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Research Article

Antimicrobial Potential, Mechanisms, and Biosynthesis Pathways of Lichen-Derived Bioactive Compounds; A Systematic Review

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ABSTRACT

Lichens, symbiotic organisms comprising fungi and photosynthetic partners, have gained particular attention due to their rich nutritional profile, which includes significant bioactive compounds with strong antimicrobial potential. This review collectively highlights the antimicrobial activity, its mechanism of action, and synthesis of lichen-derived compounds, advocating for their effective use as novel agents against microbial infections. Lichen metabolites, especially usnic acid and atranorin, exhibited significant activity against various multidrug-resistant bacterial strains and also antifungal activity, especially against *Candida albicans* and *Aspergillus* species. Their mechanism of action against infectious microbes involves cell wall and cell membrane formation inhibition, RNA/DNA synthesis disruption, and efflux pump inhibition. Recent advanced genomic and metabolomics studies have explored the biosynthesis pathways of these bioactive compounds with the involvement of several key enzymes, especially polyketide synthases (PKSs), and genes such as biosynthetic gene clusters (BGCs). Despite significant studies, there remain gaps in evaluating the pharmacogenomics, toxicity, and in vivo efficiency of these bioactive compounds. However, there is also a need for further study on sustainable enhanced extraction techniques and nano-encapsulation for improved and enhanced availability. This review synthesizes evidence that lichen compounds target microbial cell structures, nucleic acid synthesis, and efflux pumps, with emerging potential for drug development, also urges for advanced approaches such as nano-encapsulation and AI-driven drug discovery to utilize their complete potential.

Keywords: Bioactive compounds, Antimicrobial potential, Microbial infections, Biosynthesis pathways, Pharmacogenomics, Drug development.

INTRODUCTION

Lichens, which are symbiotic entities formed from fungi and photosynthetic organisms like cyanobacteria or green algae (Honegger, 2009; Lutzoni & Miadlikowska, 2009; Grimm et al., 2021), have garnered considerable scientific attention because of their capacity to generate a wide range of bioactive substances that possess strong antimicrobial properties. These extraordinary organisms thrive in harsh conditions and produce specialized metabolites that exhibit significant activity against various pathogenic microorganisms. Among the many compounds derived from lichens, usnic acid, atranorin, salazinic acid, and protolichesterinic acid have shown particularly potent antimicrobial effects against antibiotic-resistant strains (Furmanek et al., 2019; Macedo et al., 2021). The escalating threat posed by antimicrobial resistance has spurred investigations into these natural products as potentially novel therapeutic agents.

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The effectiveness of lichen extracts against various bacteria, Gram-positive and Gram-negative, such as Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa, as well as harmful fungi, like Candida albicans and Aspergillus species have already been proven in numerous studies (Mitrović et al., 2014). Specifically, usnic acid has proven to be incredibly effective against methicillin-resistant S. aureus (MIC: 0.002 µg/µL) (Gupta et al., 2012) and atranorin has proven its efficacy against Mycobacterium tuberculosis (MIC: 0.25 0.5g/L) with antiviral properties observed against the Zika virus by acting on viral envelope proteins (Thuan et al., 2022; Huang et The antimicrobial activity of the said substances may also differ significantly depending on the methods of extraction, and non-polar solvents like ethyl acetate tend to produce a stronger extract than polar solvents like methanol (Mitrović et al., 2014; Kocovic et al., 2022).

The action by which lichen compounds act as antimicrobials is diverse and will act on multiple processes important to the microorganisms. Such effects involve the destruction of cell wall and membrane integrity, as seen with the effect of vulpinic acid on the membrane permeability of MRSA (Shrestha et al., 2016), blockage of efflux pumps by compounds such as rhizocarpic acid (Kokubun et al., 2007), and disruption of nucleic acid synthesis through the activity of usnic acid on the production of RNA in Bacillus subtilis (Maciąg-Dorszyntska et al., 2014). These multifaceted processes make the lichen metabolic particularly useful when investigating the growing problem of antimicrobial resistance, since they may reduce the risks of pathogen resistance formation, which is unlikely when using standard single-target antibiotic agents (Figure 1).

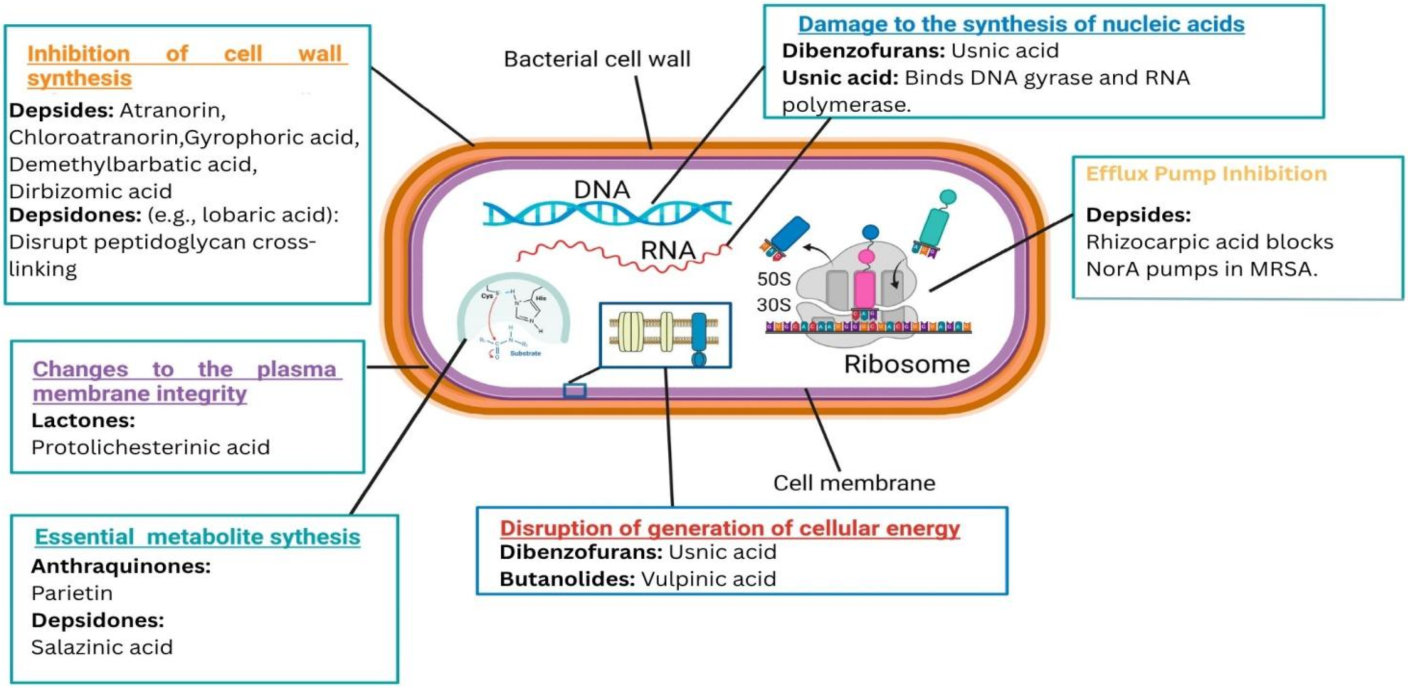

Figure 1. Lichen compounds target all major microbial processes: (1) cell wall/membrane synthesis (depsides/depsidones/lactones), (2) nucleic acid function (dibenzofurans), (3) efflux pumps (anthraquinones), (4) essential metabolites (anthraquinones/depsidones), and (5) energy production (dibenzofurans/butanolides) (modified from Eshboev et al., 2024).

Although these in vitro findings are promising, there are a series of vital issues that need to be surpassed in order to apply lichen compounds into clinical practice. Many bioactive metabolites exhibit a low water solubility such as with atranorin and no profiles are described comprehensively in terms of pharmacokinetics and toxicity. Also, the overall biosynthesis pathways of many lichen metabolites remain unknown although recent advances in genomics have identified key enzymes such as polyketide synthases (PKSs) and biosynthetic gene clusters (BGCs) involved in their production (Kim et al., 2021; Singh et al., 2021). Moreover, large-scale extraction and synthesis must be developed in a sustainable manner that would make these compounds appropriate in large-scale therapeutic use.

This review methodically explores the existing body of knowledge regarding antimicrobial compounds derived from lichens, focusing particularly on their mechanisms of action, biosynthetic routes, and potential applications in clinical settings. By integrating findings from various studies, we intend to underscore both the therapeutic promise of these natural products and the significant challenges that must be addressed to fulfill their clinical potential. Special emphasis is placed on innovative strategies such as nano-encapsulation for enhanced drug delivery and AI-driven approaches for drug discovery and optimization, which could help bridge the divide between laboratory discoveries and practical medical applications.

MATERIALS AND METHODS

Search Strategy and Dates

A systematic literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar between January 1–10, 2024. The search covered publications from 2000 to 2024.

Boolean search strings included:

("lichen" OR "lichen-derived" OR "lichen metabolites") AND ("antimicrobial" OR "antibacterial" OR "antifungal" OR "antiviral")

("lichen" AND "biosynthesis" AND ("PKS" OR "polyketide synthase" OR "biosynthetic gene cluster" OR "BGC"))

("usnic acid" OR "atranorin" OR "depside" OR "depsidone") AND ("mechanism of action" OR "MIC")

Reference lists of included articles were also screened. Only peer-reviewed studies reporting MIC values, antimicrobial assays, mechanisms, or biosynthetic evidence were included.

Extraction and Analysis

72 out of 305 (Initially identified studies) studies were selected after applying systemic inclusion and exclusion criteria for relevant and in-depth study (Figure. 2). Inclusion criteria involved relevant studies focused on major classes of lichen metabolites, their biosynthesis and mechanisms of actions (Table 1) while exclusion criteria involved the publications irrelevant to antimicrobial activity such anticancer, and other diseases resistance via lichen derived compounds.

Table 1. Summary of included studies: compound, organism, MIC, and method.

Compound	Organism Tested	MIC (µg/µL)	Method Used
Atranorin	*B. subtilis*, *Listeria monocytogenes*	0.31	Broth microdilution
Atranorin	*M. tuberculosis*	0.25	Broth microdilution
Usnic acid	MRSA	0.025–0.05	Broth microdilution
Usnic acid	*Candida albicans*	0.001–0.1	Broth dilution
Fumarprotocetraric acid	*B. mycoides*	0.5–5	Broth microdilution
Lobaric acid	*S. aureus*	0.04	Broth microdilution
Diffractaic acid	Zika virus	1.05	Viral inhibition assay
Salazinic acid	*B. cereus*, *L. monocytogenes*	1.51–11.9	Disk diffusion / microdilution
Vulpinic acid	MRSA	0.004–0.042	Broth microdilution
Parietin	*C. albicans*	0.032	Microdilution / photodynamic assay

Quality Assessment

A simplified quality appraisal was applied based on four criteria: (1) clarity of extraction method, (2) identification of compound purity, (3) use of standardized antimicrobial assays (CLSI/EUCAST), and (4) reporting of MIC values.

Most studies showed moderate quality, with consistent descriptions of extraction and antimicrobial testing. However, risk of bias remained due to:

inconsistent reporting of compound purity,
use of non-standardized assays in some studies (e.g., disk diffusion only),
limited replication or lack of positive/negative controls in several studies,
selective reporting (many studies only report strongest results).

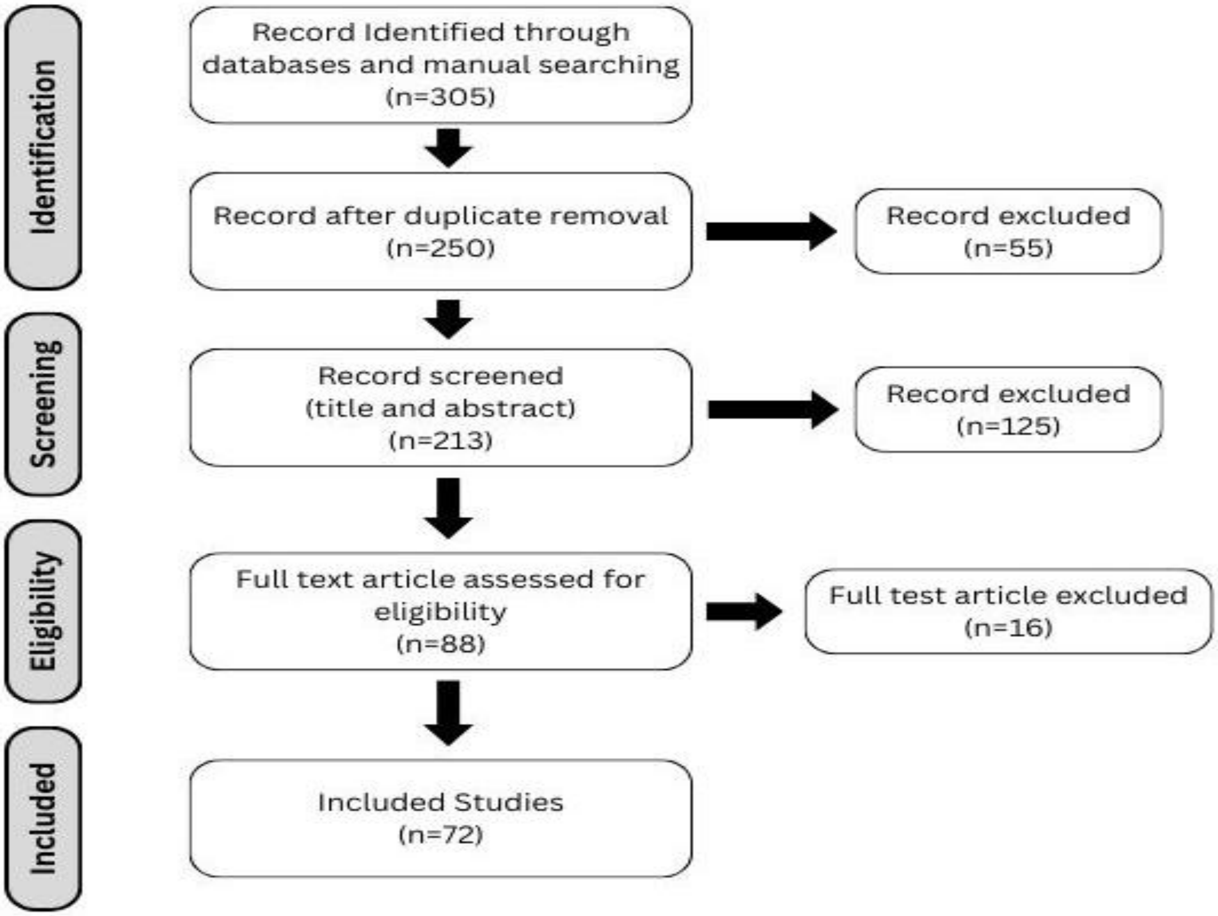

Figure 2. PRISMA diagram flow chart. (n) represents the number of papers.

RESULTS AND DISCUSSION

Lichens Metabolites

Lichens exhibit diverse metabolic diversity which mainly be classified into six classes includes depside, depsidone, lactone, dibenzofuran, anthraquinone, and butanolide (Table 2; Figure. 5).

Depside

This class contain a prominent compound named atranorin, formed by ester linkage of two aromatic cycles (Zhou *et al.,* 2017; Sepahvand *et al.,* 2021). Yilmaz *et al.,* (2004) demonstrated the antibacterial activity of atranorin extracted from *Cladonia foliacea* as it exhibited highest action against *B. subtilis* and *Listeria monocytogenes* with the 0.31 ug/uL of minimal inhibitory concentration (MIC). In another study by Rankovi´c *et al.,* (2008), with the MIC of 0.031 to 0.5 ug/uL, atranorin extracted from *Physcia aipolia* showed strong antibacterial activity, however *Klebsiella pneumoniae*, *Bacillus* spp., *E. coli*, *Enterobacter cloacae* and *S. aereus* experienced lowest MIC. Neeraj et al. (2011) demonstrated the antibacterial properties of atranorin extracted from three lichen species: *Parmotrema nilgherrensis, P. sanctiangelii*, and *Cladonia ochrochlora*. They reported a minimum inhibitory concentration (MIC) of 0.005–0.07 µg/µL against various Gram-positive and Gram-negative bacteria, particularly *Escherichia coli and C. diffluens*. The study also highlighted atranorin's ability to inhibit colony-forming units (CFUs) of both Gram-positive and Gram-negative bacteria during incubation. Similarly, Ranković et al. (2013) observed an MIC range of 0.015–1 µg/µL for atranorin extracted from *Hypogymnia physodes* against *Bacillus mycoides* and *Candida albicans*. Kosanić et al. (2014) reported a comparable MIC range of 0.015–1 µg/µL for atranorin derived from *Cladonia furcata* against *B. mycoides*. In contrast, Micheletti et al. (2021) found that atranorin isolated from *Parmotrema dilatatum* exhibited an MIC of 0.25 µg/µL against *Enterococcus faecium*, *E. coli*, *Staphylococcus aureus*, and *Enterococcus faecalis*.

Goel *et al.,* (2011) carried a study on antifungal activity of atranorin extracted from *Parmelia reticulata* against many pathogenic fungi. MIC of 0.04 ug/uL was observed against the fungi strain of *Sclerotium rolfsii*. In another study by Thuan *et al.,* (2022) atranorin shows MIC of 0.25 ug/uL against *M. tuberculosis* while 65-250 µg/µL against other different strains when extracted from lichen *C. pyxidata*.

Regarding the antiviral activity of atranorin, Vu *et al.,* (2015) demonstrated the virus entry inhibiting and interfering viral replication ability of atranorin when extracted from the *S. evolutum* lichen. Atranorin exhibit the MIC of 0.004–0.006 µg/µL over anti-hepatitis C virus (HCV), however lowest MIC of 0.004-0.005 µg/µL was presented by derivatives of atranorin.

Putra et al. (2020) investigated the inhibitory potential of atranorin on angiotensin-converting enzyme 2 (ACE2), the receptor for SARS-CoV-2, which is the virus responsible for COVID-19. Using advanced computational techniques such as molecular docking and simulation, the study revealed that atranorin could effectively interact with ACE2. Additionally, the researchers evaluated the absorption, distribution, metabolism, and elimination (ADME) properties of atranorin and found that its optimal molecular mass makes it a promising candidate for oral absorption. This highlights atranorin's potential as a biologically active compound with therapeutic relevance. Atranorin also showed an optimum cell membrane permeability with the low level of solubility in aqueous medium and high level of gastrointestinal absorption. Moreover, a strong coupling capability with ACE2 was observed as indicated by value of low energy resulted from the Gibbs free energy calculations of 7.0 kcal/mol.

Huang *et al.,* (2024) carried out an advanced study to observe its antiviral activity against Zika virus using western blot, RT-qPCR, and immunofluorescence by inhibiting viral protein envelope of Zika virus. A detailed illustration of viral protein envelope is shown in Figure 3.

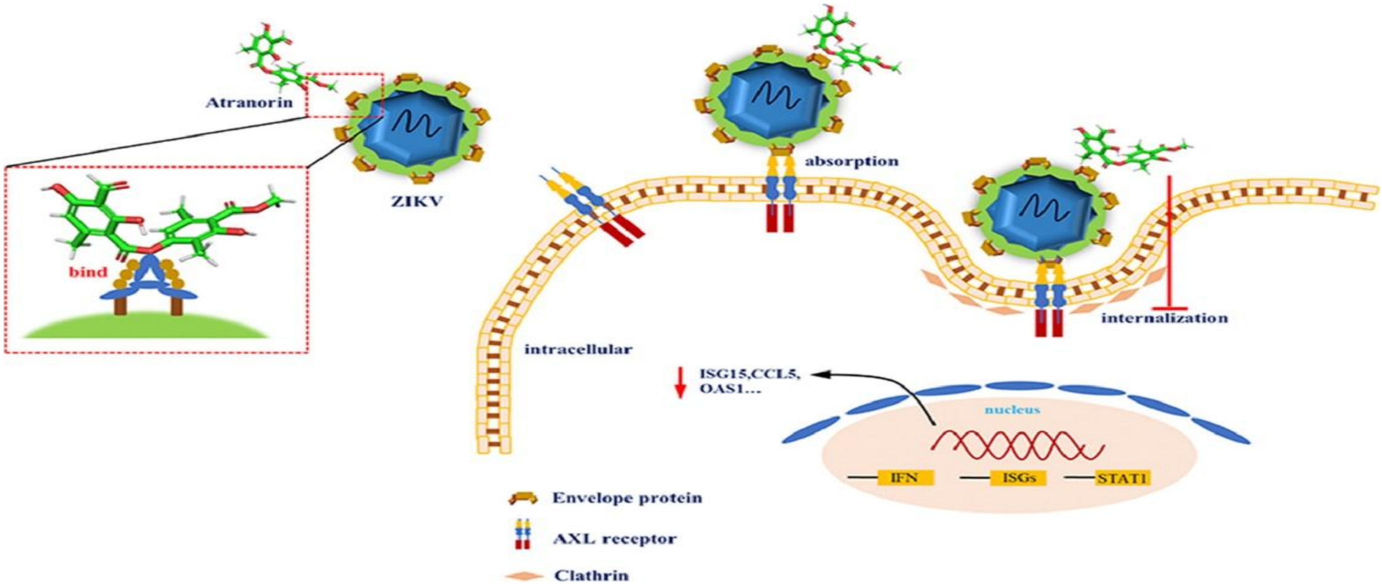

Figure 3. Atranorin inhibition activity against protein envelope of Zika virus (Huang *et al.,* 2024).

Türk *et al.,* (2006) demonstrated the antibacterial activity of another compound of depside class, the chloroatranorin when extracted from *P. furfuracea* lichen via Kirby and Baur disk diffusion method. From 3.14 to 12.5 ug/uL of MIC was observed over the *L. monocytogenes* and *A. hydrophila*. Antifungal activity with MIC of 7.52 ug/uL was reported against *Gaeumannomyces graminis*, *Fusarium* spp., *Penicillium notattum*, and *Aspergillus* spp.

By using the same diffusion method, Candan *et al.,* (2006) determined the antimicrobial activity of gyrophoric acid isolated from *Xanthoparmelia pokornyi* with the MIC of 0.5 to 7.5 ug/uL against *Candida* spp. and *Bacillus* spp. However, MIC value of 0.125 ug/uL was presented against B. mycoides via method of broth microdilution in a study by Kosani´c & Rankovi´c, (2011). Another application of the broth dilution method for determining the antibacterial activity of diffractaic acid, extracted from *Protousnea magellanica*, was conducted by Celenza et al. (2013). This study utilized the broth dilution technique to evaluate the efficacy of diffractaic acid against various bacterial strains, providing insights into its potential as an antimicrobial agent. The method allowed for precise measurement of the compound's inhibitory effects, contributing to a better understanding of its antibacterial properties. In this study, MIC value of 0.064 ug/uL was presented against *S. aureus*.

For the evaluation of diffractaic acid antiviral activity extracted from *U. aciculifera* lichen, Loeanurit *et al.,* (2023) carried a study on chikungunya virus, zika virus, enterovirus, and dengue virus. Diffractiac acid showed a significant activity against dengue and zika virus with MIC value of 0.9 to 1.83 ug/uL and 1.05 ug/uL respectively (Figure 4).

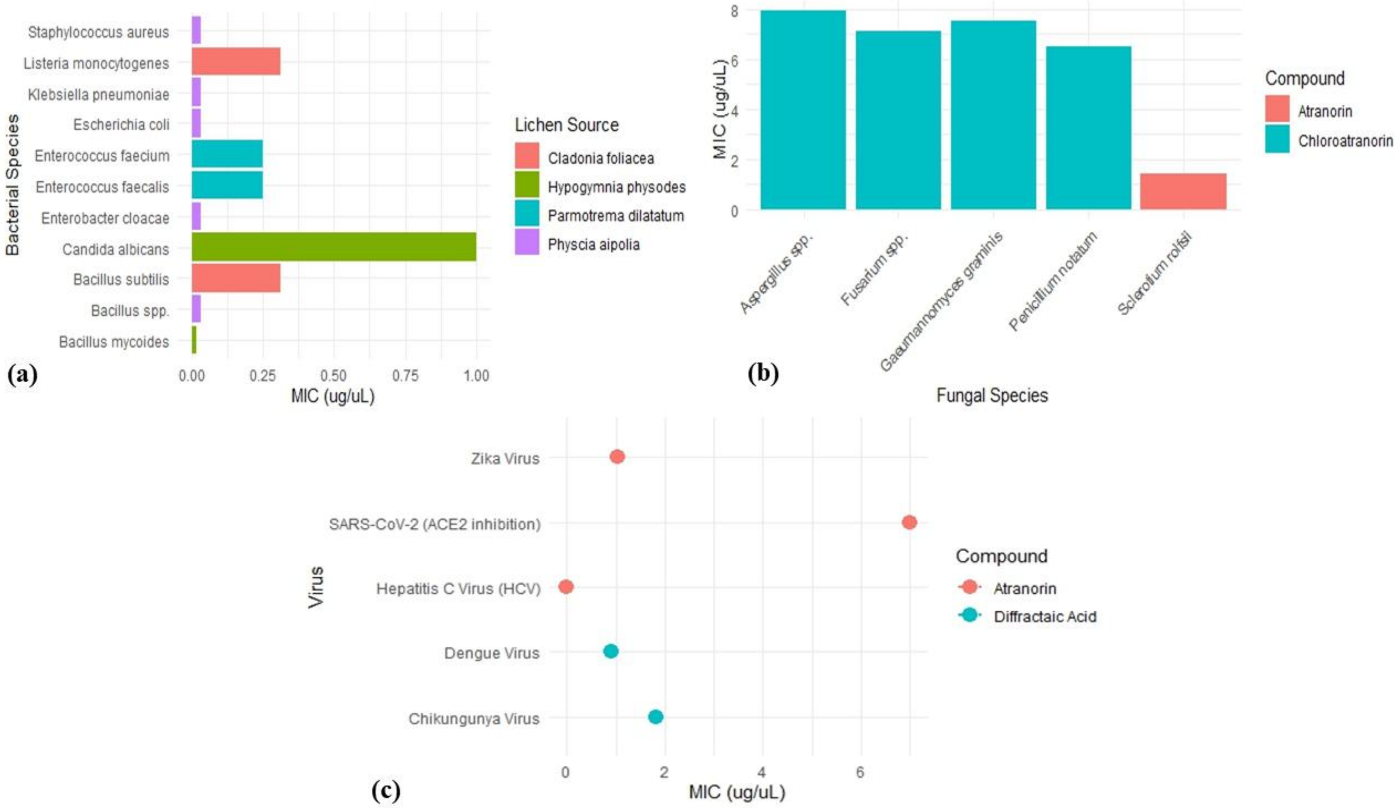

Figure 4. Antimicrobial activity of lichen-derived depsides (a) Antibacterial (b) Antifungal (c) Antiviral Depsidone.

Psoromic acid is most abundant and prominent compound of the depsidone class, having a heterocyclic unit of ester and ether group. Sweidan *et al.,* (2017) investigated its antibacterial activity with the MIC value of 0.0011 to 0.0015 ug/uL and also against *P. gingivalis* with 0.005 ug/uL. In another study by Hassan *et al.,* (2018), its inhibitory effect was observed against teo mycobacterium enzymes; arylamine-N-acetyltransferase and UDP-galactopyranose mutase with the inhibition percentage of 77.4 and 85.8 respectively. Hassan *et al.,* (2019) evaluated its antiviral activity via inhibitory action against human simplex virus 1 and 2 (HSV-1 and HSV-2).

Fumarprotocetraric acid, another compound of the same class exhibits anti-bacterial activity. Fumarprotocetraric acid extracted from *C. foliacea* with the MIC value of 0.5 to 5 ug/uL. Moreover, lowest MIC value was presented against *L. monocitogenes* and *Bacillus* spp. (Yilmaz *et al.,* 2004). However, Neeraj *et al.,* (2011) determined its activity against *C. diffluens* and *P. vulgaris* with MIC values of 24.4 and 24 µg/µL respectively. Thuan *et al.,* (2022) determined its activity against multi-drug resistant isolates with a MIC value of 0.5 ug/uL and also against *M. tuberculosis* H37Ra presenting MIC value of 0.031 ug/uL when extracted from *C. pyxidate*.

Thadhani *et al.,* (2012), carried a study on the antimicrobial activity of another compound of this class; lobaric acid against *E. coli*, *B. subtilis*, *Serovar typhi* and *Salmonella enterica*. However, its antifungal activity was also observed against *A. flavus* via inhibition percentage of 90 and MIC of 0.2 ug/uL. Bhattarai *et al.,* (2013) also demonstrated its inhibition activity against *S. aureus* with MIC of 0.04 ug/uL. An inhibition activity was also observed by Maslowska *et al.,* (2019), against the triphosphate production by RecA enzyme of *E. coli* with the inhibition percentage of 96.8. Paguirigan *et al.,* (2022) also investigated the antimicrobial response of lobaric acid against an actinomycete *Clavibacter michiganensis* subsp *michiganensis* with MIC value of 0.25 ug/uL via method of broth microdilution.

Lobaric acid has demonstrated antiviral activity by inhibiting key viral targets, including the chikungunya virus, non-structural protein 1 (NSP1), and SARS-CoV-2. Studies have shown that lobaric acid exhibits strong binding affinity to these viral components, with a binding energy of -8.6 kcal/mol. This significant binding ability highlights its potential as a promising antiviral agent, particularly in targeting viruses such as chikungunya and SARS-CoV-2, which are of global health concern (Feibelman *et al.,* 2018; Vankadari *et al.,* 2020)

Salazinic acid, another significant compound of this class has been reported to be a strong antimicrobial agent against several fungi and bacteria including *B. cereus, L. monocytogenes, B. subtilis, Aeromonas hydrophila, E. faecalis, Y.*

enterocolitica, S. aureus, P. vulgaris, C. albicans, C. glabrata, P. notatum, A. fumigatus, and *A. niger* with MIC of 1.51 to 11.9 ug/uL (Candan *et al.,* 2007). Another study by Sultana & Afolayan, (2011), determined the MIC value of 0.125 ug/uL against, *E. coli, B. subtilis* and *B. cereus* of salazinic acid when extracted from *U. undulata*. However, Manojlovi´c *et al.,* (2012) observed MIC value of 0.015 to 1 ug/uL against Gram +ve, and –ve bacteria when extracted from *P. saxatilis*. Moreover, salazinic acid extracted from *P. lichexanthonicum* also exhibit antibacterial activity with MIC value of 0.031 ug/uL against *E. faecalis* (Micheletti *et al.,* 2021).

Dibenzofuran

This class includes one of the strongest antimicrobial compound, usnic acid which has effective antibacterial inhibiting activity ability. Sultana and Afolayan, (2011), studied its antibacterial response with MIC value of 0.008 µg/µL against *B. subtilis* and *B. cereus* when extracted from *P. caperata*, however same activity was observed against *B. mycoides* and *B. subtilis* with MIC of 0.8 µg/µL by Manojlovi´c *et al.,* (2012). Another extraction aided by method of broth microdilution, showed strong antibacterial activity against *U. barbata* with MIC of 0.8 ug/uL (Rankovi´c *et al.,* 2012). Maciąg-Dorszy´nska et al. (2014), observed no antibacterial response by usnic acid but determined a phenomenon of RNA synthesis inhibition in *Vibrio harveyi*. Mechanism behind RNA synthesis inhibition was also determined as usnic acid stops the entry of precursors to nucleic acid and protein synthesis in *B. subtilis* and *S. aureus*.

Methicillin-resistant *Staphylococcus aureus* (MRSA) strain experienced strong antimicrobial activity by usnic acid with MIC value of 0.025 to 0.05 ug/uL via method of broth microdilution (Gupta *et al.,* 2012). However, an interactive study based on usnic acid relative activity with other antibiotics against MRSA present MIC value of .002 to 0.004 ug/uL (Segatore *et al.,* 2012). Another investigation carried out along with the norfloxacin via method of checkerboard microdilution determined MIC value of 0.25 to 0.5 ug/uL when observed in *M. abscessus* strains (Ramis *et al.,* 2018).

Regarding the evaluation of its antifungal and antibacterial activity, (Pires *et al.,* 2012), determined the inhibition activity of usnic acid against several bacteria with MIC value of 0.001-0.1 ug/uL via method of broth dilution. However, antifungal response was also determined against *Candida* spp. and *Aspergillus* spp. Another study by Micheletti *et al.,* (2021) observed the antibacterial response of usnic acid against *E. faecalis* with MIC value of 0.002 ug/uL when extracted from *U. subcavata*.

Lactone

Protolichesterinic acid is prominent member of lactone class, it exhibits strong antimicrobial activity against several infectious microbes such as B. *subtilis, E. coli, L. monocytogenes* and *Pseudomonas aeruginosa*. In a study by Bellio *et al.,* (2015), it has been determined the antibacterial response of protolichesterinic acid via method of checkerboard microdilution against several Gram +ve and –ve bacteria presented MIC value of 0.00024–0.064 µg/µL. Goel *et al.,* (2011), have explored its antimicrobial activity over *Rhizoctonia solani* and *Phytium debaryanum* with MIC value of 0.063 ug/uL and inhibition percentage of 67 and 78% respectively. Sasidharan *et al.,* (2014), determined it activity against four fungal strain with MIC value of 0.00012–0.008 µg/µL. However, *Trichophyton rubrum* presented lowest MIC value**.**

Butanolide

Vulpinic acid is another notable antimicrobial compound within this class, demonstrating potent antibacterial activity against both anaerobic and aerobic bacteria. It has shown effectiveness against pathogens such as *Clostridium perfringens*, *Bacteroides thetaiotaomicron*, *B. vulgatus*, *B. fragilis*, *B. ruminicola* subsp. *brevis*, *B. loeschii*, *Propionibacterium acnes*, *Enterococcus faecalis*, *E. faecium*, and methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The minimum inhibitory concentration (MIC) values for vulpinic acid range from 0.004 to 0.042 µg/µL, underscoring its strong antibacterial potential against a broad spectrum of bacteria. (Paguirigan *et al.,* 2022).

To assess antiviral activity of lichen extracted compounds, Joshi et al. (2021) carried out a study on more than 400 compounds extracted from lichens and determined their inhibition activity against protease which is responsible for viral replication and transcription in SARS-CoV-2. However, scientists carried out the applications of computational tools to investigate about drug resembles properties, profile of toxicity level, interaction of protein-ligand of these compounds. Results shows rhizocarpic acid and calycin as strong inhibitors of protease. Calycin and rhizocarpic acid bind to the active site through hydrogen bonds and hydrophobic interactions with key amino acids, yielding binding energies of -8.4 kcal/mol and -8.7 to -9.11 kcal/mol, respectively.

Furthermore, protein-ligand stability analyses revealed binding free energy values of –42.42 kJ/mol for calycin and –57.85 kJ/mol for rhizocarpic acid, indicating that both formed stable complexes with MproCalycin and rhizocarpic acid demonstrate promising antiviral potential against SARS-CoV-2, with binding free energies comparable to reference molecule X77 (-91.78 kJ/mol), warranting further research for development as novel antiviral agents (Joshi *et al.,* 2021).

Anthraquinone

This class contain Parietin as prominent compound as extracted form *Xanthoria parietina* as it shows antimicrobial activity over *S. aureus, E. faecalis* and *P. mirabilis* with MIC of 0.008 to 0.06 µg/uL. However, it also exhibits antifungal activity against *Rhyzoctonia solani*, *Botrytis cinerea* and *C. albicans* with MIC value of 0.032 ug/uL (Basile *et al.,* 2015). In another study, a compound isolated from the lichen *Teloschistes flavicans* was assessed for its bactericidal properties using the microdilution method. The evaluation focused on its activity under light exposure against *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli,* and *Pseudomonas aeruginosa*. Under dark conditions, the minimum inhibitory concentration (MIC) exceeded 0.25 µg/µL for all tested bacterial strains. However, when actinic light irradiation was applied, the MIC dropped to values below 0.00013 to 0.25 µg/µL. Specifically, a MIC of less than 0.13 µg/µL was observed for *S. epidermidis* ATCC 12228. Notably, no minimum bactericidal concentration (MBC) was detected in the absence of light. Under actinic irradiation, however, an MBC of 0.5 µg/µL was recorded for *P. aeruginosa* ATCC 27853 (Comini *et al.,* 2017).

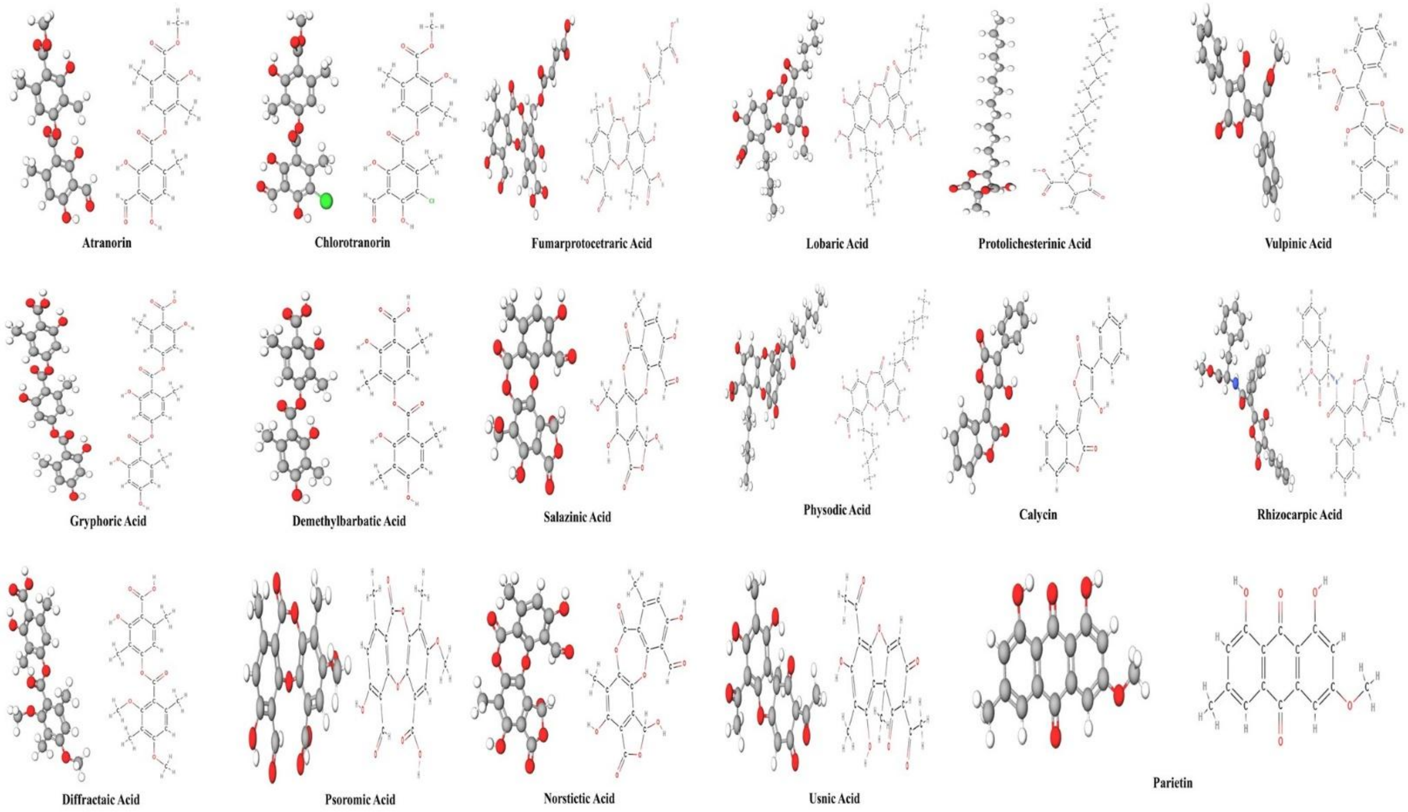

Figure 5. Compounds discussed in this review. Atranorin, Chloroatranorin, Diffractaic Acid, Gryphoric Acid, Demethyl barbatic Acid, Psoromic Acid, Salazinic Acid, Lobaric Acid, Physodic Acid, Fumarprotocetraric Acid, Norstictic Acid, Usnic Acid, Protoliches-terinic Acid, Vulpinic Acid, Calycin, Rhizocarpic Acid, Parietin.

Table 2. Antimicrobial activities of lichen derived compounds, their class, and extraction source.

Class	Compound	Extraction Source	Activity	Affected Microbes
Depside	Atranorin	*Cladonia foliacea, Physcia aipolia, Gherrensis, Hypogymnia physodes, C. furcate, P. dilatatum, Parmelia reticulate, Stereocaulon alpinum,*	Antibacterial	*Mycobacterium tuberculosis, B. mycoides, Enterococcus cloacae, E. faecium*

		Cladonia foliacea, Physcia aipolia, C. ochrochlora, Parmotrema nil Gherrensis, P. sancti-angelii, Hypogymnia physodes, C. furcate, P. dilatatum, Parmelia reticulate, Stereocaulon alpinum	Antifungal	*Candida albicans, C. glabrata, C. diffluens, Rhizoctonia bataticola, R. solani, Fusarium oxysporum, F. udum, Pythium debaryanum, P. aphanidermatum, Aspergillus fumigatus, A. flavus, Botrytis cinerea, Mucor mucedo, Paecilomyces variotii, Penicillium verrucosum, P. purpurescens, Trichoderma harzianum, Sclerotium rolfsii*
		S. evolutum,	Antiviral	SARS-CoV-2, Anti-hepatitis C virus (HCV)
	Chloroatranorin	*Cladonia foliacea, Physcia aipolia, C. ochrochlora, Parmotrema nil Gherrensis, P. sancti-angelii, Hypogymnia physodes, C. furcate, P. dilatatum, Parmelia reticulate, Stereocaulon alpinum,*	Antibacterial	*Listeria monocytogenes, Aeromonas hydrophila, B. subtilis, B. cereus, P. vulgaris, S. aureus*
		P. furfuracea, C. furcate, C. ochrochlora	Antifungal	*Penicillium notatum, Gaeumannomyces graminis, Fusarium spp., Aspergillus spp., C. glabrata, C. albicans*
	Gyrophoric acid	*Xanthoparmelia pokornyi, Ramalina siliquosa*	Antibacterial	*B. subtilis, B. cereus, B. mycoides, E. cloacae, E. faecalis, E. coli, Klebsiella pneumonia, Listeria monocytogenes, Staphylococcus aureus*
		Xanthoparmelia pokornyi, Ramalina siliquosa	Antifungal	*Fusarium oxysporum, Botrytis cinerea, Mucor mucedo, Trichoderma harzianum, Aspergillus fumigatus, A. flavus, C. albicans, C. glabrata, P. verrucosum, P. purpurescens, Paecilomyces variotii*
	Demethylbarbatic acid	*Ramalina siliquosa*	Antibacterial	*S. gordonii, P. gingivalis*
	Dirbizomic acid	*Protousnea magellanica, Usnea subcavata,*	Antibacterial	*Staphylococcus haemolyticus, S. warneri, S. aureus, Mycobacterium tuberculosis*
		U. aciculifera,	Antiviral	Dengue virus, Zika virus, Enterovirus and Chikungunya Virus
Depsidone	Parellic acid	*Protousnea magellanica*	Antibacterial	*S. gordonii, P. gingivalis*
	Fumarprotocetraric acid	*C. foliacea, C. rangiferina,*	Antibacterial	*Bacillus mycoides, B. cereus, S. aureus*
		C. pyxidate	Antifungal	*Aspergillus fumigatus, A. flavus, C. diffluens, Botrytis cinerea, Trichoderma harzianum, P. purpurescens, Paecilomyces variotii*
	Lobaric acid	*S. alpinum,*	Antibacterial	*Clostridium sporogenes, C. tertium, C. butyricum, Clostridium sordelli, Mycobacterium aurum, Bacillus subtilis, Escherichia coli, Salmonella enterica (S. enterica), Aspergillus flavus (A. flavus) Staphylococcus aureus (including MRSA strains)*

		S. alpinum	Antiviral	SARS-COV-2, Chikungunya Virus
	Salazinic acid	*U. undulata, P. saxatilis, P. lichexanthonicum*	Antibacterial	*Bacillus subtilis (B. subtilis), B. cereus, B. mycoides, Aeromonas hydrophila (A. hydrophila), Proteus vulgaris, S. epidermidis, Enterococcus faecium (E. faecium), S. faecalis, Shigella sonnei (S. sonnei)*
		U. undulata	Antifungal	*Candida glabrata (C. glabrata), C. albicans, Penicillium notatum, Aspergillus fumigatus (A. fumigatus), A. niger*
	Physodic acid	*P. furfuracea*	Antibacterial	*Escherichia coli, Klebsiella pneumonia, Bacillus cereus (B. cereus), B. subtilis,*
		P. furfuracea	Antifungal	*C. albicans, Aspergillus flavus*
	Norstictic acid	*Tonina candida*	Antibacterial	*B. mycoides (B. mycoides), B. subtilis, Escherichia coli, Klebsiella pneumonia*
		Tonina candida	Antifungal	*C. glabrata (C. glabrata), C. albicans, Aspergillus flavus, Penicillium purpurescens (P. purpurescens), P. verrucosum*
Dibenzofuran	Usnic acid	*P. caperata, U. barbata, U. subcavata,*	Antibacterial	*Mycobacterium aurum, Mycobacterium spp. Staphylococcus aureus (including MRSA strains), Staphylococcus haemolyticus, Staphylococcus epidermidis, Bacillus subtilis*
		U. barbata	Antifungal	*Candida spp., C. albicans, Aspergillus flavus Aspergillus spp. Penicillium purpurescens*
Lactone	Protolichesterinic acid	*P. lichexanthonicum*	Antibacterial	*Bacillus subtilis, Escherichia coli, Staphylococcus aureus (including MRSA strains)*
		P. lichexanthonicum	Antifungal	*Aspergillus flavus, Candida albicans, Rhizoctonia solani, Pythium debaryanum, Trichophyton rubrum (T. rubrum)*
Butanolide	Vulpinic acid	*Letharia vulpina*	Antibacterial	*B. vulgatus, Clostridium perfringens, E. faecalis, Staphylococcus aureus*
		Letharia vulpina	Antifungal	*Sclerotinia sclerotiorum, Diaporthe eres (D. eres)*
	Calycin	*Letharia vulpina*	Antiviral	Coronavirus
	Rhizocarpic acid(L-Phenylalanine)	*Letharia vulpina*	Antiviral	Coronavirus
Anthraquinone	Parietin	*Xanthoria parietina,*	Antibacterial	*E. coli, P. aeruginosa, P. mirabilis, E. faecalis, S. epidermidis*
		Teloschistes flavicans	Antifungal	*Botrytis cinerea, Rhizoctonia solani, C. albicans*

Bioactive Compounds Synthesis

Depsides

Kim *et al.,* (2021) carried a genetically advanced study on several families of lichens to investigate and point out the genes involved in atranorin synthesis. This study extensively analyzed the polyketide synthases (PKSs) enzyme to confirm the biosynthetic involvement of biosynthetic gene cluster (BGC) in atranorin production. A comprehensive analysis of polyketide synthases in *Cladonia* and other several Antarctic lichens confirms the extensive diversity of BGC in 45 lichen families which involved in atranorin production. Expression of PKS gene named atr1 was found extensively in many lichens as precursor of atranorin and other depsides production. Moreover, phylogenetic investigation also confirms the depsides synthesis ability of Atr1 gene (Kim *et al.,* 2021).

Singh *et al.,* (2021), observed production of depsides from lichens aided by an enzyme named reducing polyketide synthases (NR-PKSs). NR-PKSs synthesize depsides by linking different aromatic rings via ester linkages. This study was carried out on *Pseudevernia furfuracea,* revealed that NR-PKSs synthesizes the depsides compounds with the help of a specific gene cluster known as biosynthetic gene clusters (BGCs). Besides NR-PKSs, Fatty acid synthases such as HexA and HexB also helps in the production of depsides by synthesizing hexanoyl which acts as starter and also attach side branches and chains for completion and diversification of depsides compound (Singh *et al.,* 2021).

Depsidone

Depsidone production is same as that of depsides but with an additional ether linkage of aromatic ring as investigated by Sing *et al.,* (2021). Cytochrome P450 enzymes with NR-PKSs encoded with BGCs initiates the ether linkage between depsides aromatic rings. This expression of cytochrome P450 enzymes enables the conversion of depsides to depsidones. Moreover, Ureña-Vacas *et al.,* (2022), identified PKSs involvement along with fatty acid synthases (HexA and HexB) via different methods like advance genomics and metatranscriptomics in the production of depsidones.

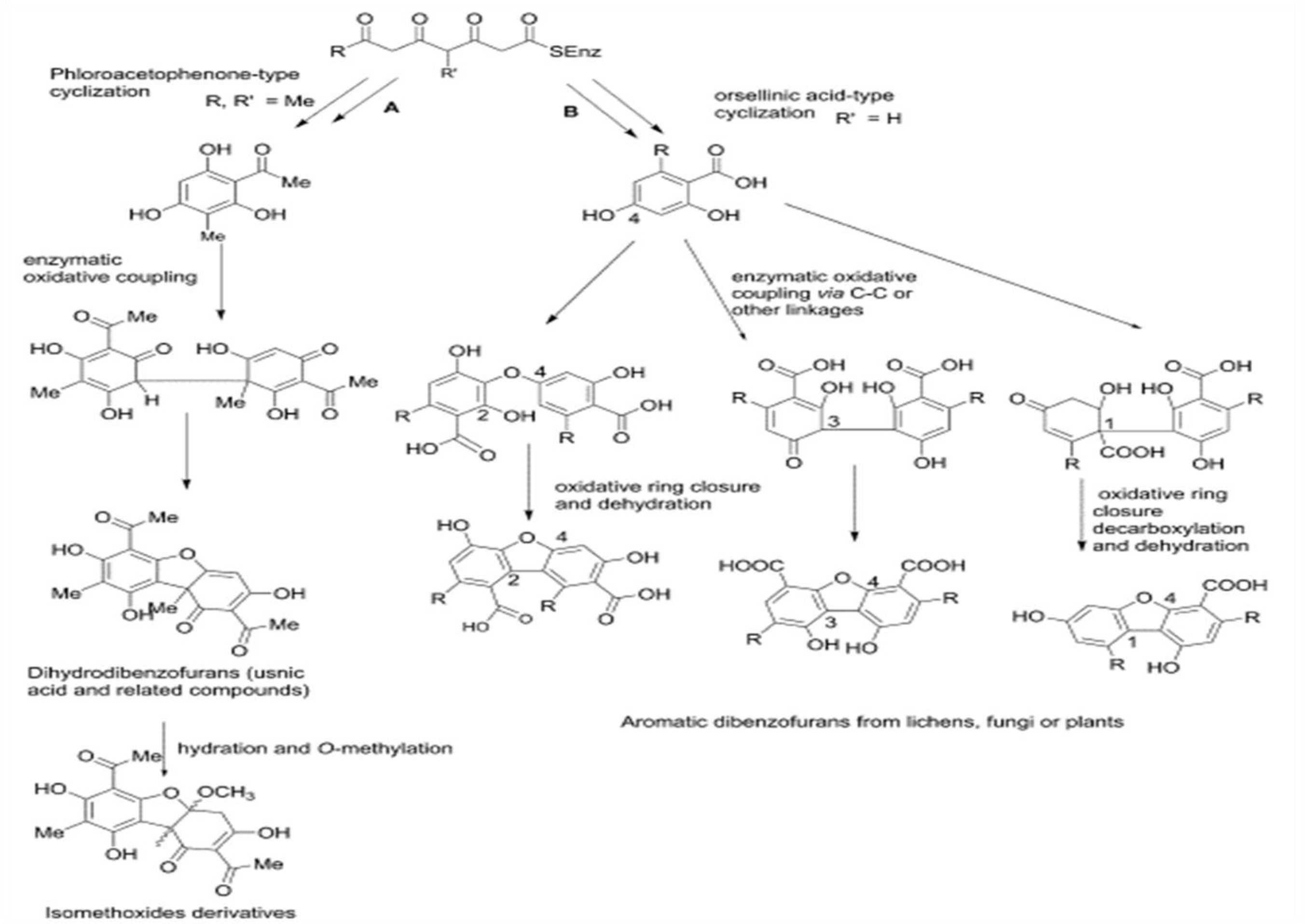

Figure 6. Dibenzofuran and its derivatives synthesis overview.

Dibenzofuran

PKSs in addition with acetyl-CoA and 3-malonyl-CoA develop a backbone of tetraketide in linear sequence for dibenzofurans and its derivatives production as studied by Talapatra & Talapatra, (2015) (Figure 6). Production of compounds of dibenzofurans are formed via two pathways either by linkage of carboxylic group and hydroxyl group or via C-C bonding of orsellinic acid with further dehydration and decarboxylation (Talapatra & Talapatra, 2015). Abdel-Hameed *et al.,* (2016) explored the BGCs involvement in usnic acid production in *Cladonia uncialis* using methylphloroacetophenone.

Lactone

PKSs are involved in lactone compounds synthesis but aided by acyl-CoA as precursor to rearrange and assemble the polyketides chains (Pichler *et al.,* 2023). Uriac *et al.,* (2024), investigated the production hydroxy-lactones via δ-keto acids isomerization influenced by aromatic carboxylic acid skeleton and ortho-substituted 2-oxoalkyl chains. A recent study by Sepúlveda *et al.,* (2022), identified new lactone compounds in *Cladonia metacorallifera* (Fumarprotocetraric acid, peak 5 and 7) formed by acetate-polymalonate condensation via oxidation and localization (Figure 7).

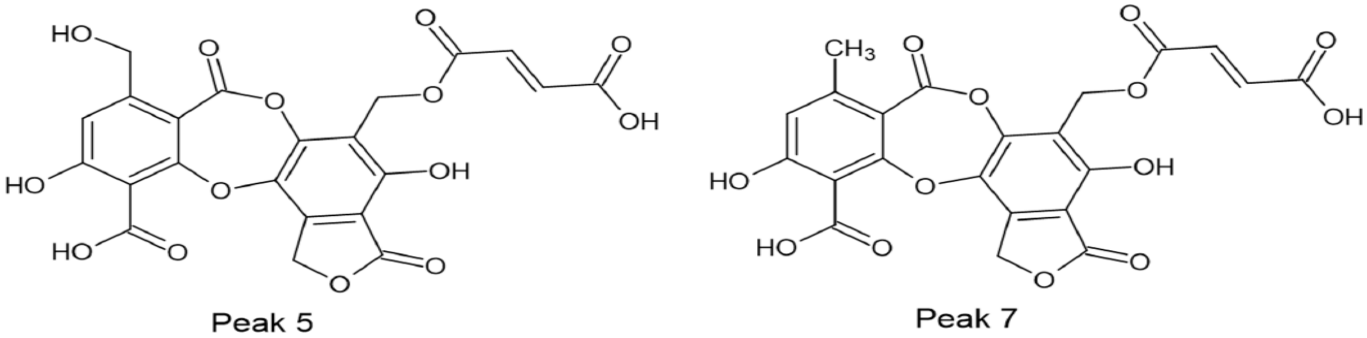

Figure 7. Newly identified fumarprotocetraric acid, Peak 5 & Peak 7 (Sepúlveda *et al.,* 2022).

Butanolide

PKSs with acetyl-polymalonyl (polyketide) pathway encoded in BGCs aided by microorganisms prepare butanolide in lichens. BGCs encodes the key enzymes that are involved in butanolide compounds synthesis such as polyketides and nonribosomal peptides which then initiates the butanolide compounds synthesis (Shishido *et al.,* 2021). However, specific biosynthesis pathway of butanolides production is still unexplored.

Anthraquinone

Anthraquinone production mechanism is different from previous classes. Its production involves the multifunctional enzymatic domains such as ketoacyl synthase and acyltransferase. Ketoacyl synthase and acyltransferase extensively adds the acetate or malonate units to growing chain of polyketides to produce anthraquinone (Gershenzon & Dudareva, 2007). A structured comparison of computational and experimental biosynthesis evidence is provided in Table 3 to support the above distinctions.

Table 3. Comparison of computational vs. experimental biosynthesis evidence of lichen-derived compounds

Category	Evidence Type	Key Findings	Compounds / Pathways	References
Experimental Evidence	Gene cluster (BGC) identification validated by laboratory methods	De novo genome sequencing identified a putative usnic acid biosynthetic gene cluster; supported by chemical profiling and correlation analyses.	Usnic acid (dibenzofuran class)	Abdel-Hameed et al., 2016
	Heterologous expression confirming PKS function	Genetic dereplication + heterologous expression linked a PKS gene (atr1) directly to atranorin biosynthesis.	Atranorin (depside class)	Kim et al., 2021

	Metabolomics + genomics confirmation of BGC roles	Comparative genomics identified NR-PKS and cytochrome P450 enzymes responsible for depside/depsidone interconversion.	Olivetoric & Physodic acid pathways	Singh et al., 2021
	Metatranscriptomics showing active pathways	Transcript-level expression of PKSs and fatty-acid synthases supports active biosynthesis of depsidones.	Depsidone class (e.g., salazinic, fumarprotocetraric acid)	Ureña-Vacas et al., 2022
	Chemical structure confirmation of new lactones	Structural elucidation by NMR confirmed novel lactone derivatives from *Cladonia metacorallifera*.	Fumarprotocetraric-acid-derived lactones	Sepúlveda et al., 2022
Computational Evidence	In silico BGC prediction	Genome mining predicted numerous putative BGCs associated with polyketides and nonribosomal peptides in *Cladonia* spp	Butanolide, depside, depsidone precursors	Shishido et al., 2021
	Molecular docking studies (drug interaction predictions)	Docking simulations predicted strong binding of atranorin to ACE2 and viral proteins; not validated experimentally.	Atranorin; antiviral pathways	Putra et al., 2020; Huang et al., 2024
	Docking for SARS-CoV-2 protease inhibitors	Computational screening found rhizocarpic acid and calycin to strongly bind Mpro (main protease).	Rhizocarpic acid, calycin	Joshi et al., 2021
	Predicted PKS catalytic mechanisms	Predicted tetraketide formation and rearrangement in dibenzofuran synthesis using theoretical PKS models.	Usnic acid and related dibenzofurans	Talapatra & Talapatra, 2015
	Computational modeling of anthraquinone formation	Enzymatic pathway proposed for anthraquinone synthesis; lacks biochemical validation.	Parietin and related anthraquinones	Gershenzon & Dudareva, 2007

Antimicrobial Activity Mechanisms

Inhibition of Cell Wall Formation and Cell Division

Vulpinic acid from extracted from *Letharia vulpine,* significantly inhibits the cell wall formation and disrupts the cell division in microbes. Different studies on methicillin-resistant Staphylococcus aureus (MRSA) revealed that *L. vulpine* extracted compounds inhibits the cell membrane permeability, as confirmed by the uptake of propidium iodide, which glows while binding with DNA in cells (Shrestha *et al.,* 2016). Further transmission electron microscopy also reveals the disturbed cell division by interfering with FtsZ proteins that are main protein in cell division of bacteria (Shrestha *et* *al.,* 2016). Although the extracts don't directly interfere the cell division but it significantly reduces the bacterial potential thus highlighting the as novel bacterial pathway targeting antimicrobial agent.

Inhibition of Efflux Pump

Efflux pumps are the active transporter proteins in microbes that actively reduce the antibiotic effects in microbes this induces the resistance against antibiotic compounds. Kokubun *et al.,* (2007), revealed in his study about the inhibition of efflux pumps in methicillin- and multidrug-resistant *S. aureus* by lichen derived antimicrobial compounds such as rhizocarpic acid and hybocarpone. Both the compounds were actively possessing inhibitory activity against MRSA strains but hybocarpone was found to be more active with an MIC value of 4 to 8 ug/uL. Both the compounds inhibit efflux pumps via interfering efflux pump compounds assembly, efflux pump powering energy sources blockage, or altering the genotypic modulation of efflux pump regulating genes (Ahirrao *et al.,* 2022).

Inhibition of RNA/DNA Protein Synthesis

Lichen-derived compounds such as usnic acid actively inhibits the RNA and DNA synthesis in microbes via inhibiting their replication and transcription processes (Dorszyńska *et al.,* 2014). Dorszyńska *et al.,* (2014), investigated in his study about the RNA and DNA inhibition in *B. subtilis* and *S. aureus* by usnic acid which interfere the replication and transcription process via preventing elongation and suppressing RNA synthesis. However, variable resistance results shown by *E. coli* and *Vibrio harveyi* indicates that the mechanism may vary across different bacteria.

CONCLUSIONS

Despite an existed extensive research on lichen-derived antimicrobial compounds, there still remains some significant research gaps on understanding a complete antimicrobial potential and applicability. Most of the existing studies are carried out as in vitro, but there is lack of sufficient research on their pharmacogenomics, toxicity and in vivo effectiveness. Moreover, bioactive compounds biosynthesis pathways are poorly explained, requiring further genomic and metabolic investigations. Future research must focus on advancements in extraction methods for increased availability and explore advanced formulations such as nano-encapsulation regarding antimicrobial resistance (AMR). Advanced bioinformatics and computational techniques such AI-driven drug discovery and molecular docking can further enhance the identification of novel significant lichen-derived antimicrobial compounds.

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COMPETING OF INTEREST

No conflicts of interest have been disclosed by the authors.

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