, catechol equivalent; MDA, malodialdehyde; ChE, chloroform extract; ME, metanol extract; PE, petrol ether extract; AcE, acetone extract; DmE, dimethyl sulfoxide extract; EE, ethanol extract; WE, water extract; DE, diethyl-ether extract; BE, benzene extract; BuE, butanol extract; DcmE, dichlorometane extract; EaE, ethyl acetate extract.

chemical assays, such as DPPH free radical scavenging activity, superoxide anion radical scavenging activity, reducing power, and lipid peroxidation inhibition. Methanol arises as one of the most used solvents for an efficient extraction of lichens bioactive compounds with antioxidant activities and, therefore, many antioxidant activity assays have been performed on methanol extracts (Stojanović et al., 2010; Kosanić & Ranković, 2011; Zambare & Christopher, 2012).

In the last part of our review, we focus on antioxidant responses of these natural products to oxidative stress occurring at intracellular level and *in vivo* trials. Therefore, we collect the more recent investigations on antioxidant activity of lichens species (both purified metabolites and extracts) on *in vitro* cellular substrates (Table 3) and *in vivo* animal models (Table 4).

Apart from all species and assays shown in the tables, some authors have measured similar parameters by other methods (e.g., other radical scavenging properties) and also different parameters related to the antioxidant potential of the aforementioned lichens and compounds. Regarding other radical scavenging properties, Papadopolou et al. (2007) evaluated the hydroxyl radical scavenging activity of β-orcinol metabolites of the lichen *Hypotrachyna revoluta* (Flörke) Hale (Parmeliaceae); this $OH^{\cdot}$-radical scavenging activity has also been measured in *Toninia candida* (Weber) Th.Fr. (Ramalinaceae) (Manojlovic et al., 2012b), *Usnea ghattensis* G. Awasthi (Parmeliaceae) (Verma et al., 2008a), and *Umbilicaria cylindrica* (L.) Delise ex Duby (Umbilicariaceae) (Manojlovic et al., 2012c). Nitric oxide radical scavenging activity was assayed on *Usnea complanata* (Müll. Arg.), Motyka (Parmeliaceae) (Behera et al., 2012), *Usnea ghattensis* (Verma et al., 2008b), psoromic and usnic acids (Behera et al., 2012), and on other 14 lichen-purified metabolites (Thadhani et al., 2011). Moreover, hydrogen peroxide scavenging activity was investigated on *Parmelia saxatilis* (Özen & Kinalioglu, 2008) and the TEAC value (Trolox equivalent antioxidant capacity) has been determined using the ABTS radical assay in several polar lichen species (Paudel et al., 2008; Singh et al., 2011), as well as in *Usnea ghattensis* (Behera et al., 2005a; Verma et al., 2008a), *Laurera benguelensis* Zahlbr. (Zahlbr.) (Manojlovic et al., 2010), and ramalin compound (Paudel et al., 2011).

Behera et al. (2003, 2006a) assessed the xanthine oxidase inhibitory capacity for many species of the family Graphidaceae; the ferrous ion-chelating activity was investigated in *Umbilicaria cylindrica* (Manojlovic et al., 2012c) and *Toninia candida* (Manojlovic et al., 2012b); and the tyrosinase inhibitory activity has been studied in some lichens and isolated compounds (Behera et al., 2006b; Kim & Cho, 2007; Paudel et al., 2011).

Finally, it is remarkable that the work conducted by Lopes et al. (2008) assayed the radical scavenging properties for many semisynthetic derivatives from the lecanoric acid obtained from a *Parmotrema tinctorum* (Delise ex Nyl.) Hale (Parmeliaceae) specimen and treated with alcohols. They obtained the three most active compounds at scavenging DPPH radical that were orsellinic acid, orcinol and resorcinol, and the lowest activity was displayed by methyl orsellinate.

Table 2. Antioxidant activities of isolated compounds from lichens.

Compound	Origin	LP inhibition (IC_{50} or %INH)	DPPH (IC_{50} or %INH)	SO RSA (IC_{50} or %INH)	Reducing power (A_{700} or IC_{50})	Reference
1,8-Dihydroxy-5-methoxy-3-methylxanthone	*Pyrenula japonica* Kurok [DE]	Not studied (NS)	Numeric Value Not Reported (NVNR)	NS	NS	Takenaka et al. (2000)
1,5,8-Trihydroxy-3-methylxanthone	*Pyrenula japonica* Kurok [DE]	NS	NVNR	NS	NS	Takenaka et al. (2000)
1,7-Dihydroxy-3-methylxanthone	*Pyrenula japonica* Kurok [DE]	NS	NVNR	NS	NS	Takenaka et al. (2000)
1,2,8-Trihydroxy-5-methoxy-3-methylxanthone	*Pyrenula japonica* Kurok [DE]	NS	NVNR	NS	NS	Takenaka et al. (2000)
1-Chloropannarin	*Erioderma chilense* Mont.	30% In rat brain homogenate: 27–66%	NS	NS	NS	Hidalgo et al. (1994)
7-Chlorocanarione	*Lethariella cashmeriana* Krog [ME]	NS	NS	Activity: 142.7	NS	Kinoshita et al. (2010)
2-*O*-Methylsekikaic acid	*Ramalina asahinae* W.L. Culb & C.F. Culb. [ME, AcE]	NS	$1/IC_{50} = 0.052$	NS	NS	Valencia-Islas et al. (2007)
Atranol	*Lethariella canariensis* (Ach.) Krog [ME]	NVNR	NS	NS	NS	Toledo-Marante et al. (2003)
Atranorin	*Placopsis* sp.	6.5% In rat brain homogenate: 7.3–9.5%	NS	NS	NS	Hidalgo et al. (1994)
	Parmotrema stuppeum (Taylor) Hale [BE, AcE]	14.0%	NS	NS	NS	Jayaprakasha et al (2000)
	Lethariella canariensis (Ach.) Krog [ME]	Unable to prevent lipid peroxidation	NS	NS	NS	Toledo-Marante et al. (2003)
	Usnea articulata (L.) Hoffm. [various extracts]	NS	NVNR	NVNR	NS	Lohézic-Le Dévéhat et al. (2007)
	Parmotrema stuppeum (Taylor) Hale [ME, AcE]	NS	$1/IC_{50} = 0.576$	NS	NS	Valencia-Islas et al. (2007)
	Parmotrema grayana Hue. [DcmE], *Heterodermia obscurata* (Nyl.) Trevisan [DcmE], and *Cladonia* sp. [DcmE]	NS	No activity	1.6%	NS	Thadhani et al. (2011)
Barbatic acid	*Usnea articulata* (L.) Hoffm. [various extracts]	NS	NVNR	NVNR	NS	Lohézic-Le Dévéhat et al. (2007)
Boninic acid	*Ramalina asahinae* W.L. Culb & C.F. Culb. [ME, AcE]	NS	$1/IC_{50} = 0.014$	NS	NS	Valencia-Islas et al. (2007)
Canarione	*Lethariella sernanderi* (Motyka) Obermayer [AcE]	NS	NS	Activity: 137.2	NS	Kinoshita et al. (2010)
Chloroatranol	*Lethariella canariensis* (Ach.) Krog [ME]	50.0–60.0%	NS	NS	NS	Toledo-Marante et al. (2003)
Chloroatranorin	*Lethariella canariensis* (Ach.) Krog [ME]	50.0–57.0%	NS	NS	NS	Toledo-Marante et al. (2003)
	Parmotrema stuppeum (Taylor) Hale [ME, AcE]	NS	$1/IC_{50} = 0.589$	NS	NS	Valencia-Islas et al. (2007)
Chlorohematommic acid	*Lethariella canariensis* (Ach.) Krog [ME]	NVNR	NS	NS	NS	Toledo-Marante et al. (2003)
Chlororubrocashmeriquinone	*Lethariella sernanderi* (Motyka) Obermayer [AcE], *L. sinensis* J.C.Wei & Y.M.Jiang [ME], and *L. cashmeriana* Krog [ME]	NS	NS	Activity: 277.4	NS	Kinoshita et al. (2010)
Cryptostictinolide	*Usnea articulata* (L.) Hoffm. [various extracts]	NS	18.0%	NVNR	NS	Lohézic-Le Dévéhat et al. (2007)
Diffractaic acid	*Usnea longissima* Ach. [EE]	NVNR – no antioxidant activity	No scavenging activity	NS	NS	Atalay et al. (2011)
	Protousnea magellanica (Mont.) Krog	NS	No scavenging activity	NS	NS	Brisdelli et al. (2013)
Divaricatic acid	*Protousnea malacea* (Stirt.) Krog	8.6% In rat brain homogenate: 1.7–8.4%	NS	NS	NS	Hidalgo et al. (1994)
	Parmotrema grayana Hue [DcmE]	NS	27.0%	92.5%	NS	Thadhani et al. (2011)
Ergosterol peroxide	*Usnea articulata* (L.) Hoffm. [various extracts]	NS	NVNR	NDR	NS	Lohézic-Le Dévéhat et al. (2007)
	Lobaria pulmonaria L. (Hoffm.) [AcE]	LNVNR	NVNR	NS	NS	Atalay et al. (2011)
Erythrin	*Roccella montagnei* Bel. [AcE]	NS	No scavenging activity	84.1%	NS	Thadhani et al. (2011)
Ethyl chlorohematommate	*Lethariella canariensis* (Ach.) Krog [ME]	50.0–60.0%	NS	NS	NS	Toledo-Marante et al. (2003)
Ethyl hematommate	*Lethariella canariensis* (Ach.) Krog [ME]	NVNR	NS	NS	NS	Toledo-Marante et al. (2003)
Evernic acid	*Evernia prunastri* Ach. [AcE]	NS	322.4 μg/ml	561.8 μg/ml	500 μg/ml: 0.091	Kosani ć et al. (2013)
Fumarprotocetraric acid	*Usnea articulata* (L.) Hoffm. [various extracts]	NS	20.0%	566.0 μM	NS	Lohézic-Le Dévéhat et al. (2007)

Gyrophoric acid	*Umbilicaria virginis* Schaerer	NS	50.9%	NS	NS	Buçukoglu et al. (2012)
Hematommic acid	*Lethariella canariensis* (Ach.) Krog [ME]	50.0–60.0%	NS	NS	NS	Toledo-Marante et al. (2003)
Isidiophorin	*Lobaria pulmonaria* L. (Hoffm.) [AcE]	NVNR	NVNR – high scavenging activity	NS	NS	Atalay et al. (2011)
Lecanoric acid	*Parmotrema stuppeum* (Taylor) Hale [BE, AcE]	12.0–36.0%	NS	NS	NS	Jayaprakasha et al (2000)
	Parmotrema tinctorum (Nyl.) Hale	NS	42.87 mM	NS	NS	Lopes et al. (2008)
Lecanoric acid	*Sticta nylanderiana* Zahlbr. [ME]	51.5%	35.4%	NS	NS	Luo et al. (2010)
	Parmotrema grayana Hue. [ME]	NS	34.0%	98.4%	NS	Thadhani et al. (2011)
	Umbilicaria aprina var. halei Nyl. [ME]	NS	32.5%	NS	NS	Buçukoglu et al. (2012)
Lobaric acid	*Cladonia* sp. [ME]	NS	No scavenging activity	96.8%	NS	Thadhani et al. (2011)
	Stereocaulon alpinum Laur.	NS	No scavenging activity	NS	NS	Brisdelli et al. (2013)
Methyl chlorohematommate	*Lethariella canariensis* (Ach.) Krog [ME]	66.0–70.0%	NS	NS	NS	Toledo-Marante et al. (2003)
Methyl hematommate	*Lethariella canariensis* (Ach.) Krog [ME]	NVNR	NS	NS	NS	Toledo-Marante et al. (2003)
	Parmotrema grayana Hue. [DcmE], and *Heterodermia obscurata* (Nyl.) Trevisan [DcmE]	NS	No scavenging activity	20.4%	NS	Thadhani et al. (2011)
Methyl orcinol carboxylate	*Usnea articulata* (L.) Hoffm. [various extracts]	NS	NVNR	NVNR	NS	Lohézic-Le Dévéhat et al. (2007)
	Heterodermia obscurata (Nyl.) Trevisan [DcmE], and *Cladonia* sp. [DcmE]	NS	No scavenging activity	1.5%	NS	Thadhani et al. (2011)
Methyl orsellinate	*Parmotrema stuppeum* (Taylor) Hale [BE, AcE]	18.0–40.0%	NS	NS	NS	Jayaprakasha et al (2000)
Methyl orsellinate	*Lethariella canariensis* (Ach.) Krog [ME]	NVNR	NS	NS	NS	Toledo-Marante et al. (2003)
	Parmotrema grayana Hue. [ME], *Heterodermia obscurata* (Nyl.) Trevisan [DcmE], and *Cladonia* sp. [ME]	NS	2.4%	21.2%	NS	Thadhani et al. (2011)
Montagnetol	*Roccella montagnei* Bél. [AcE]	NS	No scavenging activity	9.9%	NS	Thadhani et al. (2011)
Norstictic acid	*Usnea articulata* (L.) Hoffm. [various extracts]	NS	NVNR	580.0 µM	NS	Lohézic-Le Dévéhat et al. (2007)
	Toninia candida (Weber) Th. Fr. [AcE]	NS	102.7 µg/ml	133.5 µg/ml	500 µg/ml: 0.547	Rankovic et al. (2012)
Orcinol	*Parmotrema grayana* Hue. [ME]	NS	49.7%	38.2%	NS	Thadhani et al. (2011)
Orsellinic acid	*Parmotrema stuppeum* (Taylor) Hale. [BE, AcE]	26–50%	NS	NS	NS	Jayaprakasha et al (2000)
	Parmotrema grayana Hue. [ME]	NS	39.7%	7.9%	NS	Thadhani et al. (2011)
Pannarin	*Erioderma chilense* Mont.	23.0% In rat brain homogenate: 13.0–36.0%	NS	NS	NS	Hidalgo et al. (1994)
Physodic acid	*Pseudoevernia furfuraceae* (L.) Zopf.[AcE]	NS	69.1 µg/ml	118.2 µg/ml	500 µg/ml: 0.664	Kosanić et al. (2013)
Protolichesterinic acid	*Cornicularia aculeata* (Schreb.) Ach.	NS	No scavenging activity	NS	NS	Brisdelli et al. (2013)
Protrocetraric acid	*Parmelia caperata* (L.) Ach. [AcE]	NS	138.2 µg/ml	177.6 µg/ml	500 µg/ml: 0.090	Manojlovic et al. (2012a)
Psoromic acid	*Usnea complanata* (Müll. Arg.) Motyka [total extract]	0.2 mg/ml	0.271 mg/ml	NS	NS	Behera et al. (2012)
Pulmonarianin	*Lobaria pulmonaria* L. (Hoffm.) [AcE]	NVNR	NVNR – low scavenging activity	NS	NS	Atalay et al. (2011)
Ramalin	*Ramalina terebrata* Hook. f. & Taylor. [ME]	NS	0.990 µg/ml	10.2 µg/ml	0.4 µg of BHT equivalent	Paudel et al. (2011)
Rhizonaldehyde	*Lobaria pulmonaria* L. (Hoffm.) [AcE]	NVNR	NVNR	NS	NS	Atalay et al. (2011)
Rhizonyl alcohol	*Lobaria pulmonaria* L. (Hoffm.) [AcE]	NVNR	NVNR	NS	NS	Atalay et al. (2011)
Rubrocashmeriquinone	*L. sernanderi* (Motyka) Obermayer [AcE], and *L. sinensis* Wei & Jiang. [ME]	NS	NS	Activity: 87.2	NS	Kinoshita et al. (2010)
Salazinic acid	Parmelia sp. (*P. saxatilis* (L.) Ach.and *P. sulcata* Taylor.) [AcE]	NS	91.6 µg/ml	119.1 µg/ml	500 µg/ml: 0.184	Manojlovic et al. (2012a)
	Parmotrema stuppeum (Taylor) Hale. [ME, AcE]	NS	$1/IC_{50} = 0.014$	NS	NS	Valencia-Islas et al. (2007)
Sekikaic acid	*Heterodermia obscurata* (Nyl.) Trevis. [ME]	NS	32.6%	98.2%	NS	Thadhani et al. (2011)
Solorinine	*Peltigera aphthosa* (L.) Willd. [EE]	NS	120.0 µmol/ml	NS	NS	Hara et al. (2011)
Stictic acid	*Usnea articulata* (L.) Hoffm.[various extracts]	NS	NVNR	NVNR	NS	Lohézic-Le Dévéhat et al. (2007)
	Lobaria pulmonaria L. (Hoffm.) [AcE]	NVNR	NVNR	NS	NS	Atalay et al. (2011)
Umbilicaric acid	*Umbilicaria nylanderiana* (Zahlbr.) H. Magn [ME]	NS	68.1%	NS	NS	Buçukoglu et al. (2012)

(*continued*)

Table 2. Continued

Compound	Origin	LP inhibition (IC_{50} or %INH)	DPPH (IC_{50} or %INH)	SO RSA (IC_{50} or %INH)	Reducing power (A_{700} or IC_{50})	Reference
Usnic acid	*Lethariella canariensis* (Ach.) Krog [ME]	Unable to prevent lipid peroxidation	NS	NS	NS	Toledo-Marante et al. (2003)
	Usnea articulata (L.) Hoffm.[various extracts]	NS	NVNR	NVNR	NS	Lohézic-Le Dévéhat et al. (2007)
	Ramalina asahinae W. L. Culb. & C. F. Culb. [ME, AcE]	NS	$1/IC_{50} = 0.112$	NS	NS	Valencia-Islas et al. (2007)
	Usnea longissima Ach. [EE]	NVNR – no antioxidant activity	No scavenging activity	NS	NS	Atalay et al. (2011)
	Parmotrema grayana Hue. [DcmE]	NS	No scavenging activity	59.9%	NS	Thadhani et al. (2011)
	Usnea complanata (Müll. Arg.) Motyka [Total extract]	0.214 mg/ml	0.195 mg/ml	NS	NS	Behera et al. (2012)
	Parmelia caperata (L.) Ach. [AcE]	NS	60.7 µg/ml	97.3 µg/ml	500 µg/ml: 0.547	Manojlovic et al. (2012a)
	Usnea barbata Motyka [AcE]	NS	130.7 µg/ml	197.3 µg/ml	500 µg/ml: 0.664	Rankovic et al. (2012)
	Cladonia lepidophora Ahti & Kashiw	NS	No scavenging activity	NS	NS	Brisdelli et al. (2013)
Variolaric acid	*Ochrolechia deceptionis* (Hue) Darb.	NS	No scavenging activity	NS	NS	Brisdelli et al. (2013)
Vesuvianic acid	*Lobaria pulmonaria* L. (Hoffm.) [AcE]	NVNR	NS	NS	NS	Atalay et al. (2011)
Vicanicin	*Psoroma pallidum* Nyl	NS	No scavenging activity	NS	NS	Brisdelli et al. (2013)
Zeorin	*Cladonia* sp. [DcmE]	NS	No scavenging activity	1.6%	NS	Thadhani et al. (2011)

NS, not studied; NVNR, numeric value not reported; LP, lipoperoxidation; %INH, percentage of inhibition; SO RSA, superoxide radical scavenging activity; GA, gallic acid; PE, pyrocatechol equivalent; RE, rutin equivalent; AA, ascorbic acid; T, tocopherol; TBA, thiobarbituric acid; CE, catechol equivalent; MDA, malodialdehyde; ChE, chloroform extract; ME, metanol extract; PE, petrol ether extract; AcE, acetone extract; DmE, dimethyl sulfoxide extract; EE, ethanol extract; WE, water extract; DE, diethyl-ether extract; BE, benzene extract; BuE, butanol extract; DcmE, dichlorometane extract; EaE, ethyl acetate extract.

Table 3. Evaluations of antioxidant parameters on cellular substrates.

Lichen specie/isolated compound	Solvent/origin	Cell line	LP inhibition	Antioxidant activity markers	Reference
Atranorin	Comercial	Human neuron-like cells (SH-SY5Y)	↑ Peroxyl radical-induced lipoperoxidation *in vitro*	Good antioxidant capacity in TRAP/TAR assays ↑ H_2O_2 and NO production and $SO^{\cdot-}$ scavenging activity Protection of SH-SY5Y cells against H_2O_2-induced cell viability impairment	Melo et al. (2011)
Cetraria islandica (L.) Ach.	Methanol	Human lymphocytes	↓ MDA levels	↑ SOD and GPx activities	Kotan et al. (2011)
Diffractaic acid	*Protousnea magellanica* (Mont.) Krog	HeLa cell line	Not studied (NS)	No effect on intracellular ROS level No protection against t-BHP-induced increase in intracellular ROS level	Brisdelli et al. (2013)
Evernia prunastri (L.) Ach.	Methanol	Human lymphocytes	↓ MDA levels	↑ GSH levels, SOD and GPx activities	Alpsoy et al. (2015)
Lobaric acid	*Stereocaulon alpinum* Laurer ex Funck	HeLa cell line	NS	No effect on intracellular ROS level No protection against t-BHP-induced increase in intracellular ROS level	Brisdelli et al. (2013)
Peltigera horizontalis (Hudson) Baumg.	Methanol	Human lymphocytes	↓ MDA levels	↑ GSH levels, SOD and GPx activities	Nardemir et al. (2013)
Peltigera praetextata (Flörke ex Sommerf.) Zopf	Methanol	Human lymphocytes	↓ MDA levels	↑ GSH levels, SOD and GPx activities	Nardemir et al. (2013)

Protolichesterinic acid	*Cornicularia aculeata* (Schreb.) Ach.	HeLa cell line	NS	No effect on intracellular ROS level No protection against t-BHP-induced increase in intracellular ROS level	Brisdelli et al. (2013)
Ramalin	*Ramalina terebrata* Hook. f. & Taylor. [ME]	Murine macrophage Raw 264.7 cells	NS	↓ NO release and H_2O_2 production after LPS stimulation	Paudel et al. (2011)
Salazinic acid	*Xanthoparmelia cantschadalis* (Ach.) Hale [ME]	Astrocyte cell line U373-MG	NS	↑ Cell viability in H_2O_2-treated cells ↓ ROS production ORAC value: 2.7 μmol TE/mg	de Paz et al. (2010)
Stictic acid	*Xanthoparmelia conspersa* (Ach.) Hale [ME]	Astrocyte cell line U373-MG	NS	↑ Cell viability in H_2O_2-treated cells ↓ ROS production ORAC value: 2.3 μmol TE/mg	de Paz et al. (2010)
Umbilicaria vellea (L.) Ach.	Methanol	Human lymphocytes	↓ MDA levels	↑ SOD and GPx activities (doses: 5 and 10 mg/ml)	Aslan et al. (2011)
Usnic acid (UA)	*Xanthoparmelia conspersa* (Ach.) Hale and *X. cantschadalis* (Ach.) Hale [ME]	Astrocyte cell line U373 MG	NS	↑ Cell viability in H_2O_2-treated cells ↓ ROS production ORAC value: 2.9 μmol TE/mg	de Paz et al. (2010)
	Comercial	Human neuron-like cells (SH-SY5Y)	↑ Lipoperoxidation	Good antioxidant capacity in TRAP/TAR assays ↓ $OH^{\cdot}$ and NO formation No effect on CAT and SOD-like activities No protection against H_2O_2-induced cell death ↑ ROS production	Rabelo et al. (2012)
Usnic acid (UA)	*Cladonia lepidophora* Ahti & Kashiw.	HeLa cell line	NS	No effect on intracellular ROS level No protection against t-BHP-induced increase in intracellular ROS level	Brisdelli et al. (2013)
Variolaric acid	*Ochrolechia deceptionis* (Hue) Darb.	HeLa cell line	NS	No effect on intracellular ROS level No protection against t-BHP-induced increase in intracellular ROS level	Brisdelli et al. (2013)
Vicanicin	*Psoroma pallidum* Nyl.	HeLa cell line	NS	No effect on intracellular ROS level No protection against t-BHP-induced increase in intracellular ROS level	Brisdelli et al. (2013)
Xantho somloensis (Gyelnik) Hale.	Methanol	Human lymphocytes	↓ MDA levels	↑ SOD and GPx activities (doses: 5 and 10 mg/ml)	Aslan et al. (2011)
Xanthoparmelia cantschadalis (Ach.) Hale	Methanol	Astrocyte cell line U373 MG	NS	↑ Cell viability in H_2O_2-treated cells ↓ ROS production ORAC value: 4.9 μmol TE/mg	de Paz et al. (2010)
Xanthoparmelia conspersa (Ach.) Hale	Methanol	Astrocyte cell line U373 MG	NS	↑ Cell viability in H_2O_2-treated cells ↓ ROS production ORAC value: 8.8 μmol TE/mg	de Paz et al. (2010)
Xanthoria elegans (Link) Th. Fr.	Water	Human lymphocytes	NS	↑ TAC level without changing TOS level	Turkez et al. (2011)

TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; GPx, gluthathione peroxidase; GSH, reduced gluthathione; AFB_1, aflatoxin B_1; AE, water extract; ME, methanol extract; ROS, reactive oxygen species; $OH^{\cdot}$, hydroxyl radical; CAT, catalase; TAC, total antioxidant capacity; TOS, total oxidative stress; MPx, myeloperoxidase; cNOS, constitutive nitric oxide synthase; iNOS, inducible nitric oxide synthase; GR, gluthathione reductase; GST, glutathione transferase; DE, diethyl ether extract; AcE, acetone extract.

Table 4. *In vivo* evaluations of antioxidant activities.

Lichen specie/isolated compound	Solvent/origin	LP inhibition	Antioxidant enzymes and other antioxidant markers	Reference
Cetraria islandica (L.) Ach.	–	↓ MDA levels	↑ GSH levels ↓ CAT and GPx activities Association of magnesium augmented the antioxidant effect	Cernescu et al. (2011)
Diffractaic acid	*Usnea longissima* Ach. [DE]	↓ lipoperoxidation level in tissues	↑ SOD and GPx activities and GSH levels ↓ CAT and MPx activities ↑ cNOS activity and ↓ iNOS activity	Bayir et al. (2006)
Fumarprotocetraric acid	*Cladonia verticillaris* (Raddi) Fr. [AcE]	↓ endotoxin-induced lipid peroxidation	Not studied (NS)	de Barros Alves et al. (2014)
Lobaria pulmonaria (L.) Hoffm.	Methanol	↓ lipoperoxidation level in tissues	↑ SOD, GPx and GSH levels in tissues No effect on CAT and MPx levels	Karakus et al. (2009)
Peltigera rufescens (Weiss) Humb.	Methanol	↓ lipoperoxidation	↑ SOD, CAT, GSH, GR and GPx levels ↓ MPx and iNOS activities	Tanas et al. (2010)
Usnea ghattensis G. Awasthi	Methanol	↓ MDA formation in liver tissue	Depletion in antioxidant enzymes (SOD, CAT, GPx) and GSH	Verma et al. (2008a)
Usnea longissima Ach.	Water	47.1% inhibition	↑ SOD and GST levels ↓ CAT activity. Reducing power (A_{700}): 0.1; phenolic content: 18.3 mg GA/g	Halici et al. (2005)
Usnic acid	*Usnea longissima* Ach. [DE]	↓ lipoperoxidation level in tissues	↑ SOD, GSH and GPx levels ↓ CAT, GR and MPx activities ↑cNOS activity and ↓iNOS activity	Odabasoglu et al. (2006)

TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; GPx, gluthathione peroxidase; GSH, reduced gluthathione; AFB_1, aflatoxin B_1; AE, water extract; ME, methanol extract; ROS, reactive oxygen species; $OH^{\cdot}$, hydroxyl radical; CAT, catalase; TAC, total antioxidant capacity; TOS, total oxidative stress; MPx, myeloperoxidase; cNOS, constitutive nitric oxide synthase; iNOS, inducible nitric oxide synthase; GR, gluthathione reductase; GST, glutathione transferase; DE, diethyl ether extract; AcE, acetone extract.

Conclusions

The present review reports the biological activity of more than 75 different lichen species, as well as more than 65 purified metabolites, isolated from these or other species. The study of their antioxidant activities has recently been started and they have been determined by various chemical *in vitro* assays as first approach, with some of them showing interesting results. Further knowledge of this potential implies deeper research on their activities in order to understand the implied mechanisms. Thus, in this report, we also reflect the few available data about *in vitro* antioxidant activities of some lichen species and purified metabolites on cellular substrates and *in vivo* on animal models.

Concerning antioxidation, the most interesting compounds are polyphenols. The antioxidant properties of polyphenols are due to the presence of their many phenolic hydroxyl groups, which confer high potential for scavenging free radicals (Dai & Mumper, 2010; Sawa et al., 1999). For instance, phenolic compounds are able to donate hydrogen to reactive radicals and break the chain reaction of lipid oxidation at the initiation step (Gülçin et al., 2004).

Then, the strong antioxidant activity shown by some lichen extracts or metabolites, and assessed by different systems, can be attributed to their high total polyphenolic contents (specially depsides, depsidones, dibenzofurans, etc.), since a positive correlation between phenolic composition and antioxidant activity has been proved for most of them (Kosanić et al., 2011; Manojlovic et al. 2012c); at least, it suggests that polyphenols might be the major antioxidant compounds in studied lichens. Nevertheless, there have been other studies in which results did not show any positive correlation between antioxidant activity of certain lichens and total phenolic contents (Odabasoglu et al., 2004; Stojanović et al., 2010). This fact implies that other minor compounds should not be ignored but antioxidant activity might be as well attributed to the presence of non-phenolic compounds, antagonistic or synergistic interactions between constituents, and even distinct antioxidant activities of individual phenolics.

In the previous tables, the great diversity of lichens and their substances is shown, and one might deduce that the increasing interest in the study of its pharmacological properties is promoting further phylogenetic studies in an evolutionary context. Based on molecular data mainly, they are leading to a more complex classification of lichen families and species (Crespo et al., 2010). Moreover, phylogenetic analysis of biosynthetic genes can facilitate the discovery of novel compounds, novel genes, and, therefore, unknown producers of pharmaceutical relevant compounds, including antioxidants: the greatest challenges would be to find the biosynthetic gene of interest or assign function to each of the biosynthetic genes found in a lichen genome (Schmitt & Barker, 2009). Considering the difficulties still found for the *in vitro* culture of lichens and different culture conditions result in different antioxidant activities of lichen extracts (due to the production of different amount and type of secondary metabolites depending on culture characteristics) (Behera et al., 2005b), a global approach to the lichen metabolomic features seems to be crucial for the development of new and viable biotechnological processes. These will allow production of suitable amounts of unique isolated antioxidant compounds from lichens (Boustie & Grube, 2005).

Through this review of literature, we can conclude that lichens are a potential source of natural antioxidants but, at the same time, there is still a need for a deeper research in order to establish their possibilities and a better understanding of their mechanisms of action. This goal can be achieved by the better isolation of purified metabolites and more studies on appropriate cell lines and *in vivo*, in order to identify molecular targets, active compounds, and structure–activity correlations.

Declaration of interest

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