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# 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 (Piddock,

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**List of abbreviations**

| | |
|---|---|
| B | *Bryoria* |
| U | *Umbilicaria* |
| L | *Lethariella* |
| T | *Thamnolia* |
| E | *Everniastum* |
| J | *Juniperus* |
| R | *Rhododendron* |
| O | *Ochrolechia* |
| C | *Cryptococcus* |
| P | *Pseudomonas* |
| S | *Staphylococcus* |
| K | *Klebsiella* |
| NA | Not available |
| ACE | Acetone |
| CHL | Chloroform |
| MeOH | Methanol |
| EtOH | Ethanol |
| PE | Petroleum ether |
| AQ | Aqueous |
| HX | Hexane |
| DEE | Diethyl ether |
| EA | Ethyl acetate |
| Conc | Concentration |
| IC | Inhibitory concentration |
| LC | Lethal concentration |
| MIC | Minimum Inhibitory Concentration |
| IZ | Inhibitory Zone |
| OD | Optical density |
| Sig | Significant |
| SI | Selectivity index |
| SEC | Solid Ehrlich Carcinoma |
| COX | Cyclooxygenase |
| LOX | Lipoxygenase |
| AchE | Acetyl cholinesterase |
| ROS | Reactive Oxygen Species |
| PD | Petri dish |
| SEM | Scanning Electron Microscopy |
| TEM | Transmission Electron Microscopy |
| CBMN | Cytokinesis-block Micronucleus |
| MSD | Meso Scale Discovery |
| ORAC | Oxygen Radical Antioxidant Capacity |
| DPPH | 1,1-diphenyl-2-picrylhydrazyl |
| FRAP | Ferric Reducing Antioxidant Power |
| ABTS | 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) |
| TBARS | Thiobarbituric Acid Reactive Substance |
| BSL | Brine Shrimp Lethality |
| MTT | 2, 5-diphenyl-2H-tetrazolium bromide |
| $H_2O_2$ | Hydrogen peroxide |
| IL | Interleukin |
| LT | Leukotriene |
| IFN | Interferon |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| NO | Nitric oxide |
| NOS | Nitric oxide synthase |
| 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 pharmaceutics 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), antineurodegenerative (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, 2021) 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 (Kranner 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. sernanderi* (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.) ZablBr., *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 *Roccella 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 bioresource 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 (ZoharSerri, 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) | *Bryoria fremontii* (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) |
| | *Lobothallia alphoplaca* (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) |
| | *Umbilicaria muhlenbergii* (Ach.) Tuck. | Umbilicariaceae | Plated rocktripe lichen | | |
| | *Xanthoparmelia mexicana* (Gyelnik) Hale | Parmeliaceae | Salted rock-shield | | |
| Brazil | *Heterodermia galactophylla* (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 | *Umbilicaria muhlenbergii* (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 | *Lethariella cashmeriana* Krog | Parmeliaceae | NA | In Yunnan, the lichens are taken as health foods and health-promoting teas | Wang et al. (2001) |
| | *Lethariella sernanderi* (Motyka) Obermayer | | | | |
| | *Lethariella sinensis* Wei & Jiang | | | | |
| | *Lobaria isidiophora* Yoshim | Peltigeraceae | Lung lichen | | |
| | *Lobaria kurokawae* Yoshim | | | | |
| | *Ramalina conduplicans* Vain | Ramalinaceae | Bushy lichen | | |
| | *Ramalina sinensis* Jatta | | Burning bush lichen | | |
| | *Thamnolia subuliformis* (Ehrh.) Culb | Icmadophilaceae | Awl shaped whiteworm lichen | | |
| | *Thamnolia vermicularis* (Swartz) Ach. ex Schaerer | | Alpine lichen | | |
| India | *Heterodermia diademata* (Taylor) D.D.Awasthi | Physciaceae | Shield lichen | The lichen is mixed with *Parmotrema* 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) |
| | *Parmelia perlata* (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) |
| | Usnea sikkimensis Biswas | Parmeliaceae | Old man's beard lichen | The herdsmen 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) |
| Italy | Lobaria pulmonaria (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) |
| Japan | Usnea diffracta Vain | Parmeliaceae | Beard lichen | It is used for the relief of pain and fever | Okuyama et al. (1995) |
| Libya | *Evernia furfuracea* (L.) Mann | Parmeliaceae | Oakmoss lichen | The lichens are mixed and used to prepare medicinal decoctions and food spices | De Natale and Pollio (2012) |
| | *Ramalina calicaris* (L.) Fr. | Ramalinaceae | Strap lichen | | |
| | *Ramalina farinacea* (L.) Ach. | Ramalinaceae | Farinose cartilage lichen | | |
| | *Usnea plicata* (L.) Fries | Parmeliaceae | Beard lichen | | |
| Nepal | *Everniastrum cirrhatum* (Fr.) Hale ex Sipman. | Parmeliaceae | NA | Extracts or juices of *Eupatorium odoratum* or *Artemisia vulgaris* are mixed with the lichen species and applied on fresh wounds, cuts and moles | Devkota et al. (2017) |
| | *Everniastrum nepalense* (Taylor) Hale ex Sipman | | NA | | |
| | *Heterodermia diademata* (Taylor) D.D.Awasthi | Physiaceae | Shield lichen | | |
| | *Parmotrema cetratum* (Ach.) Hale | Parmeliaceae | NA | | |
| | *Ramalina* species | Ramalinaceae | Strap lichen | | |
| | *Thamnolia vermicularis* (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 |
|---|---|---|---|---|---|
| | *Usnea longissima* Ach. | Parmeliaceae | Methuselah's beard lichen | | |
| Papua New Guinea | *Parmotrema saccatilobum* (Taylor) Hale | Parmeliaceae | Ruffle lichen | The people of Milne Bay province use the lichen for relief of pain and fever | Bugni et al. (2009) |
| Turkey | *Lobaria pulmonaria* (L.) Hoffm | Peltigeraceae | Lung lichen | Prepared as a tea and taken as a laxative | Suleyman et al. (2003) |
| Western Sahara (Algeria, Morocco, Mauritania) | Tequilit 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 | *Usnea barbata* (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 (Ingolfsdottir, 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, isolichenin, 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 anthelminthic (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, supressing 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), neuroprotective 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 (Kosanic 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 |
|---|---|---|---|---|---|---|---|
| *Acarospora fuscata* (Nyl.) Th.Fr. (Brown cobblestone lichen) | Acarosporaceae (Acarospora - 128 species) | Atranorin, chloroatranorin, stictic, norstictic, gyrophoric, usnic acids | Antioxidant | *In vitro* (DPPH, FRAP methods) | Gyrophoric acid isolated from ACE extract had high scavenging activity ($IC_{50}$: 105.75 μg/ml) | Serbia | Kosanic et al. (2014a) |
| | | | Antimicrobial | *In vitro* (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 | *In vitro* (human cell culture – MTT assay) | Gyrophoric acid showed moderate cytotoxic activity | | |
| *Alectoria sarmentosa* (Ach.) Ach. (Witch's hair lichen) | Parmeliaceae (Alectoria - 10 species) | Alectosarmentin,dibenzofuran, usnic, alectoronic acids | Antibacterial | *In vitro* (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) |
| *Bryoria capillaris* (Ach.) Brodo & D. Hawksw. (Horsehair lichen) | Parmeliaceae (Bryoria - 36 species) | Atranorin, usnic, fumarprotocetraric, confumarprotocetraric, stictic, lobaric, gyrophoric, vulpinic, barbatolic acids | Antibacterial | *In vitro* (disc diffusion method) | ACE extract showed broad spectrum antibacterial activity against both Gram + ve and Gram -ve bacteria | Turkey | Tas et al. (2017) |
| | | | Antioxidant | *In vitro* (DPPH assay) | 100 μg/ml conc. caused 67.4% free radical scavenging activity | | |
| | | | Antiproliferative | *In vitro* (human cell culture – MTT assay) | Weak antiproliferative activity was observed ($IC_{50}$: >200 μg/ml) | | |
| *Bryoria fuscescens* (Gyeln.) Brodo and D.Hawksw (Pale-footed horsehair lichen) | | Fumarprotocetric acid, atranorin | Antibacterial | *In vitro* (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) |
| *Bulbothrix setschwanensis* (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 | *In vitro* (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 S. aureus (1.56 mg/ml) and C. neoformans (6.25 mg/ml) | India | Maurya et al. (2018) |
| *Candelariella vitellina* (Hoffm.) Mull. Arg. (Egg-yolk lichen) | Candelariaceae (Candelariella - 35 species) | Physodic, physodalic acids | Antigenotoxic, anthelminthic, antioxidant | *In vitro* (human cell culture – MTT assay, antioxidant – DPPH assay, antigenotoxic – Comet assay, anthelminthic – Protoscoleces assay, SEM) | 80% MeOH/$H_2O$ extract exhibited very low cytotoxicity towards normal human peripheral lymphocytes with $IC_{50}$ >1000 μg/ml. There was sig. ($p \leq 0.05$) 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 | *In vitro* (human cell culture – MTT assay, cholesterol assay kit) and *in vivo* (SEC model in mice) | 32 mg/ml 80% MeOH/$H_2O$ extract reduced cholesterol conc. to 100 ± 0% after 96 h of incubation and antirotavirus activity was seen with a therapeutic index of 11 | | Elkhateeb et al. (2020) |
| *Cetraria aculeata* (Schreb.) Fr. (Spiny Iceland lichen) | Parmeliaceae (Cetraria- 20 species) | Norstistic, protolichesterinic acids | Genotoxic, antigenotoxic, cytotoxic | *In vitro* (cell culture – MTT, CBMN assays, Ames test) | ACE extract showed a sig. ($p \leq 0.05$) antigenotoxic activity in bacterial systems, but not in mammalian cells | Turkey | Zeytinoglu et al. (2008) |
| *Cetraria islandica* L. (Ach.) (True Iceland lichen) | | Protolichesterinic, fumarprotocetraric acids, isolichenan, lichenan, thamnolan | Anti-inflammatory | *In vivo* (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 $H_2O_2$ | 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 |
|---|---|---|---|---|---|---|---|
| | | | | *In vitro* (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 | *In vitro* (ORAC, DPPH assays) | Lichen extract reversed oxidative damage caused by $H_2O_2$, thus promoting astrocyte survival | Spain | Fernández-Moriano et al. (2015a) |
| | | | Anticancer | *In vitro* (human cell culture - MTT assay) | Extract had anticancer activity, with $IC_{50}$ values between 19.51 and 181.05 μg/ml | | |
| | | | Antioxidant, neuroprotective | *In vitro* (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 | *In vitro* (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) |
| *Cetrelia braunsiana* (Müll. Arg.) W. L. Culb. & C. F. Culb (Giant shield lichen) | Parmeliaceae (Cetrelia- 19 species) | Alectoronic acid | Antioxidant, neuroprotective | *In vitro* (DPPH, MTT assays | Sig. ($p \leq 0.05$) antioxidant and cytoprotective activities were observed | Spain | Fernández-Moriano et al. (2015a) |
| *Cladia aggregata* (Sw.) Nyl. (Reindeer lichen) | Cladoniaceae (Cladia - 20 species) | Barbatic acid | Antibacterial | *In vitro* (antibacterial – biochromatography method) | Barbatic acid isolated from the DEE extract showed sig. ($p \leq 0.05$) antibacterial activity (MIC: 50 μg/ml) against the four resistant *S. aureus* strains tested | Brazil | Martins et al. (2010) |
| | | | Anthelminthic, molluscidal | *In vitro* (immersion test) | 1 μg/ml presented cercaricidal activity against L2 Schistosoma mansoni after 60 min of exposure. Barbatic acid exhibited no embryotoxicity, but showed molluscicidal effects against Biomphalaria glabrata at 20 and 25 μg/ml | | Martins et al. (2017) |
| | | | Insecticidal | *In vitro* (Nasutitermes corniger - 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) |
| | | | Anthelminthic | *In vitro* (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 Schistosoma mansoni was 99.43 μM. Extensive damage to the worm's tegument was observed from 25 μM | | Silva et al. (2020) |
| *Cladonia borealis* S. Stenroos (Boreal cup lichen) | Cladoniaceae (Cladonia - 30 species) | Usnic, barbatic, 4-*O*-demethylbarbatic acids | Antibacterial | *In vitro* (broth microdilution method) | Extract inhibited five bacteria strains tested (MIC: 7.8–31.25 μg/ml) | Brazil | Micheletti et al. (2021) |
| *Cladonia convoluta* (Lam) Anders (Cup lichen) | | 9′-(O-methyl)protocetraric, usnic, fumarprotocetraric acids | Anticancer | *In vitro* (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) |
| *Cladonia kalbii Ahti* (Reindeer lichen) | | Atranorin | Antioxidant, cytoprotective | *In vitro* (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 $H_2O_2$ | 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 |
|---|---|---|---|---|---|---|---|
| | | | | | was observed for atranorin isolated from the CHL extract | | |
| *Cladonia rangiferina* (L.) F. H. Wigg. (Grey reindeer lichen) | | Fumarprotocetraric acid, atranorin | Hepatoprotective | *In vitro* (DPPH, FRAP, MTT assays) and *in vivo* (acute toxicity test in rats) | $IC_{50}$ 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) |
| *Cladonia rangiformis* Hoffm. (Reindeer lichen) | | Atranorin, usnic, fumarprotocetraric acids | Anticancer | *In vitro* (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 | *In vitro* (disk diffusion method) | *Escherichia coli* was particularly sensitive to the MeOH and AQ extracts | Algeria | Rafika and Monia (2018) |
| **Cladonia* sp. | | Zeorin, methyl β-orcinolcarboxylate, atranorin, methylorsellinate,lobaric acid | Antidiabetic (α-glucosidase inhibitor) | *In vitro* (Antidiabetic assay, spectrophotometry) | Zeorin isolated showed excellent α-glucosidase inhibition ($IC_{50}$: 100.0 ± 0.3 μM) | Sri Lanka | Karunaratne et al. (2014) |
| Cladonia substellata Vain. (Reindeer lichen) | | Usnic, norstictic, stictic acids | Trypanocidal | *In vitro* (*Trypanosoma cruzi,* spectromorphometry, TEM) | Usnic acid isolated caused a strong decrease of OD values, in a dose-dependent manner | Brazil | De Calvarho et al. (2005) |
| | | | Insecticidal | *In vitro* (Nasutitermes corniger - 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 | *In vitro* (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 | *In vitro* (microdilution method) | The growths of *S. aureus, Escherichia coli* and *K. pneumoniae* were inhibited, but the organic extracts showed the highest activity | | |
| | | | Molluscicidal | In vivo (Biomphalaria glabrata 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) |
| | | | Anthelminthic | In vitro (Schistosoma mansoni-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) |
| *Cladonia verticillaris* (Raddi) Fr. (Ladder lichen) | | Fumarprotocetraric acid | Expectorant | *In vivo* (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 | *In vivo* (Albino Swiss mice – TBARS assay) | Lipid peroxidation was reduced by 50% in the lung tissue | | |
| | | | Insecticidal | *In vitro* (Nasutitermes corniger - 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 |
|---|---|---|---|---|---|---|---|
| *Dirinaria aegialita* (Afzel. ex Ach.) B.J. Moore (NA) | Caliciaceae (Dirinaria - 35 species) | Lichexanthone, atranorin, divaricatic acid | Antimicrobial | *In vitro* (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 | *In vitro* (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 | | |
| *Evernia prunastri* (L.) Ach. (Oakmoss lichen) | Parmeliaceae (Evernia - 5 species) | Evernic, usnic, physodic acids, atranorin, chloroatranorin | Anticancer | *In vitro* (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 | *In vitro* (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 | *In vitro* (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 | *In vitro* (CNS-like cell culture – MTT, ORAC, DPPH assays | Evernic acid isolated displayed sig. ($p \leq 0.05$) protection against $H_2O_2$-induced cytotoxic damage in both models used | Spain | Fernández-Moriano et al. (2017b) |
| | | | Antibacterial | *In vitro* (disc diffusion method) | *S. aureus* was highly sensitive to the MeOH extract (IZ = 43 mm) | Algeria | Rafika and Monia (2018) |
| *Heterodermia diademata* (Taylor) D.D.Awasthi (Shield lichen) | Physciaceae (Heterodermia - 80 species) | Atranorin, chloroatranorin, zeorin, norstictic, salazinic, lobaric acids | Antifungal | *In vitro* (disc diffusion method) | ACE and MeOH extracts were active against all the seven tested fungi while the CHL extract showed activity against only two pathogenic fungi (*Alternaria alternata* and *Penicillium citrinum*). The maximum IZ of 19 mm was exhibited by the MeOH extract. | India | Tiwari et al. (2011) |
| | | | Antioxidant | *In vitro* (DPPH, LOX inhibition assays) | 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 | | Behera et al. (2016) |
| | | | Antimicrobial | *In vitro* (disc diffusion method) | EA extract showed strong antimicrobial activity with *Candida albicans* being very sensitive (MIC: 0.23 mg/ml) | | |
| *Heterodermia microphylla* Trevis. (NA) | | Atranorin, chloroatranorin, zeorin, norstictic, salazinic, lobaric acids, methyl-β-orcinolcarboxylate | Antifungal | *In vitro* (spore germination assay) | Atranorin was comparable in activity to the standard antifungal agent benlate (methyl-1-(butylcarbonyl)-2-benzamidizolecarbamate) | Sri Lanka | Bombuwela et al. (2008) |
| | | | Insecticidal | *In vitro* (PD assay) | Atranorin isolated exhibited moderate larvicidal activity against the 2nd instar larvae of *Aedes aegypti* (90 and 100% mortality at 100 ppm conc. after 24 and 48 h, respectively) | | |
| *Heterodermia obscurata* (Nyl.) (Orange tinted fringe lichen) | | Atranorin, chloroatranorin, zeorin, emodin, 7-chloroemodin | Antinociceptive | *In vivo* (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 | *In vivo* (acetic-acid writhing method) | The fraction also reduced leukocyte migration by 58%, but did not alter plasmatic extravasation to the peritoneal cavity | | |
| *Heterodermia speciosa* (Wulfen) Trevis. (Centipede lichen) | | Atranorin, zeorin, norstictic, salazinic, lobaric acids | Antioxidant | *In vitro* (DPPH, BSL assays) | Medium activity (50–80% death of brine shrimp) was observed | Nepal | Jha et al. (2017) |
| | | | Antimicrobial | *In vitro* (disc diffusion method) | Antibacterial activity against *S. aureus* was observed (IZ: 7 mm) | | |
| *Hypogymnia physodes* (L.) Nyl. (Monk's hood lichen) | Parmeliaceae (Hypogymnia - 90 species) | Physodalic, physodic, 3-hydroxy-physodic, isophysodic acids | Cytotoxic, antiproliferative | *In vitro* (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 | *In vitro* (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) |
| *Lethariella zahlbruckneri* (Du Rietz) Krog (NA) | Parmeliaceae (Lethariella - 11 species) | Atranorin, tolypyridone A | Antiproliferative | *In vitro* (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) |
| *Lobaria pulmonaria* (L.) Hoffm (Lung lichen) | Peltigeraceae (Lobaria - 21 species) | Stictic, constictic, norstictic, cryptostictic acids | AchE inhibition | *In vitro* (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 | *In vitro* (PD assay) | Silver nanoparticles extracted were highly effective on the six bacterial species tested | Slovak Republic | Goga et al. (2021) |
| | | | Antioxidant | *In vitro* (DPPH assay) | Silver nanoparticles extracted had lower antioxidant properties (19.4%) than the extract (44.7%) | | |
| *Melanelixia fuliginosa* (Duby) O. (NA) | Parmeliaceae (Melanelixia - 15 species) | Atranorin, lecanoric, gyrophoric, anziaic, 2′-*O*-methyl anziaic, usnic acids | Antioxidant | *In vitro* (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 | *In vitro* (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 | *In vitro* (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) | | |
| *Melanelixia subaurifera* (Nyl) (Abraded camouflage lichen) | | Atranorin, lecanoric, gyrophoric, anziaic, 2′-*O*-methyl anziaic, usnic acids | Antioxidant | *In vitro* (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 | *In vitro* (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 | *In vitro* (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 |
|---|---|---|---|---|---|---|---|
| | | | | | (IC50: 9.88, 123.97, 151.79 μg/ml, respectively) | | |
| *Myelochroa irrugans* (Nyl.) Elix & Hale (Axil bristle lichen) | Parmeliaceae (Myelochroa - 30 species) | Atranorin, zeorin | Antioxidant, | *In vitro* (ORAC, DPPH, FRAP assays) | MeOH extract showed strong radical scavenging activity (EC50: 384 μg/ml) | Spain | Fernández-Moriano et al. (2016a), b |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay) | MeOH extract reduced significantly ($p \leq 0.05$), the viability of the cells (LD50: 22 μg/ml) | | |
| *Parmelia arseneana* Gyeln. (NA) | Parmeliaceae (Parmelia - 40 species) | Atranorin, stictic, norstictic, usnic acids | Antioxidant | *In vitro* (DPPH, FRAP assays) | ACE extract had high scavenging activity ($IC_{50}$: 612.75 μg/ml) | Serbia | Kosanic et al. (2014a) |
| | | | Antimicrobial | *In vitro* (broth microdilution method) | ACE extract showed moderate antibacterial and antifungal activities, inhibiting the microorganisms tested at 0.08–10 mg/ml | | |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay) | ACE extract expressed strong anticancer activity against all cell lines tested ($IC_{50}$: 11.61–47.06 μg/ml) | | |
| *Parmelia caperata* (L.) Ach. (Common greenshield lichen) | | Protocetraric, usnic, caperatic acids, ergosterol peroxide | Anticancer | *In vitro* (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 | France | Bézivin et al. (2003) |
| | | | Antimicrobial | *In vitro* (broth microdilution method) | 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 | Serbia | Manojlović et al. (2012) |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay) | Protocetraric and usnic acids demonstrated cytotoxic activity with $IC_{50}$ of 58.68 and 12.72 μg/ml, respectively | | |
| | | | Antioxidant | *In vitro* (DPPH, FRAP, Superoxide assays) | 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 | | |
| | | | Antibacterial | *In vitro* (bioautography, broth microdilution method) | MIC of usnic, caperatic and protocetraric acids were between 7.25 and 12.5 μg/ml | France | Dieu et al. (2020) |
| *Parmelia erumpens* Kurok. (Shield lichen) | | Atranorin, usnic, 2-hydroxy-4-methoxy-3,6-dimethylbenzoic acids | Antimicrobial | *In vitro* (agar disc diffusion, broth microdilution methods) | 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 | India | Aravind et al. (2014) |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay) | Growth of cancer cells was suppressed by 2-hydroxy-4-methoxy-3,6-dimethylbenzoic acid in both dose- and time-dependent manners | | |
| *Parmelia nepalensis* Taylor (Schield lichen) | | Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids | Antiproliferative | *In vitro* (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 | Germany | Kumar and Müller (1999a) |
| | | | Antioxidant | *In vitro* (DPPH assay) | Atranorin, diffractaic and protolichesterinic acid inhibited $LTB_4$ biosynthesis in polymorphonuclear leukocytes | | Kumar and Müller (1999b) |
| *Parmelia perlata* (Huds.) Ach. (Stone flower lichen) | | Salazinic, stictic acids, atranorin, chloroatranorin | Anticancer | *In vitro* (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 | France | Bézivin et al. (2003) |
| | | | Antimicrobial | *In vitro* (broth microdilution methods) | The MeOH extract was more active than the ACE extract with a MIC of 39.1 mg/ml | Serbia | Manojlović et al. (2021) |
| | | | Antioxidant | *In vitro* (DPPH assay) | 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) | | |

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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 | *In vitro* (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 | | |
| *Parmelia saxatilis* (L.) Ach. (Salted shield lichen) | | Salazinic acid, atranorin, chloroatranorin | Anticancer | *In vitro* (human cell culture – MTT assay) | Demonstrated cytotoxic activity and the $IC_{50}$ for salazinic acid was 35.67 μg/ml | Serbia | Manojlović et al. (2012) |
| | | | Antimicrobial | *In vitro* (broth microdilution method) | Antibacterial activity of salazinic acid was stronger than its antifungal, with MIC as low as 0.015 mg/ml | | |
| | | | Antioxidant | *In vitro* (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 | | |
| *Parmelia sulcata* Taylor (Hammered shield lichen) | | Salazinic acid, atranorin, chloroatranorin | Anticancer | *In vitro* (human cell culture – MTT assay) | Demonstrated cytotoxic activity and the $IC_{50}$ for salazinic acid was 35.67 μg/ml | Serbia | Manojlović et al. (2012) |
| | | | Antimicrobial | *In vitro* (broth microdilution method) | Antibacterial activity of salazinic acid was stronger than its antifungal, with MIC as low as 0.015 mg/ml | | |
| | | | Antioxidant | *In vitro* (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 | | |
| | | | Antimicrobial | *In vitro* (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 | Armenia | Sargsyan et al. (2021) |
| | | | Antioxidant | *In vitro* (DPPH assay) | The MeOH extract showed good radical scavenging activity (71%), which was only slightly lower than ascorbic acid (96%) | | |
| *Parmotrema cetratum* (Ach.) Hale (Ruffle lichen) | Parmeliaceae (Parmotrema - 300 species) | Salazinic acid | Anticancer | *In vitro* (human and murine cell culture – MTT, flow cytometry assays) and *in vivo* (acute toxicity and experimental melanoma model in mice) | 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). *In vivo,* 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) |
| *Parmotrema saccatilobum* (Taylor) Hale (Ruffle lichen) | | Atranorin, chloroatranorin, protocetraric acid | Anti-inflammatory | *In vitro* (COX 1 and 2 enzyme inhibition assay) | Atranorin inhibited COX-1 in a dose dependent manner | USA | Bugni et al. (2009) |
| *Parmotrema tinctorum* (Delise ex Nyl.) Hale (Palm ruffle lichen) | | Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids | Antiproliferative | *In vitro* (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 | Germany | Kumar and Müller (1999a) |
| | | | Antioxidant | *In vitro* (DPPH assay) | Atranorin, diffractaic and protolichesterinic acid inhibited $LTB_4$ biosynthesis in polymorphonuclear leukocytes | | Kumar and Müller (1999b) |
| | | | Macrofilaricidal | *In vitro* (cell culture – MTT, worm motility assays) and *in vivo* (acute toxicity test) | MeOH extract was active against adult male worms (IC50: 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 |
|---|---|---|---|---|---|---|---|
| *Peltigera rufescens* (Weis.) Humb. (Dog lichen) | Peltigeraceae (Peltigera - 100 species) | Peltigerin, 3-*O*-β-glucopyranosyl-d-mannitol, d-mannitol | Antioxidant | *In vitro* (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 | *In vitro* (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 | *In vitro* (immersion test) | There was sig. ($p \leq 0.05$) insecticidal activity against adults of *Sitophilus zeamais* as 20 mg ml extract caused mortality of 95.96% | Egypt | Yildirim et al. (2012) |
| *Platismatia glauca* (L.) W.L.Culb. & C.F. Culb (Ragbag lichen) | Parmeliaceae (Platismatia - 10 species) | Atranorin, gyrophoric, usnic, diffractaic, protolichesterinic acids | Anticancer | *In vitro* (human cell culture – MTT assay) | Extract demonstrated interesting activity on human cancer cell lines tested (SI > 3) | France | Bézivin et al. (2003) |
| *Pleurosticta acetabulum* (Neck.) Elix & Lumbsch (NA) | Parmeliaceae (Pleurosticta - 2 species) | Cytochalasin E, atranorin, salazinic, norstictic, protocetraric, evernic acids | Anticancer | *In vitro* (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 | *In vitro* (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 | *In vitro* (DPPH, FRAP assays) | ACE extract exhibited moderate free radical scavenging activity ($IC_{50}$: 151.73 μg/ml) | | |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay) | $IC_{50}$ values ranged from 24.09 to 45.94 μg/ml | | |
| *Pseudevernia furfuracea* (L.) Zopf (Tree moss lichen) | Parmeliaceae (Pseudevernia - 9 species) | Olivetoric, physodic, atraric, 3-hydroxyphysodalic, physodalic acids, methyl haematommate, atranorin, chloroatranorin | Antioxidant | *In vitro* (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 | *In vitro* (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 | *In vitro* (PD assay) | Silver nanoparticles extracted were highly effective on the six bacterial species tested | | Goga et al. (2021) |
| | | | Antioxidant | *In vitro* (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 | *In vitro* (agar disk diffusion, broth microdilution methods) | MeOH, EtOH, ACE and AQ extracts showed low antibacterial activity, but the MeOH extract demonstrated antifungal activity against *Candida albicans* (IZ: 12 mm) | Armenia | Sargsyan et al. (2021) |
| | | | Anticancer | *In vitro* (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 | *In vitro* (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 |
|---|---|---|---|---|---|---|---|
| | | | | | Olivetoric and physodic acids strongly augmented all antioxidant enzymes gene expressions in HepG2 cells | | |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay, molecular docking) | 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) |
| *Pseudoparmelia sphaerospora* (Nyl.) Hale (NA) | Parmeliaceae (Pseudoparmelia – 27 species) | Hypostictic acid | Anticancer | *In vitro* (human and murine cell culture – MTT, flow cytometry assays) and *in vivo* (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). *In vivo,* 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) |
| *Ramalina conduplicans* Ach. (Strap lichen) | Ramalinaceae (Ramalina – 246 species) | Usnic, salazinic, sekikaic, homosekikaic acids | Antioxidant | *In vitro* (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 | *In vitro* (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) |
| *Ramalina cuspidata* (Ach). Nyl (Strap lichen) | | Usnic acid | Anticancer | *In vitro* (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) |
| *Ramalina hossei* Vain. (Strap lichen) | | Usnic, sekikaic acids | Antimicrobial | *In vitro* (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) |
| *Ramalina pacifica* Asahina (Strap lichen) | | Usnic, salazinic acids | Antimicrobial | *In vitro* (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) |
| *Ramalina fastigiata* (Pers.) Ach. (Cartilage lichen) | | Atranorin, usnic, fumarprotocetraric, obtusatic, protocetraric acids | Anticancer | *In vitro* (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 | *In vitro* (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 | *In vitro* (broth microdilution method) | Methyl evernate showed the strongest antimicrobial properties with the least MIC value being 0.125 mg/ml | | |
| | | | Antioxidant | *In vitro* (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 | *In vitro* (agar well diffusion method) | ACE extract showed maximum activity against *K. pneumonia* with IZ of 2.1 mm. An IZ of 1.1 cm was seen for *Candida albicans* and 1.3 cm for *Candida krusei* at 100 μg/ml | | |
| *Ramalina fraxinea* (L.) Ach. (Bush lichen) | | | Anticancer | *In vitro* (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 |
|---|---|---|---|---|---|---|---|
| | | Atranorin, usnic, salazinic, sekikaic, obtusatic, protocetraric acids | | | ACE extract exhibited strong anticancer activities against tested cells ($IC_{50}$: 24.63–161.37 μg/ml) | | |
| | | | Antioxidant | *In vitro* (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 32.63 μg | | |
| | | | | Antimicrobial | *In vitro* (broth microdilution method) | | |
| Methyl evernate showed the strongest antimicrobial properties with the least MIC value being 0.125 mg/ml | | | | | | | |
| *Ramalina sinensis* Jatta (Burning bush lichen) | | Betulin, betulinic acid, nanoparticles | Antibacterial | *In vitro* (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 | Abdolmaleki and Sohrabi (2016) |
| | | | Antioxidant | *In vitro* (DPPH assay) | Demonstrated good antioxidant properties and was able to remove toxic free radicals | Iran | Nazari et al. (2018) |
| | | | Antibacterial | *In vitro* (agar well diffusion method) | 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 *S. aureus* and *P. aeruginosa*, respectively | Iran | Safarkar et al. (2020) |
| | | | Antimicrobial | *In vitro* (agar disc diffusion, broth microdilution methods) | MeOH and EtOH extracts showed the largest IZs (25 mm and 23 mm, respectively) against *Bacillus subtilis.* The MIC was between 0.9 and 1.8 mg/ml | Armenia | Sargsyan et al. (2021) |
| | | | Anticancer | *In vitro* (human cell culture – MTT assay) | The $IC_{50}$ values estimated for the MeOH extract in HeLa cell line was 1.75 mg/ml, and considered as non-cytotoxic | | |
| *Ramalina terebrata* Hook. & Taylor. (Strap lichen) | | Usnic acid, usimine A, B, C, ramalin | Antibacterial | *In vitro* (disk diffusion method) | MeOH extract and usnic acid showed antibacterial activity against *S. aureus* and *Bacillus subtilis.* MIC values against *Bacillus subtilis* were from 1.0 to 26.0 g/ml | South Korea | Paudel et al. (2010) |
| *Ramalina usnea* (L.) R. Howe (Cartilage lichen) | Usnic acid, 2-hydroxy-4-methoxy-6-propyl-methyl benzoate | Insecticidal | *In vitro* (*Aedes aegypti* – 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) | |
| *Stereocaulon alpinum* 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 | *In vitro* (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) |
| | | Lecanoric acid | Antioxidant | | | Korea | Luo et al. (2010a) |

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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 |
|---|---|---|---|---|---|---|---|
| *Sticta nylanderiana* Zahlbr. (Spotted felt lichen) | Peltigeraceae (Sticta - 114 species) | | | *In vitro* (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 | | |
| *Teloschistes flavicans* (Sw.) Norman (Golden hair lichen) | Teloschistaceae (Teloschistes - 8 species) | Vicanicin | Antidiabetic | *In vitro* (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) |
| *Thamnolia vermicularis* (Sw.) Schaer. (White worm lichen) | Icmadophilaceae (Thamnolia – 6 species) | Thamnolan, β-glucan | Immunomodulating | *In vitro* (Anticomplementary assay) | The polysaccharides isolated caused stimulation of rat spleen cells proliferation, induction to secrete IL-10 above background levels and stimulated TNF-a secretion by rat peritoneal macrophages | Iceland | Olafsdottir et al. (2003)<br>Omarsdottir et al. (2007) |
| *Umbilicaria esculenta* (Miyoshi) (Minks rock tripe lichen) | Umbilicariaceae (Umbilicaria – 65 species) | Constictic, lecanoric acids, laminaran, pustulan | Antithrombotic | *In vitro, ex vivo, in vivo* (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 | *In vitro* (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 | | Wang et al. (2019) |
| | | | | | Isolated metabolite promoted the phagocytic activity and production of NO in RAW 264.7 cells in a dose-dependent manner. It also significantly ($p \leq 0.05$) improved the proliferation effect of RAW 264.7 cells at 50 μg/ml | | Shi et al. (2021) |
| *Umbilicaria hirsuta* (Sw. ex Westr.) Hoffm. (Hairy navel lichen) | | Atranorin, parietin, usnic, gyrophoric acids | Anticancer | *In vitro* (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) |
| *Umbilicaria mammulata* (Ach.) Tuck. (Smooth rock tripe lichen) | | Glycophoric, constictic, lecanoric acids | Antibacterial | *In vitro* (Micro-well dilution method) | ACE extract was active against *P. aeruginosa* (MIC: 50 μg/ml) | USA | Shrestha et al. (2014) |
| *Umbilicaria muhlenbergii* (Ach.) Tuck. (Plated rock tripe lichen) | | Glycophoric, constictic, lecanoric acids | Anticancer | *In vitro* (human cell culture – MTT assay) | Good anticancer activity reported | USA/ Canada | Mohammadi (2021)<br>Mohammadi et al. (2022) |
| *Usnea antarctica* Du Rietz (Antartic shrub lichen) | Parmeliaceae (Usnea- over 600 species) | Usnic acid | Antibacterial | *In vitro* (broth microdilution method) | Antibacterial activity was demonstrated against S. aureus. The MIC was 94.76% at 31.25 μg/ml | Peru | Londoñe-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 |
|---|---|---|---|---|---|---|---|
| | | | Antioxidant | *In vitro* (ABTS method) | MeOH/ACE extract showed radical inhibition values of 9.05 μM | | |
| | | | Cytotoxic | *In vitro* (monkey kidney cell culture – MTT assay) | MeOH/ACE extract showed activity against Vero cell line achieving an $IC_{50}$ of 169.64 μg/ml | | |
| *Usnea articulata* L. (Hoffm) (Old man's beard) | | Usnic acid | Antibacterial | *In vitro* (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) |
| | | | | *In vitro* (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 | *In vitro* (monkey kidney cells - MTT assay) | MeOH extract was not cytotoxic ($IC_{50}$: 56.58–278.50 μg/ml) | | |
| *Usnea barbata* (L.) F. H.Wigg (Beard lichen) | | Usnic acid | Antimicrobial | *In vitro* (agar disc diffusion method) | 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 Bacillus subtilis and S. aureus, and some G-ve bacteria. The ACE extract had the highest fungal inhibitory activity ranging from 51.60% against Schizophyllum commune to 100% against Alternaria alternaria at 10 mg/ml | South Africa | Madamombe and Afolayan (2003) |
| | | | Antibacterial | *In vitro* (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 *Bacillus subtilis* and *Bacillus megaterium,* respectively | Turkey | Cansaran et al. (2006) |
| | | | Antibacterial | *In vitro* (agar gel diffusion, broth microdilution methods) | The MeOH and EA extracts showed variable antimicrobial activities against thirteen *S. aureus* 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 | *In vivo* (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 | *In vitro* (disc diffusion, DPPH, BSL assays) | AQ extract did not have any inhibitory activity on any pathogens (IZ = 0 mm). Gram + ve bacteria especially Enterococcus casseliflavus displayed the most sig. susceptibility (IZ: 20–22 mm) and the most susceptible Gram -ve bacterium was P. aeruginosa (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 |
|---|---|---|---|---|---|---|---|
| | | | | | Cytotoxicity was inversely proportional to the antioxidant effect | | |
| *Usnea ceratina* Ach. (Warty beard lichen) | | Ceratinalone, bailesidone, stictic, 8′-*O*-methylstictic, 8′-*O*-ethylstictic acids | Cytotoxic | *In vitro* (human cell culture - MTT assay) | Isolated compounds showed moderate cytotoxic activity against cell lines tested | Vietnam | Bui et al. (2022) |
| *Usnea florida* (L.) F.H. Wigg (Beard lichen) | | Usnic, thamnolic, evernic, physodic, 3-hydroxyphysodic acids, 5,7-dihydroxy-6-methylphtalide | Antibacterial | *In vitro* (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 *Bacillus subtilis* and *Bacillus megaterium,* respectively | Turkey | Cansaran et al. (2006) |
| | | | Antibacterial | *In vitro* (bioautography, broth microdilution method) | Antibacterial activity of usnic acid reported (MIC: 7.25 μg/ml) | France | Dieu et al. (2020) |
| | | | Antibacterial | *In vitro* (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 | *In vitro* (monkey kidney cells - MTT assay) | MeOH extract was not cytotoxic ($IC_{50}$: 56.58–278.50 μg/ml) | | |
| *Usnea ghattensis* G. Awasthi (Beard lichen) | | Usnic, stictic, constictic acids | Antimicrobial | *In vitro* (agar well diffusion, poisoned food methods) | Usnic acid isolated from MeOH extract inhibited test fungi and bacteria especially *K. pneumoniae* in a conc.- dependent manner (20 mg/ml caused IZ of 2.8 cm) | India | Mesta et al. (2016) |
| | | | Cytoprotective, antioxidant | *In vitro* (CNS-like cell culture – MTT, ORAC, DPPH assays) | Usnic acid isolated displayed moderate protection against $H_2O_2$-induced cytotoxic damage in both models | Spain | Fernández-Moriano et al. (2017b) |
| *Usnea longissima* Ach. (Methuselah's beard) | | Longissiminone A, B, glutinol | Anti-inflammatory, cytotoxic | *In vitro* (anti-inflammatory, MTT assays) | 200 μg/ml of Longissiminone A possesses potent anti-inflammatory activity and caused 100% cell viability | Pakistan | Choudhary and Jalil (2005) |
| | | | Antibacterial | *In vitro* (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 Bacillus subtilis and Bacillus megaterium, respectively | Turkey | Cansaran et al. (2006) |
| *Usnea rubicunda* Stirt. (Red beard lichen) | | Usnic acid | Anticancer | *In vitro* (murine and human cell culture – MTT assay) | HX fraction had $IC_{50}$ of 8.1 μg/ml. The highest SI was 10.8 for the DEE fraction | France | Bézivin et al. (2003) |
| *Usnea subcavata* (Motyka) (Beard lichen) | | Atranorin, usnic, diffractaic, lecanoric, protocetraric, salazinic, hypostictic, norstictic acids | Antimycobacterial | *In vitro* (*Mycobacterium tuberculosis* - microplate alamar blue assay) | Diffractaic acid was the most active metabolite (MIC:15.6 μg/ml, 41.6 μM), followed by norstictic acid (MIC: 62.5 μg/ml, 168 μM) and usnic acid (MIC: 62.5 μg/ml, 182 μM). Hypostictic acid (MIC: 94.0 μg/ml, 251 μM) and protocetraric acid (MIC:125 μg/ml, 334 μM) showed moderate inhibitory activities | Brazil | Honda et al. (2010) |
| *Usnea undulata* Stirt (Beard lichen) | | Usnic, galbinic, norstictic, salazinic acids | Antimicrobial | *In vitro* (agar well diffusion, poisoned food methods) | Usnic acid isolated from MeOH extract inhibited test fungi and bacteria especially *K. pneumoniae* in a conc.- dependent manner (20 mg/ml caused IZ of 2.5 cm) | India | Mesta et al. (2016) |
| *Vulpicida canadensis* (Rasanen) J.-E. Mattsson & M. J. Lai. (Brown-eyed sunshine lichen) | Parmeliaceae (Vulpicida- 6 species) | Pulvinic, vulpinic, usnic acids | Antioxidant | *In vitro* (ORAC, DPPH assays) | Lichen extract reversed oxidative damage caused by $H_2O_2$, thus promoting astrocyte survival | Spain | Fernández-Moriano et al. (2015b) |
| | | | Anticancer | *In vitro* (human cell culture - MTT assay) | Extract had anticancer activity, with $IC_{50}$ values of 19.51–181.05 μg/ml | | |
| *Xanthoparmelia plitti* (Gyelnik) Hale | | Usnic acid, nanoparticles | Antibacterial | *In vitro* (agar gel diffusion method) | MeOH extract showed weak antibacterial activity | Cameroon | Bate et al. (2020) |

(*continued on next page*)

**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 | *In vitro* (cell culture – MTT assay) | The $IC_{50}$ of the MeOH extract was >30 μg/ml, the cut point for lack of cytotoxicity | | |
| *Xanthoria parietina* (L.) Beltr. (Common orange lichen) | Teloschistaceae (Xanthoria - 20 species) | Parietin | Antiproliferative | *In vitro* (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 | Italy | Basile et al. (2015) |
| | | | Antimicrobial | *In vitro* (broth microdilution method) | ACE extract inhibited all the tested microorganisms at conc. of 7.8–62.5 μμg/ml. Parietin likewise displayed a robust antibacterial activity, with MICs ranging from 7.8 to 62.5 μg/ml | | |

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, LC – Lethal 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, 5-diphenyl-2H-tetrazolium bromide, SEM - Scanning Electron Microscopy, TEM - Transmission 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, $H_2O_2$ - 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.

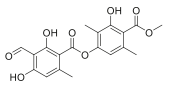
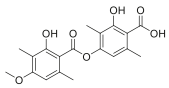
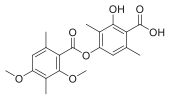
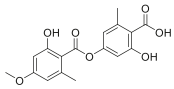
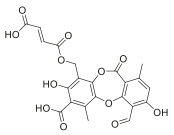
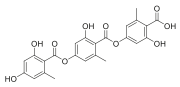
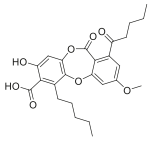
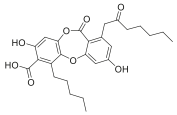
## 5. Recommendations for further research

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.

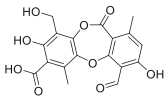
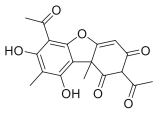
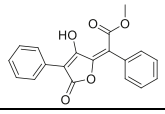
Improved *in vitro* culture techniques could be developed for lichen species with a high commercial value and demand. This would help with

**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-dimethyl-phenyl ester] | Depside | $C_{19}H_{18}O_8$<br>374.34<br>  | Cladonia kalbii Anti.<br>*Heterodermia* species<br>*Everniastrum vexans* (W. L. Culb. & C.F. Culb.) Sipman *Parmotrema praesorediosum* (Nyl.) Hale<br>*Lepraria jackii* Tonsberg | Antioxidant (100 μg/ml), anti-inflammatory, (17 μg/ml), anti-cancer (5.36 ± 0.85 μM), wound healing modulation, DNA-interacting agent, anticancer | Bačkorová et al., 2012<br>Barreto et al. (2013)<br>Plsíkova et al., 2014<br>Zhou et al. (2017)<br>Studzinska-Sroka et al. (2017)<br>Studzinska-Sroka and Dubina (2018)<br>Harikrishnan et al., 2021 |
| Barbatic acid [2-hydroxy-4-(2-hydroxy-4-methoxy-3,6-dimethylbenzoyl)oxy-3,6-dimethylbenzoic acid] | Depside | $C_{19}H_{20}O_7$<br>360.36<br>  | *Cladia aggregate* (Sw.) Nyl<br>*Cladonia cristatella* Tuck.<br>*Lecanora chrysoleuca* (Sm.) Ach. | Antibacterial against *S. aureus* (MIC: 50 μg/ml) | Martins et al. (2010) |
| Diffractaic acid [4-[(2,4-Dimethoxy-3,6-dimethylbenzoyl)oxy]-2-hydroxy-3,6-dimethylbenzoic acid] | Depside | $C_{20}H_{22}O_7$<br>374.38<br>  | Usnea diffracta Vainio<br>Usnea longissimi Ach.<br>*Parmelia nepalensis* Taylor<br>*Parmelia tinctorum* 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)<br>Kumar and Muller, 1999<br>Bayir et al. (2006)<br>Honda et al. (2010)<br>Odabasoglu et al. (2012)<br>Karagoz et al. (2015) |
| Evernic acid [2-hydroxy-4-(2-hydroxy-4-methoxy-6-methylbenzoyl)oxy-6-methylbenzoic acid] | Depside | $C_{17}H_{16}O_7$<br>332.09<br>  | *Evernia* species<br>Ramalina species<br>Hypogymnia species | Antifungal, antioxidant, anti-inflammatory, neuroprotective | Halama and Van Haluwin (2004)<br>Gökalsın and Sesal, 2016<br>Ahamed et al. (2019)<br>Lee et al. (2021)<br>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] | ß-orcinol depsidone | $C_{22}H_{16}O_{12}$<br>472.36<br>  | *Cladonia rangiformis* Hoffm.<br>*Cladonia foliacea* (Huds) Willd.<br>*Cladonia verticullaris* P. Browne<br>*Cetraria islandica* (L.) Ach. | Cytoprotective, expectorant, antioxidant (50 mg/kg), antimicrobial (0.33 mM) | Yılmaz et al., 2004 de Barros Alves et al., 2014<br>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 | $C_{24}H_{20}O_{10}$<br>468.41<br>  | *Xanthoparmelia porkonyi* 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 | $C_{25}H_{28}O_8$<br>456.49<br>  | *Stereocaulon* species | Anti-oxidant (97.9 μmol), antiproliferative (15.2–63.9 μg/ml), enzyme inhibitory (0.87 μM) | Haraldsdóttir et al. (2004)<br>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 | $C_{26}H_{30}O_8$<br>470.51<br>  | | 175.8 μM | Sahin et al. (2021) |
| Protocetraric acid [10-formyl-3,9-dihydroxy-4-(hydroxymethyl)-1,7- | Depsidone | $C_{18}H_{14}O_9$<br>374.30 | *Usnea albopunctata*<br>*Cetraria islandica* (L.) | Antibacterial (0.5 μg/ml), antifungal (1 μg/ml), anticancer | Brandão et al., 2012<br>Nishanth et al. (2015) |

(*continued on next page*)

**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. *Cetraria ericetorum* Opiz | | |
| Thamnolan (NA) | Heteroglycan | Has not been adequately described | *Thamnolia* species | Immunomodulatory | Omarsdottir et al. (2007) |
| Usnic acid [2,6-Diacetyl-7,9-dihydroxy-8,9 b-dimethyldibenzo [*b*,*d*]furan-1,3(2*H*,9b*H*)-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 | Ingolfsdottir (2002) Verma et al. (2012) Bačkorová et al., 2012 Brisdelli et al., 2013 Maulidiyah et al. (2020) |
| Vulpinic acid [Methyl (2*E*)-2-(5-hydroxy-3-oxo-4-phenylfuran-2-ylidene)-2-phenylacetate] | Dibenzofuran (butenolide) | $C_{19}H_{14}O_5$ 322.32  | *Cladonia* 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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