Lichen Depsidones with Biological Interest

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ABSTRACT

Depsidones are some of the most abundant secondary metabolites produced by lichens. These compounds have aroused great pharmacological interest due to their activities as antioxidants, antimicrobial, and cytotoxic agents. Hence, this paper aims to provide up-to-date knowledge including an overview of the potential biological interest of lichen depsidones. So far, the most studied depsidones are fumarprotocetraric acid, lobaric acid, norstictic acid, physodic acid, salazinic acid, and stictic acid. Their pharmacological activities have been mainly investigated in *in vitro* studies and, to a lesser extent, in *in vivo* studies. No clinical trials have been performed yet. Depsidones are promising cytotoxic agents that act against different cell lines of animal and human origin. Moreover, these compounds have shown antimicrobial activity against both Gram-positive and Gram-negative bacteria and fungi, mainly *Candida* spp. Furthermore, depsidones have antioxidant properties as revealed in oxidative stress *in vitro* and *in vivo* models. Future research should be focused on further investigating the mechanism of action of depsidones and in evaluating new potential actions as well as other depsidones that have not been studied yet from a pharmacological perspective. Likewise, more *in vivo* studies are prerequisite, and clinical trials for the most promising depsidones are encouraged.

Introduction

Lichens are a unique symbiosis between a fungus belonging to Ascomycota and Basidiomycota phylum (mycobiont) and a chlorophyll-containing partner (photobiont), which is an alga or a cyanobacterium. Moreover, recent studies have identified specific bacterial microbiomes as the third component of lichen [1, 2]. Lichens have been traditionally used for their medicinal value as healing (i.e., *Heterodermia diademata* [Taylor] D.D. Awasthi) and cold (i.e., *Everniastrum cirrhatum* [Fr.] Hale ex Sipman.), for their culinary value for preparing tea, curry, soup, pickle, and sausages (i.e., *Everniastrum nepalense* [Taylor] Hale ex Sipman; *Cladonia rangiferina* [L.] Weber ex F.H. Wigg.), and for their ritual, spiritual, and aesthetic values (i.e., *Thamnolia vermicularis* [Sw.] Ach. ex Schaer.) [3–5].

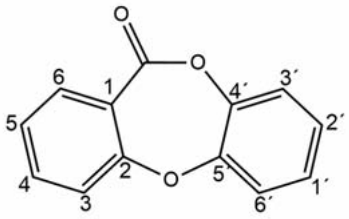
Lichens produce unique and diverse secondary metabolites. So far, over 1000 compounds have been identified, including depsidones, depsides, dibenzofurans, and xanthones, which are synthesized via the acetate-malonate pathway, pulvinic acid derivatives formed in the shikimic acid pathway, and terpenes and steroids via the mevalonic acid pathway. The amount of these secondary metabolites may vary from 0.1% to 30% of the dry weight of the thallus, and they are deposited in both the cortex and the medullary layers. Hence, depsides and dibenzofurans, such as usnic acid (major) and atranorin (trace) in *Flavoparmelia caperata* L. (Hale) and atranorin and chloroatranorin in *Hypogymnia physodes* (L.) Nyl., are found in the cortex, whereas depsidones, such as physodic acid, 3-hydroxyphysodic acid, and physodalic acid as major compounds in *H. physodes* (L.) Nyl., norstictic acid in *Parmotrema perforatum* (Jacq.) A. Massal., and salazinic acid (major) and consalazinic acids (minor) in *Parmelia saxatilis* (L.) Ach., are found in the medullary layer [6–9]. These secondary metabolites play a key role in chemotaxonomy and systematics [6]. Moreover, they exert diverse biological functions including protection against

ABBREVIATIONS

8-OH-dG	8-Oxo-2′-deoxyguanosine
Axin2	axis inhibition protein 2
Bax	Bcl-2 associated X-protein
Bcl-2	B-cell lymphoma 2
BDNF	brain-derived neurotrophic factor
COX	cyclooxygenase
DPPH	2,2-diphenyl-1-picrilhidrazil
FabZ	3-hydroxyacyl-[acyl-carrier-protein] dehydratase
FAS	fatty acid biosynthesis
GSH	reduced glutathione
HGF	hepatocyte growth factor
Hsp70	70 kD heat shock proteins
HSV	herpes simplex virus
IL-1	interleukin-1
JAK/STAT	janus kinase/signal transducers and activators of transcription
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinases
MIC	minimum inhibitory concentration
MMP7	matrix metalloproteinase-7
MPP1	M-Phase Phosphoprotein 1
MRSA	methicillin-resistant *Staphylococcus aureus*
NF-κβ	nuclear Factor kappa-light-chain-enhancer of activated B cells
NGF	nerve growth factor
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
NOS	nitric oxide synthase
Nrf2	nuclear factor E2-related factor 2
nsP1	nonstructural protein 1
ORAC	oxygen radical absorbance capacity
PAR2	proteinase-activated receptor-2
PARP	poly (ADP-ribose) polymerase
PF-UVA	protection Factor-ultraviolet A
PI3K	phosphatidylinositol 3-kinase
PKS	polyketide synthase
Plk1	polo-like kinase-1
PTP1B	protein tyrosine phosphatase 1B
RNS	reactive nitrogen species
ROS	reactive oxygen species
SLIGKV-NH_2	Ser-Leu-Ile-Gly-Lys-Val-amide
SOR	scavenging superoxide radicals
TNF-α	tumor necrosis factor- α
TRAIL	TNF-related apoptosis-inducing ligand
Trp-P-2	tryptophan pyrolysis product-2

pathogens, herbivores, and UV irradiation [7]. Furthermore, these secondary metabolites of lichens arouse great pharmacological interest due to their activities, mainly as antioxidants, antimicrobials, and cytotoxic agents [10–12].

Some of the most abundant groups of secondary metabolites in lichens are depsidones (around 100) [13]. Structurally, depsidones consist of a polycyclic system linked through an ether group and an ester group, giving the rigid 11H-dibenzo[b,e][1,4] dioxepin-11-one ring (▶ **Fig. 1**) [14–16]. The biosynthesis of depsidones occurs via the acetate-malonate pathway, with acetyl-Coenzyme A as the precursor and PKS as the responsible enzyme (▶ **Fig. 2**) [17]. Several bioactive depsidones such as stictic acid, salazinic acid, and psomoric acid have been identified [18–20]. The chemical structures of different depsidones of lichens are depicted in ▶ **Fig. 3**.



▶ **Fig. 1** General structure of depsidones.

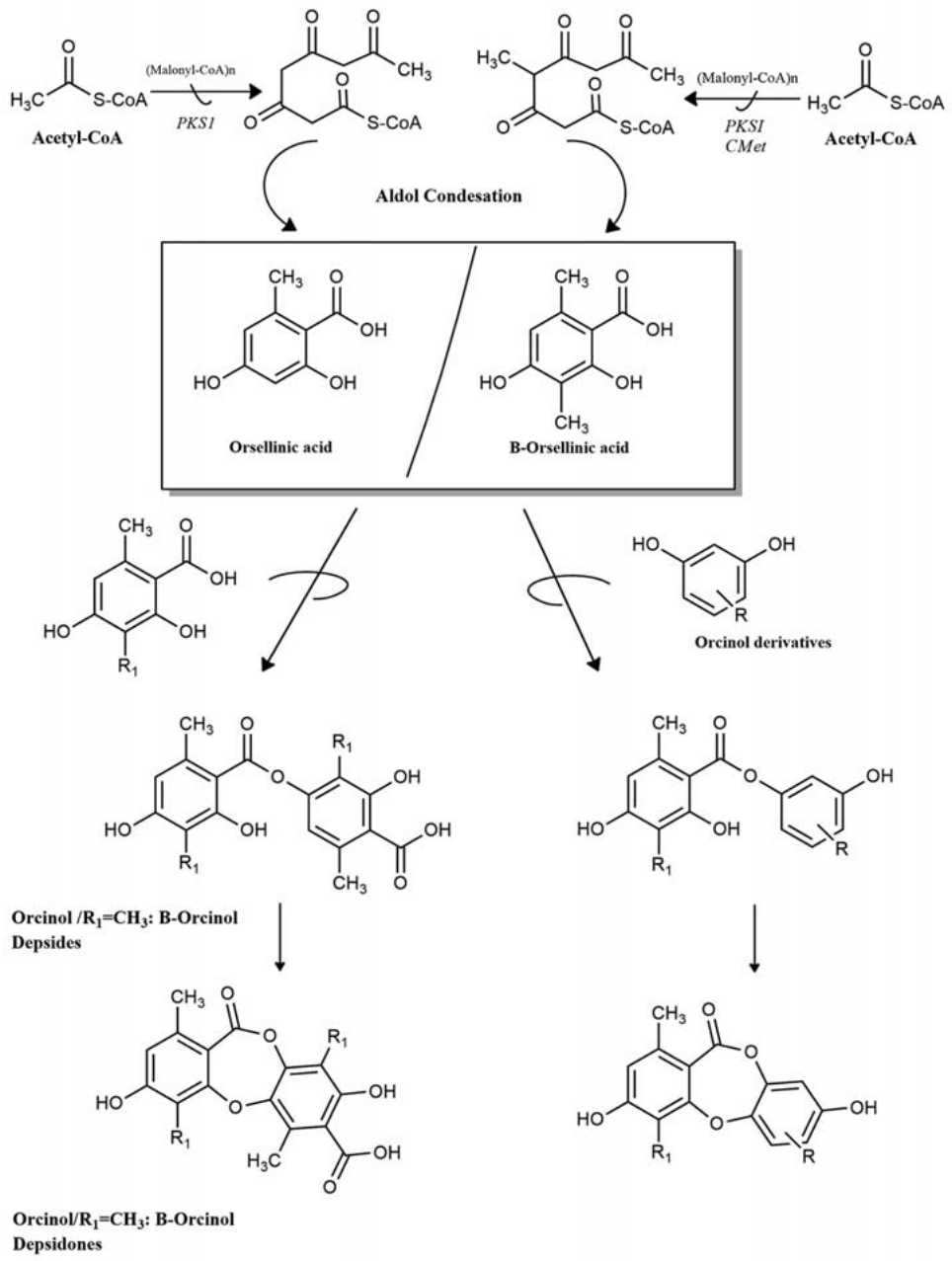
This paper aims to provide up-to-date knowledge and an overview of the biological interest of lichen depsidones. This review includes pharmacological information for those depsidones that have been investigated with potential bioactivity. Original papers published in English in PubMed/Medline and Scholar Google without date restriction were included. Those articles with lichen extracts rich in depsidones were excluded from this review. It is important to emphasize that more depsidones have been identified, such as notatic acid, nortotatic acid, and diploicin, but their pharmacological activities have not been investigated yet.

Chemistry and Biochemical Origin

The depsidones and the majority of other secondary metabolites in lichens are produced by lichen-forming fungi and are deposited on the outer surface of the hyphal cell walls in the medullary layer of the lichen thallus (▶ **Fig. 4**) [21]. The interactions between the mycobiont and photobiont affect the production of secondary metabolites in lichens. For example, several studies have shown that mycobionts within the lichen thallus produce a variety of secondary metabolites in contrast with axenic mycobiont cultures [22–24]. The production of secondary metabolites in the lichen thallus has also been found to be affected by environmental factors (i.e., UV-radiation, climatic conditions, habitats, and presence of non-photosynthetic bacteria and other fungi in lichen thallus) [25–30].

Depsidones consist of 2 or rarely 3 aromatic rings joined by ester linkages and an ether linkage between the rings. The rings are based on the structure of orsellinic acid. Depsidones are grouped in an orcinol or B-orcinol series, depending on the presence of a CH_3 on the C3 carbon of their rings (▶ **Fig. 1**) [31–33].

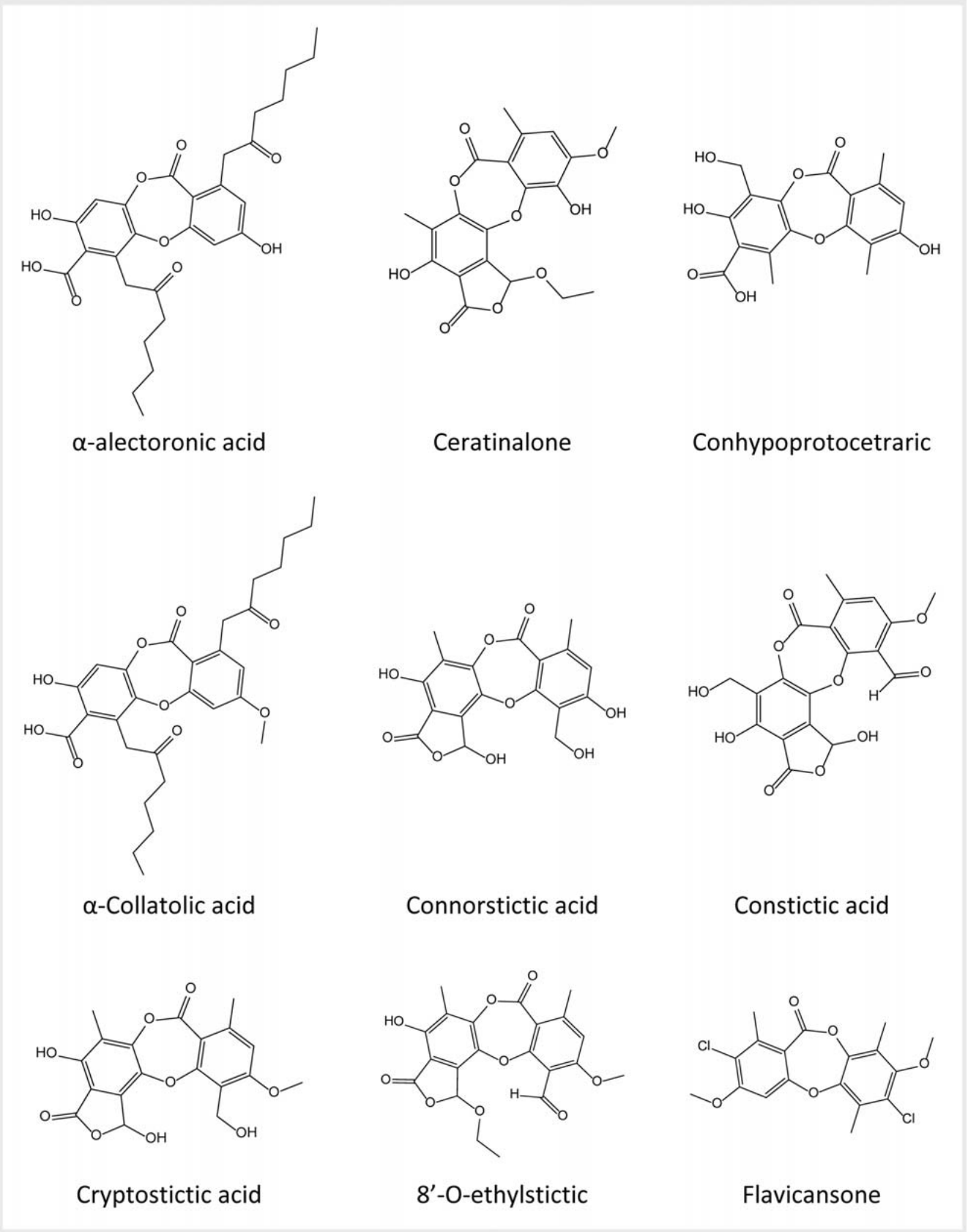
Acetate and malonate units are condensed to form orsellinic acid or B-orsellinic acid that is a precursor for the biosynthesis of several secondary metabolites in lichens and fungi in general (▶ **Fig. 2**). Depsides are produced by the condensation of 2 or



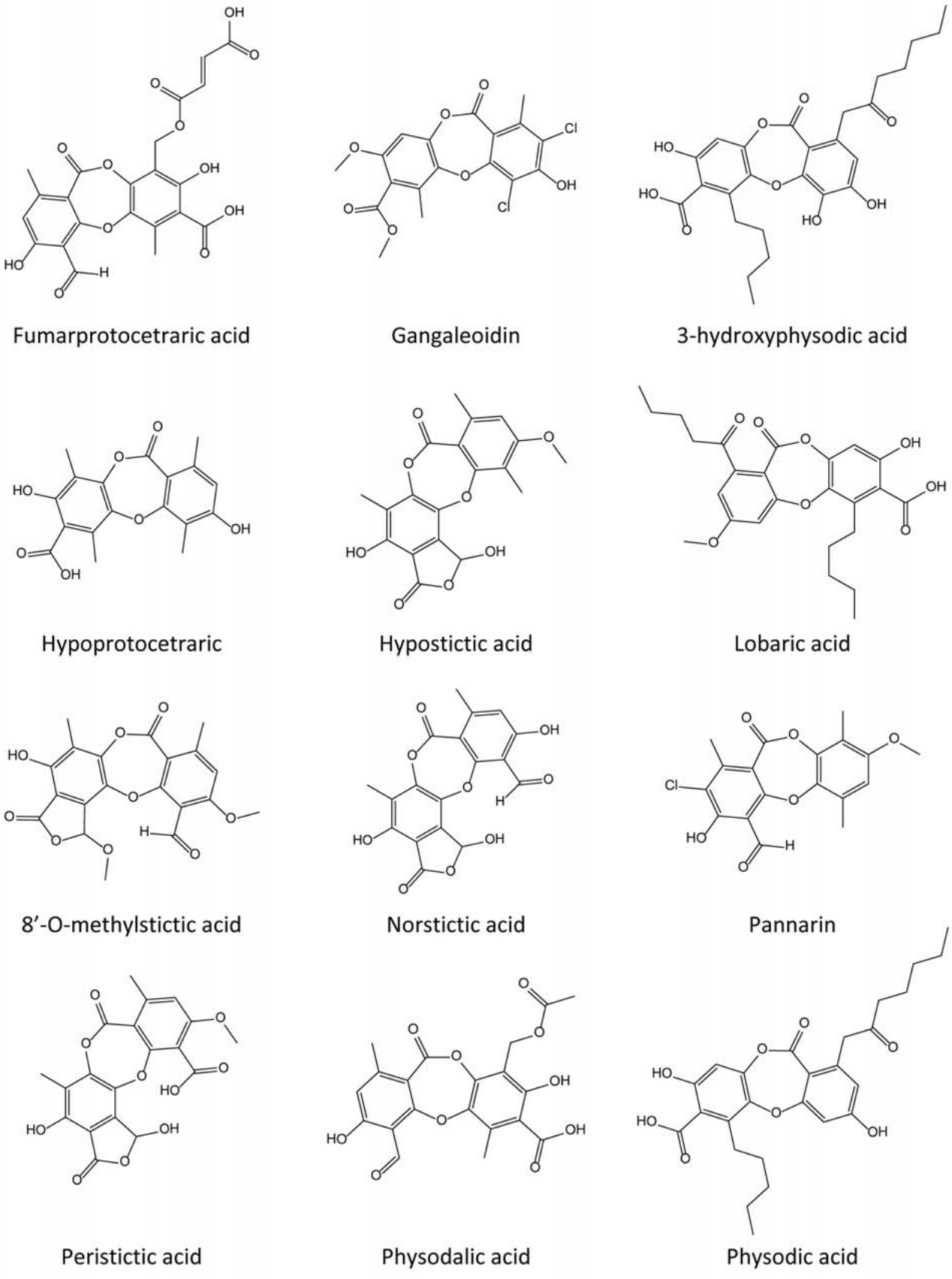
▶ **Fig. 2** Biosynthesis of depsidones.

more hydroxybenzoic acids through which the carboxyl group of 1 molecule is esterified with a phenolic hydroxyl group of a second molecule. Depsides are precursors for the biosynthesis of depsidones [34]. It is widely accepted that the depsidones are formed from depsides by a loss of hydrogen in an oxidative cyclization process (▶ **Fig. 2**) [35, 36]. Several depside-depsidone pairs are found in lichens, for example, *Pseudevernia furfuracea* contains the depside-depsidone pair (i.e., olivetoric acid and physodic acid) [37]. O-methylation (methylation of oxygen) is a common process and the cause of chemical variation in depsidones in lichens [36]. However, from chemical synthesis producing high yields of several depsidones, it is proposed that depsidones are biosynthesized in 4 steps: by hydroxylation, acyl group migration, Smiles rearrangement, and esterification [38].

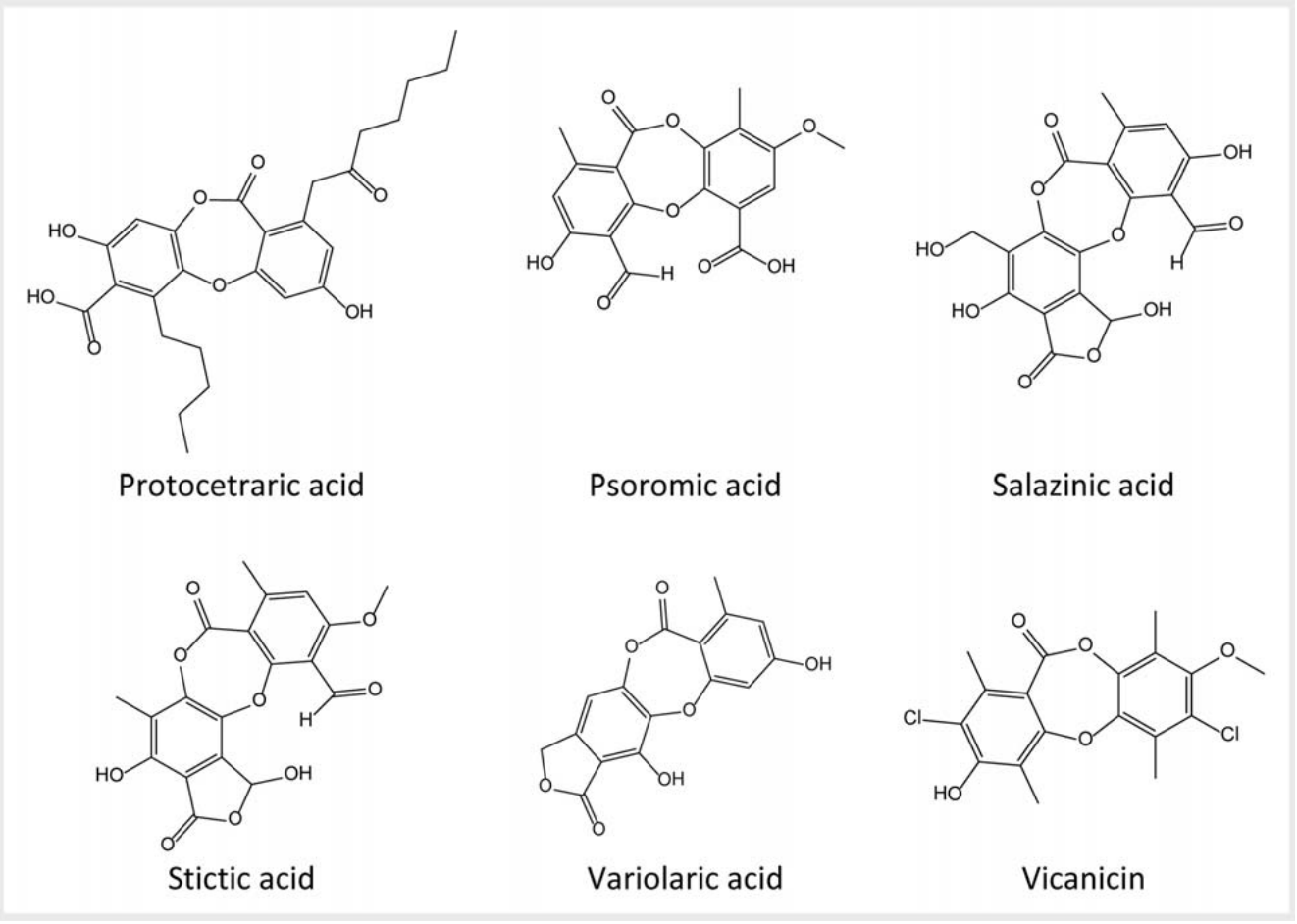
Both the depside and depsidones are products of a nonreducing PKS encoded in the genome of the mycobiont [26, 39]. Therefore, the phylogenetic studies of PKS domains, sequencing of complete PKS gene clusters, and the availability of whole-genome sequence data have enabled a more detailed study of the biosynthetic origin of the nonreducing polyketides in lichens [40–44].



▶ **Fig. 3** Chemical structure of different depsidones of lichens. *continued*



▶ **Fig. 3** *Continued*



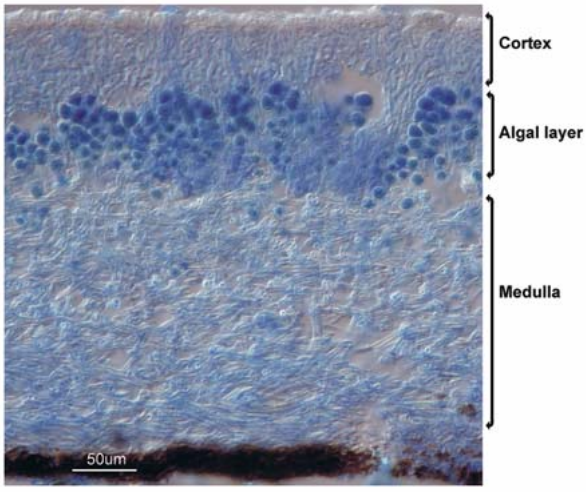
▶ **Fig. 3** *Continued*

Molecular Mechanism of Action of Lichen Depsidones

Little is known about the molecular mechanisms through which depsidones exhibit their activities. This review presents some examples; however, further studies are needed to elucidate the diverse properties of this group of secondary metabolites in lichens.

One of the most investigated activities in lichens is their antioxidant activity. Depsidones have been demonstrated to act as antioxidants by directly scavenging ROS and RNS and by modulating redox enzyme activity and expression (i.e., superoxide dismutase and catalase) and transcription factors expression (i.e., Nrf2) [45]. Depsidones can incorporate into cellular lipid microdomains that make them more efficient as antioxidants than other lichen secondary metabolites [46].

Depsidones have also shown cytotoxic activity against diverse cancer cell lines (i.e., melanoma, breast, and colon). These bioactive compounds exert cytotoxic effects through diverse signaling pathways. Hence, depsidones can attenuate cell tumor growth by acting as selective inhibitors of Plk1 activity. Plk1 is a serine/threonine kinase that is overexpressed in human tumors, and it is related to invasive potential and lower cancer-related survival [47]. In addition, depsidones also directly target antiapoptotic Bcl-2



▶ **Fig. 4** Cross-section of lichen thallus showing cortical and medullary hyphae.

family proteins [48]. High expression of antiapoptotic Bcl-2 family proteins (i.e., Bcl-2) contributes to the expansion of malignant cells and reduces the therapeutic efficacy of cytotoxic drugs [49]. Moreover, these secondary metabolites are promising cytotoxic agents via oxidative stress induction; the overproduction of ROS disrupts redox homeostasis and leads to severe structural and functional injury in cancer cells [50]. Furthermore, depsidones inhibit lipoxygenases, which are involved in cell viability and proliferation, and migration, invasion, and metastasis of cancer cells [51]. Besides, depsidones can suppress carcinomas by targeting the HGF-c-Met signaling pathway [52]. c-Met is a receptor tyrosine kinase, and HGF is the ligand for this receptor. Dysregulation of the HGF-c-Met signaling pathway promotes tumor progression and metastasis by stimulating different signaling pathways as JAK/STAT and PI3K/AKT [53]. Finally, other depsidones act as cytotoxic agents by targeting the aberrant Wnt/β-catenin signaling [20].

Depsidones have also antimicrobial properties against Gram-positive bacteria, Gram-negative bacteria, and fungi. Particularly, some depsidones are RecA inhibitors, which potentiate bactericidal activity and reduce antibiotic resistance [54]. Moreover, depsidones have also targeted the β-hydroxyacyl-acyl carrier protein FabZ of the bacterial system for FAS [55]. Furthermore, depsidones have proven to be promising antiviral agents against alphaviruses via nsP1 GTP binding and guanylation inhibition. These RNA viruses need a 5′cap structure in whose formation viral protein nsP1 participates and which is necessary to avoid viral RNA degradation [56].

Other depsidones are reported for pharmacological inhibition of protein tyrosine phosphatase 1B (involved in insulin resistance) [57]. Moreover, these compounds act in other signal transduction pathways such as epidermal growth factor receptor, integrin signaling pathways, and cell cycle regulation [58]. Furthermore, they have anti-inflammatory properties by inhibiting cytokine expression and NO production through NF-κB/MAPK and inflammasome NLRP3 pathways [59, 60].

Pharmacological Activity of Lichen Depsidones

Pharmacological activities of lichen depsidones are summarized in ▶ **Table 1**.

Alectoronic acid

Alectoronic acid has been shown to have cytotoxic activity against the B16 murine melanoma cell line. It reduced cancer cell viability with a higher potency than the reference compound cisplatin (IC_{50} of 10.3 µM for alectoronic acid and IC_{50} of 30.3 µM for cisplatin) [61].

Collatolic acid

Collatolic acid showed antimicrobial properties against methicillin-resistant clinical isolates strains of *Staphylococcus aureus* with an MIC_{90} value of 128 µg/mL. Moreover, combinations of collatolic acid and gentamicin led to a synergistic antimicrobial effect, whereas antagonism occurred when collatolic acid and levofloxacin were associated [62]. Additional antimicrobial action against *Escherichia coli* RecA protein has been reported for collatolic acid. This compound exhibited a percentage of RecA inhibition of 103.4%, and it acted as a noncompetitive inhibitor for ATP binding site [63].

Fumarprotocetraric acid

Fumarprotocetraric acid has been mainly investigated for its antimicrobial properties. Hence, this compound showed antimicrobial action against Gram-positive bacteria (especially *Bacillus cereus* and *Bacillus subtilis* with MIC values of 4.6 µg/mL), Gram-negative bacteria (especially, *Listeria monocytogenes* with MIC value of 4.6 µg/mL), and fungi (*Candida albicans* and *Candida glabrata* with MIC values of 18.7 µg/mL) in the disk diffusion method [64]. In another study, this depsidone was more active against bacteria than fungi, and its action against *Klebsiella pneumoniae* (MIC value of 0.031 mg/mL) was particularly remarkable [65]. However, fumarprotocetraric acid has resulted to be ineffective towards MRSA strains [66]. Apart from its antibacterial activity, fumarprotocetraric acid showed antitrypanosomal activity against *Trypanosoma brucei brucei* [67].

In addition to antimicrobial properties, fumarprotocetraric acid is a promising antioxidant compound. The neuroprotection exerted in neuroblastoma and astrocytoma cell lines by fumarprotocetraric acid has been related to its ability to reduce ROS formation, lipid peroxidation, and GSH depletion [68]. Moreover, fumarprotocetraric acid demonstrated *in vivo* expectorant and antioxidant properties in an albino Swiss mice model at 25 and 50 mg/kg as evidenced in an increase of excretions and a reduction of lipid peroxidation in lung tissue [69].

Finally, fumarprotocetraric acid did not show photoprotective properties (SPF value [1.91] and PF-UVA value [1.75]) [70].

3-Hydroxyphysodic acid

This compound induced cytotoxicity against rat thymocytes and diminished their proliferation via antioxidant/oxidant imbalance [71]. In addition, 3-hydroxyphysodic showed antimicrobial activities. It acted as a larvicidal agent against second and third instar larvae of the mosquito *Culiseta longiareolata* (LC_{50} values 0.97 ppm) as well as antibacterial and antifungal agent with MIC values from 0.08 to 2.57 mM against *B. cereus, E. coli, L. monocytogenes, Salmonella typhimurium, S. aureus*, and *C. albicans* [72, 73].

Lobaric acid

The *in vitro* cytotoxic activity of lobaric acid has been tested in many different cancer cell lines such as human breast adenocarcinoma MCF-7 cells, human colon carcinoma HCT-116 cells, and human malignant glioma U87MG cells [48, 50, 74–77]. Lobaric acid effectively reduced cancer cell viability and proliferation, targeting the anti-apoptotic Bcl-2 protein and the cleaved form of the PARP [48]. This depsidone also exerted cytotoxic action via oxidative stress induction as evidenced in high levels of 8-OH-dG (DNA damage) [50]. Further, lobaric acid reduced cancer cell growth through the inhibition of 5-lipoxygenase and 12-lipoxygenase [74, 75, 77]. Furthermore, this compound inhibited the polymerization of tubulin in a concentration-dependent manner, and this activity is structurally related to hydroxyl groups at C-1′ and C-2′ and carboxylic acid [78]. Finally, lobaric acid also inhibited mitochondrial thioredoxin reductase in rat lungs [79].

▶ **Table 1** Pharmacological activity of lichen depsidones.

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
α-Alectoronic acid	*Ochrolechia parella* (L.) Massal	*In vitro*	Mouse melanoma B16 cell line	Cytotoxic	Cytotoxic activity (IC_{50} = 10.3 µM)	[61]
Ceratinalone	*Usnea ceratina* Ach.	*In vitro*	Human epithelial carcinoma HeLa, Human lung cancer NCI-H46, Liver hepatocellular carcinoma HepG2, Human breast cancer MCF-7 cell lines	Cytotoxic	Moderate activity	[133]
α-Collatolic acid	*Lecanora atra* (Huds.) Ach.	*In vitro*	*Escherichia coli* RecA protein	Antimicrobial	High RecA inhibition (103.4 %) Uncompetitive inhibitors for ATP binding	[63]
	Lecanora atra (Huds.) Ach.	*In vitro*	Methicillin-resistant *S. aureus* strains	Antimicrobial	Antimicrobial activity (MIC_{90} = 128 µg/mL) Synergism with gentamicin	[62]
Conhypoprotocetraric acid	*Ramalina* genus	*In silico*	Computational studies	Antioxidant	Hydroxyl and superoxide anion radical scavengers in polar environments	[131]
Connorstitic acid	*Ramalina* genus	*In silico*	Computational studies	Antioxidant	Hydroxyl and superoxide anion radical scavengers in polar environments	[131]
Cryptostictic acid	*Ramalina* genus	*In silico*	Computational studies	Antioxidant	Hydroxyl and superoxide anion radical scavengers in polar environments	[131]
Deoxystictic acid	*Hypotrachyna revoluta* (Flörke) Hale.	*In vitro*	Radical scavenging activity	Antioxidant	↑ scavenger (13.176 Trolox equivalents)	[126]
8′-O-ethylstictic	*Usnea ceratina* Ach.	*In vitro*	Human epithelial carcinoma HeLa cell line Human lung cancer NCI-H460 cell line Hepatocellular carcinoma HepG2 cell line Human breast cancer MCF-7 cell line	Cytotoxic	Moderate cytotoxicity against all cancer lines	[133]
Flavicansone	*Teloschistes flavicans* (Sw.) Norman.	*In vitro*	Human promyelocytic leukemia HL 60 cell line	Cytotoxic	Moderate activity (IC_{50} value of 58.18 µM)	[130]
Fumarprotocetraric acid	*Cetraria islandica* (L.) Ach.	*In vitro*	*T. brucei brucei*	Antimicrobial	Antitrypanosomal activity	[67]
	–	*In vitro*	Methicillin-resistant *S. aureus* strains	Antimicrobial	No activity	[66]
	Cladonia foliacea (Huds.) Willd.	*In vitro*	Gram-positve bacteria: *B. cereus*, *B. subtilis*, *S. aureus*, *S. faecali* Gram-negative bacteria: *P. vulgaris*, *L. monocytogenes*, *A. hydrophila* Fungi: *C. albicans*, *C. glabrata*	Antimicrobial	Antimicrobial activity against all microorganisms	[64]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	Cladonia furcata (Hudson) Schrade	*In vitro*	Gram-positve bacteria: *B. mycoides*, *B. subtilis*, *S. aureus* Gram-negative bacteria: *E. cloaceae*, *E. coli*, *K. pneumoniae* Fungi: *A. flavus*, *A. fumigatu*, *B. cinerea*, *C. albicans*, *F. oxysporum*, *M. mucedo*, *P. variotii*, *P. purpurescens*, *P. verrucosum*, *T. harsianum*	Antimicrobial	More activity against bacteria than fungi The lowest MIC value (0.031 mg/mL) against *K. pneumoniae*	[65]
	Cetraria islandica (L.) Ach.	*In vitro*	Human neuroblastoma SH-SY5Y cell line Human U373 MG astrocytoma cell line Hydrogen peroxide-induced oxidative stress model	Antioxidant	↑ Cell viability ↓ ROS formation, lipid peroxidation, and GSH depletion ↓ Apoptosis, ↓ caspase-3 activity, and expression; ↓ Bax and ↑ Bcl-2 proteins levels ↑ CAT, SOD-1, and HO-1 expression	[68]
	Cladonia verticillaris (Raddi) Fr.	*In vivo*	Albino Swiss mice	Antioxidant Expectorant	↑ Expectorant activity ↓ Lipid peroxidation	[69]
	Lasallia pustulata (L.) Mérat	*In vitro*	Sun protection factor (SPF) protection Factor-UVA (PF-UVA)	Photoprotection	SPF value: 1.91 (commercial filters ranged 3.91 to 11.16) PF-UVA value: 1.75. Commercial filter: 2.76	[70]
Gangaleoidin	*Ramalina* genus	*In silico*	Computational studies	Antioxidant	Hydroxyl and superoxide anion radical scavengers in polar environments	[131]
3-Hydroxyphysodic acid	*Hypogymnia tubulosa* (Schaer.) Hav.	*In vitro*	Second and third instar larvae of the mosquito *Culiseta longiareolata*	Antimicrobial	Larvicidal activity (LC_{50} values 0.97 ppm)	[72]
	Hypogymnia tubulosa (Schaerer) Hav.	*In vitro*	Gram-positive bacteria: *Bacillus cereus*, *Staphylococcus aureus* Gram-negative bacteria: *Escherichia coli*, *Salmonella typhimurium* Fungi: *Candida albicans*	Antimicrobial	MIC values from 0.08 to 2.57 mM	[73]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Rat thymocytes	Cytotoxic	↑ cytotoxicity ↓ proliferation No effects on MMP and ROSA	[71]
Hypoprotocetraric	*Ramalina* genus	*In silico*	Computational studies	Antioxidant	Hydroxyl and superoxide anion radical scavengers in polar environments	[131]
Hypostictic acid	*Pseudoparmelia sphaerospora* (Nyl.) Hale.	*In vitro*	*M. tuberculosis*	Antimicrobial	Antitubercular activity Moderate inhibitory activity (MIC = 94.0 µg/mL)	[93]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
Lobaric acid	*Stereocaulon alpinum* Laurer	*In vitro*	Human breast adenocarcinoma MCF-7 Human cervix adenocarcinoma HeLa Human colon carcinoma HCT-116 cell lines	Cytotoxic	↓ HeLa and HCT-116 cell viability	[76]
	Stereocaulon alpinum Laurer	*In vitro*	Peripheral venous blood	Cytotoxic	Potent 12(S)-LOX inhibitor (93.4%)	[75]
	Usnea longissima Ach.	*In vitro*	Papillary renal cell carcinoma cell line Human malignant glioma U87MG cell line	Cytotoxic	↑ LDH and 8-oxo-dG levels PRCC cells (IC_{50} = 9.08 mg/L) U87MG (IC_{50} = 5.77 mg/L)	[50]
	Stereocaulon alpinum Laurer	*In vitro*	Pancreas cell cancer (Capan-1, Capan-2) Breast cell cancer (T47-D) Prostate cell cancer (PC-3) Lung cell cancer (NCI-H1417) Ovary cell cancer (NIH: OVCAR-3) Stomach cell cancer (AGS) Colorectal cell cancer (WiDr) Blood cell cancer (HL-60, K-562) cell lines	Cytotoxic	5-LOX and 12-LOX inhibitory activity ↑ Inhibitory effect against all cell lines (EC_{50} = 15.2–65.5 µg/mL)	[77]
	Stereocaulon paschale (L.) Hoffm.	*In vitro*	LPS-stimulated macrophages	Anti-inflammatory	↓ NF-κB activation ↓ IL-1β and TNF-α secretion	[59]
	Stereocaulon alpinum Laurer	*In vitro*	Porcine leucocytes	Anti-inflammatory	Inhibitory effects on 5-LOX (IC 50 7.3 µM)	[84]
	–	*In vitro*	Human HaCaT keratinocytes cell line	Anti-inflammatory	Block trypsin-induced and SLIGKV-NH2-induced PAR2 activation ↓ mobilization of intracellular Ca^{2+} ↓ expression of IL-8 PAR2 antagonist	[82]
	Stereocaulon alpinum Laurer	*In vitro*	TNF-α-Stimulated Vascular Smooth Muscle Cells	Anti-inflammatory	↓ VCAM-1 and TNF-R1 expression	[83]
	Stereocaulon alpinum Laurer	*In vitro*	LPS-stimulated macrophages	Anti-inflammatory	↓ NO production, COX-2 expression, and PG2 expression ↓ TNF-α, IL-1, β IL-6, and IL-18 production Inhibition of NLRP3 inflammasome activation Downregulating NF-κB/MAPK pathways	[60]
	Stereocaulon alpinum Laurer	*In vitro*	*E. coli* RecA protein	Antimicrobial	High RecA inhibition (96.8%)	[63]
	Stereocaulon alpinum Laurer	*In vitro*	Methicillin-resistant *S. aureus* strains	Antimicrobial	Antimicrobial activity (MIC_{50} = 32 µg/mL MIC_{90} = 64 µg/mL) Synergic only for gentamicin	[62]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	–	*In vitro*	Baby hamster kidney BHK17 cell line Monkey Vero E6 cell line Human liver Huh7 cell line Sindbis virus and Chikungunya virus	Antimicrobial	Anti-alphaviral ↓ CHIKV nsP1 GTP-binding and guanylation activities ↓ virus growth	[56]
	Stereocaulon alpinum Laurer	*In vitro*	*M. aurum*	Antimicrobial	Antimycobacterial activity (MIC values ≥ 125 µg/mL)	[85]
	–	*In silico*	Drug-binding studies on the structure of Nsp1 from SARS-CoV-2	Antimicrobial	Lobaric acid bind to Nsp1 Potential inhibitor blocking viral RNA binding	[86]
	Cladonia sp.	*In vitro*	SOR assay, NO assay, DPPH assay	Antioxidant	SOR (IC_{50} = 97.9 µmol) No DPPH activity	[87]
	Stereocaulon alpinum Laurer	*In vitro*	Human cervix adenocarcinoma HeLa cell line Colon carcinoma HCT116 cell line	Cytotoxic	↓ Hela and HCT116 cells proliferation ↑ Apoptosis ↓ Bcl-2 ↑ PARP	[48]
	Stereocaulon sasakii Zahlbr.	*In vitro*	Tubulin protein	Cytotoxic	Inhibition tubulin polymerization (IC_{50} = 100 µM)	[78]
	Stereocaulon alpinum Laurer	*In vitro*	Breast cell cancer (T-47D and ZR-75-1) Erythro-leukemia cell cancer (K-562) Normal skin fibroblasts Peripheral blood lymphocytes	Cytotoxic	↓ DNA synthesis in malignant cells ↑ Cell death in malignant cells 5-LOX inhibitory activity	[74]
	–	*In vitro*	Mitochondrial TrxR purified from rat lung	Cytotoxic	↑ Inhibitory effect	[79]
	Stereocaulon alpinum Laurer	*In vitro*	PTP1B inhibition assay	Enzyme inhibition	PTP1B inhibitory activity	[81]
	Stereocaulon alpinum Laurer	*In vitro*	PTP1B inhibition assay	Enzyme inhibition	Potent PTP1B inhibitory activity (IC_{50} = 0.87 µM)	[80]
	Stereocaulon alpinum Laurer	*In vivo*	*T. coli* from guinea pigs	Muscle relaxant	↓ Spontaneous muscle contractile activity	[88]
8′-O-methylstictic	*Hypotrachyna revoluta* (Flörke) Hale.	*In vitro*	Radical scavenging activity	Antioxidant	(61.85) Trolox® equivalents	[126]
	Hypotrachyna caraccensis (Taylor) Hale	*In vitro*	DPPH assay	Antioxidant	Low-moderate scavenging activity	[132]
Norstictic acid	*Ramalina* sp.	*In vitro*	*M. tuberculosis*	Antimicrobial	Antitubercular activity (MIC = 62.5 µg/mL)	[93]
	Toninia candida (Weber) Th.Fr.	*In vitro*	Gram-positive bacteria: *B. mycoides*, *B. subtilis*, *S. aureus* Gram-negative bacteria: *E. coli*, *K. pneumoniae* Fungi: *A. flavus*, *A. fumigatus*, *C. albicans*, *P. purpurescens*, *P. verrucosum*	Antimicrobial	Moderate antimicrobial activity (MIC value = 0.25 to 1 mg/mL)	[90]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	Ramalina farinacea (L.) Ach.	*In vitro*	Gram-positive bacteria: *B. subtilis*, *L. monocytogenes*, *P. vulgaris*, *S. aureus*, *E. faecalis* Gram-negative bacteria: *A. hydrophila* Fungi: *C. albicans*, *C. glabrata*	Antimicrobial	Low antimicrobial activity	[92]
	Rhizoplaca aspidophora (Vain.) Redón	*In vitro*	*E. coli* RecA protein	Antimicrobial	Low RecA inhibition (18.2 %)	[63]
	Stereocaulon montagneanum I. M. Lamb.	*In vitro*	DPPH assay SOR assay	Antioxidant	Low DPPH radical scavenging activity High SOR scavenging activity	[91]
	Toninia candida (Weber) Th.Fr.	*In vitro*	DPPH assay SOR assay	Antioxidant	High antioxidant activity (DPPH IC_{50} = 102.65 µg/mL and SOR IC_{50} = 133.46 µg/mL)	[90]
	Ramalina sp.	*In vitro*	Human melanoma UACC-62 cell line Mouse melanoma B16-F10 cell line Mouse 3T3 normal cells	Cytotoxic	↑ Stronger activity against UACC-62 melanoma cells Selective action against malignant cells	[89]
	Usnea strigosa (Ach.)	*In vitro*	Human breast cancer (MDA-MB-231, MDA-MB-468, MCF-7, T-47D, BT-474, SK-BR-3) cell lines Human mammary epithelial (MCF-10A) cell line Female athymic nude mice	Cytotoxic	↓ MDA-MB-231 cell proliferation, migration, and invasion ↓ Tumor size and tumor weight ↑ Tolerability	[52]
	Stereocaulon montagneanum I. M. Lamb.	*In vitro*	Murine melanocytes B16 cell line Human keratinocyte HaCaT cell line UV-model	Cytotoxic	No cytotoxic No sunscreen action	[91]
	Toninia candida (Weber) Th.Fr.	*In vitro*	Human melanoma FemX cell line Human colon carcinoma LS174 cell line	Cytotoxic	High cytotoxic activity ↑ Number of cells in sub-G1 phase	[90]
Pannarin	*Psoroma sp.*	*In vitro*	*E. coli* RecA protein	Antimicrobial	Low RecA inhibition (13.1 %)	[63]
	Psoroma spp.	*In vitro*	Methicillin-resistant *S. aureus*	Antimicrobial	Bactericidal (MIC_{50} = 4 µg/mL; MIC_{90} = 8 µg/mL)	[97]
	Psoroma pallidum Nyl.	*In vitro*	Promastigotes forms of *Leishmania* ssp	Antimicrobial	Total lysis of parasites (50 µg/mL)	[98]
	Psoroma spp.	*In vitro*	pBR322 plasmid DNA model SOR assay	Antioxidant	↓ NO-induced DNA damage Dose-dependent SOR scavenging effect	[95]
	Psoroma spp.	*In vitro*	Human PBMC cell line	Cytotoxic	Moderate cytotoxic effect	[97]
	Psoroma spp.	*In vitro*	Red blood cells	Cytotoxic	Significant hemolytic capacity	[96]
	Psoroma spp.	*In vitro*	Normal human prostatic epithelial DU-145 cell line	Cytotoxic	↓ Cell growth ↑ LDH release at 50 mM ↑ DNA fragmentation ↑ ROS	[94]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	Psoroma spp.	*In vitro*	Human melanoma M14 cell line	Cytotoxic	↓ Cell growth ↑ LDH release at 50 mM ↑ DNA fragmentation ↑ ROS	[95]
	Psoroma spp.	*In vitro*	8-MOP-human serum albumin photobinding	Photoprotection	Inhibition of photobinding (35.2%)	[99]
Peristictic acid	*Stereocaulon montagneanum* I. M. Lamb.	*In vitro*	DPPH assay SOR assay	Antioxidant	DPPH scavenging activity (10%) High SOR scavenging activity	[91]
	Stereocaulon montagneanum I. M. Lamb.	*In vitro*	Murine melanocytes B16 cell line Human keratinocyte HaCaT cell line UV-model	Cytotoxic	No cytotoxic No sunscreen action	[91]
Physodic acid	*Pseudevernia furfuracea* (L.) Zopf	*In silico* *In vitro*	Virtual screening using validated pharmacophore models Microsomal fraction IL-1β -stimulated A549 cells	Anti-inflammatory	Potential inhibitors of microsomal prostaglandin E2 synthase 1 Inhibitors of mPGES-1 (IC50 = 0.4 µM)	[107]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Gram-positive bacteria: *B. mycoides*, *B. subtilis*, *S. aureus* Gram-negative bacteria: *E. coli*, *K. pneumoniae* Fungi: *A. flavus*, *A. fumigatu*, *C. albicans*, *P. purpurescens*, *P. verrucosum*	Antimicrobial	Antimicrobial activity (especially against *B. subtilis* and *B. mycoides* with MIC values of 0.0008 and 0.0016 mg/mL, respectively)	[101]
	Pseudevernia furfuracea (L.) Zopf	*In vitro*	Cultured human amnion fibroblasts	Antioxidant	< 50 mg/L no oxidative stress and genotoxicity	[108]
	Pseudevernia furfuracea (L.) Zopf	*In vitro*	Cultured Human lymphocytes (HLs)	Antioxidant	↑ Total antioxidant capacity (0.5–10 mg/L)	[109]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	DPPH assay SOR assay Reducing power	Antioxidant	High DPPH radical scavenging activity (IC_{50} 69.11 µg/mL) High SOR scavenging activity (IC_{50} = 118.17 µg/mL) High reducing power	[101]
	Hypogymnia lugubris (Pers.) Krog	*In vitro*	A375 melanoma cancer cell line	Cytotoxic	Apoptosis ↓ Hsp70 expression	[100]
	Pseudevernia furfuracea (L.) Zopf	*In vitro*	Human U87MG-GBM cell lines Primary rat cerebral cortex (PRCC) cells	Cytotoxic	↓ Cell viability (IC_{50} values of 698.19 mg/l for PRCC cells and 410.72 mg/L for U87MG cells) ↑ 8-OH-dG levels	[103]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Human melanoma FemX cell line Human colon carcinoma LS174 cell line	Cytotoxic	Cytotoxic activity (IC_{50} = 19.52 µg/mL for FemX, IC_{50} = 17.89 µg/mL for LS174) ↑ Number cells in sub-G1 phase ↓ Number cells in S phase and G2/M phase	[101]
	Hypogymnia enteromorpha (Ach.) Nyl.	*In vitro*	*S. typhimurium* TA 98	Cytotoxic	Inhibition of reactive metabolites formation	[111]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
Physodic acid	*Hypogymnia physodes* (L.) Nyl.	*In vitro*	Colorectal cancer cell lines (HCT116 and DLD-1) Human keratinocytes HaCaT cell line	Cytotoxic	↓ Axin2 expression (especially in HCT116 cells) ↓ Survivin and MMP7 expression	[20]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Isolated rat thymocytes	Cytotoxic	↓ Thymocytes proliferation ↑ Cytotoxicity ↑ ROS production ↓ MMP	[71]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Human cancer HeLa cell lines	Cytotoxic	↓ Cell viability: IC_{50} (24 h incubation) of 171 µg/mL and IC_{50} (72 h incubation) of 63 µg/mL	[105]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Peripheral human lymphocytes	Cytotoxic	↓ Frequency of MN (28.2 %)	[104]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Breast cancer cell lines (MDA-MB-231, MCF-7, and T-47D) Nontumorigenic MCF-10A cell line	Cytotoxic	Cytotoxic activity (IC_{50} 46.0–93.9 µM)	[102]
	–	*In vitro*	Human colon cancer HTC116 cell line Human leukemic K562 cell line Bladder cancer J82 and UM-UC-3 cell lines Human primary pancreatic adenocarcinoma BxPC-3 cell line	Cytotoxic	Inhibition of M-Phase Phosphoprotein 1 (MPP1) ATPase activity Weak cancer cell inhibitor (EC_{50} values ≈ 30 µM)	[106]
	Pseudevernia furfuracea (L.) Zopf	*In vitro* *Ex vivo*	Murine neuroblastoma Neuro2A cells Murine hippocampal primary cultures	Neuroprotection	No cytotoxic effects Neurotrophic and neurogenic activity Modulation gene expression of BDNF and NGF	[110]
Physodalic acid	*Hypogymnia enteromorpha* (Ach.) Nyl.	*In vitro*	*S. typhimurium* TA 98	Cytotoxic	Inhibition mutagenicity of a heterocyclic amine, Trp-P-2	[111]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Isolated rat thymocytes	Cytotoxic	↓ Thymocytes proliferation ↑ Cytotoxicity ↑ ROS production ↓ MMP	[71]
	Hypogymnia enteromorph (Ach.) Nyl.	*In vitro*	*S. typhimurium* strain TA 100	Cytotoxic	↑ Mutagenicity	[111]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Human cancer HeLa cell lines	Cytotoxic	↓ Cell viability: IC_{50} (24 h incubation) of 964 µg/mL and IC_{50} (72 h incubation) of 283 µg/mL	[105]
	Hypogymnia physodes (L.) Nyl.	*In vitro*	Peripheral human lymphocytes	Cytotoxic	↓ Frequency of MN (30.3 %)	[104]
Protocetraric acid	*Hypogymnia lugubris* (Pers.) Krog	*In vitro*	*E. coli* RecA protein	Antimicrobial	Low RecA inhibition (11.5 %)	[63]
	Flavoparmelia caperata L.	*In vitro*	*S. aureus*	Antimicrobial	Antibacterial activity (MIC 12.5 µg/mL)	[113]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	Usnea albopunctata Nyl.	*In vitro*	Gram-positive bacteria: *B. subtilis*, *S. faecalis*, *S. aureus*, *S. epidermis*, *M. smegmatis* Gram-negative bacteria: *E. coli*, *P. mirabilis*, *P. vulgaris V. cholerae K. pneumoniae P. aeruginosa S. typhi* Fungi: *A. flavus C. albicans,C. tropicalis C. glabrata*, *C. gastri*, *T. rubrum*	Antimicrobial	High activity against *S. typhi* (MIC value = 0.5 mg/mL), *K. pneumoniae* (MIC value = 1 mg/mL) and *T. rubrum* (MIC value = 1 mg/mL)	[112]
	Cetraria islandica (L.) Ach.	*In vitro*	*T. brucei brucei*	Antimicrobial	Antitrypanosomal activity	[67]
	Parmelia caperata (Ehrh. ex Ach.) Ach	*In vitro*	Gram-positve bacteria: *B. mycoides*, *B. subtilis*, *S. aureus* Gram-negative bacteria: *E. coli*, *K. pneumoniae* Fungi: *A. flavus*, *A. fumigatus*, *C. albicans*, *P. purpurescens*, *P. verrucosum*	Antimicrobial	↑ Antibacterial activity than antifungal activity High activity against *B. mycoides*, *B. subtilis*, and *S. aureus* (MIC value = 0.015 mg/mL)	[19]
	Parmotrema dilatatum (Vain.) Hale.	*In vitro*	*M. tuberculosis*	Antimicrobial	Antitubercular activity (MIC value = 125 µg/mL)	[93]
	Ramalina farinacea (L.) Ach.	*In vitro*	Gram-positive bacteria: *B. subtilis*, *L. monocytogenes*, *S. aureus*, *S. faecalis* Gram-negative bacteria: *A. hydrophila*, *P. vulgaris* Fungi: *C. albicans*, *C. glabrata*	Antimicrobial	Active against *C. albicans* and *C. glabrata*	[92]
	Parmelia caperata (Ehrh. ex Ach.) Ach	*In vitro*	DPPH assay SOR assay	Antioxidant	Strong antioxidant activity (IC_{50} = 119.10 µg/mL for DPPH and 177.60 µg/mL for SOR)	[19]
	Parmotrema dilatatum (Vain.) Hale.	*In vitro*	Human melanoma UACC-62 cell line Mouse melanoma B16-F10 cell line Mouse 3T3 normal cells	Cytotoxic	↑ Stronger activity against UACC-62 melanoma cells Selective action against malignant cells	[89]
	Parmelia caperata (Ehrh. ex Ach.) Ach	*In vitro*	Human melanoma FemX cell line Human colon carcinoma LS174 cell line	Cytotoxic	Cytotoxic activity (IC_{50} = 58.68 µg/mL for FemX, IC_{50} = 60.18 µg/mL for LS174) ↑ Number cells in sub-G1 phase ↓ Number cells in S phase	[19]
Psoromic acid	–	*In vitro*	Monkey kidney epithelial Vero cell line HSV-1 and HSV-2 models of infection	Antimicrobial	Antiherpetic activity HSV-1 replication inhibition (IC_{50} = 1.9 µM) HSV-2 replication inhibition (IC_{50} = 2.7 µM) HSV-1 DNA polymerase inactivation (IC_{50} = 0.7 µM)	[116]
	Squamarina cartilaginea (With.) P. James	*In vitro*	*S. gordonii*, *P. gingivalis*	Antimicrobial	Antibacterial activity against *S. gordonii* (MIC value = 11.72 µg/mL) and *P. gingivalis* (MIC value = 5.86 µg/mL)	[117]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	–	*In vitro*	*M. tuberculosis* strains	Antimicrobial	Antituberculosis activity (MIC values = 3.2–4.1 µM) Remarkable inhibition UGM (85.8 %) and TBNAT (77.4 %)	[118]
	–	*In vitro*	*S. aureus* *E. coli* *M. tuberculosis* *P. berghei* liver stage (LS) parasites *P. falciparum* blood-stage (BS) parasites	Antimicrobial	Antibacterial/Antimycobacterial Activity ↓ Growth bacterial Antiplasmodial activity Moderate LS activity (IC_{50} = 31.6 µM), high BS potential (IC_{50} = 29.2 µM) Plasmodial FAS-II enzyme (PfFabI, PfFabG, and PfFabZ) inhibition	[119]
	Usnea complanata (Müll. Arg.) Motyka.	*In vivo*	FRSA assay NORSA assay LPI assay HMGR inhibitory activity ACE inhibitory activity	Antioxidant	Moderate-to-strong antioxidant activity (IC_{50} values 0.174–0.271 mg/mL) Competitive type of HMGR inhibition and mixed type of ACE inhibition	[120]
	–	*In vitro*	Fluorometric Assay	Cytotoxic	↑ RabGGTase inhibition (IC_{50} = 1.3 µM)	[114]
	–	*In vitro*	Splicing assay	Cytotoxic	Pre-mRNA splicing inhibitor	[115]
	–	*In vitro*	Primary cultures of rat hepatocytes	Cytotoxic	↑ Caspase 3 activity ↑ Subdiploid nuclei %	[18]
	Usnea sp	*In vitro*	Human melanoma UACC-62 cell line Mouse melanoma B16-F10 cell line Mouse 3T3 normal cells	Cytotoxic	↑ Stronger activity against UACC-62 melanoma cells Selective action against malignant cells	[89]
	–	*In vivo*	Zebrafish embryos *(B. rerio)* model	Toxicity	Hepatotoxicity (≥ 40 %)	[119]
Salazinic acid	*Parmelia saxatilis* (L.) Ach	*In vitro*	*E coli* RecA protein	Antimicrobial	Low RecA inhibition (8.4 %)	[63]
	Parmelia sulcata Taylor	*In vitro*	Gram-positve bacteria: *B. cereus, B. subtilis, L. monocytogenes, S. aureus, S. faecalis* Gram-negative bacteria: *A. hydrophila, P. vulgaris, Y. enterocolitica, P. aeruginosa, S. typhimurium* Fungi: *C. albicans, C. glabrata, A. niger, A. fumigatus, P. notatum*	Antimicrobial	Antimicrobial activity specially against *B. cereus* (MIC values = 63 µg/mL)	[121]
	Parmelia reticulata Taylor.	*In vitro*	Fungi: *S.rolfsii, R. solani, R. bataticola, F. udum, P. aphanidermatum, P. debaryanum*	Antimicrobial	Moderate active against *F. udum* (IC_{50} = 88.20 µg/mL)	[122]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
	Parmelia saxatilis (L.) Ach. *Parmelia sulcata* Taylor	*In vitro*	Gram-positve bacteria: *B. mycoides*, *B. subtilis*, *S. aureus* Gram-negative bacteria: *E. coli*, *K. pneumoniae* Fungi: *A. flavus*, *A. fumigatus*, *C. albicans*, *P. purpurescens*, *P. verrucosum*	Antimicrobial	↑ Antibacterial activity than antifungal activity	[19]
	Xanthoparmelia camtschadalis (Ach.) Hale.	*In vitro*	ORAC assay Human U373 MG astrocytoma cell line Hydrogen peroxide-induced oxidative stress model	Antioxidant	ORAC value (2.74 µmol Trolox equivalents per milligram) ↑ Cell viability ↓ ROS production	[124]
	Everniastrum cirrhatum (Fr.) *Hale ex* Sipman *Rimelia cetrata* (Ach.) Hale & Fletcher	*In vitro*	DPPH assay Anti-linoleic acid peroxidation assay Trolox-equivalent antioxidant capacity assay	Antioxidant	Antioxidant activity (46.4 to 57.2 %)	[123]
	–	*In vitro*	DPPH assay NBT assay Human keratinocytes HaCaT cell line	Antioxidant	Superoxide anion scavenger Good PF-UVA candidate (PF-UVA > 2)	[70]
	Parmelia saxatilis (L.) Ach. *Parmelia sulcata* Taylor	*In vitro*	DPPH assay SOR assay	Antioxidant	Strong antioxidant activity (IC_{50} = 91.57 for DPPH and 138.23 µg/mL for SOR)	[19]
	–	*In vitro*	Primary cultures of rat hepatocytes	Cytotoxic	↑ Caspase 3 activity ↑ Subdiploid nuclei %	[18]
	Parmelia saxatilis (L.) Ach. *Parmelia sulcata* Taylor	*In vitro*	Human melanoma FemX cell line Human colon carcinoma LS174 cell line	Cytotoxic	Cytotoxic activity (IC_{50} = 39.02 µg/mL for FemX and IC_{50} = 5.67 µg/mL for LS174) ↑ Number cells in sub-G1 phase ↓ Number cells in S phase	[19]
	Parmelia sulcata Taylor	*In vitro*	Colorectal cancer HCT116 and DLD-1 cell lines.	Cytotoxic	Moderate cytotoxic effects (100 µM)	[20]
	Everniastrum cirrhatum (Fr.) Hale *ex* Sipman *Rimelia cetrata* (Ach.) Hale & Fletcher	*In vitro*	*L. casei*	Probiotic	Moderate growth stimulating activity	[123]
	Xanthoparmelia somloensis (Gyeln.) Hale	*In vitro*	Malignant mesothelioma MM98 cell line Vulvar carcinoma A431 cell line Human keratinocyte HaCaT cell line	Wound healing	Intermediate wound closure	[125]

continued

▶ **Table 1** *Continued*

Depsidone	Botanical origin	Type of study	Experimental model	Activities	Results	References
Stictic acid	*Rhizoplaca aspidophora* (Vain) Redon	*In vitro*	*E. coli* RecA protein	Antimicrobial	Low RecA inhibition (16.7%)	[63]
	–	*In vitro*	*F. tularensis*, *Y. pestis*	Antimicrobial	Inhibition of FabZ (*F. tularensis*, IC_{50} = 13.0 µM and *Y. pestis*, IC_{50} = 27.8 µM)	[55]
	Xanthoparmelia camtschadalis (Ach.) Hale.	*In vitro*	ORAC assay Human U373 MG astrocytoma cell line Hydrogen peroxide-induced oxidative stress model	Antioxidant	ORAC value (2.32 µmol Trolox equivalents per milligram) ↑ Cell viability ↓ ROS production	[124]
	Stereocaulon montagneanum I. M. Lamb.	*In vitro*	DPPH assay SOR assay Murine melanocytes B16 cell line Human HaCaT keratinocyte cell lines	Antioxidant	Low DPPH radical scavenging activity ↑ SOR scavenging activity	[91]
	Hypotrachyna revoluta (Flörke) Hale.	*In vitro*	Hydroxyl radical scavenging assay	Antioxidant	Noteworthy antioxidant activity	[126]
	–	*In vitro*	Primary cultures of rat hepatocytes	Cytotoxic	↑ Caspase 3 activity ↑ Subdiploid nuclei %	[18]
	–	*In silico*	Docking studies	Cytotoxic	p53 activator ↓ Toxic adverse effects	[128]
	–	*In vitro* *In silico*	Human Saos-2 cells expressing cancer mutant R175H Docking studies	Cytotoxic	p53 activity restoration Cell cycle inhibitor p21 inductor	[127]
Variolaric acid	*Ochrolechia deceptionis* (Hue) Darb	*In vitro*	*E. coli* RecA protein	Antimicrobial	Low RecA inhibition (3.2%)	[63]
	Ochrolechia deceptionis (Hue) Darb.	*In vitro*	Human breast adenocarcinoma MCF-7 cell line Human cervix adenocarcinoma HeLa cell line Human colon carcinoma HCT-116 cell line	Cytotoxic	No effect	[76]
Vicanicin	*Psoroma pallidum* Nyl., *P. pulchrum* Malme	*In vitro*	*E. coli* RecA protein	Antimicrobial	Moderate RecA inhibition (73.7% inhibition)	[63]
	Psoroma pallidum Nyl. *P. pulchrum* Malme	*In vitro*	Human breast adenocarcinoma MCF-7 cell line Human cervix adenocarcinoma HeLa cell line Human colon carcinoma HCT-116 cell line	Cytotoxic	↓ Cell viability (HeLa, IC_{50} = 67 µM and HCT-116, IC_{50} = 40.5 µM)	[76]
	Psoroma dimorphum Malme	*In vitro*	Androgen-sensitive LNCaP and androgen-insensitive DU-145 human prostate cancer cells	Cytotoxic	↓ Cell viability ↑ Apoptosis	[129]
	Teloschistes flavicans (Sw.) Norman.	*In vitro*	HL-60 cells	Cytotoxic	Higher cytotoxicity against HL-60 cells	[130]

Lobaric acid showed high inhibition of PTP1B with an IC_{50} value of 0.87 µM [80, 81]. Tyrosine phosphatase protein is overexpressed in insulin-resistant states [80]. Indeed, Klaman et al. showed that PTP-1B regulates energy balance, insulin sensitivity, and body fat stores in *in vivo* studies [58].

Lobaric acid could inhibit inflammation in LPS-activated macrophages through regulation of NF-κB/MAPK pathways, NLRP3 inflammasome activation, proinflammatory cytokines suppression (TNF-α, IL-1, IL-6, and IL-18), and NO production inhibition [59, 60]. Moreover, lobaric acid reduced IL-8 expression and targeted PAR2 in an *in vitro* SLIGKV-NH_2-induced atopic dermatitis model in HaCaT keratinocytes [82]. Additionally, lobaric acid exerted anti-inflammatory activity by inhibiting NF-κB and MAPK signaling pathways in TNF-α-stimulated mouse vascular smooth muscle cells [83]. Furthermore, lobaric acid turned out to be a potent arachidonate-5-lipoxygenase inhibitor (IC_{50} value of 7.3 µM) [84].

Lobaric acid also showed antimicrobial activity against bacteria and viruses. Thus, this depsidone inhibited RecA from *E. coli* by noncompetitively binding the ATP site [63]. While it showed moderate activity against *Mycobacterium aurum* [85], the activity against methicillin-resistant clinical isolates strains of *S. aureus* with an MIC_{90} value of 64 µg/mL was good [62]. Moreover, lobaric acid showed anti-alphaviral activity against *Chikungunya* virus via NsP1 GTP binding and guanylation inhibition in hamster BHK21 and human Huh 7 cell lines [56]. Furthermore, binding studies of Nsp1 from SARS-CoV-2, a nonstructural protein 1 related to viral processes as viral replication and translation regulation, showed greater binding affinities with lobaric acid [86].

Other assayed activities were its antioxidant activity (superoxide radical scavenging action with IC_{50} value of 97.9 µmol) [87] and muscle relaxant as evidenced in the reduction of spontaneous muscle contractile activity in guinea-pig taenia coli [88].

Norstictic acid

The cytotoxic and antitumor role of norstictic acid has been evaluated in diverse *in vitro* (using different cancer cell lines) and *in vivo* models. Therefore, this compound has been shown to be effective for breast cancer treatment and prevention by targeting the c-Met signaling pathway and by suppressing the MDA-MB-231/GFP tumor growth in mammary cancer cells and breast cancer xenograft models in athymic nude mice [52]. Moreover, norstictic acid exerted a noticeable cytotoxic effect against different human melanoma cell lines (FemX, UACC-62, and B16-F10) [89, 90] by increasing apoptotic cells in the sub-G1 phase [89]. Contrary, other studies reported that norstictic acid was not cytotoxic for melanocyte cells [91].

Concerning its antimicrobial activity, norstictic acid showed low to moderate antibacterial and antifungal action against a wide range of Gram-positive bacteria, Gram-negative bacteria, and fungi [63, 90, 92, 93]. For instance, norstictic acid inhibited *Mycobacterium tuberculosis* growth with a MIC value of 62.5 µg/mL [93] and *E. coli* with a value of 18.2% [63].

Norstictic acid has also been shown to be a promising antioxidant agent against superoxide anion. On the other hand, its DPPH radical scavenging activity is not entirely clear, since its activity is contradictory in published works [90, 91].

Pannarin

Pannarin was able to inhibit the growth of the human melanoma M14 cell line and the human prostatic epithelial DU-145 cell line. Its cytotoxic activity has been related to oxidative stress induction as evidenced in ROS overproduction and DNA fragmentation [94, 95]. Moreover, pannarin showed cytotoxic activity against blood cells through a mechanism of hemolysis [96, 97].

Regarding antimicrobial activity, pannarin acted as bactericidal against methicillin-resistant *S. aureus*, and it also had a low capacity to inhibit *E. coli* RecA protein [63, 97]. Moreover, pannarin was effective as an antiparasitic agent against promastigote forms of *Leishmania* spp [98].

Pannarin also showed antioxidant properties as evidenced in its superoxide radical scavenging capacity and NO-induced DNA damage [95], and it has photoprotector capacity (35.2%) [99].

Physodic acid

There are several studies on the cytotoxic activity of physodic acid against different cancer and nontumorigenic cell lines from diverse origins (human or animal). Against A375 melanoma cancer cell line, physodic acid exhibited good cytotoxicity via apoptosis with a concentration-response relationship (range 6.25–50 µM), showing inhibition of Hsp70 expression [100]. Other studies on FemX and LS174 cell lines revealed significant cytotoxic activity (IC_{50} value of 19.52 µg/mL for FemX, IC_{50} value of 17.89 µg/mL for LS174) with moderate proapoptotic activity. The number of cells in the sub-G1 phase increased, and the number of cells in the S phase and G2/M phase was lower, indicating a G0/G1 cell cycle arrest [101]. Moreover, physodic acid was cytotoxic on different breast cancer cell lines (MDA-MB-231, MCF-7, and T-47D) with IC_{50} values that ranged from 46.0 to 93.9 µM [102]. Physodic acid displayed weak cytotoxic activity on human U87MG-GBM cell lines and primary rat cerebral cortex (PRCC) cells (IC_{50} value of 698.19 mg/mL for PRCC cells and IC_{50} value of 410.72 mg/mL for U87MG cells) [103]. Moreover, physodic acid reduced thymocyte proliferation-induced cytotoxicity via oxidative stress mainly through ROS production [71]. On lymphocytes, this depsidone significantly decreased micronucleus frequency (28.2%) compared to the positive control [104]. Furthermore, this compound proved to significantly reduce human cancer HeLa cell viability (IC_{50} [24 h] value of 171 µg/mL and IC_{50} [72 h] value of 63 µg/mL) [105]. In another study, Talapatra et al. concluded that physodic acid was a weak cancer cell inhibitor (EC_{50} values ≈ 30 µM) on multiple cancer cell lines (human colon cancer HTC116 cell line, human leukemic K562 cell line, bladder cancer J82 and UM-UC-3 cell lines, and human primary pancreatic adenocarcinoma BxPC-3 cell line) [106]. Physodic acid was studied as a modulator of β-catenin-dependent transcription on colorectal cancer (HCT116 and DLD-1). β-catenin transcription is related to cell survival and proliferation. Physodic acid reduced Axin2 (β-catenin target gene) expression (especially in HCT116 cells) and decreased survivin and MMP7 expression [20]. Also, this depsidone was probed as an inhibitor of MPP1, essential for the cytokinesis process, indicating noncompetitive ATP binding in *in silico* studies [106].

Antimicrobial activity was also examined in bacteria and fungi. Physodic acid had strong inhibitory capacity especially against

B. subtilis and *B. mycoides* with MIC values of 0.0008 and 0.0016 mg/mL, respectively [101].

In addition to cytotoxic and antimicrobial properties, *in vitro* and *in silico* models showed the anti-inflammatory activity of physodic acid. Virtual screening evaluation revealed that this depsidone inhibits microsomal prostaglandin E2 synthase-1 [107]. Determination of mPGES-1 inhibition was performed using a microsomal fraction of IL-1β-stimulated A549 cells (IC_{50} = 0.43 µM) [107].

Physodic acid was also investigated as an antioxidant agent, showing high DPPH radical scavenging activity (IC_{50} value of 69.11 µg/mL), high SOR scavenging activity (IC_{50} value of 118.17 µg/mL), and high reducing power [101]. Lower concentrations of physodic acid tested in cultured human amnion fibroblasts (< 50 mg/L) and cultured human lymphocytes (0.5–10 mg/L) showed antioxidant capacities [108, 109].

Moreover, physodic acid showed neuroprotective properties, exhibiting neurotrophic and neurogenic activity via modulation of gene expression of BDNF and NGF in *ex vivo* (murine hippocampal primary cultures) and *in vivo* (murine neuroblastoma Neuro2A cells) assays [110].

Physodalic acid

Cytotoxic activity of physodalic acid is also described. However, compared to physodic acid, physodalic presented weaker activity. Physodalic acid demonstrated a weak reduction of viability (IC_{50} [24 h] value of 964 µg/mL and IC_{50} [72 h] value of 283 µg/mL) on human cancer HeLa cell lines [105].

This compound also diminished the proliferation of thymocytes inducing cytotoxicity via ROS production. Physodalic acid reduced the frequency of micronucleus (30.3 %) on lymphocytes [71, 104].

Despite being reported as mutagenic in *S. typhimurium* TA 100 [83], physodalic acid inhibited the mutagenicity of a heterocyclic amine, Trp-P-2, in *S. typhimurium* TA 98 [111].

Protocetraric acid

Most of the studies on protocetraric acid referred to its antimicrobial activity. Particularly, this depsidone inhibited pathogenic bacteria growth such as *S. aureus* (MIC value of 12.5 µg/mL), *M. tuberculosis* (MIC value of 125 µg/mL), *S. typhi* (MIC value of 0.5 mg/mL), *K. pneumoniae* (MIC value of 1 mg/mL), and *B. mycoides, B. subtilis*, and *S. aureus* (MIC value of 0.015 mg/mL) [19, 93, 112, 113]. Moreover, protocetraric acid revealed a marked antifungal activity against *T. rubrum* (MIC value of 1 mg/mL), *C. albicans,* and *C. glabrata* (MIC value of 3.9 µg/µl) [92, 112]. Furthermore, protocetraric acid showed trypanocidal activity against *T. brucei brucei* with a MIC value of 6.30 µM [67].

Protocetraric acid also demonstrated cytotoxic activity against melanomas cell lines (IC_{50} values of 0.52 µg/mL for UACC-62 cells and 58.68 µg/mL for FemX cells) and colon carcinoma cell line (IC_{50} value of 60.18 µg/mL for LS174 cells) [19, 89].

This depsidone had also an effective antioxidant action as evidenced in DPPH and superoxide anions radical scavenging activity [19].

Psoromic acid

Psoromic acid presented an inhibitory effect against melanoma cell lines (UACC-62 and B16-F10) and primary cultures of rat hepatocytes [18, 89]. The cytotoxic activity of psomoric acid was related to its capacity to induce an apoptotic response and to inhibit splicing and Rab GTPase [18, 114, 115].

Psoromic acid was also of interest as an antiviral agent, as it blocked HSV-1 and HSV-2 replication and DNA synthesis [116]. Moreover, this depsidone reduced bacterial growth of *Streptococcus gordonii* (MIC value of 11.72 µg/mL), *Porphyromonas gingivalis* (MIC value of 5.86 µg/mL), and *M. tuberculosis* strains (3.2–4.1 µM) [116–118]. Furthermore, psoromic acid acts as an inhibitor of *Plasmodium* liver stages targeting the plasmodial FAS-II pathway [119]. *In vivo* studies determined that psoromic acid was hepatotoxic in fabp10a: DsRed2 zebrafish larvae (≥ 40 %) [119].

Using different *in vitro* antioxidant assays, Behera et al. revealed that psomoric acid had moderate to strong antioxidant activity [120].

Salazinic acid

Salazinic acid displayed cytotoxic activity against colorectal cancer cell lines (HCT116, DLD-1, and LS174), melanoma cancer cell lines (FemX), and primary cultures of rat hepatocytes by inducing apoptosis and cell cycle arrest [18–20].

Considering its antimicrobial activity, salazinic acid inhibited *B. mycoides* and *B. subtilis* growth with a MIC value of 0.0008 µg/m and *B. cereus* with a MIC value of 63 µg/mL [19, 121]. However, this depsidone was ineffective as an *E. coli* Rec A protein inhibitor [63]. Moreover, salazinic acid showed moderate antifungal activity against *Fusarium udum* (IC_{50} value of 88.20 µg/mL) [122]. Furthermore, this compound promoted growth effects on probiotic bacteria *Lactobacillus casei* [123].

Salazinic acid has also turned out to be interesting as an antioxidant compound as revealed in different *in vitro* assays (DPPH assay, SOR assay, ORAC assay) [19, 70, 123, 124] Because of its antioxidant properties, this depsidone increased cell viability and reduced ROS production in a hydrogen peroxide-induced oxidative stress model in the human U373 MG astrocytoma cell line [124]. Moreover, salazinic acid proved to protect against UVA sunrays (PF-UVA > 2) [70].

Another property attributed to salazinic action is its ability to heal wounds on HaCaT keratinocytes [125].

Stictic acid

Stictic acid has been investigated for its antioxidant, antimicrobial, and cytotoxic properties. This promising compound showed antioxidant activity in diverse *in vitro* test models. Despite its low DPPH radical scavenging activity (less than 10 %), stictic acid exhibited moderate ORAC values (2.32 µmolTE/mg), high SOR scavenging activity (IC_{50} value of 35 µM), and good hydroxyl radical scavenging activity (7.63 Trolox equivalents) [91, 124, 126]. Furthermore, in hydrogen peroxide-induced oxidative stress conditions, this depsidone protected human U373 MG astrocytoma cell line at 5, 10, and 25 g/mL concentrations via inhibition of ROS production [124]. These findings showed that stictic acid may be a potential neuroprotective compound.

On the other hand, cytotoxicity evaluation on murine melanocytes B16 cells and human HaCaT keratinocyte cell lines showed no safety; therefore, its possible cosmetic use was dismissed [91].

Enzymes involved in fatty acid biosynthesis processes such as FabZ are excellent targets for developing broad-spectrum antibiotics. Differences between FAS systems (bacterial and human) imply that the inhibition process does not interfere with the host. Stictic acid exhibited a significant inhibitory effect against *Francisella tularensis* (IC_{50} value of 13 µM) and *Yersinia pestis* (IC_{50} value of 27 µM) *β*-hydroxyacyl-acyl carrier protein dehydratase (FabZ) [55]. Stictic acid's antimicrobial properties have been investigated, along with other depsidones through *E. coli* RecA protein inhibition. RecA is related to bacterial SOS response regulation, which is involved in resistance to antimicrobials. Stictic acid exhibited low RecA inhibition (16.7%) [63].

In vitro and *in silico* assays reported cytotoxic activity of this compound. In human cancer, p53 genes mutate frequently. Using docking studies, stictic acid showed potential p53 reactivation by binding to a transiently open L1/S3 pocket of the p53 core domain [127]. In another study, stictic acid showed great potential as a p53 activator and less adverse effect but poor pharmacokinetic properties [128]. To support *in silico* assays, stictic acid was biologically evaluated in human Saos-2 cells expressing cancer mutant R175H, restoring p53 activity via induction of the cell cycle inhibitor p21 [127]. Moreover, stictic acid displayed cytotoxic activity in different cell lines. In primary cultures of rat hepatocytes, this depsidone showed significant concentration-dependent activation of caspase 3 and an increased percentage of subdiploid nuclei (DNA fragmentation) [18].

Variolaric acid

While variolaric acid was tested to evaluate its cytotoxic and antimicrobial activity, the viability assays reported no significant effect on human breast adenocarcinoma cell line MCF-7, human cervical adenocarcinoma cell line HeLa, and human colon carcinoma HCT-116 [76]. Moreover, this depsidone had a low capacity to inhibit *E. coli* RecA protein (3.2%) [63].

Vicanicin

Cytotoxic activity of vicanicin was evaluated in different cell cancer lines, showing significant loss of viability in a concentration-dependent manner on human cervix adenocarcinoma HeLa cell lines and human colon carcinoma HCT-116 (IC_{50} values of 67 µM and 40.5 µM, respectively). However, vicanicin did not have effects on human breast adenocarcinoma MCF-7 cells. This depsidone neither exhibited antiradical activity nor reduced intracellular ROS level, dismissing both as the potential mechanism of cytotoxicity [76].

In the model of androgen-sensitive (LNCaP) and androgen-insensitive (DU-145) human prostate cancer cells, vicanicin decreased cell growth by the induction of apoptosis. The expression of Bcl-2, Bax, TRAIL, COX-2, NOS2, and Hsp70 proteins was analyzed, and the inhibition of Hsp70 proteins expression as a mediator of the process should be highlighted [129]. Moreover, this depsidone exhibited moderate activity against HL-60 cells as revealed on antileukemic assay [130]. Regarding its antimicrobial activity, this depsidone showed moderate inhibition of *E. coli* RecA protein (73%) [63].

Other Depsidones

Many depsidones have been identified but barely studied. Computational studies have revealed that connorstictic acid, cryptostictic acid, conhypoprotocetraric acid, hypoprotocetraric acid, and gangaleoidin, among other depsidones, are potent hydroxyl and superoxide anion radical scavengers in polar environments [131]. Other stictic acid derivatives also displayed antioxidant activities such as peristictic acid and cryptostictic acid that showed weak DPPH radical scavenging activity (about 10%) and potent superoxide anion radical scavenging activity equivalent to that of ascorbic acid. These compounds showed no cytotoxicity on B16 murine melanoma and HaCaT human keratinocyte cell lines (IC_{50} higher than 100 µM) [91]. The compounds 8′-O-methylstictic and deoxystictic acid showed radical scavenging activity (61.85 and 13.176 Trolox equivalents, respectively) [126]. Moreover, 8′-O-methylstictic acted as a DPPH scavenger and had good properties for skin penetration (lipophilicity and permeability) [132].

These derivatives have also displayed other activities. For example, hypostictic acid showed antimicrobial properties due to its moderate inhibitory activity against *M. tuberculosis* (MIC value of 94 µg/mL) [93]. The compound 8′-O-ethylstictic presented moderate cytotoxicity against human epithelial carcinoma HeLa, human lung cancer NCI-H460, liver hepatocellular carcinoma HepG2, and human breast cancer MCF-7 cell lines [133].

Other depsidones recently identified, such as ceratinalone and flavicansone, isolated from *Usnea ceratina* Ach. and *Teloschistes flavicans* (Sw.) Norman, respectively, have also shown cytotoxic properties [130, 133]. Ceratinalone has been tested against different cancer cell lines such as human epithelial carcinoma HeLa, human lung cancer NCI-H460, liver hepatocellular carcinoma HepG2, and human breast cancer MCF-7. It acted as a moderate cytotoxic agent [133]. On the other hand, flavicansone exhibited cytotoxic activity as evidenced in an antileukemic assay against HL-60 cells (IC_{50} value of 58 µM) [130].

Conclusions and Future Perspectives

Indeed, lichens produce unique bioactive secondary metabolites such as depsidones. Most pharmacological studies of depsidones focus on fumarprotocetraric acid, lobaric acid, norstictic acid, physodic acid, salazinic acid, and stictic acid compounds. Lichen depsidones have proven their ability to perform diverse biological activities, with cytotoxic, antimicrobial, and antioxidant the most studied. While many published works are on *in vitro* studies, the *in vivo* studies are very limited, and no clinical trials are yet available.

The cytotoxic activity has been evaluated against different cell lines of animal and human origin. Most of these works on cytotoxic activity are based on assessing their effect on cell viability, however, there are fewer studies that clarify the molecular targets and signaling pathways. The most interesting depsidones with cytotoxic activity included lobaric and physodic acids. Regarding the antimicrobial activity, most of the studies evaluated antibacterial

activity against both Gram-positive bacteria and Gram-negative bacteria and fungi, mainly *Candida* spp. Among depsidones, fumarprotocetraric and protocetraric acids are emphasized for their antimicrobial properties. The antioxidant activity has been investigated using techniques such as the DPPH method and ORAC assay as well as in cellular and animal models of oxidative stress. The compounds salazinic acid and stictic acid stand out for their antioxidant properties.

Our study revealed that the future perspectives of pharmacological research on depsidones should focus on:

1. Deepening the activities for these depsidones, clarifying the mechanism of action.
2. Evaluating other and novel potential actions and properties of depsidones.
3. Investigating the potential therapeutic activity of unstudied depsidones from a pharmacological perspective as notatic acid, nortotatic acid, constictic acid, and diploicin.
4. Performing more *in vivo* studies confirming the activity shown in *in vitro* studies.
5. Conducting clinical trials for those depsidones that have shown potential pharmacological activities.

Contributors' Statement

Data collection: I. M. Ureña-Vacas, E. González-Burgos; drafting the manuscript: I. M. Ureña-Vacas, E. González-Burgos; critical revision of the manuscript: P. K. Divakar, M. P. Gómez-Serranillos.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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