SCICELL

Nova Biotechnol Chim (2022) 21(1): e1075
DOI: 10.36547/nbc.1075

Nova Biotechnologica *et* Chimica

Biologically active orcinol-based secondary metabolites originated from lichens

Boddu Rama Krishna[1,✉], Narayana Rao Gundoju[2], Tiruveedhula Somasekhar[3], Waill Elkhateeb[4], Ghoson Daba[4]

[1]*Department of Energy Engineering and School of Energy and Chemical Engineering, Ulsan National Institute of Science and Technology, Ulsan 44919, Republic of Korea*
[2]*Department of Chemistry, M. R. Degree College, Fort, Andhra Pradesh 535002, India*
[3]*Department of Chemistry, S.V.R.M College Nagaram, Guntur, Andhra Pradesh 522268, India*
[4]*Chemistry of Natural and Microbial Products Department, Pharmaceutical Industries Division, National Research Centre, Dokki, Giza 12622, Egypt*

✉Corresponding author: *bodduramakrishna87@gmail.com*

Article info

Article history:
Received: 1st August 2021
Accepted: 8th November 2021

Keywords:
Lichens
Natural products
Secondary metabolites

Abstract

Lichens have attracted considerable interest since ancient time due to their medicinal properties. Lichen produce a variety of orcinol-based compounds such as xanthones, anthraquinones, dibenzofurans, depsides, and depsidones. Several related compounds have shown potent bioactivities as antiviral, antioxidant, anti-herbivore, insecticidal, antifungal, and anticancer. Lichens have been employed as traditional medicines, and these are continuing to be of great interest for their biotechnological potential. The purpose of this review was to systematically evaluate the literature on the orcinol based biologically active secondary metabolites of lichen.

Introduction

Lichens are extraordinary self-supporting symbiotic microorganisms, formed by both alga (cyanobacteria) and fungi. This association is very useful for both organisms. The alga carries chlorophyll and is called photobiont. The fungi build the structure of the lichen thalli, the partner may be referred to as the mycobiont (De Priest 2004). Alga produces primary metabolites by photosynthesis (sugars, amino acids, carotenoids, and starch) for fungus growth and, which in turn gives a surface to the algae for the protection against dehydration (Podterob 2008). The fungus and the alga are in a mutualistic relation and they are capable of dealing with ecological conditions, that neither of them would be able to survive on its own (Margulis and Barreno 2003; Bates *et al.* 2011).

Some lichenized fungi synthesized secondary metabolites without photobiont under certain conditions, for example the lichen *Lecanora dispersa* contains 2,7-dichlorolichexanthone as the main secondary metabolite, but cultured spore isolates, growing in absence of the alga, produced from lichen genus *Pannarin* (Leuckert *et al.* 1990). A lichen thalli consist of cortex layers, algal layer and medulla. Naturally, lichens grow in a very slow and radial manner that is measured in millimeters per year. Lichen produces different secondary metabolites (SMs), and most of them occur exclusively in this symbiotic organism (Boustie and Grube 2005; Jayanthi *et al.* 2012; Xu *et al.* 2016).

During the complex metabolic interaction between mycobiont and photobiont, the mycobiont produce important secondary metabolites and accumulate as extracellular tiny crystals on the external sides of the hyphae. Lichen-derived secondary metabolites are small and complex molecules, which represent about 20 % of lichens total dry weight (Muggia *et al.* 2009). They act as protectors of the thalli against attacks by pathogens, herbivores, competitors, and different external abiotic conditions including high UV irradiation. Approximately 1,050 lichen secondary metabolites have been extracted and identified to date. Most well-known lichen substances are members of phenolic compounds such as dibenzofurans, anthraquinones, depsides, depsidones, depsidones, triterpenes, gamma lactones, and pulvinic acid derivatives.

Lichens synthesized SMs, mainly Acetyl-Polymalonate pathway (APP), Shikimic acid pathway (SAP) and Mevalonic acid pathway (MAP) (Culberson and Armaleo 1992; Çobanoğlu *et al.* 2016). The polyketide biosynthetic pathway seems to be in charge of majority of the phenolic lichen compounds, while pulvinic acid derivatives derived from shikimic pathway and the abundance of di and triterpenoids, carotenoids, steroids found in lichens are synthesized via the mevalonate pathway (Stocker-Wörgötter 2008). On the other hand, secondary metabolites originated from the fungal partner of the lichen, are placed on the surface of the fungal hyphae. Most of these fungal secondary metabolites are phenolics, crystalline in nature and soluble in organic solvents. However, the carbon is essential for lichen secondary substances biosynthesis and is obtained by the algal partner during photosynthesis. The carbohydrates involved in this process depend mainly on the algae itself and are mostly glucose and sugar alcohols (polyols) (El-Garawani *et al.* 2020).

Orcinol based lichen secondary metabolites

Orcinol and its derivatives have been considered the most common mono-hydric phenolic compounds found in lichens (Stepanenko *et al.* 2002; Férnandez-Morano *et al.* 2015; Moreira *et al.* 2015). As shown in Fig. 1, the major orcinol based compounds of lichens are produced by the polyketide route. In this pathway, two coenzymes such as acetyl-CoA and malonyl-CoA are utilized in lichen substances biosynthesis. Particularly, orcinol-based secondary metabolites produced by orsellinate type of cyclization. Orsellinic acid and its homologues are the most existing mononuclear structural units of polyketide-related lichen substances.

Orcinol type of secondary metabolites (orcinol and orsenillic acid based derivatives, e.g. lecanoric acid, montagnetol, trivaricacid, gyrophoric acid, evernic acid, methyl orsenillate, and erythrin) (Subba Rao and Seshadri 1941; Boustie and Grube 2005; Thadhani *et al.* 2011).

β-orcinol type of secondary metabolites (β-orcinol and β-orsenillic acid based derivatives, (e.g. diffractic acid, pannarin, stictic acid, atranorin and vicanicin acid (Kathirgamanathar *et al.* 2004; Papadopoulou *et al.* 2007).

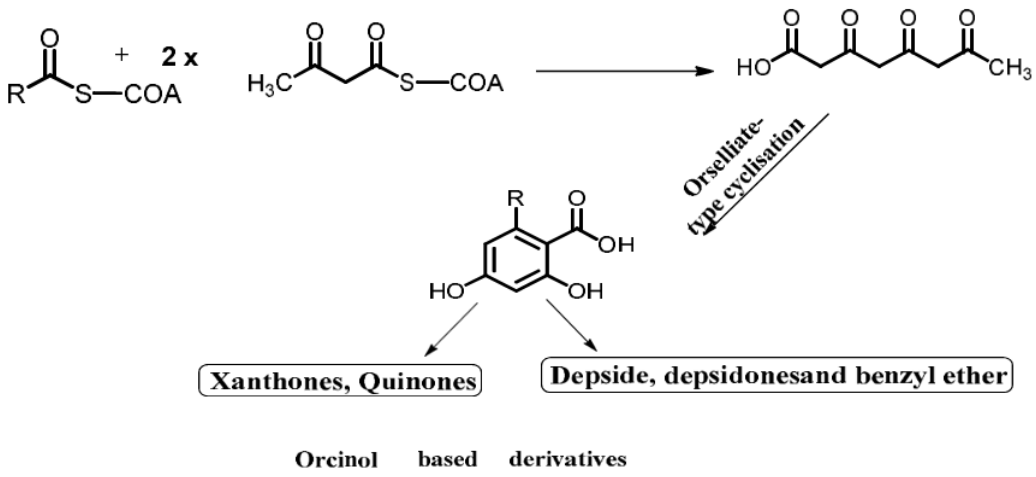

Fig. 1. Biosynthesis of orcinol based lichen secondary metabolites.

Depsides

Depsides are phenolic compounds, constructed through intermolecular esterification of two or more orsenillic acid units. For example, the carboxylic acids of one unit are joined to the hydroxyl para to the carboxylic acid of the second unit, such esterification leads to para-depside. If the esterification occurs through meta hydroxyl with respect to the carboxylic acid called meta-depside (Seshadri 1944; Elix and Wardlaw 1986). Some of the important examples of this class are lecanoric acid, gyrophoricacid, erythrin, etc.

Depsidones

Depsidones are the important class of oxygenated heterocyclic compounds derived from lichen species. Depsidones consist of both ester and ether linkage synthesized from the depsides. The depsidones biosynthesis involves oxidative coupling of depsides, which are normally biosynthesized from the condensation of orsellinic acid and orcinol derivatives. However, depsidones biosynthesis may actually operate through a depside intermediate pathway (Hirayama *et al.* 1974; Llah *et al.* 1993). Some of the important examples of this class are diploicin, psoromic acid, virensic acid, and norstictic acid.

Dibenzofurans

Dibenzofurans are essentially unique to lichens, produced via the polyketide pathway. Dibenzofurans are formed by carbon-carbon coupling and cyclodehydration of two phenolic units (orcinol and orsenillic acid derivatives). Notable examples of this class are didymic acid, pannaric acid, schizopeltic acid, subbidymic acid, and usnic acid (Millot *et al.* 2016).

Xanthones

Lichens produces poly-substituted aromatic xanthones, formed through internal cyclization of a single folded polyketide chain. Majority of the lichen xanthones are synthesized via folding of a polyketide intermediate, which results in formation of structures having a methyl group in position 8. Both, aldol condensation and Claisen-type cyclization yield a benzophenone intermediate that might then dehydrate to form the central pyrone core. Two different series of xanthones are resulting according to this folding pattern. This biosynthetic scheme gives rise to the common oxygen substitution pattern of lichexanthone and norlichexanthone (Rezanka *et al*. 2003; Masters and Bräse 2012; LePogam and Boustie 2016). Some of the important examples of this class are lichexanthone, nor lichexanthone and arthothelin.

Biphenyls

In lichens, biphenyls form via phenolic couplings of two methyl pholoroacetate to phoneunits, followed by O-methylation of hydroxyl groups. Since the mechanism for carbon bond formation between two mono-aromatic units is common in lichens, as exemplified in the usnic acids, dibenzofurans, and depsidones formation. It is interesting to note that contortin is the only lichen biphenyl known so far. Another compound also formed from two mono aromatic units bound by a carbon-carbon linkage is the diphenyl methane, bis-(2,4-dihydroxy-6-n-propylphenyl) methane, which are found in *Protousnea* sp., eg. contortin (Rezanka *et al.* 2003).

Biological activity of orcinol based lichen secondary metabolites

In nature, lichen fungi grow under the most extremely different ecological conditions. Lichenized fungi produce variety of low molecular weight orcinol based secondary metabolites possess several biological activities, including anti-bacterial, anti-fungal, anti-oxidant, anti-diabetic, anti-cancer, and anti-inflammatory activities (Lawrey 1986; Boustie and Grube 2005; Shukla *et al*. 2010; Shrestha and Clair 2013). However, lichens are pharmaceutically unexplored secondary metabolites. Extracts and isolated compounds from different lichen species antimicrobial activities. From literature surveys, it was found that lichen genus such as *Usnea, Parmelia, Parmotrema, Cetraria, Pseudevernia and Hypogymnia* showed potent antimicrobial and antifungal activities (Türk *et al.* 2006; Kamal *et al*. 2015; Özyiğitoğlu *et al.*

2017). The major metabolites gyrophoric acid (1), stenosporic acid (2) isolated from the lichen, *Xanthoparmelia pokornyi* showed antimicrobial activity towards some known food borne bacteria and fungi. These acid derivatives showed significant anti-microbial activity again sleight organisms (Candan *et al.* 2006). Methyl-β-orcinol carboxylate is an orcinol derivative isolated from the lichen, *Everniastrum irrhatum*, tested against polyene and azole-resistant strains of *Candida albicans* and capable of inhibiting drug-resistant strains in a dose dependant manner (Candan *et al.* 2006). New dibenzofuran derivatives (3 – 5) obtained from the *Cladonia incrassate* showed anti-bacterial activity against *S. aureus* organism. The major metabolites, (-)usnic acids (3), didymic acid (4) and condidymic acid (5) (Fig. 2), were found to be potent molecules (MIC : 7.5 $\mu g.mL^{-1}$). Phenonip was used as a positive control (IC_{50}: 150 $\mu g.mL^{-1}$) in this assay (Dieu *et al.* 2014).

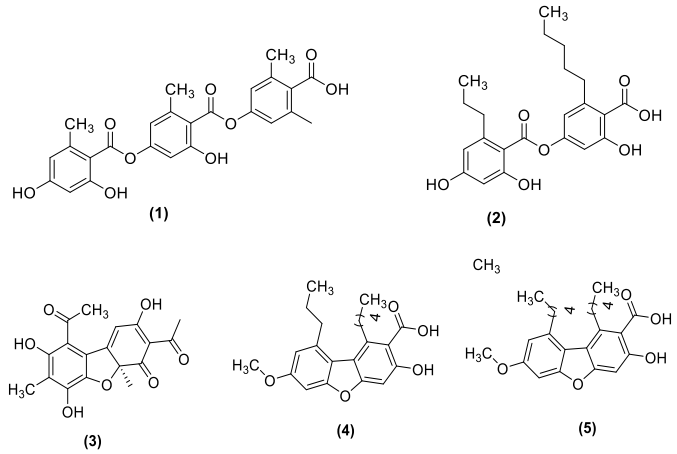

Fig. 2. Structures of 1-5.

Hirtusneanoside A (6) was first extracted from the *Usnea hirta* by Rezanka and Sigler (2007) and found to be an L-rhamnose-O-deoxyglycoside of an unsymmetrical dimeric tetra-hydro xanthone. It is potent when tested against *Staphylococcus aureus* and *Bacillus subtilis* (Rezanka and Sigler 2007). Depside anziaic acid (7) was discovered from lichen (*Hypotrachyna* sp.) as an inhibitor for both *Yersinia pestis* and *Escherichia coli* topoisomerase I and it was also found to act as an inhibitor of human topoisomerase II (with little effect on human topoisomerase I), an important enzyme in cancer processes (Lin *et al.* 2013). Some lichen compounds such as (+) usnic acid (8), vicanicin (9), and diffractic acid (10) were identified as anticancer molecules (Fig. 3). Usnic acid, a di-benzo furan derivative, isolated from *Cladonia lepidophora* lichen species. It is one of the well-studied lichen secondary metabolite, showed potent anti-cancer activity against HCT-116 and HeLa cancer cell lines with IC_{50} values of 17.7 µM and 23.7 µM respectively, and was found to be more active than the standard etoposide (IC_{50} = 40.3 µM). Vicanicin (9) showed moderate anti-cancer activities against HCT-116, HeLa and MCF-7 cell lines (Cocchietto *et al.* 2002). Evernic acid (11) and physodic acid (12) were isolated from the acetone extract of *Evernia prunastri* and *Pseudevernia furfuracea* showed cytotoxicity against FemX (human melanoma) and LS174 (human colon carcinoma) cell lines. Particularly, physodic acid (12) exhibited the better cytotoxic activity (IC_{50} values of 19.52 for Fem Xcell line and 17.89 $\mu g.mL^{-1}$ for LS 174) (Kosanić *et al.* 2013).

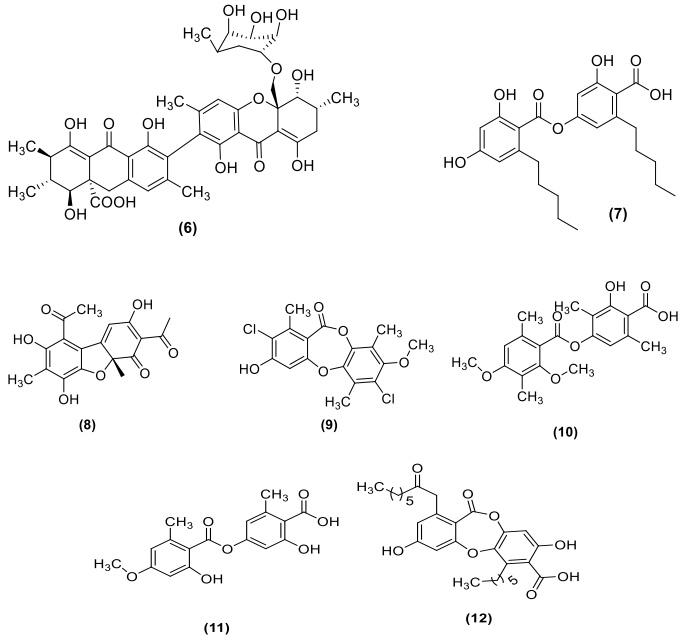

Fig. 3. Structures of 6-12.

A new di-phenyl ether (13) and secalonic acid D (14) were isolated from the lichen, *Diploicia canescens* and evaluated for their anti-cancer activity against the B16 murine melanoma cells. The di-phenyl ether (IC_{50} = 0.25 µM) and secalonic acid (IC_{50} = 0.28 µM) showed anti-cancer activity similar to standard etoposide (IC_{50} 0.28 µM) against B16 cell line (Millot *et al.* 2009). (-)usnic acid (15), a dibenzofuran derivative

isolated from different lichens genera such as *Cladonia, Usnea, Hypotrachyna, Ramalina, Evernia, Lecanora, Parmelia* and most extensively studied lichen compound in search of anticancer agents (Lumbsch *et al.* 1995; Cocchietto *et al.* 2002; Cansaran-Duman *et al.* 2008). It has been shown moderate to potent proliferative activities against multiple cell lines, such as L-929 mouse fibroblast cells, K-562 human leukemia cells, HeLa human cervix carcinoma, FemX human melanoma, LS174 human colon carcinoma 37 and UACC-62 human melanoma cells (Schinkovitz *et al.* 2014). (-)Usnic acid and M-scrobiculin were extracted from the lichen *Lobaria scrobiculata* and exhibited cytotoxicity against HL-60 cells. Both the isolated compounds showed IC_{50} values of 7.6 and 1.7 µM for (15 and 16 in Fig. 4). Doxorubicin was positive control in this assay (IC_{50} = 0.04µM).

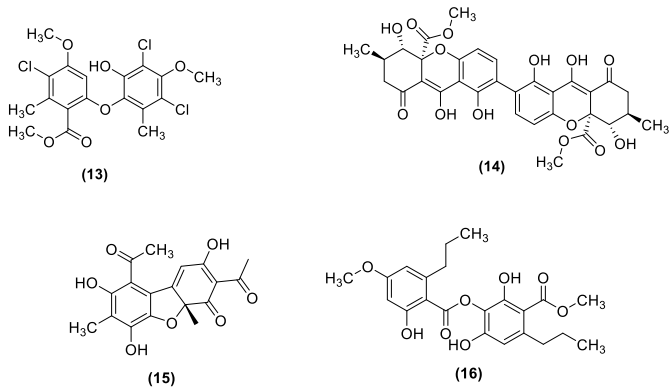

Fig. 4. Structures of 13-16.

Anti-oxidants inhibit undesirable oxidation processes by reacting with free radicals (reactive oxygen species) and their ability to protect the body from damage caused by oxidative stress. Most of the secondary metabolites have been identified as phenolic compounds in lichens, which are strong antioxidants. Some orcinol based secondary metabolites such aslobariellin and methyl haematommate isolated from *L. pallida* and *S. strictum var. compressum* exhibited promising antioxidants, able to prevent skin and neurodegenerative damage caused by oxidative stress. Depsidones such as norstictic acid (17), fumarprotocetraric acid (18) and methyl haematommate (19) isolated from the lichen *Usnea articulata* showed better superoxide anion scavenging activity with IC_{50} 566 and 580 µM, respectively, than standard quercetin (IC_{50} = 754 µM) (Lohézic-Le Dévéhat *et al.* 2007). Orsellinic acid (20) and methyl orsellinate (21) were isolated from *Parmotrema stuppeum* and *Heterodermia obscurata* together with methyl-β-orcinol carboxylate (22). Significant activity was observed for both the compound in the β-carotene-linoleate model system and in the NOR assay (Jayaprakasha and Rao 2000; Thadhani *et al.* 2011). The *para*-depsides lecanoric acid (23), erythrin (24) and the meta-depside sekikaic acid (25), along with the depsidone lobaric acid (26) showed exceptionally potent radical scavenging activity in the SOR assay (Fig. 5). Interestingly, the IC_{50} values of the sekikaic acid (81.9 µM) lecanoric acid (91.4 µM) and lobaric acid (97.9 µM) were found lower than standard propylgallate standard (106 µM) (Fig. 5).

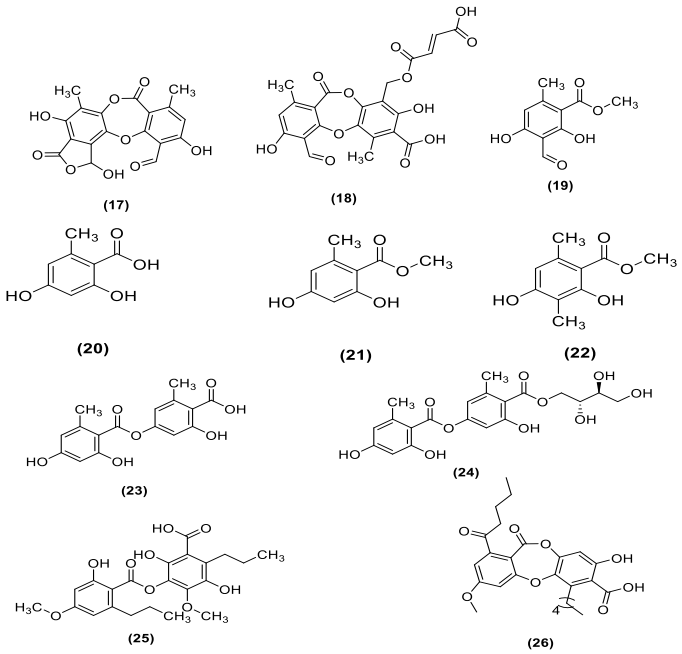

Fig. 5. Structures of 17-26.

Taborga *et al.* (2016) reported the new prenylated orcinol derivatives (27-29) from the direct reaction between orcinol and geraniol in the presence of BF_3OEt as catalyst. The cytotoxic activity of synthesized compounds was *in vitro* investigated against various cancer cell lines including (HT-29, PC-3, MDA- MB231, DU-145). All the tested compounds were found to exhibit anti-cancer activity. Orsellinates were synthesized by alcoholysis of lecanoric acid, a natural product isolated from the lichen *Parmotrema tinctorum*. Increasing the aliphatic alkyl chain at the ester functionality of orsellinic acid causes enhancement

in the cytotoxic activity. The ethyl, propyl, butyl and pentanyl orsellinates (30 – 33) showed LC_{50} values range from 495 – 31 µM against brine shrimp (*Artemia salina*) (Gomesa *et al.* 2006). Among tested ones, pentanyl orsellinate (33) possess potent inhibitory activity, whereas standard Podophyllotoxin showed cytotoxicity15 µM. Lichen genus *Parmelia* is a rich source for depsides (Aravind *et al.* 2014). Atranorin (34) and diffractaic acid (35) isolated from the *Parmelia nepalensis and Parmelia tinctorum*, showed highly potent inhibitory activity against leukotriene B4 biosynthesis by a non-Redox mechanism with IC_{50} values 6 and 8 µM respectively (Fig. 6). Nordihydroguaiaretic acid and anthralin were used as standard inhibitors (IC_{50} = 0.4 and 37 µM respectively) (Kumar and Müller 1999).

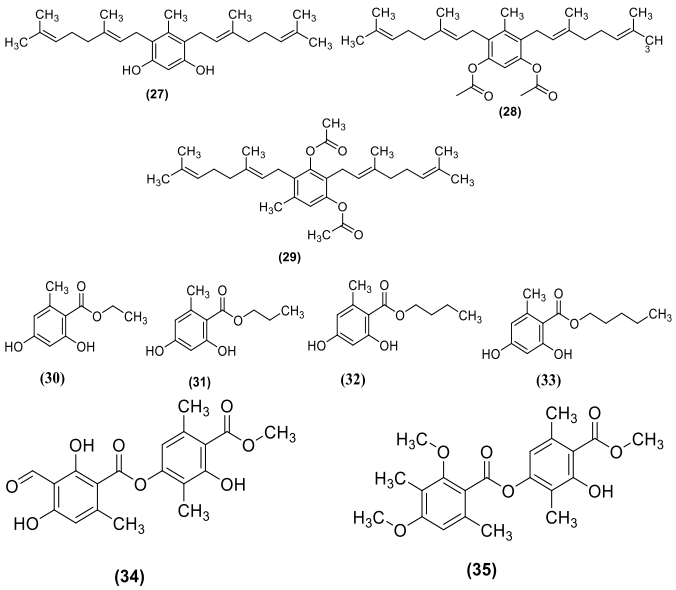

Fig. 6. Structures of 27-35.

Conclusion

From the above review it is evident that the orcinol form is an important building block for several phenolic compounds isolated from lichens. Orcinol has very useful functionalities like phenolic, hydroxyl, and one methyl group, which are enable for a wide range of chemical transformations. Chemical modification of orcinol is expected to elaborate wide range of diverse analogs and hybrid molecules. Due to their structural diversity these compounds are expected to exhibit newer and enhanced biological activities.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

Aravind SR, Sreelekha TT, Kumar BD, Kumar SN, Mohandas C (2014) Characterization of three depside compounds from a Western Ghat lichen Parmelia erumpens Kurok with special reference to antimicrobial and anticancer activity. RSC Adv. 4: 34632-34643.

Bates ST, Cropsey GW, Caporaso, JG, Knight R, Fierer N (2011) Bacterial communities associated with the lichen symbiosis. Appl. Environ. Microbiol. 77: 1309-1314.

Boustie J, Grube M (2005) Lichens – A promising source of bioactive secondary metabolites. Plant Genet. Resour.-C. 3: 273-287.

Candan M, Yilmaz M, Tay T, Kivanç M, Türk H (2006) Antimicrobial activity of extracts of the lichen *Xanthoparmelia pokornyi* and its gyrophoric and stenosporic acid constituents. Z Naturforsch. C. 61: 319-323.

Cansaran-Duman D, Aras S, Atakol O (2008) Determination of usnic acid contentin some lichen species found in Anatolia. J. Appl. Biol. Sci. 2: 41-44.

Çobanoğlu G, Açikgöz B, Sesal C (2016) Lichen secondary metabolites: Synthesis pathways and biological activities. Acta Biol. Turcica. 29: 150-163.

Cocchietto M, Skert N, Nimis PL, Sava G (2002) A review on usnic acid, an interesting natural compound. Naturwissenschaften 89: 137-146.

Culberson CF, Armaleo D (1992) Induction of a complete secondary-product pathway in a cultured lichen fungus. Exp. Mycol. 16: 52-63.

De Priest TP (2004) Early molecular investigation of lichen forming symbionts: 1986–2001. Annu. Rev. Microbiol. 58: 273-301.

Dieu A, Millot M, Champavier Y, Mambu L, Chaleix V, Sol V, Gloaguen V (2014) Uncommon chlorinated xanthone and other antibacterial compounds from the lichen *Cladonia incrassate*. Planta Med. 80: 931-935.

Eix JA, Wardlaw JH (1986) The synthesis of new meta-depsides from Ramalina lichens. Aust. J. Chem. 39: 227-231.

El-Garawani I, Emam M, Elkhateeb W, El-Seedi H, Khalifa S, Oshiba S, Daba G (2020) In vitro antigenotoxic, antihelminthic and antioxidant potentials based on the extracted metabolites from lichen, *Candelariella vitellina*. Pharmaceuticals 12(5): 477.

Férnandez-Moriano C, Gómez-Serranillos MP, Crespo A (2015) Antioxidant potential of lichen species and their secondary metabolites. A systematic review. Pharm. Biol. 54: 1-17.

Gomesa AT, Hondaa NK, Roesea FM, Muzzia RM, Sauerb L (2006) Cytotoxic activity of orsellinates. Z. Naturforsch. C. 61: 653-657.

Hirayama T, Fujikawa F, Yosioka I, Kitagawa I (1974) A new depsidone oxyphysodic acid isolated from a lichen

Parmelia enteromorpha Ach. Chem. Pharm. Bull. 22: 1678-1680.

Jayanthi S, Priya P, Devi M, Benila Smily M (2012) Lichens: Origin, types, secondary metabolites and applications. J. Acad. Indus. Res. 1: 45-49.

Jayaprakasha K, Rao LJ (2000) Phenolic constituents from the lichen *Parmotrema stuppeum* (Nyl.) Hale and their antioxidant activity. Z. Naturforsch. C. 55: 1018-1022.

Kamal S, Manish S, Savita J, Jasumati I (2015). Assessment of antibacterial activity of *Usnea species* of Shimla Hills. Int. J. Curr. Microbiol. App. Sci. 4: 413-425.

Kathirgamanathar S, Williams DE, Andersen RJ, Bombuwela K, DeSilva D, Karunaratne V. (2004) β-Orcinol depsidones from the lichen *Usnea sp*. from Sri Lanka. Nat. Prod. Res. 19: 695-701.

Kosanić M, Manojlović N, Janković S, Stanojković T, Ranković B (2013) *Evernia prunastri* and *Pseudoevernia furfuracea* lichens and their major metabolites as antioxidant, antioxidant, antimicrobial and anticancer agents. Food Chem. Toxicol. 53: 112-118.

Kumar K, Müller K (1999). Lichen metabolites 1. Inhibitory action against leukotriene B4 biosynthesis by a non-redox mechanism. J. Nat. Prod. 62: 817-820.

Lawrey JD (1986) Biological role of lichen substances. Bryologist 89: 111-122.

LePogam P, Boustie J (2016) Xanthones of lichen source: A 2016 Update. Molecules 21: 294.

Leuckert C, Ahmadjian V, Culberson C, Johnson A (1990) Xanthones and Depsidones of the Lichen *Lecanora dispersa* in nature and of its mycobiontin culture. Mycol. 82: 370-378.

Lin H, Annamalai T, Bansod P, Tse-Dinh, Y, Sun D (2013) Synthesis and antibacterial evaluation of anziaic acid and its analogues as topoisomerase inhibitors. Med. Chem. Commun. 4: 1613-1618.

Llah Bin Hamat A, BinDin L, Wahid Bin Samsudin M (1993) Two new depsidones from the lichen *Erioderma phaeorhizum Vainio sensu lato*. Austr. J. Chem. 46: 153-156.

Lohézic-Le Dévéhat F, Tomasi S, Elix JA, Bernard A, Rouaud I, Uriac P, Boustie J (2007) Stictic acid derivatives from the lichen *Usnea articulata* and their antioxidant activities. J. Nat. Prod. 70: 1218-1220.

Lumbsch HT, Feige GB, Elix JA (1995) A revision of the usnic acid containing taxa belonging to *Lecanora sensu stricto* (Lecanorales: lichenized Ascomycotina). Bryologist 561-577.

Margulis L, Barreno E (2003) Looking at lichens. Biol. Sci. 53. 776-778.

Masters K, Bräse S (2012) Xanthones from fungi, lichens, and bacteria: The natural products and their synthesis. Chem. Rev. 112: 3717-3776.

Millot M, Dieu A, Tomasi S (2016) Dibenzofurans and derivatives from lichens and ascomycetes. Nat. Prod. Rep. 33: 801-811.

Millot M, Tomasi S, Studzinska E, Rouaud E, Boustie J (2009) Cytotoxic constituents of the lichen *Diploicia canescens*. J. Nat. Prod. 72: 2177-2180.

Moreira A, Braz-Filho R, Mussi-Dias V, Vieira IJ (2015) Chemistry and biological activity of Ramalina lichenized fungi. Molecules 20: 8952-8987.

Muggia L, Schmitt I, Grube M (2009) Lichens as treasure chests of natural products. SIM News 59: 85-97.

Özyiğitoğlu G, Açıkgöz B, Tahiroğlu G, Sesal NC (2017) Comparison of antibacterial and antibiofilm activity properties of *Hypogymniatubulosa* (Schaer.) Hav. lichen extracts from different locations in Turkey. Mycosphere 8: 994-1002.

Papadopoulou P, Tzakou O, Vagias C, Kefalas P, Roussis V (2007) β-Orcinol Metabolites from the lichen *Hypotrachynarevolute*. Molecules 12: 997-1005.

Podterob AP (2008). Chemical composition of lichens and their medical applications. Pharm. Chem. J. 42: 582-588.

Rezanka T, Jáchymová J, Dembitsky VM (2003) Prenylated xanthone glucosides from Ural's lichen *Umbilicaria proboscidea*. Phytochemistry 62: 1-10.

Rezanka T, Sigler K (2007) Hirtusneanoside, an unsymmetrical dimerictetrahydr oxanthone from the lichen *Usnea hirta*. J. Nat. Prod. 70: 1487-1491.

Schinkovitz A, Kaur A, Urban E, Zehl M, Páchniková G, Wang Y, Kopp B (2014) Cytotoxic constituents from *Lobaria scrobiculata* and a comparison of two bioassays for their evaluation. J. Nat. Prod. 77: 1069-1073.

Seshadri TR (1944) A theory of biogenesis of lichen Depsides and Depsidones. Proc. Indian Acad. Sci. 20: 1-14.

Shrestha G, Clair LL (2013) Lichens: A promising source of antibiotic and anticancer drugs. Phytochem. Rev. 12: 229-244.

Shukla V, Joshi G, Rawat, MS (2010). Lichens as a potential natural source of bioactive compounds: a review. Phytochem. Rev. 9: 303-314.

Stepanenko L, Krivoshchekova O, Skirina I (2002) Functions of phenolic secondary metabolites in lichens from Far East Russia. Symbiosis 32: 119-131.

Stocker-Wörgötter E (2008). Metabolic diversity of lichen-forming ascomycetous fungi: culturing, polyketide and shikimate metabolite production, and PKS genes. Nat. Prod. Rep. 25: 188-200.

Subba Rao V, Seshadri T (1941) Chemical investigation of Indian lichens. Proc. Ind. Acad. Sci. (A) 13: 199-202.

Taborga L, Espinoza L, Moller A, Carrasco H, Cuellar M, Villena J (2016) Antiproliferative effect and Apoptotic activity of linear geranyl phenol derivatives from phloroglucinol and orcinol. Chem Biol Interact. 247: 22-29.

Thadhani VM, Choudhary M, Ali S, Omar I, Siddique H, Karunaratne V (2011) Antioxidant activity of some lichen metabolites. Nat. Prod. Res. 25: 1827-1837.

Türk H, Yilmaz M, Tay T, Türk A, Kivanç M (2006) Antimicrobial activity of extracts of chemical races of the lichen *Pseudevernia furfuracea* and theirphysodic acid, chloro atranorin, atranorin, and olivetoric acid constituents. Z Naturforsch. C. 61: 499-507.

Xu, M, Heidmarsson S, Olafsdottir E, Buonfiglio R, Kogej T, Omarsdottir S (2016) Secondary metabolites from cetrarioid lichens: Chemotaxonomy, biological activities and pharmaceutical potential. Phytomed. 23: 41-59.