



Lichens: An update on their ethnopharmacological uses and potential as sources of drug leads

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ABSTRACT

Ethnopharmacological relevance: Lichens, a unique symbiotic association between an alga/cyanobacterium and a fungus, produce secondary metabolites that are a promising source of novel drug leads. The beauty and importance of lichens have not been adequately explored despite their manifold biological activities such as anticancer, antimicrobial, antioxidant, anti-inflammatory, analgesic, antipyretic and antiparasitic.

Aim of the study: The present review collates and discusses the available knowledge on secondary metabolites and biological activities of lichens (*in vitro* and *in vivo*).

Materials and methods: Using relevant keywords (lichens, secondary metabolites, bioactivity, pharmacological activities), five electronic databases, namely ScienceDirect, PubMed, Google Scholar, Scopus and Recent Literature on Lichens, were searched for past and current scientific contributions up until May 2022. Literature focusing broadly on the bioactivity of lichens including their secondary metabolites were identified and summarized.

Results: A total of 50 review articles and 189 research articles were searched. Information related to antioxidant, antimicrobial, anti-inflammatory, anticancer and insecticidal activities of 90 lichen species (from 13 families) and 12 isolated metabolites are reported. Over 90% of the studies comprised *in vitro* investigations, such as bioassays evaluating radical scavenging properties, lipid peroxidation inhibition and reducing power, cytotoxicity and antimicrobial bioassays of lichen species and constituents. *In vivo* studies were scarce and available only in fish and rats. Most of the studies were done by research groups in Brazil, France, Serbia, India and Turkey. There were relatively few reports from Asia and Africa despite the ubiquitous nature of lichens and the high occurrence in these continents.

Conclusion: Secondary metabolites from lichens are worthy of further investigation in terms of their potential therapeutic applicability, including better understanding of their mechanism(s) of action. This would be of great importance in the search for novel drugs.

1. Introduction

Natural products are low molecular weight molecules produced by living organisms (plants, animals, and microbes) and have been traditional leads for medicines for ages (Harvey, 2000). They have a historic significance as important novel compounds which are useful as drugs, models for synthetic/semisynthetic structure modifications and optimization, biochemical and/or pharmacological probes, and inspiration for generations of synthetic organic chemists, biologists,

pharmacologists, clinicians and bioinformaticians (Balandrin et al., 1993; Heinrich, 2008; Khan et al., 2018). Natural product molecules, and/or their synthetic modifications, have been particularly useful for chemotherapy of cancer and malaria (Phillipson, 2007). With the discovery of penicillin (from the fungus *Penicillium chrysogenum* Thom) in 1928, an era to herald the end of infectious diseases was thought to have been reached (Sengupta et al., 2013). However, introduction of new therapeutic agents has not kept pace with the increase in the evolution of multi-drug resistant microbial strains, making many infections untreatable. There is therefore a dire need for novel drugs (Pidcock,

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List of abbreviations

B	<i>Bryoria</i>	Sig	Significant
U	<i>Umbilicaria</i>	SI	Selectivity index
L	<i>Lethariella</i>	SEC	Solid Ehrlich Carcinoma
T	<i>Thamnolia</i>	COX	Cyclooxygenase
E	<i>Everniastum</i>	LOX	Lipoxygenase
J	<i>Juniperus</i>	AchE	Acetyl cholinesterase
R	<i>Rhododendron</i>	ROS	Reactive Oxygen Species
O	<i>Ochrolechia</i>	PD	Petri dish
C	<i>Cryptococcus</i>	SEM	Scanning Electron Microscopy
P	<i>Pseudomonas</i>	TEM	Transmission Electron Microscopy
S	<i>Staphylococcus</i>	CBMN	Cytokinesis-block Micronucleus
K	<i>Klebsiella</i>	MSD	Meso Scale Discovery
NA	Not available	ORAC	Oxygen Radical Antioxidant Capacity
ACE	Acetone	DPPH	1,1-diphenyl-2-picrylhydrazyl
CHL	Chloroform	FRAP	Ferric Reducing Antioxidant Power
MeOH	Methanol	ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
EtOH	Ethanol	TBARS	Thiobarbituric Acid Reactive Substance
PE	Petroleum ether	BSL	Brine Shrimp Lethality
AQ	Aqueous	MTT	2, 5-diphenyl-2H-tetrazolium bromide
HX	Hexane	H ₂ O ₂	Hydrogen peroxide
DEE	Diethyl ether	IL	Interleukin
EA	Ethyl acetate	LT	Leukotriene
Conc	Concentration	IFN	Interferon
IC	Inhibitory concentration	ALT	Alanine aminotransferase
LC	Lethal concentration	AST	Aspartate aminotransferase
MIC	Minimum Inhibitory Concentration	NO	Nitric oxide
IZ	Inhibitory Zone	NOS	Nitric oxide synthase
OD	Optical density	TNF	Tumour necrosis factor
		IP	Intraperitoneal

2012). Microbial symbioses have a high potential of affording a wide variety of unique structures, hence, are very promising in yielding new drug classes (Hutchings et al., 2019). A source of biodiversity that has been largely underestimated and not extensively explored are the lichens.

Lichens are composite organisms that arise from algae or cyanobacteria (the photobiont) living among filaments of multiple fungal species (the mycobiont) in a symbiotic relationship. The algal or cyanobacterial cells are photosynthetic, and reduce atmospheric carbon dioxide into organic carbon sugars to feed both symbionts. The fungal filaments in turn, protect the algae or cyanobacteria, and supply moisture and nutrients from the environment (Spribille et al., 2016). Research on the potential uses of lichens in pharmaceuticals and medicine has grown substantially in recent years. This is evident from many comprehensive periodic reviews on different subject areas - [traditional uses (Malhotra et al., 2008; Crawford, 2019), biological activities (Perez-Llano, 1944; Lawrey, 1986; Molnár and Farkas, 2010; Bhattacharyya et al., 2016; Ramya and Thirunalasundari, 2017; Kekuda et al., 2018; Elkhateeb and Daba, 2019; Lendemer, 2022), bioactive metabolites (Müller, 2001; Boustie and Grube, 2005; Podterob, 2008; Shukla et al., 2010; Boustie et al., 2011; Mitrović et al., 2011; Moreira et al., 2015; Xu et al., 2016; Dar et al., 2021; Ranković and Kosanić, 2021; Thadhani et al., 2021; Mohammadi et al., 2022), anticancer (Srivastava and Sarethy, 2003; Shrestha and St. Clair, 2013; Kim et al., 2015; Basnet et al., 2018; Marques, 2019; Solárová et al., 2020; Dar et al., 2021), antioxidant (White et al., 2014; Fernández-Moriano et al., 2016b; Thadhani and Karunaratne, 2017), antidiabetic (Thadhani and Karunaratne, 2017; Kosanić and Ranković, 2019a), antimicrobial (Shrestha and St. Clair, 2013; Basnet et al., 2018; Milovanović et al., 2018; Furmanek et al., 2019; Kumar and Khurana, 2019; Kosanić and Ranković, 2019b; Sepahvand et al., 2021; Furmanek et al., 2022), anti-neurodegenerative (Kosanić and Ranković, 2019a), immunomodulatory

(Shrestha et al., 2015), insecticidal/pesticidal (Dayan and Romagni, 2001; Sachin et al., 2018), nutritional value (Yusuf, 2020; Zhao et al., 2021), nanoparticles (Rattan et al., 2021), biomonitoring (Abas, 2012) and biopharmaceutical applications (Zambare and Christopher, 2012; Alam et al., 2020; Sharma and Mohammad, 2020; Elkhateeb et al., 2021)]. Despite these, the traditional utilization patterns and market potentiality of lichens as sources of drugs have not been fully explored.

2. Materials and methods

For this review, a detailed and extensive literature search was carried out on the secondary metabolites, biological properties and use of lichens as medicines globally. Five search engines - ScienceDirect, PubMed, Google Scholar, Scopus and Recent Literature on Lichens were used. Available information on commonly used lichen species is summarized and discussed thoroughly on their efficacy, bioactive constituents and possible mechanism(s) of action. Lichen species and secondary metabolites with very good efficacy are highlighted. This review may serve as an updated, simplified reference to facilitate and guide future research on these unique natural products.

3. Results and discussion

3.1. Taxonomy and classification

A lichen bears the same scientific/binomial name as the fungus species in the lichen. The alga or cyanobacterium bears its own scientific name, which has no relationship to that of the lichen or fungus (Kirk et al., 2008). Nearly 20% of known fungal species, belonging to the order Ascomycota or Basidiomycota, are associated with lichens (Sharnoff, 2014). *Trebouxia* is the most common genus of green algae in lichens, occurring in about 40% of all lichens. Other genera are

Trentepohlia, *Pseudotrebouxia* or *Myrmecian*. The two most commonly occurring cyanobacterium genera are *Nostoc* and *Scytonema* (Dobson, 2011).

There are about 20 000 known lichen species globally (Ramya and Thirunalasundari, 2017). When growing by itself, the fungus, alga, or cyanobacterium has very different properties from that of the lichen. Thus, the anatomy, physiology and biochemistry of each lichen varies, depending on the different fungal, algae, or cyanobacteria combinations (Ramya and Thirunalasundari, 2017). Studies have shown that lichens are miniature ecosystems, where the fungi, algae or cyanobacteria can connect with coexisting bacteria, endolichenic fungi and basidiomycete yeasts, evolving as an even more complex composite organism (Hawksworth and Grube, 2020).

3.2. Habitat and geographic distribution

It is estimated that 8% of the earth's land surface is covered by lichens (Ahmadjian, 1995). They are ubiquitous, occurring in a wide variety of habitats, from sea level to high mountains, and constitute the sole vegetation of extreme environments such as the Arctic tundra, hot dry deserts, rocky coasts and slag heaps (Gadd, 2010). They are considered to be among the oldest living organisms, as an arctic species, *Rhizocarpon geographicum* (L.) DC (Map lichen), is dated as being 8600 years old (Bradwell and Armstrong, 2007). Lichens are also slow-growing organisms and have been measured to grow from 0.5 mm to 0.5 m yearly (Bradwell and Armstrong, 2007). These properties (long lifespan with slow and regular growth rate) of lichens have been used to date events (lichenometry) (Loso and Doak, 2006).

Another major ecophysiological advantage of lichens is that they are poikilohydric (tolerate irregular and extended periods of severe desiccation) (Lange and Green, 2005). They, like some mosses, liverworts, and ferns, enter a cryptobiotic state of metabolic suspension or stasis, in which the cells of the lichen symbionts are dehydrated to a degree that halts most biochemical activities, thereby enhancing their survival (Kranter et al., 2008).

3.3. Economic importance

3.3.1. Nutritional uses

It is estimated that approximately one billion people globally consume lichens as part of their diet (Burlingame, 2000). Lichens are used to prepare indigenous foods, beverages, spices and animal feed among different cultures around the world. *Bryoria fremontii* (Tuck.) Brodo & D. Hawksw., is an important food in parts of North America, where it is usually pitcooked. In Scandinavian countries such as Denmark, Norway and Sweden, *Cetraria islandica* (L.) Ach., *Umbilicaria mammulata* (Ach.) Tuck., *U. muhlenbergii* (Ach.) and *B. fremontii* are mixed with grain flour to prepare bread, porridge, pudding, soups and salads (Devkota et al., 2017). In India, *Everniastrum cirrhatum* (Fr.) Hale is used as a spice and flavouring agent for vegetables and meats (Upreti et al., 2005). *Lethariella cashmeriana* Krog, *L. sermanderi* (Motyka) Obermayer, *L. sinensis* Wei & Jiang, *Thamnolia vermicularis* (Sw.) Ach. ex Schaer and *T. subuliformis* (Ehrh.) Culb. are used to prepare tea in the Yunnan Province of China (Wang et al., 2001), while *U. esculenta* (Miyoshi) Minks is used in a variety of traditional Korean and Japanese foods. Lichens are the primary food source for reindeers/caribou and the northern flying squirrel. *Cladonia* species are of economic importance to reindeer herders, such as the Sami in Scandinavia or the Nenets in Russia (Devkota et al., 2017). All these lichens play crucial roles in the subsistence strategy of rural communities, especially in developing countries (Zemede and Mesfin, 2001).

3.3.2. Spiritual uses

In many Asian countries, there is a myth that lichens ward off evil spirits and maintain peace among family members (Devkota et al., 2017). In India, *E. cirrhatum* is used as holy material for sacrificial fire in

ceremonies (Upreti et al., 2005). In Nepal, dried *Usnea longissima* Ach. and *T. vermicularis* are mixed with dried leaves of *Juniperus indica* Bertol., *J. squamata* Buch. Ham ex D. Don, *Rhododendron anthopogon* D. Don, *R. decorum* Franch., *R. lepidotum* Wall. ex G. Don and roots of *Jurinea dolomiaea* Boiss. as ingredients in incense powder. The incense powder is burnt during morning prayers and religious ceremonies, above the main entrance of a house (Devkota et al., 2017).

3.3.3. Industrial uses

The use of lichens in perfumery dates back more than 3500 years. It has been estimated that approximately 7800 to 9200 lichen species are collected to manufacture perfume in Morocco, Yugoslavia, and France (Moxham, 1986). There are also reports of lichens being used to make purple and red dyes, dating almost 2000 years ago (Casselman, 1994; Ferreira et al., 2004). *Bryoria fremontii*, *E. cirrhatum*, *Letharia vulpine* (L.) Hue, *Ochrolechia oregonensis* H. Magn., *O. tartarea* (L.) Zahlbr., *Parmelia omphalodes* (L.) Ach., *Parmotrema nilgherrensis* Nyl. and *Rocella* species produce pigments which are being used as natural dyes in different parts of the world (Shukla et al., 2014a, b). The pH indicator litmus test dyes (acidic and basic) are extracted from the lichen *Rocella tinctoria* DC. by boiling. In the Highlands of Scotland, dyes for Harris tweed and other traditional cloths were made from lichens such as *Xanthoria parietina* (L.) Th. Fr. and *Parmelia saxatilis* (L.) Ach. (Casselman, 2001). In addition, *Usnea longissima* is used in Western Himalayas to clean religious cups, butter lamps and water bowls, while *Ramalina thrausta* (Ach.) Nyl., *Usnea* and *Bryoria* species are used by Svaneti hunters in Georgia as a field-bedding (Kupradze et al., 2015) and *Usnea longissima* is used as bedding for Nepal herdsmen, calves, colts and chicks (Devkota et al., 2017).

3.3.4. Environmental uses

Many lichens are used to assess air pollution, ozone depletion, heavy metal contamination, radionuclides and other environmental pollutants. This is due to their efficiency as bio-accumulators (as they retain heavy metals such as lead, mercury and copper) and bio-indicators of air quality (Monnet et al., 2005; Bačkor and Loppi, 2009; Shukla et al., 2014c). In areas of clean air, shrubby, hairy and leafy lichens are abundant, while lichens may not be present in badly polluted areas, just green algae will be found. A few lichen species can tolerate high levels of pollution and are commonly found on pavements, walls and tree bark in urban areas (Rotherham, 2017). Lichens are therefore, a valuable bio-resource for environmental monitoring and sustainable development (Negi, 2003).

3.3.5. Ethnomedical and ethnoveterinary uses

The medicinal uses of lichens can be traced back to the 18th century (1700-1800 BC) where *Pseudevernia furfuracea* (L.) Zopf was first used as a drug (Ramya and Thirunalasundari, 2017). Ancient herbal medicinal texts such as *Materia Medica* and *Naturalis Historiae* had accounts of several genera such as *Cladonia*, *Evernia*, *Lobaria*, *Parmelia*, *Peltigera*, *Pertusaria*, *Physica*, *Rocella*, *Usnea* and *Xanthoria* (Yavuz, 2012, 2013). In European traditional medicine, *Lobaria pulmonaria* (L.) Hoffm., due to its lung-like appearance, was used to treat diseases affecting the respiratory system. Similarly, *Peltigera leucophlebia* (Nyl.) Gyeln. was used as a cure for thrush, due to the resemblance of its cephalodia to the appearance of the disease (Dobson, 2011). The tenth century Arab physician, Al-Tamimi, reported the use of lichens dissolved in vinegar and rose water for the treatment of skin diseases (Zohar Serri, 2004).

Lichens have been used for the treatment of various ailments in humans and animals by cultures across the Himalayas, Europe, Africa and Asia (Crawford, 2019; Yang et al., 2021). They are employed in traditional systems of medicine including Traditional Indian Medicine (Ayurveda), Traditional Chinese Medicine, Homeopathic and Western Medicine. Crawford (2019) listed 60 lichen genera in traditional medicine and reported that they were most commonly used for treating wounds, skin disorders, respiratory, gastrointestinal, obstetric and

Table 1

The use of lichens in ethnomedicine and ethnoveterinary medicine in some regions of the world.

Country	Lichen species	Family	Common name	Mode of preparation and route of administration for disease treated	Reference
America (North America)	<i>Bryoria fremontii</i> (Tuck.) Brodo & D. Hawksw	Parmeliaceae	Black tree lichen	The Okanagan and the Nlaka'pmx of British Columbia use the lichen for baby medicines and for removing warts respectively. The Atsugewi of California use it as a poultice for swellings. The interior Indian people of western North America, from northern British Columbia to northern California, also use it for medicinal purposes	Garth (1953) Milovanović et al. (2018)
	<i>Lobothallia alphoplaca</i> (Wahlenb.) Hafellner	Megasporaceae	Variable sunken disk lichen	The Cree of Manitoba mix flakes from lichens into fish broth which is taken orally to treat gastrointestinal disorders	Letwin (2017)
	<i>Umbilicaria muhlenbergii</i> (Ach.) Tuck.	Umbilicariaceae	Plated rocktripe lichen		
	<i>Xanthoparmelia mexicana</i> (Gyelnik) Hale	Parmeliaceae	Salted rock-shield		
Brazil	<i>Heterodermia galactophylla</i> (Tuck.) Culb.	Physciaceae	Fringe lichen	The lichen is taken orally for epilepsy and gastrointestinal disorders such as diarrhoea and vomiting	Londoño-Castañeda et al. (2017)
Canada	<i>Umbilicaria muhlenbergii</i> (Ach.) Tuck.	Umbilicariaceae	Plated rocktripe lichen	The Dena'ina of Alaska and the Inuit of Northern Quebec boil the lichen and take it orally to treat tuberculosis and prolonged bleeding	Letwin (2017)
China	<i>Lethariella cashmeriana</i> Krog	Parmeliaceae	NA	In Yunnan, the lichens are taken as health foods and health-promoting teas	Wang et al. (2001)
	<i>Lethariella sernanderi</i> (Motyka) Obermayer				
	<i>Lethariella sinensis</i> Wei & Jiang				
	<i>Lobaria isidiophora</i> Yoshim	Peltigeraceae	Lung lichen		
	<i>Lobaria kurokawae</i> Yoshim				
	<i>Ramalina conduplicans</i> Vain	Ramalinaceae	Bushy lichen		
	<i>Ramalina sinensis</i> Jatta		Burning bush lichen		
India	<i>Thamnolia subuliformis</i> (Ehrh.) Culb	Icmadophilaceae	Awl shaped whiteworm lichen		
	<i>Thamnolia vermicularis</i> (Swartz) Ach. ex Schaerer		Alpine lichen		
	<i>Heterodermia diademata</i> (Taylor) D.D.Awasthi	Physciaceae	Shield lichen	The lichen is mixed with <i>Parmotrema</i> species and applied topically as a plaster to protect wounds from infection. It is also dried, ground and applied on fresh wounds in cattle	Vinayaka et al. (2012)
	<i>Parmelia perlata</i> (Huds.) Ach.	Parmeliaceae	Stone flower lichen	The lichen is taken orally as a food supplement in the treatment of wounds, infections, inflammation, skin diseases, diarrhoea, dysentery and fever	Shailajan et al. (2014)
Italy	Usnea sikkimensis Biswas	Parmeliaceae	Old man's beard lichen	The herdsman of North Sikkim put the lichen in their shoes to prevent or treat foot blisters, skin eruptions and boils. They also insert it in a bag and used as pillow or it is inserted in the nostril to treat bleeding, lung troubles and asthma	Pradhan and Badola (2008)
	<i>Lobaria pulmonaria</i> (L.) Hoffm	Peltigeraceae	Lung lichen	It is used in central Italy for the treatment of sciatica. The thallus is applied on cuts in southern Italy	Guarrera et al. (2008)
	<i>Usnea diffracta</i> Vain	Parmeliaceae	Beard lichen	It is used for the relief of pain and fever	Okuyama et al. (1995)
Japan	<i>Evernia furfuracea</i> (L.) Mann	Parmeliaceae	Oakmoss lichen	The lichens are mixed and used to prepare medicinal decoctions and food spices	De Natale and Pollio (2012)
	<i>Ramalina calicaris</i> (L.) Fr.	Ramalinaceae	Strap lichen		
	<i>Ramalina farinacea</i> (L.) Ach.	Ramalinaceae	Farinose cartilage lichen		
Libya	<i>Usnea plicata</i> (L.) Fries	Parmeliaceae	Beard lichen		
	<i>Everniastrum cirrhatum</i> (Fr.) Hale ex Sipman	Parmeliaceae	NA	Extracts or juices of <i>Eupatorium odoratum</i> or <i>Artemisia vulgaris</i> are mixed with the lichen species and applied on fresh wounds, cuts and moles	Devkota et al. (2017)
	<i>Everniastrum nepalense</i> (Taylor) Hale ex Sipman		NA		
	<i>Heterodermia diademata</i> (Taylor) D.D.Awasthi	Physciaceae	Shield lichen		
	<i>Parmotrema cetratum</i> (Ach.) Hale	Parmeliaceae	NA		
	<i>Ramalina species</i>	Ramalinaceae	Strap lichen		
	<i>Thamnolia vermicularis</i> (Swartz) Ach. ex Schaerer	Icmadophilaceae	Alpine lichen		

(continued on next page)

Table 1 (continued)

Country	Lichen species	Family	Common name	Mode of preparation and route of administration for disease treated	Reference
	<i>Usnea longissima</i> Ach.	Parmeliaceae	Methuselah's beard lichen		
Papua New Guinea	<i>Parmotrema saccatilobum</i> (Taylor)	Parmeliaceae	Ruffle lichen	The people of Milne Bay province use the lichen for relief of pain and fever	Bugni et al. (2009)
Turkey	Hale <i>Lobaria pulmonaria</i> (L.) Hoffm	Peltigeraceae	Lung lichen	Prepared as a tea and taken as a laxative	Suleyman et al. (2003)
Western Sahara (Algeria, Morocco, Mauritania)	Tequilil lichen ^a	NA	NA	Sahrawi refugees add the lichen to some plants to make perfumes and incense for therapeutic purposes	Volpato et al. (2012)
South Africa	<i>Usnea barbata</i> (L.) Weber ex F.H.Wigg	Parmeliaceae	Old man's beard lichen	The Xhosa clan of South Africa use the lichen for the treatment of mammary infection in cattle	Afolayan et al. (2002)

^a Lichen is known by only its traditional name; NA – Common name not available; Other traditional uses of lichens are reported in Yang et al. (2021)..

gynaecological disorders. *Parmelia caperata* (L.) Ach. and *Umbilicaria* species are used for many diseases in Chilean traditional medicine (Shahid et al., 2020). *Usnea densirostra* Taylor is used in Argentina's traditional medicine, while *Ramalina thrausta* is used in Finland for the treatment of several skin diseases (Ingolfssdottir, 2002; Paliya et al., 2016). Further ethnomedical and ethnoveterinary uses of lichen species are highlighted in Table 1.

3.4. Lichen secondary metabolites and reported biological activities

Metabolites synthesized by lichens are divided into primary and secondary metabolites. Primary metabolites, such as amino acids, vitamins, enzymes, disaccharides, chitin (in hyphal walls), lichenin, iso-lichenin, hemicellulose, pectins, polyalcohols, and pigments have structural functions and roles in cellular metabolism, as in other organisms (Podterob, 2008). Secondary metabolites on the other hand, are produced due to adaptations for survival in different environments (Ramya and Thirunalasundari, 2017). Approximately 1050 chemically diverse, relatively low molecular weight, and unique secondary metabolites (lichen substances) have been identified, produced primarily by the mycobiont (Molnár and Farkas, 2010). Many of these metabolites are structurally and functionally similar to some broad-spectrum antibiotics while a few are associated with antiseptic properties (Dini et al., 2016).

Secondary metabolites identified from lichens include phenolic compounds (e.g. orcinol and β -orcinol), anthraquinones (e.g. parietin), dibenzofurans (e.g. usnic acid), depsides (e.g. gyrophoric acid), depsidones (e.g. norstictic acid), depsones (e.g. picrolichenic acid), γ -lactones (e.g. protolichesterinic acid), and pulvinic acid derivatives (e.g. vulpinic acid) (Podterob, 2008). The majority of the compounds synthesized through the polyketide pathway are unique to lichens (Blanco et al., 2005). Reported biological activities of some metabolites include antibacterial (Ranković et al., 2008), antiviral (Odimegwu et al., 2019), antibacterial, antifungal (Pathak et al., 2016a, b, c), anti-oxidant (Sisodia et al., 2013; Kosanić and Ranković, 2019a), analgesic, antipyretic (Okuyama et al., 1995), antinociceptive, anti-inflammatory (Pereira et al., 2010a, b), anti-inflammatory, anti-ulcerogenic (Suleyman et al., 2003), cytotoxic (Brisdelli et al., 2013), hepatoprotective (Shailajan et al., 2014), antioxidant, antimicrobial, anticancer (Ristic et al., 2016; Jha et al., 2017), antidiabetic (Maulidiyah et al., 2020), insecticidal (Karthik et al., 2011), and anthelmintic (Anke and Sterner, 1997). Other biological activities of lichen species and their metabolites are highlighted in Tables 2 and 3.

3.5. Proposed mechanism(s) of action

Though not yet extensively explored, many mechanisms of action have been proposed for the different biological activities observed in lichen species and their metabolites. Lichen metabolites such as lobarstin, protolichesterinic, lobaric, vulpinic, gyrophoric and lecanoric acids

may exert anticancer activity via several mechanisms. Such include inducing cell cycle arrest, inhibiting growth factor signalling, activating anti-tumour immunity, inhibiting telomerase activity, inhibiting tumour-promoting inflammation, inhibiting invasion and metastasis, blocking angiogenesis, suppressing genome instability, inducing apoptotic, autophagic and necrotic cell death, activating apoptosis through G0/G1/G2/M arrest, nuclear blebbing and initiator caspases, programmed cell death through the mitochondrial pathway and modulating energy metabolism (Bessadóttir et al., 2014, 2015; Hong et al., 2018; Marques, 2019; Cansaran-Duman et al., 2021b; Noh et al., 2021; Shendge et al., 2021; Roser et al., 2022; Mohammadi et al., 2022). For antioxidant activity, the most commonly reported mechanisms of action for metabolites such as evernic, usnic and fumarprotocetraric acids included scavenging of ROS, enzymatic activation and inhibition of inducible NOS, expression of intracellular phase-II antioxidant enzymes through a plausible involvement of the nuclear factor erythroid 2-related factor cytoprotective pathway (White et al., 2014), neuro-protective potential of fumarprotocetraric acid was reported to be via intracellular redox modulation (Fernández-Moriano et al., 2017a), anti-inflammatory activity of atraric acid through inhibition of lipopolysaccharide-stimulated inflammatory responses, strongly associated with the suppression of nuclear factor kappa B activation (Mun et al., 2020; Hong et al., 2021), while cell wall damage was proposed for the antibacterial activities of diffractic acid and butyrolactone derivatives (Maurya et al., 2018; Sweidan et al., 2019; Maulidiyah et al., 2021).

3.6. Toxicity potential

There is a dearth of information on the toxicity potential of lichens and most lichens are assumed to be non-poisonous. *Letharia vulpina*, *Cetraria pinastri*, *Bryoria fremontii* and *Bryoria tortuosa*, however, are well known poisonous lichens, as they contain high amounts of vulpinic, usnic and pinastrinic acids (Emmerich et al., 1993). Factors such as pH and concentration gradient are thought to affect the toxicity of lichen acids (Gardner and Mueller, 1981).

3.7. Research achievements

Promising therapeutic potential of lichens is apparent as many tested lichen extracts and isolated metabolites have been found to possess strong antioxidant activity using various oxidative systems *in vitro* and *in vivo*. The strong antioxidant activity of tested samples may be correlated with a high content of total phenols. In many experiments, the tested lichen extracts showed a relatively strong antimicrobial activity, though the antimicrobial activity of their metabolites was much stronger (Kosanić et al., 2014a). Three potent α -glucosidase inhibitors showed several fold higher inhibitory activities than those of acarbose, an anti-diabetic drug used to manage type II diabetes mellitus (Karunaratne et al., 2014). Lichens were also effective against various cancer cell lines,

Table 2
Biological activities of some commonly used lichen species and their secondary metabolites.

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Acarospora fuscata</i> (Nyl.) Th.Fr. (Brown cobblestone lichen)	Acarosporaceae (Acarospora - 128 species)	Atranorin, chloroatranorin, stictic, norstictic, gyrophoric, usnic acids	Antioxidant	<i>In vitro</i> (DPPH, FRAP methods)	Gyrophoric acid isolated from ACE extract had high scavenging activity (IC ₅₀ : 105.75 µg/ml)	Serbia	Kosanac et al. (2014a)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	As low as 0.019 mg/ml gyrophoric acid inhibited all species of bacteria and fungi tested (MIC: 0.019–1.25 mg/ml)		
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Gyrophoric acid showed moderate cytotoxic activity		
<i>Alectoria sarmentosa</i> (Ach.) Ach. (Witch's hair lichen)	Parmeliaceae (Alectoria - 10 species)	Alectosarmentin, dibenzofuran, usnic, alectoronic acids	Antibacterial	<i>In vitro</i> (disc diffusion method)	20 µl ACE and CHL extracts inhibited three species of bacteria tested (IZ: 9.50–10.30 mm)	Turkey	Cobanoglu et al. (2010)
<i>Bryoria capillaris</i> (Ach.) Brodo & D. Hawksw. (Horsehair lichen)	Parmeliaceae (Bryoria - 36 species)	Atranorin, usnic, fumarprotocetraric, confumarprotocetraric, stictic, lobaric, gyrophoric, vulpinic, barbatolic acids	Antibacterial	<i>In vitro</i> (disc diffusion method)	ACE extract showed broad spectrum antibacterial activity against both Gram + ve and Gram -ve bacteria	Turkey	Tas et al. (2017)
			Antioxidant	<i>In vitro</i> (DPPH assay)	100 µg/ml conc. caused 67.4% free radical scavenging activity		
			Antiproliferative	<i>In vitro</i> (human cell culture – MTT assay)	Weak antiproliferative activity was observed (IC ₅₀ : >200 µg/ml)		
<i>Bryoria fuscescens</i> (Gyeln.) Brodo and D.Hawksw (Pale-footed horsehair lichen)		Fumarprotocetraric acid, atranorin	Antibacterial	<i>In vitro</i> (disc diffusion method)	20 µl ACE and CHL extracts inhibited three species of bacteria tested (IZ: 8.00–10.30 mm)	Turkey	Cobanoglu et al. (2010)
<i>Bulbothrix setschwanensis</i> (Zahlbr.) Hale (NA)	Parmeliaceae (Bulbothrix - 36 species)	2,3-bis(2-methylpentanoyloxy) propyl 2-methylpentanoate, Ethyl 2-[(2R,3R,4aR,8aS)-3-hydroxy-2,3,4,4a,6,7,8,8a-octahydropyrano [3,2-b]pyran-2-yl]acetate	Antimicrobial	<i>In vitro</i> (broth microdilution method)	ACE, CHL and MeOH extracts showed antimicrobial activities against six bacteria and seven fungi species tested. ACE extract showed promising activity against <i>S. aureus</i> (1.56 mg/ml) and <i>C. neoformans</i> (6.25 mg/ml)	India	Maurya et al. (2018)
<i>Candelariella vitellina</i> (Hoffm.) Mull. Arg. (Egg-yolk lichen)	Candelariaceae (Candelariella - 35 species)	Physodic, physodalic acids	Antigenotoxic, anthelmintic, antioxidant	<i>In vitro</i> (human cell culture – MTT assay, antioxidant – DPPH assay, antigenotoxic – Comet assay, anthelmintic – Protoscolices assay, SEM)	80% MeOH/H ₂ O extract exhibited very low cytotoxicity towards normal human peripheral lymphocytes with IC ₅₀ >1000 µg/ml. There was sig. (<i>p</i> ≤ 0.05) dose and time-dependent scolicidal effects. A conc. of 1.0 mg/ml exhibited strong DPPH scavenging activity (99.5%)	Egypt	El-Garawani et al., 2019, 2020
			Hypocholesterolemic, antiviral	<i>In vitro</i> (human cell culture – MTT assay, cholesterol assay kit) and <i>in vivo</i> (SEC model in mice)	32 mg/ml 80% MeOH/H ₂ O extract reduced cholesterol conc. to 100 ± 0% after 96 h of incubation and antitrovirus activity was seen with a therapeutic index of 11		
<i>Cetraria aculeata</i> (Schreb.) Fr. (Spiny Iceland lichen)	Parmeliaceae (Cetraria- 20 species)	Norstictic, protolichesterinic acids	Genotoxic, antigenotoxic, cytotoxic	<i>In vitro</i> (cell culture – MTT, CBMN assays, Ames test)	ACE extract showed a sig. (<i>p</i> ≤ 0.05) antigenotoxic activity in bacterial systems, but not in mammalian cells	Turkey	Zeytinoglu et al. (2008)
<i>Cetraria islandica</i> L. (Ach.) (True Iceland lichen)		Protolichesterinic, fumarprotocetraric acids, isolichenan, lichenan, thamnolan	Anti-inflammatory	<i>In vivo</i> (anti-inflammatory – antigen-induced arthritis model in rats)	AQ extract caused upregulated secretion of both IL-10 and IL-12p40. MeOH extract reversed oxidative damage caused by H ₂ O ₂	Iceland	Freysdottir et al. (2008)
			Anticancer				

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
				<i>In vitro</i> (cell culture – MTT, MSD assays)	Protolichesterinic acid isolated from the PE extract showed anti-proliferative effects on several cancer cell lines.		Bessadóttir et al. (2014), 2015
			Antioxidant	<i>In vitro</i> (ORAC, DPPH assays)	Lichen extract reversed oxidative damage caused by H ₂ O ₂ , thus promoting astrocyte survival	Spain	Fernández-Moriano et al. (2015a)
			Anticancer	<i>In vitro</i> (human cell culture - MTT assay)	Extract had anticancer activity, with IC ₅₀ values between 19.51 and 181.05 µg/ml		
			Antioxidant, neuroprotective	<i>In vitro</i> (ORAC, DPPH assay)	Fumarprotocetraric acid has cytoprotective property as it attenuated intracellular ROS formation, lipid peroxidation and glutathione depletion		Fernández-Moriano et al. (2015b), 2017a
			Antibacterial, antioxidant, antiproliferative	<i>In vitro</i> (disc diffusion method, DPPH, MTT assays)	ACE extract was active against Gram + ve bacteria (IZ: 20.3–28.0 mm). Strong antiproliferative activity was not observed (IC ₅₀ : >200 µg/ml)	Turkey	Tas et al. (2017)
<i>Cetrelia braunsiana</i> (Müll. Arg.) W. L. Culb. & C. F. Culb (Giant shield lichen)	Parmeliaceae (<i>Cetrelia</i> - 19 species)	Alectoronic acid	Antioxidant, neuroprotective	<i>In vitro</i> (DPPH, MTT assays)	Sig. (p ≤ 0.05) antioxidant and cytoprotective activities were observed	Spain	Fernández-Moriano et al. (2015a)
<i>Cladonia aggregata</i> (Sw.) Nyl. (Reindeer lichen)	Cladoniaceae (<i>Cladonia</i> - 20 species)	Barbatic acid	Antibacterial	<i>In vitro</i> (antibacterial – biochromatography method)	Barbatic acid isolated from the DEE extract showed sig. (p ≤ 0.05) antibacterial activity (MIC: 50 µg/ml) against the four resistant <i>S. aureus</i> strains tested	Brazil	Martins et al. (2010)
			Anthelmintic, molluscidal	<i>In vitro</i> (immersion test)	1 µg/ml presented cercaricidal activity against L2 <i>Schistosoma mansoni</i> after 60 min of exposure. Barbatic acid exhibited no embryotoxicity, but showed molluscicidal effects against <i>Biomphalaria glabrata</i> at 20 and 25 µg/ml		Martins et al. (2017)
			Insecticidal	<i>In vitro</i> (<i>Nasutitermes corniger</i> - PD assay)	Barbatic acid isolated and tested at 5, 7 and 10 mg/ml, had termiticidal activity (~100%) on worker termites after 8 days of treatment, in comparison with controls		Martins et al. (2018)
			Anthelmintic	<i>In vitro</i> (immersion test, SEM)	Barbatic acid showed a schistosomicidal effect after 3 h of exposure. At the end of 24 h the conc. of 50–200 µM presented lethality in the worms. IC ₅₀ obtained by the cell viability assay for <i>Schistosoma mansoni</i> was 99.43 µM. Extensive damage to the worm's tegument was observed from 25 µM		Silva et al. (2020)
<i>Cladonia borealis</i> S. Stenroos (Boreal cup lichen)	Cladoniaceae (<i>Cladonia</i> - 30 species)	Usnic, barbatic, 4-O- demethylbarbatic acids	Antibacterial	<i>In vitro</i> (broth microdilution method)	Extract inhibited five bacteria strains tested (MIC: 7.8–31.25 µg/ml)	Brazil	Micheletti et al. (2021)
<i>Cladonia convoluta</i> (Lam) Anders (Cup lichen)		9'-(O-methyl)protocetraric, usnic, fumarprotocetraric acids	Anticancer	<i>In vitro</i> (murine cell culture – MTT assay)	Usnic acid isolated from the HX extract displayed moderate, dose- and time-dependent cytotoxic activity against various cancer cell lines (IC ₅₀ : 6.0–17.8 mg/ml)	France	Bézivin et al. (2004)
<i>Cladonia kalbii</i> Ahti (Reindeer lichen)		Atranorin	Antioxidant, cytoprotective	<i>In vitro</i> (DPPH, FRAP assays, human cell culture – MTT assay)	A redox-active action, acting as a pro-oxidant or antioxidant agent depending on the radical, and cytoprotective effects on cells under oxidative stress induced by H ₂ O ₂	Brazil	Melo et al. (2011)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Cladonia rangiferina</i> (L.) F. H. Wigg. (Grey reindeer lichen)		Fumarprotocetraric acid, atranorin	Hepatoprotective	<i>In vitro</i> (DPPH, FRAP, MTT assays) and <i>in vivo</i> (acute toxicity test in rats)	was observed for atranorin isolated from the CHL extract IC ₅₀ for atranorin and fumarprotocetraric acid isolated from the EtOH extract were 128.48 and 218.46 mg/ml respectively. Reducing power of the extract was found to be quite sig. ($p \leq 0.05$), endothelial cells were less injured around the central vein and number of fat vacuoles were lesser in the hepatocytes	India	Shukla et al. (2019)
<i>Cladonia rangiformis</i> Hoffm. (Reindeer lichen)		Atranorin, usnic, fumarprotocetraric acids	Anticancer	<i>In vitro</i> (murine and human cell culture – MTT assay)	DEE fraction was cytotoxic (IC ₅₀ : 1.2 µg/ ml). The SI > 50 for the MeOH extract	France	Bézivin et al. (2003)
			Antibacterial	<i>In vitro</i> (disk diffusion method)	<i>Escherichia coli</i> was particularly sensitive to the MeOH and AQ extracts	Algeria	Rafika and Monia (2018)
* <i>Cladonia</i> sp.		Zeorin, methyl β-orcinolcarboxylate, atranorin, methyloresellinate, lobaric acid	Antidiabetic (α-glucosidase inhibitor)	<i>In vitro</i> (Antidiabetic assay, spectrophotometry)	Zeorin isolated showed excellent α-glucosidase inhibition (IC ₅₀ : 100.0 ± 0.3 µM)	Sri Lanka	Karunaratne et al. (2014)
<i>Cladonia stellata</i> Vain. (Reindeer lichen)		Usnic, norstictic, stictic acids	Trypanocidal	<i>In vitro</i> (<i>Trypanosoma cruzi</i> , spectromorphometry, TEM)	Usnic acid isolated caused a strong decrease of OD values, in a dose-dependent manner	Brazil	De Calvarho et al. (2005)
			Insecticidal	<i>In vitro</i> (<i>Nasutitermes corniger</i> - PD assay)	Usnic acid tested at 5, 7 and 10 mg/ml had a termiticidal activity (~100%) on worker termites after 8 days of treatment, in comparison with controls		Martins et al. (2018)
			Anti-oxidant	<i>In vitro</i> (ABTS assay)	Stictic, norstictic and usnic acids isolated were exhibited sig. ($p \leq 0.05$) antioxidant activity with stictic acid having the highest (82.13%)		Santiago et al. (2018)
			Antimicrobial	<i>In vitro</i> (microdilution method)	The growths of <i>S. aureus</i> , <i>Escherichia coli</i> and <i>K. pneumoniae</i> were inhibited, but the organic extracts showed the highest activity		
			Molluscicidal	<i>In vivo</i> (<i>Biomphalaria glabrata</i> toxicity tests)	Usnic acid isolated from DEE extract showed sig. ($p \leq 0.05$) molluscicidal activity (LC ₉₀ after 24 h of exposure were 4.49 and 3.45 µg/ml for embryos and adults respectively, and 2.56 µg/ml for adults after 7 days)		Araújo et al. (2015)
			Anthelmintic	<i>In vitro</i> (<i>Schistosoma mansoni</i> - MTT assay, SEM)	At 24 h, 100 µM usnic acid isolated from DEE extract caused up to 100% mortality, and reduced the cell viability of the worms by 52.82%		Araújo et al. (2015)
<i>Cladonia verticillaris</i> (Raddi) Fr. (Ladder lichen)		Fumarprotocetraric acid	Expectorant	<i>In vivo</i> (Albino Swiss mice – Phenol red quantification method)	Orally administered fumarprotocetraric acid isolated from the ACE extract at 25 and 50 mg/kg promoted sig. ($p \leq 0.05$) greater dose-dependent phenol red activity in the bronchoalveolar lavage and expectorant activity in comparison with the controls	Brazil	de Barros Alves et al. (2014)
			Antioxidant	<i>In vivo</i> (Albino Swiss mice – TBARS assay)	Lipid peroxidation was reduced by 50% in the lung tissue		
			Insecticidal	<i>In vitro</i> (<i>Nasutitermes corniger</i> - PD assay)	Fumarprotocetraric acid tested at 5, 7 and 10 mg/ml had a termiticidal activity (~100%) on worker termites after 8 days of treatment, in comparison with controls		Martins et al. (2018)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Dirinaria aegialita</i> (Afzel. ex Ach.) B.J. Moore (NA)	Caliciaceae (Dirinaria - 35 species)	Lichexanthone, atranorin, divaricatic acid	Antimicrobial	<i>In vitro</i> (agar well-diffusion method)	MeOH extract of pigment isolated did not have any antibacterial activity, but exhibited efficient antifungal activity	India	Dawoud et al. (2020)
			Antioxidant	<i>In vitro</i> (FRAP, ABTS assays)	The pigment also exhibited antioxidant activity with ascorbic acid equivalent of 21.45 mg/ml. The IC ₅₀ was 75.13 mg/ml		
<i>Evernia prunastri</i> (L.) Ach. (Oakmoss lichen)	Parmeliaceae (Evernia - 5 species)	Evernic, usnic, physodic acids, atranorin, chloroatranorin	Anticancer	<i>In vitro</i> (murine, human, cell culture – MTT assay)	The fractions tested were not very active against any of the cancer cell lines tested (34.5 < IC ₅₀ < 81.1 µg/ml). The highest SI was 11.4 for the MeOH fraction	France	Bézivin et al. (2003)
			Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	Physodic, evernic acids and ACE extract demonstrated very strong radical scavenging activity, with IC ₅₀ values of 69.11, 322.44 and 663.12 µg/ml respectively	Serbia	Kosanic et al. (2013)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	Physodic acid showed the highest antimicrobial activity as extremely low amounts inhibited all the species of bacteria and fungi tested (MIC: 0.0008 µg/ml) while MIC of ACE extract was 12.5 µg/ml		
			Cytoprotective, antioxidant	<i>In vitro</i> (CNS-like cell culture – MTT, ORAC, DPPH assays)	Evernic acid isolated displayed sig. (p ≤ 0.05) protection against H ₂ O ₂ -induced cytotoxic damage in both models used	Spain	Fernández-Moriano et al. (2017b)
<i>Heterodermia diademata</i> (Taylor) D.D.Awasthi (Shield lichen)	Physciaceae (Heterodermia - 80 species)	Atranorin, chloroatranorin, zeorin, norstictic, salazinic, lobaric acids	Antifungal	<i>In vitro</i> (disc diffusion method)	<i>S. aureus</i> was highly sensitive to the MeOH extract (IZ = 43 mm)	Algeria	Rafika and Monia (2018)
			Antioxidant	<i>In vitro</i> (DPPH, LOX inhibition assays)	ACE and MeOH extracts were active against all the seven tested fungi while the CHL extract showed activity against only two pathogenic fungi (<i>Alternaria alternata</i> and <i>Penicillium citrinum</i>). The maximum IZ of 19 mm was exhibited by the MeOH extract. EA extract had IC ₅₀ LOX inhibition of 0.12 mg/ml which was equal to that of LOX inhibitor indomethacin. Also showed ≤50% radical scavenging activity	India	Tiwari et al. (2011)
			Antimicrobial	<i>In vitro</i> (disc diffusion method)	EA extract showed strong antimicrobial activity with <i>Candida albicans</i> being very sensitive (MIC: 0.23 mg/ml)		Behera et al. (2016)
<i>Heterodermia microphylla</i> Trevis. (NA)		Atranorin, chloroatranorin, zeorin, norstictic, salazinic, lobaric acids, methyl-β-ornicolcarboxylate	Antifungal	<i>In vitro</i> (spore germination assay)	Atranorin was comparable in activity to the standard antifungal agent benlate (methyl-1-(butylcarbonyl)-2-benzamidazolecarbamate)	Sri Lanka	Bombuwela et al. (2008)
			Insecticidal	<i>In vitro</i> (PD assay)	Atranorin isolated exhibited moderate larvicidal activity against the 2 nd instar larvae of <i>Aedes aegypti</i> (90 and 100% mortality at 100 ppm conc. after 24 and 48 h, respectively)		
<i>Heterodermia obscurata</i> (Nyl.) (Orange tinted fringe lichen)		Atranorin, chloroatranorin, zeorin, emodin, 7-chloroemodin	Antinociceptive	<i>In vivo</i> (acetic-acid writhing method)	IP administration of a glucomannan fraction induced marked and dose-dependent inhibition of acetic acid-induced visceral pain with an IC ₅₀ of 0.6 mg/kg and inhibition of 88%	Brazil	Pereira et al. (2010)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
			Anti-inflammatory	<i>In vivo</i> (acetic-acid writhing method)	The fraction also reduced leukocyte migration by 58%, but did not alter plasmatic extravasation to the peritoneal cavity		
<i>Heterodermia speciosa</i> (Wulfen) Trevis. (Centipede lichen)		Atranorin, zeorin, norstictic, salazinic, lobaric acids	Antioxidant	<i>In vitro</i> (DPPH, BSL assays)	Medium activity (50–80% death of brine shrimp) was observed	Nepal	Jha et al. (2017)
			Antimicrobial	<i>In vitro</i> (disc diffusion method)	Antibacterial activity against <i>S. aureus</i> was observed (IZ: 7 mm)		
<i>Hypogymnia physodes</i> (L.) Nyl. (Monk's hood lichen)	Parmeliaceae (Hypogymnia - 90 species)	Physodalic, physodic, 3-hydroxy- physodic, isophysodic acids	Cytotoxic, antiproliferative	<i>In vitro</i> (rat thymocytes, human cell culture – MTT assay)	1 µg physodalic acid extracted from the MeOH extract showed sig. ($p \leq 0.05$) decreased thymocytes proliferation, increased cytotoxicity and ROS levels	Serbia	Pavlovic et al. (2013)
			Antiproliferative	<i>In vitro</i> (HeLa cell culture – MTT assay)	3-hydroxyphysodic acid extracted from the MeOH extract showed the highest activity with IC ₅₀ of 97 and 63 µg/ml after 24 h and 72 h incubation, respectively		Stojanovic et al. (2014)
<i>Lethariella zahlbruckneri</i> (Du Rietz) Krog (NA)	Parmeliaceae (Lethariella - 11 species)	Atranorin, tolypyridone A	Antiproliferative	<i>In vitro</i> (human cell culture – MTT assay)	Both ACE and MeOH extracts decreased viable cell numbers in a dose- and time- dependent manner	Korea	Ren et al. (2009)
<i>Lobaria pulmonaria</i> (L.) Hoffm (Lung lichen)	Peltigeraceae (Lobaria - 21 species)	Stictic, constictic, norstictic, cryptostictic acids	AchE inhibition	<i>In vitro</i> (AchE inhibition assay)	A depsidone isolated showed moderate activity (at 1 µg), compared with the alkaloid galantamine which inhibited AchE at 0.01 µg	Serbia	Pejin et al. (2013)
			Antibacterial	<i>In vitro</i> (PD assay)	Silver nanoparticles extracted were highly effective on the six bacterial species tested	Slovak Republic	Goga et al. (2021)
			Antioxidant	<i>In vitro</i> (DPPH assay)	Silver nanoparticles extracted had lower antioxidant properties (19.4%) than the extract (44.7%)		
<i>Melanelixia fuliginosa</i> (Duby) O. (NA)	Parmeliaceae (Melanelixia - 15 species)	Atranorin, lecanoric, gyrophoric, anziaic, 2'-O-methyl anziaic, usnic acids	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract and isolated metabolites (lecanoric, anziaic, 2'-O-methyl anziaic acids) showed dose-dependent radical scavenging activities (IC ₅₀ : 266.32, 424.51 and 121.52 µg/ml, respectively)	Serbia	Ristić et al. (2016a)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	ACE extract, lecanoric, anziaic, 2'-O-methyl anziaic acids showed sig. ($p \leq 0.05$) antimicrobial activities (MIC: 2.5, 0.5, 0.063 mg/ml, respectively)		
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	ACE extract, lecanoric, anziaic, 2'-O-methyl anziaic acids showed sig. ($p \leq 0.05$) cytotoxic activities (IC ₅₀ : 45.24, 123.97, 151.79 µg/ml, respectively)		
<i>Melanelixia subaurifera</i> (Nyl) (Abraded camouflage lichen)		Atranorin, lecanoric, gyrophoric, anziaic, 2'-O-methyl anziaic, usnic acids	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract and isolated metabolites (lecanoric, anziaic, 2'-O-methyl anziaic acids) showed dose-dependent radical scavenging activities (IC ₅₀ : 165.13, 424.51, 121.52 µg/ml, respectively)	Serbia	Ristić et al. (2016a)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	ACE extract, lecanoric, anziaic, 2'-O-methyl anziaic acids showed sig. ($p \leq 0.05$) antimicrobial activities (MIC: 1.25, 0.5, 0.06 mg/ml, respectively)		
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	ACE extract, lecanoric, anziaic, 2'-O-methyl anziaic acids showed sig. cytotoxic activities		

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference																																																																		
<i>Myelochroa irrugans</i> (Nyl.) Elix & Hale (Axil bristle lichen)	Parmeliaceae (Myelochroa - 30 species)	Atranorin, zeorin	Antioxidant,	<i>In vitro</i> (ORAC, DPPH, FRAP assays)	(IC ₅₀ : 9.88, 123.97, 151.79 µg/ml, respectively) MeOH extract showed strong radical scavenging activity (EC ₅₀ : 384 µg/ml) MeOH extract reduced significantly (p ≤ 0.05), the viability of the cells (LD ₅₀ : 22 µg/ ml)	Spain	Fernández-Moriano et al. (2016a), b																																																																		
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)				<i>Parmelia arseniana</i> Gyeln. (NA)	Parmeliaceae (Parmelia - 40 species)	Atranorin, stictic, norstictic, usnic acids	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract had high scavenging activity (IC ₅₀ : 612.75 µg/ml) ACE extract showed moderate antibacterial and antifungal activities, inhibiting the microorganisms tested at 0.08–10 mg/ml ACE extract expressed strong anticancer activity against all cell lines tested (IC ₅₀ : 11.61–47.06 µg/ml)	Serbia	Kosanic et al. (2014a)	Antimicrobial	<i>In vitro</i> (broth microdilution method)	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	<i>Parmelia caperata</i> (L.) Ach. (Common greenshield lichen)		Protocetraric, usnic, caperatic acids, ergosterol peroxide	Anticancer	<i>In vitro</i> (murine and human cell culture – MTT assay)	HX fraction had IC ₅₀ of 7.9 µg/ml. The highest SI was 25.8 for the MeOH fraction Antibacterial activities of protocetraric and usnic acids were stronger than their antifungal, with MICs as low as 0.015 and 0.0008 mg/ml, respectively Protocetraric and usnic acids demonstrated cytotoxic activity with IC ₅₀ of 58.68 and 12.72 µg/ml, respectively The IC ₅₀ values for protocetraric acid isolated from the ACE extract were 119.10 and 177.60 µg/ml for DPPH and superoxide anion radicals, respectively MIC of usnic, caperatic and protocetraric acids were between 7.25 and 12.5 µg/ml 2-hydroxy-4-methoxy-3,6-dimethylbenzoic acid recorded excellent antimicrobial activity with MIC: 0.06–4.0 µg/ml against test bacteria and 0.12–16.0 µg/ml against test fungi Growth of cancer cells was suppressed by 2- hydroxy-4-methoxy-3,6-dimethylbenzoic acid in both dose- and time-dependent manners	France	Bézivin et al. (2003)	Antimicrobial	<i>In vitro</i> (broth microdilution method)	Serbia	Manojlović et al. (2012)	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)			Antioxidant	<i>In vitro</i> (DPPH, FRAP, Superoxide assays)			<i>Parmelia erumpens</i> Kurok. (Shield lichen)		Atranorin, usnic, 2-hydroxy-4- methoxy-3,6-dimethylbenzoic acids	Antimicrobial	<i>In vitro</i> (agar disc diffusion, broth microdilution methods)	MIC of usnic, caperatic and protocetraric acids were between 7.25 and 12.5 µg/ml 2-hydroxy-4-methoxy-3,6-dimethylbenzoic acid recorded excellent antimicrobial activity with MIC: 0.06–4.0 µg/ml against test bacteria and 0.12–16.0 µg/ml against test fungi	France	Dieu et al. (2020)	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	India	Aravind et al. (2014)	<i>Parmelia nepalensis</i> Taylor (Shield lichen)		Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids	Antiproliferative	<i>In vitro</i> (human cell culture – MTT assay)	Gyrophoric, usnic and diffractaic acids were potent antiproliferative agents and inhibited cell growth, with IC ₅₀ values of 1.7, 2.1, and 2.6 µM, respectively Atranorin, diffractaic and protolichesterinic acid inhibited LTB ₄ biosynthesis in polymorphonuclear leukocytes	Germany	Kumar and Müller (1999a)	Antioxidant	<i>In vitro</i> (DPPH assay)		Kumar and Müller (1999b)	<i>Parmelia perlata</i> (Huds.) Ach. (Stone flower lichen)		Salazinic, stictic acids, atranorin, chloroatranorin	Anticancer	<i>In vitro</i> (murine and human cell culture – MTT assay)	HX fraction had IC ₅₀ of 4.9 µg/ml. The highest SI was 26.1 for the DEE fraction The MeOH extract was more active than the ACE extract with a MIC of 39.1 mg/ml The MeOH extract (IC ₅₀ : 53.45 µg/ml) had a higher radical scavenging activity than the ACE extract (IC ₅₀ : 57.11 µg/ml)	France	Bézivin et al. (2003)	Antimicrobial	<i>In vitro</i> (broth microdilution methods)
<i>Parmelia arseniana</i> Gyeln. (NA)	Parmeliaceae (Parmelia - 40 species)	Atranorin, stictic, norstictic, usnic acids	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract had high scavenging activity (IC ₅₀ : 612.75 µg/ml) ACE extract showed moderate antibacterial and antifungal activities, inhibiting the microorganisms tested at 0.08–10 mg/ml ACE extract expressed strong anticancer activity against all cell lines tested (IC ₅₀ : 11.61–47.06 µg/ml)	Serbia	Kosanic et al. (2014a)																																																																		
			Antimicrobial	<i>In vitro</i> (broth microdilution method)																																																																					
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)																																																																					
<i>Parmelia caperata</i> (L.) Ach. (Common greenshield lichen)		Protocetraric, usnic, caperatic acids, ergosterol peroxide	Anticancer	<i>In vitro</i> (murine and human cell culture – MTT assay)	HX fraction had IC ₅₀ of 7.9 µg/ml. The highest SI was 25.8 for the MeOH fraction Antibacterial activities of protocetraric and usnic acids were stronger than their antifungal, with MICs as low as 0.015 and 0.0008 mg/ml, respectively Protocetraric and usnic acids demonstrated cytotoxic activity with IC ₅₀ of 58.68 and 12.72 µg/ml, respectively The IC ₅₀ values for protocetraric acid isolated from the ACE extract were 119.10 and 177.60 µg/ml for DPPH and superoxide anion radicals, respectively MIC of usnic, caperatic and protocetraric acids were between 7.25 and 12.5 µg/ml 2-hydroxy-4-methoxy-3,6-dimethylbenzoic acid recorded excellent antimicrobial activity with MIC: 0.06–4.0 µg/ml against test bacteria and 0.12–16.0 µg/ml against test fungi Growth of cancer cells was suppressed by 2- hydroxy-4-methoxy-3,6-dimethylbenzoic acid in both dose- and time-dependent manners	France	Bézivin et al. (2003)																																																																		
			Antimicrobial	<i>In vitro</i> (broth microdilution method)		Serbia	Manojlović et al. (2012)																																																																		
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)																																																																					
			Antioxidant	<i>In vitro</i> (DPPH, FRAP, Superoxide assays)																																																																					
<i>Parmelia erumpens</i> Kurok. (Shield lichen)		Atranorin, usnic, 2-hydroxy-4- methoxy-3,6-dimethylbenzoic acids	Antimicrobial	<i>In vitro</i> (agar disc diffusion, broth microdilution methods)	MIC of usnic, caperatic and protocetraric acids were between 7.25 and 12.5 µg/ml 2-hydroxy-4-methoxy-3,6-dimethylbenzoic acid recorded excellent antimicrobial activity with MIC: 0.06–4.0 µg/ml against test bacteria and 0.12–16.0 µg/ml against test fungi	France	Dieu et al. (2020)																																																																		
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)		India	Aravind et al. (2014)																																																																		
<i>Parmelia nepalensis</i> Taylor (Shield lichen)		Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids	Antiproliferative	<i>In vitro</i> (human cell culture – MTT assay)	Gyrophoric, usnic and diffractaic acids were potent antiproliferative agents and inhibited cell growth, with IC ₅₀ values of 1.7, 2.1, and 2.6 µM, respectively Atranorin, diffractaic and protolichesterinic acid inhibited LTB ₄ biosynthesis in polymorphonuclear leukocytes	Germany	Kumar and Müller (1999a)																																																																		
			Antioxidant	<i>In vitro</i> (DPPH assay)			Kumar and Müller (1999b)																																																																		
<i>Parmelia perlata</i> (Huds.) Ach. (Stone flower lichen)		Salazinic, stictic acids, atranorin, chloroatranorin	Anticancer	<i>In vitro</i> (murine and human cell culture – MTT assay)	HX fraction had IC ₅₀ of 4.9 µg/ml. The highest SI was 26.1 for the DEE fraction The MeOH extract was more active than the ACE extract with a MIC of 39.1 mg/ml The MeOH extract (IC ₅₀ : 53.45 µg/ml) had a higher radical scavenging activity than the ACE extract (IC ₅₀ : 57.11 µg/ml)	France	Bézivin et al. (2003)																																																																		
			Antimicrobial	<i>In vitro</i> (broth microdilution methods)		Serbia	Manojlović et al. (2021)																																																																		
			Antioxidant	<i>In vitro</i> (DPPH assay)																																																																					

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Parmelia saxatilis</i> (L.) Ach. (Salted shield lichen)		Salazinic acid, atranorin, chloroatranorin	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Sig. ($p \leq 0.05$) cytotoxic activity against the three cell lines tested. IC ₅₀ values ranged from 76.33 to 163.39 µg/ml	Serbia	Manojlović et al. (2012)
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Demonstrated cytotoxic activity and the IC ₅₀ for salazinic acid was 35.67 µg/ml		
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	Antibacterial activity of salazinic acid was stronger than its antifungal, with MIC as low as 0.015 mg/ml		
<i>Parmelia sulcata</i> Taylor (Hammered shield lichen)		Salazinic acid, atranorin, chloroatranorin	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	The IC ₅₀ values for salazinic acid isolated from the ACE extract were 91.57 and 138.23 µg/ml for DPPH and superoxide anion radicals, respectively	Serbia	Manojlović et al. (2012)
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Demonstrated cytotoxic activity and the IC ₅₀ for salazinic acid was 35.67 µg/ml		
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	Antibacterial activity of salazinic acid was stronger than its antifungal, with MIC as low as 0.015 mg/ml		
<i>Parmotrema cetratum</i> (Ach.) Hale (Ruffle lichen)	Parmeliaceae (<i>Parmotrema</i> - 300 species)	Salazinic acid	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	The IC ₅₀ values for salazinic acid isolated from the ACE extract were 91.57 and 138.23 µg/ml for DPPH and superoxide anion radicals, respectively	Armenia	Sargsyan et al. (2021)
			Antimicrobial	<i>In vitro</i> (agar disc diffusion, broth microdilution methods)	The MeOH extract was more active than the EtOH, ACE, and AQ extracts with a IZ of 13 mm and MIC of 7.5 mg/ml		
			Antioxidant	<i>In vitro</i> (DPPH assay)	The MeOH extract showed good radical scavenging activity (71%), which was only slightly lower than ascorbic acid (96%)		
<i>Parmotrema saccatilobum</i> (Taylor) Hale (Ruffle lichen)		Atranorin, chloroatranorin, protocetraric acid	Anti-inflammatory	<i>In vitro</i> (COX 1 and 2 enzyme inhibition assay)	Salazinic acid showed sig. ($p \leq 0.05$) antiproliferative activity against K562, HT- 29 and B16-F10 cells (IC ₅₀ 64.36, 67.91 and 78.64 µM, respectively). <i>In vivo</i> , the animals showed no signs of systemic toxicity and the metabolite inhibited tumour growth in relation to weight, and 88% of tumour volume	Brazil	Alexandrino et al. (2019)
<i>Parmotrema tinctorum</i> (Delise ex Nyl.) Hale (Palm ruffle lichen)		Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids	Antiproliferative	<i>In vitro</i> (human cell culture – MTT assay)	Atranorin inhibited COX-1 in a dose dependent manner	USA	Bugni et al. (2009)
			Antioxidant	<i>In vitro</i> (DPPH assay)	Salazinic acid showed sig. ($p \leq 0.05$) antiproliferative activity against K562, HT- 29 and B16-F10 cells (IC ₅₀ 64.36, 67.91 and 78.64 µM, respectively). <i>In vivo</i> , the animals showed no signs of systemic toxicity and the metabolite inhibited tumour growth in relation to weight, and 88% of tumour volume	Germany	Kumar and Müller (1999a)
			Antioxidant	<i>In vitro</i> (DPPH assay)	Atranorin, diffractaic and protolichesterinic acid inhibited LTB ₄ biosynthesis in polymorphonuclear leukocytes		
			Macrophilicidal	<i>In vitro</i> (cell culture – MTT, worm motility assays) and <i>in vivo</i> (acute toxicity test)	MeOH extract was active against adult male worms (IC ₅₀ : 8.1 µg/ml) with a SI of 21.3. No mortality or adverse effects were recorded. No sig. effect on the liver enzymes, ALT and AST, but a high AST:ALT ratio (2.59) was observed, which indicates likely reversible adverse hepatic toxicity	Cameroon	Kang et al. (2022)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Peltigera rufescens</i> (Weis.) Humb. (Dog lichen)	Peltigeraceae (Peltigera - 100 species)	Peltigerin, 3-O-β-glucopyranosyl-d-mannitol, d-mannitol	Antioxidant	<i>In vitro</i> (FRAP assay)	AQ and MeOH extracts showed potent antioxidant and reducing power activities, as there was 87.80 and 74.03% inhibition of the peroxidation of linoleic acid emulsion, respectively	Turkey	Odabasoglu et al. (2005)
			Anti-inflammatory	<i>In vitro</i> (carrageenan- and cotton pellet-induced model)	MeOH extract reduced carrageenan-induced inflammation and showed a potent antiproliferative effect (63.5%) in the chronic inflammation model	Turkey	Tanas et al. (2010)
			Insecticidal	<i>In vitro</i> (immersion test)	There was sig. ($p \leq 0.05$) insecticidal activity against adults of <i>Sitophilus zeamais</i> as 20 mg/ml extract caused mortality of 95.96%	Egypt	Yildirim et al. (2012)
<i>Platismatia glauca</i> (L.) W.L.Culb. & C.F. Culb (Ragbag lichen)	Parmeliaceae (Platismatia - 10 species)	Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Extract demonstrated interesting activity on human cancer cell lines tested (SI > 3)	France	Bézivin et al. (2003)
<i>Pleurosticta acetabulum</i> (Neck.) Elix & Lumbsch (NA)	Parmeliaceae (Pleurosticta - 2 species)	Cytochalasin E, atranorin, salazinic, norstictic, protocetraric, evernic acids	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Cytochalasin E isolated from the ACE extract showed very good antiproliferative activity, with an IC ₅₀ of 8 µg/ml	France	Delebassée et al. (2017)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	ACE extract showed moderate antimicrobial activity with MIC ranging from 1.25 to 20 mg/ml	Serbia	Tomović et al. (2017)
			Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract exhibited moderate free radical scavenging activity (IC ₅₀ : 151.73 µg/ml)		
<i>Pseudevernia furfuracea</i> (L.) Zopf (Tree moss lichen)	Parmeliaceae (Pseudevernia - 9 species)	Olivetoric, physodic, atraric, 3-hydroxyphysodalic, physodalic acids, methyl haematommate, atranorin, chloroatranorin	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	IC ₅₀ values ranged from 24.09 to 45.94 µg/ml		
			Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	Physodic acid, evernic acid and the ACE extract demonstrated very strong radical scavenging activity, IC ₅₀ values of 69.11, 322.44 and 401.71 µg/ml, respectively	Serbia	Kosanić et al. (2013)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	Physodic acid showed the highest antimicrobial activity as extremely low amounts inhibited all the species of bacteria and fungi tested (MIC – 0.0008 µg/ml), while MIC of ACE extract was 12.5 µg/ml		
			Antibacterial	<i>In vitro</i> (PD assay)	Silver nanoparticles extracted were highly effective on the six bacterial species tested		Goga et al. (2021)
			Antioxidant	<i>In vitro</i> (DPPH assay)	Antioxidant activity showed the lowest effect in the presence of silver nanoparticles which positively correlated with the content of total phenols and flavonoids		
			Antifungal	<i>In vitro</i> (agar disk diffusion, broth microdilution methods)	MeOH, EtOH, ACE and AQ extracts showed low antibacterial activity, but the MeOH extract demonstrated antifungal activity against <i>Candida albicans</i> (IZ: 12 mm)	Armenia	Sargsyan et al. (2021)
			Anticancer	<i>In vitro</i> (lung cancer cell culture – MTT assay)	Physodic acid isolated was shown to have a dose-dependent cytotoxic activity in 24, 48, and 72 h, with IC ₅₀ conc. of 382.0, 235.4, and 175.8 µM, respectively	Turkey	Sahin et al. (2021a)
Antioxidant	<i>In vitro</i> (DPPH assay)	Radical scavenging activity of EtOH extract (IC ₅₀ : 158.79 mg/L) was remarkably higher than the AQ extract (IC ₅₀ : 630.33 mg/L).		Sahin et al. (2021b)			

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
			Anticancer	<i>In vitro</i> (human cell culture – MTT assay, molecular docking)	Olivetoric and physodic acids strongly augmented all antioxidant enzymes gene expressions in HepG2 cells Atraric acid showed sig. ($p \leq 0.05$) and moderate activities against ovarian and breast cancer cell lines having IC ₅₀ of 16.42 and 64.35 µg/ml, respectively	India	Kalra et al. (2022)
<i>Pseudoparmelia sphaerospora</i> (Nyl.) Hale (NA)	Parmeliaceae (Pseudoparmelia – 27 species)	Hypostictic acid	Anticancer	<i>In vitro</i> (human and murine cell culture – MTT, flow cytometry assays) and <i>in vivo</i> (acute toxicity and experimental melanoma model in mice)	Hypostictic acid showed excellent antiproliferative activity against K562, B16–F10 and 786–0 cells (IC ₅₀ : 2.20, 13.78 and 14.24 µM, respectively). <i>In vivo</i> , the animals showed no signs of systemic toxicity and 16.7 mg/kg hypostictic acid inhibited tumour growth in relation to weight and 72% of tumour volume	Brazil	Alexandrino et al. (2019)
<i>Ramalina conduplicans</i> Ach. (Strap lichen)	Ramalinaceae (Ramalina – 246 species)	Usnic, salazinic, sekikaic, homosekikaic acids	Antioxidant	<i>In vitro</i> (DPPH assay)	MeOH extract exhibited potent anti-linoleic acid peroxidation, free radical-scavenging, and reducing power activities. IC ₅₀ of extract, sekikaic and homosekikaic acids were 0.23, 0.08 and 0.28 mg/ml, respectively	China	Luo et al. (2010b)
			Antimicrobial	<i>In vitro</i> (agar well diffusion, poisoned food methods)	MeOH extract inhibited the growth of the bacteria and fungi species tested (IZ: 2.60, 2.20 mm, respectively)	India	Ankith et al. (2017)
<i>Ramalina cuspidata</i> (Ach.) Nyl (Strap lichen)		Usnic acid	Anticancer	<i>In vitro</i> (murine and human cell culture)	HX fraction had IC ₅₀ of 5.8 µg/ml. The highest SI was 17.4 for the DEE fraction	France	Bézivin et al. (2003)
<i>Ramalina hossei</i> Vain. (Strap lichen)		Usnic, sekikaic acids	Antimicrobial	<i>In vitro</i> (agar well diffusion, poisoned food methods)	MeOH extract inhibited the growth of the bacteria and fungi species tested (IZ: 2.20 mm)	India	Ankith et al. (2017)
<i>Ramalina pacifica</i> Asahina (Strap lichen)		Usnic, salazinic acids	Antimicrobial	<i>In vitro</i> (agar well diffusion, poisoned food methods)	MeOH extract inhibited the growth of the bacteria and fungi species tested (IZ: 2.70, 2.30 mm, respectively)	India	Ankith et al. (2017)
<i>Ramalina fastigiata</i> (Pers.) Ach. (Cartilage lichen)		Atranorin, usnic, fumarprotocetraric, obtusatic, protocetraric acids	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	ACE extract exhibited strong anticancer activities against tested cells (IC ₅₀ : 24.63–161.37 µg/ml)	Serbia	Ristic et al. (2016b)
			Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract showed strong free radical scavenging activity with IC ₅₀ values between 285.45 and 423.51 µg/ml. Absorbance for reducing power was from 0.004 to 0.175. Total amount of phenol conc. was 33.49 µg		
			Antimicrobial	<i>In vitro</i> (broth microdilution method)	Methyl evernate showed the strongest antimicrobial properties with the least MIC value being 0.125 mg/ml		
			Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	Maximum inhibition was observed at the conc. of 100 µg/ml with IC ₅₀ of 2.05 µg/ml	India	Soundararajan et al. (2019)
			Antimicrobial	<i>In vitro</i> (agar well diffusion method)	ACE extract showed maximum activity against <i>K. pneumonia</i> with IZ of 2.1 mm. An IZ of 1.1 cm was seen for <i>Candida albicans</i> and 1.3 cm for <i>Candida krusei</i> at 100 µg/ml		
<i>Ramalina fraxinea</i> (L.) Ach. (Bush lichen)			Anticancer	<i>In vitro</i> (human cell culture – MTT assay)		Serbia	Ristic et al. (2016b)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
Methyl evernate showed the strongest antimicrobial properties with the least MIC value being 0.125 mg/ml <i>Ramalina sinensis</i> Jatta (Burning bush lichen)		Atranorin, usnic, salazinic, sekikaic, obtusatic, protocetraric acids	Antioxidant	<i>In vitro</i> (DPPH, FRAP assays)	ACE extract exhibited strong anticancer activities against tested cells (IC ₅₀ : 24.63–161.37 µg/ml)	Iran	Abdolmaleki and Sohrabi (2016)
					ACE extract showed strong free radical scavenging activity with IC ₅₀ values between 285.45 and 423.51 µg/ml. Absorbance for reducing power was from 0.004 to 0.175. Total amount of phenol conc. was 32.63 µg		
					<i>In vitro</i> (broth microdilution method)		
					Antimicrobial		
		Betulin, betulinic acid, nanoparticles	Antibacterial	<i>In vitro</i> (agar well diffusion method)	Silver nanoparticles produced were about 50–80 nm in size, and showed good inhibitory effect against all four bacteria species tested	Iran	Nazari et al. (2018)
					Demonstrated good antioxidant properties and was able to remove toxic free radicals	Iran	Safarkar et al. (2020)
					Iron oxide nanoparticles had the highest effect on the bacterial strains tested at 0.075 mg/ml, with IZ of 13 and 11 mm for <i>S. aureus</i> and <i>P. aeruginosa</i> , respectively	Armenia	Sargsyan et al. (2021)
					MeOH and EtOH extracts showed the largest IZs (25 mm and 23 mm, respectively) against <i>Bacillus subtilis</i> . The MIC was between 0.9 and 1.8 mg/ml		
<i>Ramalina terebrata</i> Hook. & Taylor. (Strap lichen)		Usnic acid, usimine A, B, C, ramalin	Antibacterial	<i>In vitro</i> (disk diffusion method)	The IC ₅₀ values estimated for the MeOH extract in HeLa cell line was 1.75 mg/ml, and considered as non-cytotoxic	South Korea	Paudel et al. (2010)
					MeOH extract and usnic acid showed antibacterial activity against <i>S. aureus</i> and <i>Bacillus subtilis</i> . MIC values against <i>Bacillus subtilis</i> were from 1.0 to 26.0 g/ml		
<i>Ramalina usnea</i> (L.) R. Howe (Cartilage lichen)	Usnic acid, 2-hydroxy-4-methoxy-6-propyl-methyl benzoate	Insecticidal	<i>In vitro</i> (<i>Aedes aegypti</i> – larvicidal toxicity assay)	MeOH extract killed 100% of the larvae at a conc. of 150 g/ml at 24 h. Isolated compounds, 2-hydroxy-4-methoxy-6-propyl-methyl benzoate and usnic acid showed larvicidal activity, presenting LC ₅₀ values of 4.85 and 4.48 g/ml, respectively		Brazil	Moreira et al. (2016)
<i>Stereocaulon alpinum</i> Laurer ex Funck (Snow lichen)	Stereocaulaceae (Stereocaulon - 46 species)	Lobaric acid, two pseudodepsidone-type metabolites, atranorin, methyl orsellinate, methyl haematommate, 2,6-dihydroxy-4-methoxy-3-methylacetophenone	Antiprotein tyrosine phosphatase	<i>In vitro</i> (protein tyrosine phosphatase 1 B inhibition assay)	Lobaric acid and the two pseudodepsidone-type compounds exhibited potent inhibitory activity against protein tyrosine phosphatase 1 B with IC ₅₀ of 0.87, 6.86, and 2.48 µM, respectively	Korea	Seo et al. (2009)
							Korea

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Sticta nylanderiana</i> Zahlbr. (Spotted felt lichen)	Peltigeraceae (Sticta - 114 species)			<i>In vitro</i> (DPPH, FRAP, peroxidase assays)	Lecanoric acid isolated from the MeOH extract displayed 1.37 times greater anti-linoleic acid peroxidation activity than ascorbic acid. Also possessed high free radical scavenging activity, with an inhibition rate of 90.4% at conc. of 330 µg/ml		
<i>Teloschistes flavicans</i> (Sw.) Norman (Golden hair lichen)	Teloschistaceae (Teloschistes - 8 species)	Vicanicin	Antidiabetic	<i>In vitro</i> (antidiabetic activity test)	Quercetin (positive control) had a high inhibition compared to the ACE extract and vicanicin isolated, with IC ₅₀ values of 4.05, 54.05, and 197.04 µg/ml, respectively	Indonesia	Maulidiyah et al. (2020)
<i>Thamnolia vermicularis</i> (Sw.) Schaer. (White worm lichen)	Icmadophilaceae (Thamnolia – 6 species)	Thamnolan, β-glucan	Immunomodulating	<i>In vitro</i> (Anticomplementary assay)	The polysaccharides isolated caused stimulation of rat spleen cells proliferation, induction to secrete IL-10 above background levels and stimulated TNF-α secretion by rat peritoneal macrophages	Iceland	Olafsdottir et al. (2003) Omarsdottir et al. (2007)
<i>Umbilicaria esculenta</i> (Miyoshi) (Minks rock tripe lichen)	Umbilicariaceae (Umbilicaria – 65 species)	Constictic, lecanoric acids, laminaran, pustulan	Antithrombotic	<i>In vitro, ex vivo, in vivo</i> (anticoagulant assays, arteriovenous shunt thrombosis model in rats)	Polysaccharides isolated from the AQ extract increased inhibition of thrombus formation, tail transection bleeding time, preventive effect against thrombotic death or paralysis in a dose-dependent manner, at conc. greater than 50 g/ml, 5-fold more than heparin	China	Wang et al. (2014)
			Immunomodulatory	<i>In vitro</i> (murine cell culture – MTT, cytokine, NO assays)	Polysaccharides isolated from the AQ extract promoted the proliferation and phagocytic activity of macrophages RAW264.7, and induced their release of NO, NOS, TNF-α, IFN-γ and IL-1β, IL-6 and IL-10 in a dose-dependent manner Isolated metabolite promoted the phagocytic activity and production of NO in RAW 264.7 cells in a dose-dependent manner. It also significantly (p ≤ 0.05) improved the proliferation effect of RAW 264.7 cells at 50 µg/ml		Wang et al. (2019) Shi et al. (2021)
<i>Umbilicaria hirsuta</i> (Sw. ex Westr.) Hoffm. (Hairy navel lichen)		Atranorin, parietin, usnic, gyrophoric acids	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Usnic acid and atranorin induced a massive loss in the mitochondrial membrane potential, caspase-3 activation, and phosphatidylserine externalization in tested cell lines. The two metabolites were more effective anticancer compounds when compared to parietin and gyrophoric acid	Slovakia	Bačkorová et al. (2012)
<i>Umbilicaria mammulata</i> (Ach.) Tuck. (Smooth rock tripe lichen)		Glycophoric, constictic, lecanoric acids	Antibacterial	<i>In vitro</i> (Micro-well dilution method)	ACE extract was active against <i>P. aeruginosa</i> (MIC: 50 µg/ml)	USA	Shrestha et al. (2014)
<i>Umbilicaria muhlenbergii</i> (Ach.) Tuck. (Plated rock tripe lichen)		Glycophoric, constictic, lecanoric acids	Anticancer	<i>In vitro</i> (human cell culture – MTT assay)	Good anticancer activity reported	USA/ Canada	Mohammadi (2021) Mohammadi et al. (2022)
<i>Usnea antarctica</i> Du Rietz (Antartic shrub lichen)	Parmeliaceae (Usnea- over 600 species)	Usnic acid	Antibacterial	<i>In vitro</i> (broth microdilution method)	Antibacterial activity was demonstrated against <i>S. aureus</i> . The MIC was 94.76% at 31.25 µg/ml	Peru	Londoño-Bailon et al. (2019)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Usnea articulata</i> L. (Hoffm) (Old man's beard)	Usnic acid	Antioxidant	<i>In vitro</i> (ABTS method)	MeOH/ACE extract showed radical inhibition values of 9.05 μ M			
		Cytotoxic	<i>In vitro</i> (monkey kidney cell culture – MTT assay)	MeOH/ACE extract showed activity against Vero cell line achieving an IC ₅₀ of 169.64 μ g/ml			
		Antibacterial	<i>In vitro</i> (agar well diffusion method)	Silver nanoparticles (10–50 nm in size) isolated showed good inhibitory effect against all four bacteria species tested	Iran	Abdolmaleki and Sohrabi (2016)	
		Cytotoxicity	<i>In vitro</i> (disc diffusion, microdilution methods)	MeOH extract showed broad spectrum dose-dependent activity against the nine bacteria species tested with MIC of 4–10 mg/ml	Cameroon	Bate et al. (2020)	
<i>Usnea barbata</i> (L.) F. H.Wigg (Beard lichen)	Usnic acid	Antimicrobial	<i>In vitro</i> (monkey kidney cells - MTT assay) <i>In vitro</i> (agar disc diffusion method)	MeOH extract was not cytotoxic (IC ₅₀ : 56.58–278.50 μ g/ml) ACE and MeOH extracts indicated sig. ($p \leq 0.05$) activity against most of the G + ve bacteria tested with MIC as low as 0.1 mg/ml in <i>Bacillus subtilis</i> and <i>S. aureus</i> , and some G-ve bacteria. The ACE extract had the highest fungal inhibitory activity ranging from 51.60% against <i>Schizophyllum commune</i> to 100% against <i>Alternaria alternaria</i> at 10 mg/ml	South Africa	Madamombe and Afolayan (2003)	
		Antibacterial	<i>In vitro</i> (agar disc diffusion method)	Usnic acid isolated from the ACE extract indicated sig. ($p \leq 0.05$) activity against two of the seven bacteria species tested with IZ of 20 and 22 mm against <i>Bacillus subtilis</i> and <i>Bacillus megaterium</i> , respectively	Turkey	Cansaran et al. (2006)	
		Antibacterial	<i>In vitro</i> (agar gel diffusion, broth microdilution methods)	The MeOH and EA extracts showed variable antimicrobial activities against thirteen <i>S. aureus</i> strains with IZ ranging from 0 to 34 mm at 5–20 mg/ml conc. tested. Susceptibility by the bacteria species to MeOH and EA extracts was 92.31 and 53.85%, while MIC ranged from 0.04 to 10 mg/ml, and 0.16–5 mg/ml, respectively	South Africa	Idamokoro et al. (2014)	
		Immunomodulatory, antioxidant	<i>In vivo</i> (fish – antioxidant assays)	Superoxide radical, myeloperoxidase and cytokine gene expressions production were significantly ($p < 0.05$) increased in fish treated with 12 mg conc., lysozyme activity was generally decreased. No differences were observed in liver histology of experimental groups compared with control	Turkey	Bilen et al. (2019)	
		Antimicrobial, antioxidant, anticancer	<i>In vitro</i> (disc diffusion, DPPH, BSL assays)	AQ extract did not have any inhibitory activity on any pathogens (IZ = 0 mm). Gram + ve bacteria especially <i>Enterococcus casseliflavus</i> displayed the most sig. susceptibility (IZ: 20–22 mm) and the most susceptible Gram -ve bacterium was <i>P. aeruginosa</i> (IZ: 16–20 mm). The most potent anticancer property was displayed by ACE and EA extracts. The most sig. antioxidant effect was from the MeOH extract, and all the extracts showed high cytotoxicity.	Romania	Popovici et al. (2021a) , b, c, d Popovici et al. (2022a) , b	

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
<i>Usnea ceratina</i> Ach. (Warty beard lichen)		Ceratalone, baileisidone, stictic, 8'-O-methylstictic, 8'-O-ethylstictic acids	Cytotoxic	<i>In vitro</i> (human cell culture - MTT assay)	Cytotoxicity was inversely proportional to the antioxidant effect Isolated compounds showed moderate cytotoxic activity against cell lines tested	Vietnam	Bui et al. (2022)
<i>Usnea florida</i> (L.) F.H. Wigg (Beard lichen)		Usnic, thamnolic, evernic, physodic, 3-hydroxyphysodic acids, 5,7-dihydroxy-6- methylphtalide	Antibacterial	<i>In vitro</i> (agar disc diffusion method)	Usnic acid isolated from the ACE extract indicated sig. ($p \leq 0.05$) activity against two of the seven bacteria species tested with IZ of 21 and 22 mm against <i>Bacillus subtilis</i> and <i>Bacillus megaterium</i> , respectively	Turkey	Cansaran et al. (2006)
			Antibacterial	<i>In vitro</i> (bioautography, broth microdilution method)	Antibacterial activity of usnic acid reported (MIC: 7.25 $\mu\text{g/ml}$)	France	Dieu et al. (2020)
			Antibacterial	<i>In vitro</i> (disc diffusion, microdilution methods)	MeOH extract showed broad spectrum dose- dependent activity against the nine bacteria species tested with MIC of 4–10 mg/ml	Cameroon	Bate et al. (2020)
			Cytotoxicity	<i>In vitro</i> (monkey kidney cells - MTT assay)	MeOH extract was not cytotoxic (IC ₅₀ : 56.58–278.50 $\mu\text{g/ml}$)		
<i>Usnea ghattensis</i> G. Awasthi (Beard lichen)		Usnic, stictic, constictic acids	Antimicrobial	<i>In vitro</i> (agar well diffusion, poisoned food methods)	Usnic acid isolated from MeOH extract inhibited test fungi and bacteria especially <i>K. pneumoniae</i> in a conc.- dependent manner (20 mg/ml caused IZ of 2.8 cm)	India	Mesta et al. (2016)
			Cytoprotective, antioxidant	<i>In vitro</i> (CNS-like cell culture – MTT, ORAC, DPPH assays)	Usnic acid isolated displayed moderate protection against H ₂ O ₂ -induced cytotoxic damage in both models	Spain	Fernández-Moriano et al. (2017b)
<i>Usnea longissima</i> Ach. (Methuselah's beard)		Longissiminone A, B, glutinol	Anti-inflammatory, cytotoxic	<i>In vitro</i> (anti-inflammatory, MTT assays)	200 $\mu\text{g/ml}$ of Longissiminone A possesses potent anti-inflammatory activity and caused 100% cell viability	Pakistan	Choudhary and Jalil (2005)
			Antibacterial	<i>In vitro</i> (agar disc diffusion method)	Usnic acid isolated from the ACE extract indicated sig. ($p \leq 0.05$) activity against two of the seven bacteria species tested with IZ of 15 and 17 mm against <i>Bacillus subtilis</i> and <i>Bacillus megaterium</i> , respectively	Turkey	Cansaran et al. (2006)
<i>Usnea rubicunda</i> Stirt. (Red beard lichen)		Usnic acid	Anticancer	<i>In vitro</i> (murine and human cell culture – MTT assay)	HX fraction had IC ₅₀ of 8.1 $\mu\text{g/ml}$. The highest SI was 10.8 for the DEE fraction	France	Bézivin et al. (2003)
<i>Usnea subcavata</i> (Motyka) (Beard lichen)		Atranorin, usnic, diffractaic, lecanoric, protocetraric, salazinic, hypostictic, norstictic acids	Antimycobacterial	<i>In vitro</i> (<i>Mycobacterium tuberculosis</i> - microplate alamar blue assay)	Diffractaic acid was the most active metabolite (MIC:15.6 $\mu\text{g/ml}$, 41.6 μM), followed by norstictic acid (MIC: 62.5 $\mu\text{g}/$ ml, 168 μM) and usnic acid (MIC: 62.5 $\mu\text{g}/$ ml, 182 μM). Hypostictic acid (MIC: 94.0 $\mu\text{g/ml}$, 251 μM) and protocetraric acid (MIC:125 $\mu\text{g/ml}$, 334 μM) showed moderate inhibitory activities	Brazil	Honda et al. (2010)
<i>Usnea undulata</i> Stirt (Beard lichen)		Usnic, galbinic, norstictic, salazinic acids	Antimicrobial	<i>In vitro</i> (agar well diffusion, poisoned food methods)	Usnic acid isolated from MeOH extract inhibited test fungi and bacteria especially <i>K. pneumoniae</i> in a conc.- dependent manner (20 mg/ml caused IZ of 2.5 cm)	India	Mesta et al. (2016)
<i>Vulpicida canadensis</i> (Rasanen) J.-E. Mattsson & M. J. Lai. (Brown-eyed sunshine lichen)	Parmeliaceae (Vulpicida- 6 species)	Pulvinic, vulpinic, usnic acids	Antioxidant	<i>In vitro</i> (ORAC, DPPH assays)	Lichen extract reversed oxidative damage caused by H ₂ O ₂ , thus promoting astrocyte survival	Spain	Fernández-Moriano et al. (2015b)
			Anticancer	<i>In vitro</i> (human cell culture - MTT assay)	Extract had anticancer activity, with IC ₅₀ values of 19.51–181.05 $\mu\text{g/ml}$		
<i>Xanthoparmelia plitti</i> (Gyelnik) Hale		Usnic acid, nanoparticles	Antibacterial	<i>In vitro</i> (agar gel diffusion method)	MeOH extract showed weak antibacterial activity	Cameroon	Bate et al. (2020)

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Table 2 (continued)

Lichen species (Common name)	Family (Genus and number of species available)	Main constituents isolated	Reported biological activity	Type of assay done	Summary of results	Country in which assay was done	Reference
(Green rock shield lichen)	Parmeliaceae (Xanthoparmelia - 15 species)		Cytotoxicity	<i>In vitro</i> (cell culture - MTT assay)	The IC ₅₀ of the MeOH extract was >30 µg/ml, the cut point for lack of cytotoxicity		
<i>Xanthoria parietina</i> (L.) Beltr. (Common orange lichen)	Teloschistaceae (Xanthoria - 20 species)	Parietin	Antiproliferative	<i>In vitro</i> (human cell culture - MTT assay)	Antiproliferative effect was dose-dependent, with the greatest effect being observed at three days of treatment using 1.5–3.0 mg/ml of ACE extract. Parietin did not have any effect on cell cycle phases ACE extract inhibited all the tested microorganisms at conc. of 7.8–62.5 µg/ml. Parietin likewise displayed a robust antibacterial activity, with MICs ranging from 7.8 to 62.5 µg/ml	Italy	Basile et al. (2015)
			Antimicrobial	<i>In vitro</i> (broth microdilution method)			

NA - Common name is not available, * - Species name not given, ACE - Acetone, CHL - Chloroform, MeOH - Methanol, EtOH - Ethanol, PE - Petroleum Ether, AQ - Aqueous, HX - Hexane, DEE - Diethyl ether, EA - Ethyl acetate, Sig. - Significant, Conc. - Concentration, IC - Inhibitory Concentration, MIC - Minimum Inhibitory Concentration, IZ - Inhibitory Zone, OD - Optical density, SI - Selectivity index, SEC - Solid Ehrlich Carcinoma, COX - Cyclooxygenase, LOX - Lipoxygenase, AchE - Acetyl cholinesterase, ROS - Reactive Oxygen Species, NO - Nitric oxide, NOS - Nitric oxide synthase, TNF - Tumour necrosis factor, PD - Petri dish, MTT - 2, 2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), SEM - Scanning Electron Microscopy, CBMN - Cytokinesis-block Micronucleus, MSD - Meso Scale Discovery, ORAC - Oxygen Radical Antioxidant Capacity, DPPH - 1,1-diphenyl-2-picrylhydrazyl, ABTS - 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), FRAP - Ferric Reducing Antioxidant Power, TBARS - Thiobarbituric Acid Reactive Substance, BSL - Brine Shrimp Lethality, IP - Intraperitoneal, H₂O₂ - Hydrogen peroxide, IFN - Interferon, IL - Interleukin, LT - Leukotriene, ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, S. - *Staphylococcus*, C. - *Cryptococcus*, K. - *Klebsiella*, P. - *Pseudomonas*.

and some metabolites are highly cytotoxic and can terminate cell proliferation at micro-molar concentrations (El-Garawani et al., 2019). Usnic acid and atranorin were reported to be capable of inducing a massive loss in the mitochondrial membrane potential, along with caspase-3 activation and phosphatidylserine externalization in cell lines (Bačkorová et al., 2012). Gyrophoric acid has been reported as an effective anticancer drug candidate because it impinges on topoisomerase 1 activity, as well as causes cell cycle arrest. Since it also has cytostatic properties, its possible medicinal utility may become relevant to any process that is controlled by cell growth and differentiation (Mohammadi et al., 2022).

The industrial application of these substances requires large amounts of biomass and several biotechnological techniques have been developed to solve this problem. These include the technique of cell immobilization which focuses on the continuous production of lichen metabolites for a large time period, using small amounts of thallus biomass (Santiago et al., 2018). Green synthesis of silver and iron oxide nanoparticles using a solid-state mechanochemical synthesis has also been described. As microorganisms are becoming more resistant to commercial antibiotics, nanoparticles prepared in an environmentally friendly way represent an interesting alternative (Goga et al., 2021). In general, nanoparticles are considered to be superior antibacterials due to their smaller size, high surface area, and faster kinetics (Safarkar et al., 2020).

It would have been valuable to identify in which studies dose related activities or structure activity relationships were covered, to encourage readers to continue working on these cases, but the information was not always available.

4. Future considerations

Despite the considerable amount of work done thus far on investigating lichens, only a small percentage of lichen species have been screened for their biological activities and their therapeutic potential in medicine. Most experiments done were *in vitro* and localised to certain regions despite the wide global distribution of lichens. This may be due to the difficulties encountered in identification, collection of bulk quantities (slow growth rate), and isolation of pure substances for structure determination and bioactivity testing. Utilizing new opportunities and technologies will go a long way to discovering novel active metabolites, that may be synthesized subsequently, as lead compounds for novel therapeutics (Boustie and Grube, 2005).

The Parmeliaceae represents the largest, most widespread and most studied family of lichens as highlighted in this review. It includes species that attract much interest regarding pharmacological activities, due to their ability to produce unique secondary metabolites (Fernández-Moriano et al., 2016b). These deserve further study, especially on their mechanism(s) of action and structure-activity relationships. Usnic acid is mostly used as an ingredient in creams, powders, toothpastes, mouthwash, deodorants, hair shampoos and sunscreen products. The salt form, sodium usniate, has been marketed in the USA as an ingredient in food supplements for use in weight reduction (Araújo et al., 2015). Despite this, many other properties of lichen substances such as ultraviolet absorption, preserving properties, insecticidal and acaricidal properties have been little explored and investigated for their potential industrial use.

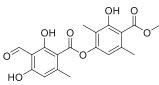
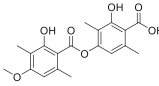
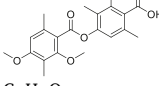
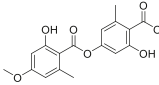
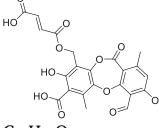
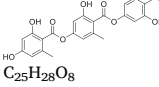
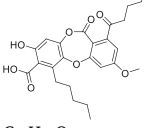
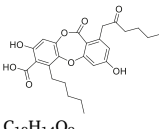
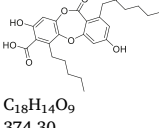
5. Recommendations for further research

To tap into the wealth of lichens, a few recommendations may be made:

Suitable conservation strategies for sustainable harvest of lichens can be deduced to reduce threatened genetic diversity of resources due to climate change and overharvesting.

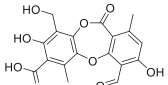
Improved *in vitro* culture techniques could be developed for lichen species with a high commercial value and demand. This would help with

Table 3
Biological activities of some promising lichen secondary metabolites.

Metabolite (IUPAC name)	Class	Chemical structure, formula and molecular weight (g/mol)	Lichen species from which the metabolite has been isolated	Biological property (IC ₅₀ /LC ₅₀)	Reference
Atranorin [3-Formyl-2,4-dihydroxy-6-methylbenzoic acid 3-hydroxy-4-(methoxycarbonyl)-2,5-dimethylphenyl ester]	Depside	 C ₁₉ H ₁₈ O ₈ 374.34	<i>Cladonia kalbii</i> Anti. <i>Heterodermia</i> species <i>Everniastrum vexans</i> (W. L. Culb. & C.F. Culb.) Sipman <i>Parmotrema praesorediosum</i> (Nyl.) Hale <i>Lepraria jackii</i> Tonsberg	Antioxidant (100 µg/ml), anti-inflammatory, (17 µg/ml), anticancer (5.36 ± 0.85 µM), wound healing modulation, DNA-interacting agent, anticancer	Báčkorová et al., 2012 Barreto et al. (2013) Plsíková et al., 2014 Zhou et al. (2017) Studzinska-Sroka et al. (2017) Studzinska-Sroka and Dubina (2018) Harikrishnan et al., 2021 Martins et al. (2010)
Barbatic acid [2-hydroxy-4-(2-hydroxy-4-methoxy-3,6-dimethylbenzoyl)oxy-3,6-dimethylbenzoic acid]	Depside	 C ₁₉ H ₂₀ O ₇ 360.36	<i>Cladia aggregate</i> (Sw.) Nyl <i>Cladonia cristatella</i> Tuck. <i>Lecanora chrysoleuca</i> (Sm.) Ach.	Antibacterial against <i>S. aureus</i> (MIC: 50 µg/ml)	
Diffraicta acid [4-[(2,4-Dimethoxy-3,6-dimethylbenzoyl)oxy]-2-hydroxy-3,6-dimethylbenzoic acid]	Depside	 C ₂₀ H ₂₂ O ₇ 374.38	<i>Usnea diffracta</i> Vainio <i>Usnea longissima</i> Ach. <i>Parmelia nepalensis</i> Taylor <i>Parmelia tinctorum</i> Despr. ex Nyl.	Antioxidant, antimycobacterial (MIC: 15.6 µg/ml, 41.6 µM), analgesic, antipyretic, hepatoprotective (50 mg/kg), antiproliferative (2.6 µM), gastroprotective	Okuyama et al. (1995) Kumar and Muller, 1999 Bayir et al. (2006) Honda et al. (2010) Odabasoglu et al. (2012) Karagoz et al. (2015)
Evernic acid [2-hydroxy-4-(2-hydroxy-4-methoxy-6-methylbenzoyl)oxy-6-methylbenzoic acid]	Depside	 C ₁₇ H ₁₆ O ₇ 332.09	<i>Evernia</i> species Ramalina species Hypogymnia species	Antifungal, antioxidant, anti-inflammatory, neuroprotective	Halama and Van Haluwin (2004) Gökalsın and Sesal, 2016 Ahamed et al. (2019) Lee et al. (2021) Girardot et al., 2021
Fumarprotocetraric acid [3-carboxyprop-2-enoyl]oxymethyl]-10-formyl-3,9-dihydroxy-1,7-dimethyl-6-oxobenzo[b][1,4]benzodioxepine-2-carboxylic acid]	β-orcinol depsidone	 C ₂₂ H ₁₆ O ₁₂ 472.36	<i>Cladonia rangiformis</i> Hoffm. <i>Cladonia foliacea</i> (Huds.) Willd. <i>Cladonia verticillaris</i> P. Browne <i>Cetraria islandica</i> (L.) Ach.	Cytoprotective, expectorant, antioxidant (50 mg/kg), antimicrobial (0.33 mM)	Yılmaz et al., 2004 de Barros Alves et al., 2014 Fernández-Moriano et al. (2017a)
Gyrophoric acid [4-[4-(2,4-Dihydroxy-6-methylbenzoyl)oxy-2-hydroxy-6-methylbenzoyl]oxy-2-hydroxy-6-methylbenzoic acid]	Tridepside	 C ₂₄ H ₂₀ O ₁₀ 468.41	<i>Xanthoparmelia porkonyi</i> Korb.	Antiproliferative, cytotoxic (7 µM), antibacterial (4 mM)	Candan et al. (2006)
Lobaric acid [3-hydroxy-9-methoxy-6-oxo-7-(1-oxopentyl)-1-pentyl-2-benzo[b][1,4]benzodioxepincarboxylic acid]	Depsidone	 C ₂₅ H ₂₈ O ₈ 456.49	<i>Stereocaulon</i> species	Anti-oxidant (97.9 µmol), antiproliferative (15.2–63.9 µg/ml), enzyme inhibitory (0.87 µM)	Haraldsdóttir et al. (2004) Seo et al. (2009)
Physodic acid [Methyl 3,8-dihydroxy-11-oxo-1-(2-oxoheptyl)-6-pentyl-11H-dibenzo[b,e][1,4]dioxepine-7-carboxylate]	β-Orcinol Depsidone	 C ₂₆ H ₃₀ O ₈ 470.51		175.8 µM	Sahin et al. (2021)
Protocetraric acid [10-formyl-3,9-dihydroxy-4-(hydroxymethyl)-1,7-	Depsidone	 C ₁₈ H ₁₄ O ₉ 374.30	<i>Usnea albopunctata</i> <i>Cetraria islandica</i> (L.)	Antibacterial (0.5 µg/ml), antifungal (1 µg/ml), anticancer	Brandão et al., 2012 Nishanth et al. (2015)

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Table 3 (continued)

Metabolite (IUPAC name)	Class	Chemical structure, formula and molecular weight (g/mol)	Lichen species from which the metabolite has been isolated	Biological property (IC ₅₀ /LC ₅₀)	Reference
dimethyl-6-oxobenzo[b][1,4]benzodioxepine-2-carboxylic acid			Ach. <i>Cetraria ericetorum</i> Opiz		
Thamnolan (NA)	Heteroglycan	Has not been adequately described	<i>Thamnolia</i> species	Immunomodulatory	Omarsdottir et al. (2007)
Usnic acid [2,6-Diacetyl-7,9-dihydroxy-8,9 b-dimethyldibenzo [b,d]furan-1,3(2 <i>H</i> ,9 <i>bH</i>)-dione]	Dibenzofuran	C ₁₈ H ₁₆ O ₇ 344.32	Usnea species Alectoria species Cladonia species Lecanora species Ramalina species Evernia species	Antibacterial (MIC: 30–40 µg/ml), α- and β-glucosidase inhibition (17.7–18.9 µg/ml), antifungal, antiviral, antiprotozoal, antimitotic, anti-inflammatory, analgesic, anticancer	Ingolfsson et al. (2002) Verma et al. (2012) Bačkorová et al., 2012 Brisdelli et al., 2013 Maulidiyah et al. (2020)
Vulpinic acid [Methyl (2 <i>E</i>)-2-(5-hydroxy-3-oxo-4-phenylfuran-2-ylidene)-2-phenylacetate]	Dibenzofuran (butenolide)	C ₁₉ H ₁₄ O ₅ 322.32	<i>Cladonia</i> species	Anti-angiogenic, cytotoxic, antimicrobial anticancer	Lauterwein et al., 1995 Koparol, 2015 Cansaran-Duman et al., 2021a

NA- Not available; ChemDraw Professional 17.0 was used to draw the chemical structures.

the production of substantial volumes of biomass for commercial harvest.

Phylogenetic analysis of biosynthetic genes can facilitate the discovery of novel compounds, novel genes, and therefore, unknown producers of pharmaceutically relevant compounds.

6. Conclusions

Although lichens are a reservoir for various biologically active metabolites, only a limited number of species have been tested for their biological significance. There appears to be a need for expanding research in this area of study. This should include in depth studies of those metabolites which have shown promising results as well as a strong focus on identifying specific mechanisms of action of extracts and purified metabolites, coupled with extensive clinical trials using the most promising lichen-based drug therapies, followed by large scale production. This goal can be achieved by enhanced methods for isolation of purified metabolites and more *in vivo* studies in order to identify molecular targets and structure–activity correlations.

CRedit authorship contribution statement

Olubukola Tolulope Adenubi: Methodology, Collation of data, Writing – original draft, preparation. **Ibukun Michael Famuyide:** Collation of data, Writing – review & editing. **Lyndy Joy McGaw:** Writing – review & editing, All authors read and approved the final version of the manuscript. **Jacobus Nicolaas Eloff:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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