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Open Access Review Article

Lichens as promising resources of enzyme inhibitors: A review

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ABSTRACT

Inhibition of some enzymes seems to be one of the therapeutic strategies for the management of certain diseases or conditions such as diabetes, Alzheimer's disease, cancer and obesity. In this review, an updated information on the enzyme inhibitory activity of lichen extracts and lichen compounds by an intensive literature survey is presented. Crude solvent extracts and isolated compounds from lichens were shown to be effective in causing inhibition of several enzymes such as amylase, lipase, lipoxygenase, aromatase, cyclooxygenase, trypsin, β-glucoronidase, prolyl endopeptidase, monoamine oxidase, urease, tyrosinase, xanthine oxidase, Thioredoxin reductase, glucosidase, topoisomerase, pancreatic elastase, phosphodiesterase, telomerase and acetylcholinesterase. Lichen metabolites such as usnic acid and its derivatives, lobaric acid, physodic acid, ramalin, protolichestrinic acid, salazinic acid, atranorin, evernic acid, zeorin, diffractic acid, psoromic acid, methyl β-orcinolcarboxylate, methylorsellinate, and anziaic acid were shown to be inhibitors of some enzymes. In conclusion, lichens can be employed as promising therapeutic agents in terms of their potential to inhibit the activity of certain enzymes that are involved in some diseases or disorders. In vitro culturing of lichen symbionts in optimized media can be carried out to isolate enzyme inhibitors in larger scale and to develop effective therapeutic agents.

Keywords: Lichens, lichen substances, enzyme inhibitors, enzyme inhibitory activity

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INTRODUCTION

Lichens are the ecologically stable, self-supporting and most successful symbiotic association between a phytosynthetic partner (photobiont; an inhabitant) comprising of an alga or a cyanobacterium and a fungal partner (mycobiont; an exhabitant) represented by an ascomycete or basidiomycete member. Mycobiont of majority of lichens belongs to Ascomycetes. Lichens are unique group of organisms as they appear as a distinct phenotype which is different from either partners. There are about 20000 species of lichens distributed worldwide. Lichens are ubiquitous in distribution (from arctic to tropical; from plains to high mountains) and occur in one of the four growth forms: crustose, squamulose, foliose and fruticose (Figure 1). Lichens appear to be the primary colonizers in many barren habitats. Lichens are slow growing organisms, adapt to extreme environmental conditions, and are able to grow on various substrates viz. bark (corticolous), rock (saxicolous), soil (terricolous), leaf (foliicolous), twigs (ramicolous), mosses (muscicolous) and plastic (plasticolous). Lichens have been considered as indicators of air pollution. Most lichens are sensitive to air pollution and disappear from regions with high air pollutants. Some lichen species are tolerant and accumulate pollutants in their thallus aiding in the study of extent of pollution in an area[1-7].

Lichens have potential utilization as food, spice, medicine, as source of dyes and as material for sacrificial fire. Lichens are used medicinally in various parts of the world. Traditional healers as well as certain indigenous systems of medicine employ several lichen species for therapy against diseases such as tuberculosis, diarrhea, vomiting, cough, bleeding, antidote, skin diseases, bronchial irritation, sore throat[5,8-12]. Lichens produce characteristic secondary metabolites (>1000 in number and termed often as lichen substances or lichen compounds) and most of these compounds do not occur in other organisms. Only a small number of such compounds (around 60) may be found in other fungi or higher plants. These metabolites majorly originate from secondary metabolism of the fungal partner. Metabolic pathways such as acetate-malonate pathway, shikimic acid pathway and mevalonic acid pathway are involved in the biosynthesis of lichen metabolites (Figure 2). These secondary metabolites are useful in lichen taxonomy. Besides, several lichen metabolites are responsible for the biological activities displayed by lichens[2,13-25].

Figure 1: Major types of lichens (Photograph by Prashith Kekuda)

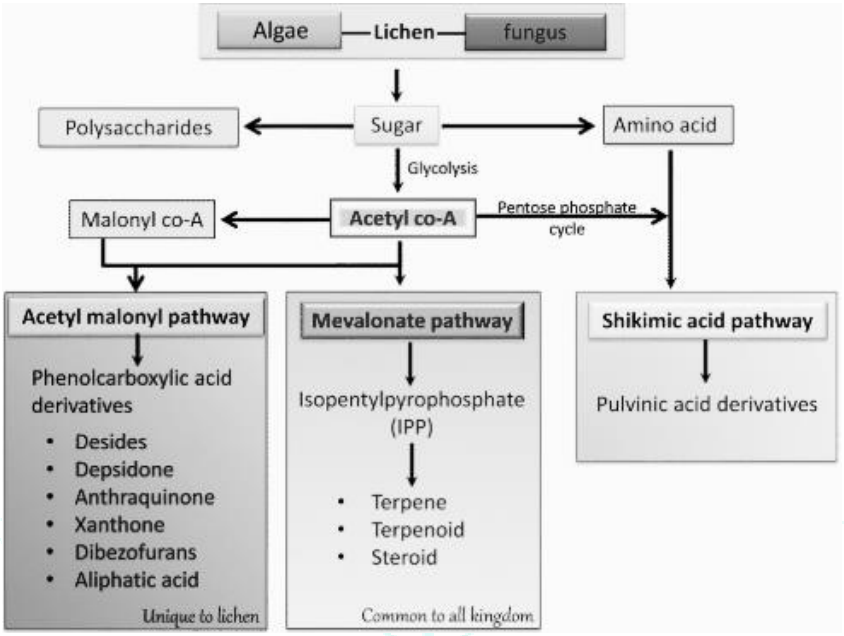

Figure 2: Metabolic pathways involved in the synthesis of lichen metabolites[21]

Enzymes are biocatalysts and are the key components of metabolism as they are involved in catalyzing biochemical reactions in the cell. However, the activity of certain enzymes (such as amylase, protein tyrosine phosphatase 1B, glucosidase, urease, and acetylcholinesterase) are known to result in certain pathological conditions such as diabetes, obesity, hypertension, congestive heart failure, gastric ulcer and cancer. Enzyme inhibitors have been extensively used as a treatment of such pathological conditions. Studies concerning discovery of enzyme inhibitors are gaining high importance nowadays because of certain negative effects that are associated with the use of existing drugs[26-33]. Table 1 shows a list of targeted enzymes (for possible therapy) that are involved in certain pathological conditions. Natural products, including lichens and their metabolites, have been screened for enzyme inhibitory studies against various key enzymes of metabolism such as acetylcholinesterase, lipase, protein tyrosine phosphatase 1B, amylase, angiotensin-converting enzyme, HMG CoA reductase, lipoxygenase, glucosidase, urease, tyrosinase, topoisomerase and xanthine oxidase[28,34-42]. In the present review, an intense literature survey was conducted to compile data available on the enzyme inhibitory activity of lichen extracts and lichen substances by referring journals, and various search engines viz. Google scholar, PubMed and ScienceDirect.

Table 1: A list of some diseases or conditions and the enzymes targeted

Disease/condition	Enzyme targeted	Reference
Diabetes	Amylase	Jayaraj *et al.*[43]
Diabetes	Glucosidase	van de Laar[44]
Diabetes	Protein tyrosine phosphatase 1B	Taylor and Hill[45]
Hyperpigmentation	Tyrosinase	Verma *et al.*[46]
Gout, hyperuricemia	Xanthine oxidase	Pacher *et al.*[47]
Gastric and urinary infections	Urease	Follmer[48]
Obesity	Pancreatic lipase	Lunagariya *et al.*[29]
Obesity	Protein tyrosine phosphatase 1B	Taylor and Hill[45]
Inflammatory diseases	Lipoxygenase	Steinhilber and Hofmann[49]
Inflammatory diseases	Cyclooxygenase	Harris and Breyer[50]
Inflammatory diseases	Prostaglandin E2 synthase-1	Psarra *et al.*[51]
Inflammatory diseases	Phosphodiesterase	Dastidar *et al.*[52]

Cancer	Telomerase	Kelland[53]
Cancer	Fatty acid synthase	Zhang *et al.*[54]
Cancer	Tyrosyl-DNA Phosphodiesterase 1	Dexheimer *et al.*[55]
Cancer	DNA polymerase	Berdis[56]
Cancer	Polo-like kinase-1	Liu *et al.*[57]
Cancer	Topoisomerase	Sinha[58]
Cancer	Rab geranylgeranyl transferase	Sane *et al.*[59]
Cancer	β-glucuronidase	Lampe *et al.*[60]
Cancer	Aromatase	Fabian[61]
Cancer	Sulfatase	Shah *et al.*[62]
Alzheimer's disease	Cholinesterase	Grossberg[63]
Cognitive disorders	Prolyl endopeptidase	Männisto *et al.*[64]
Atherosclerosis	Phospholipase A_2	Rosenson and Hurt-Camejo[65]
Diabetic peripheral neuropathy	Aldose reductase	Schemmel *et al.*[66]
Hypertension and others	Angiotensin-converting enzyme	White[67]
Hypercholesteromia	HMG CoA reductase	Pazzucconi *et al.*[68]
Central nervous disorders	Monoamine oxidase	Entzeroth and Ratty[69]
AIDS	HIV-1 reverse transcriptase	Castro *et al.*[70]
Pancreatitis and others	Trypsin	Brandl *et al.*[71]
Tuberculosis	Arylamine-N-acetyltransferase	Westwood *et al.*[72]
Tuberculosis	UDP-galactopyranose mutase	Soltero-Higgin *et al.*[73]
Cancer, neurodegenerative diseases	Thioredoxin reductase	Saccoccia *et al.*[74]

ENZYME INHIBITORY ACTIVITY OF LICHENS

Solvent extracts and purified compounds of lichens were shown to be effective enzyme inhibitors. An intensive literature survey revealed the potential of lichens to inhibit a range of enzymes such as amylase, glucosidase, lipoxygenase, telomerase, prolyl endopeptidase, tyrosinase, cyclooxygenase, xanthine oxidase, monoamine oxidase, pancreatic lipase, trypsin, pancreatic elastase, acetylcholinesterase, Thioredoxin reductase, prostaglandin E2 synthase-1, protein tyrosine phosphatase 1B, phosphodiesterase and topoisomerase. A brief description on inhibitory effect of lichens against these enzymes is presented below. Structures of some enzyme inhibitors from lichens[3,40,75-82] is shown in Figure 3 and Figure 4.

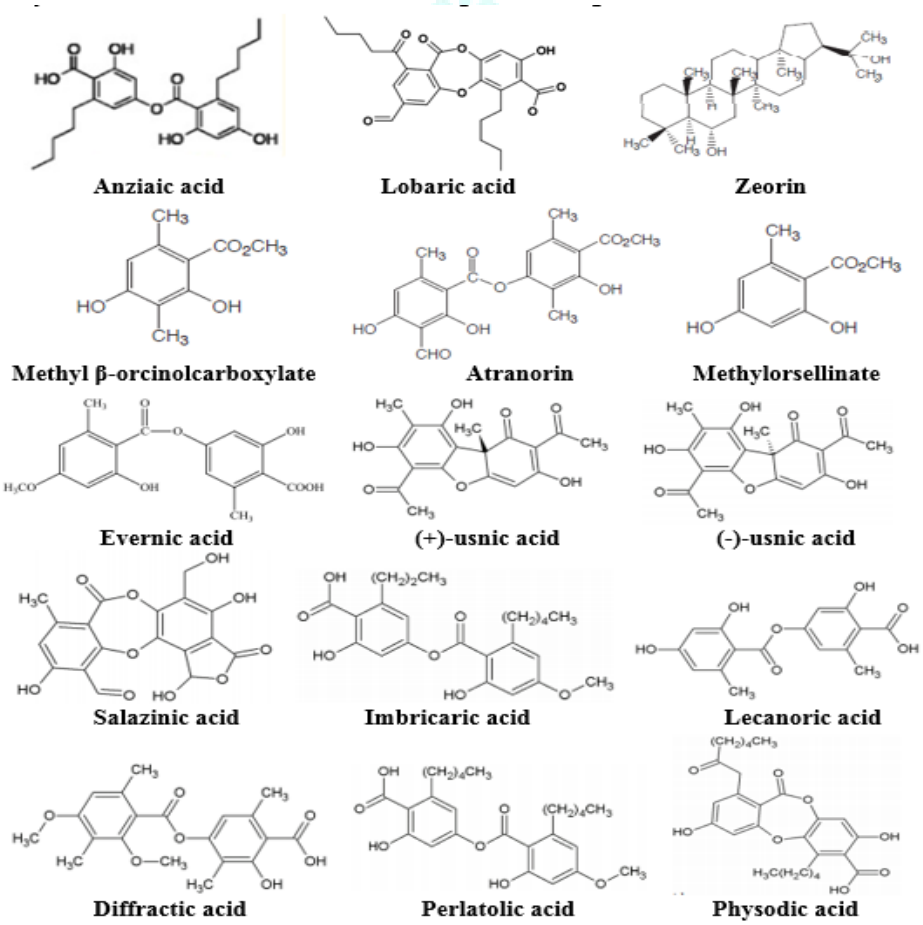

Figure 3: Structures of some lichen metabolites having enzyme inhibitory activity

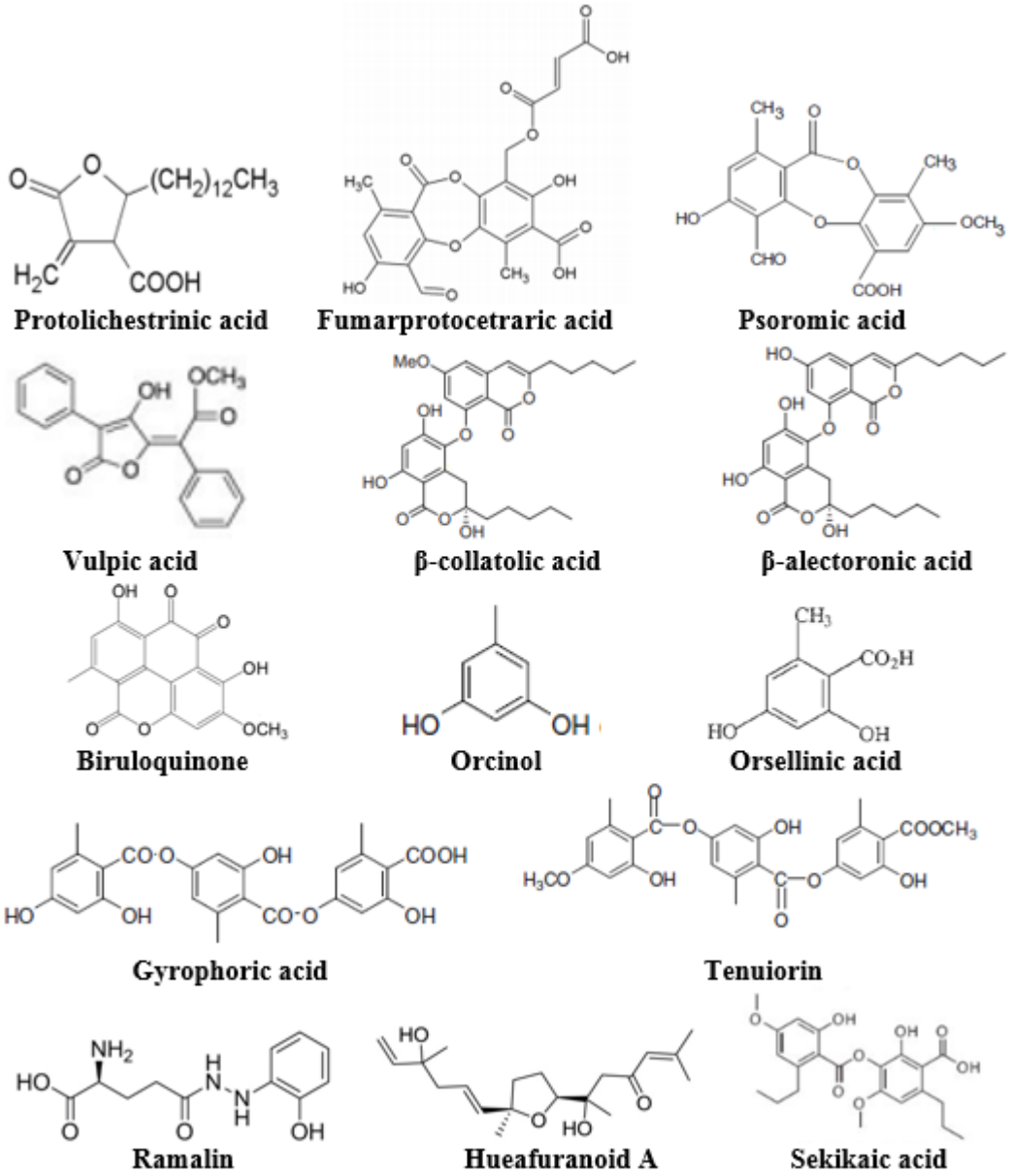

Figure 4: Structures of some lichen metabolites having enzyme inhibitory activity

Amylase inhibitory activity

Methanol extract of *Caloplaca biatorina* was shown to exhibit concentration dependent inhibition of α-amylase[83]. Various solvent extracts of lichens viz. *Ramalina sinensis*, *Heterodermia leucomelos*, *Herpothallon* sp. and *Parmatorema reticulatum* were tested against α-amylase. The extracts showed concentration dependent inhibitory activity against amylase[84]. Various solvent extracts of *Parmelia perlata* were screened for salivary amylase inhibitory activity. Highest and least inhibitory activity was observed in case of methanol extract (94.74% inhibition) and aqueous extract (40.80% inhibition) respectively[85]. Methanol and ethyl acetate extracts of two lichens viz. *Physcia aipolia* and *Flavoparmelia caperata* were effective in causing dose dependent inhibition of alpha amylase[86]. Ethyl acetate extract of a macrolichen *Parmotrema tinctorum* was shown to inhibit activity of α-amylase with an IC_{50} value of 587.74±3.27µg/ml[87].

In a study, Vinayaka *et al*.[88] investigated amylase inhibitory potential of six lichens viz. *Everniastrum cirrhatum*, *Usnea sinensis*, *Ramalina conduplicans*, *Ramalina hossei*, *Parmotrema pseudotinctorum* and *Parmotrema tinctorum* from Karnataka, India. Methanol extracts of all lichens displayed concentration dependent inhibitory activity against amylase. Extract of *R. conduplicans* was effective to highest extent. Valadbeigi and Shaddel[89] screened inhibition of amylase activity by methanol extract of ten macrolichens of Mazandaran province, Iran. A concentration dependent inhibitory activity was observed and the activity of lichens was in the order: *Usnea articulata* > *Ramalina pollinaria* > *R. hyrcana* > *Cladonia rei* > *Flavoparmelia caperata* > *Parmotrema chinense* > *Punctelia subrudecta* > *P. borreri* > *Hyperphyscia adglutinata* > *Peltigera praetextata*. Karthik *et al*.[90] showed a concentration dependent inhibition of amylase activity by methanolic extract of *H. leucomela*. At 25mg/ml concentration, the extract caused 38.57% inhibition of enzyme activity.

Glucosidase inhibitory activity

Methanol extract of *Caloplaca biatorina* exhibited concentration dependent inhibition of α-glucosidase[83]. Ethyl acetate extract of *Parmotrema tinctorum* exhibited inhibitory activity against α-glucosidase with an IC_{50} value of 58.45±1.24µg/ml[87]. Solvent extracts of lichens viz.

Herpothallon sp., *Ramalina sinensis*, *Leptogium* sp., *Heterodermia leucomelos*, *Parmotrema tinctorum*, *P. crinitum*, *P. reticulatum* and *Cladonia subradiata* were screened for β-glucosidase inhibitory. Marked inhibition of glucosidase activity was displayed by lichens *R. sinensis*, *H. leucomelos* and *Leptogium* sp. while species of *Parmotrema*, in particular *P. reticulatum*, were not so effective[91]. In a study, lobaric acid isolated from methanol extract of *Heterodermia* sp. did not show inhibitory activity against α-glucosidase[79].

Karunaratne *et al.*[78] evaluated α-glucosidase inhibitory activity of metabolites viz. zeorin, methyl β-orcinolcarboxylate, methylorsellinate, atranorin and lobaric acid isolated from a Sri Lankan lichen *Cladonia* sp. Zeorin exhibited highest α-glucosidase inhibitory activity with an IC_{50} value of 100.0±0.3μM. Methyl β-orcinolcarboxylate and methylorsellinate showed inhibition of enzyme activity with IC_{50} value of 140.0±0.6 and 165.0±1.2μM, respectively. Atranorin and lobaric acid did not show α-glucosidase inhibitory properties. Verma *et al.*[92] studied glucosidase inhibitory activity of solvent extracts of *Ramalina celastri*, *R. nervulosa* and *R. pacifica*. Extracts were effective in inhibiting α and β-glucosidases. Marked inhibitory activity was shown by methanol extract whereas acetone extract showed least activity. *Ramalina* derived metabolites viz. usnic acid, sekikaic acid and salazinic acid were shown to be effective against glucosidases with marked activity shown by sekikaic acid. Lee and Kim[93] screened β-glucosidase inhibitory activity of extract of *Umbilicaria esculenta*. The extract caused strong inhibition of glucosidase of mammalian and mold origin. 1-deoxynojirimycin (1,5-dideoxy-1,5-immino-D-glucitol) was shown to be the active component in the extract.

Protein tyrosine phosphatase 1B (PTP1B) inhibitory activity

Usnic acid and three usnic acid derivatives (Usimines A-C) were isolated from methanol extract of *Stereocaulon alpinum*. The compounds have shown moderate inhibitory activity against PTP1B[94]. Methanol extract of an Antarctic lichen *Umbilicaria antarctica* was shown to exhibit significant inhibitory activity against PTP1B. Three compounds viz. gyrophoric acid, lecanoric acid and methyl orsellinate, isolated from the lichen exhibited PTP1B inhibitory activity with IC_{50} value of 3.6±0.04μM, 31±2.7μM, and 277±8.6μM, respectively[95]. Lobaric acid and two pseudodepsidone-type compounds (2 and 3), isolated from methanol extract of *S. alpinum* showed potent inhibitory activity against PTP1B with IC_{50} values of 0.87μM, 6.86μM, and 2.48μM, respectively[96]. Four diterpene furanoids compounds designated as hueafuranoids A-D were isolated from the methanol extract of *Huea* sp. Hueafuranoid A displayed inhibitory activity (in a noncompetitive manner) against PTP1B with an IC_{50} value of 13.9μM[76]. Compounds viz. hopane-6α,22-diol, brialmontin 1, and atraric acid, isolated from the methanolic extract of an Antarctic lichen *Lecidella carpathica*, showed inhibitory activity against PTP1B dose-dependently with an IC_{50} values of 3.7, 14.0 and 51.5μM, respectively[97].

Tyrosinase inhibitory activity

In the study of Higuchi *et al.*[98], the methanol extracts obtained from tissues (from axenic cultures) of *Hypogymnia physodes*, *Letharia vulpina*, and *Cetraria juniperina* were shown to strongly inhibit tyrosinase activity, however, the extracts of the corresponding natural thalli of lichens revealed weaker inhibitory activity. In case of *Hypogymnia physodes*, the mycobiont exhibited a higher inhibitory potential when compared to the photobiont. Behera *et al.*[99] investigated the potential of some graphidaceous lichens against tyrosinase enzyme activity. Methanolic extracts of lichens viz. *Graphina glaucorufa*, *G. multistriata*, *G. salacinilabiata*, *Graphis assamensis*, *G. nakanishiana* and *Phaeographopsis indica* exhibited inhibitory activity against tyrosinase with IC_{50} value of 9.32, 8.40, 6.82, 10.06, 7.91 and 10.35μg/ml, respectively. Behera *et al.*[100] also showed inhibitory activity against tyrosinase by lichen species such as *Graphina glaucorufa*, *G. multistriata*, *G. salacinilabiata*, *Graphis assamensis*, *G. nakanishiana*, and *Phaeographopsis indica*. Methanol extracts were more effective than other extracts. Behera *et al.*[101] found inhibitory activity of methanol extract of natural thalli and in vitro grown cultures of *Graphis guimarana, G. nakanishiana* and *G. schizograpta* against tyrosinase. The study of Paudel *et al.*[102] revealed the anti-tyrosinase activity of a compound designated as Ramalin, isolated from the lichen *Ramalina terebrata*. The compound was more potent than kojic acid. In a similar study, Chang *et al.*[103] reported the melanogenesis inhibition by Ramalin, produced by *R. terebrata*, through its inhibitory activity against tyrosinase and by down-regulation of melanogenic proteins.

Orsellinates, the derivatives of lecanoric acid isolated from *Parmotrema tinctorum*, were shown to exhibit inhibitory activity against mushroom tyrosinase. Other compounds viz. orcinol, resorcinol and orsellinic acid were also effective against tyrosinase activity[104]. Behera and Makhija[105] determined tyrosinase inhibitory activity of extracts from natural thallus as well as *in vitro* grown cultures of the lichen *Bulbothrix setschwanensis*. Extracts were effective in causing inhibition of enzyme with IC_{50} values of >18%. Extract from natural thallus inhibited the enzyme with an IC_{50} value of 26.1μg/ml. The study carried out by Verma *et al.*[46] revealed tyrosinase inhibitory activity of extracts from cultured lichen-symbionts of three lichens viz. *Arthothelium awasthii* (IC_{50} value 8.71μg/ml), *Heterodermia podocarpa* (IC_{50} value 14.55μg/ml) and *Parmotrema tinctorum* (IC_{50} value 12.44μg/ml). Honda *et al.*[106] showed tyrosinase inhibitory activity of the extracts of lichens viz. *Cladia aggregata*, *Cladonia dimorphoclada*, *Stereocaulon ramulosum* and *Stereocaulon microcarpum*. Highest and least activity was exhibited by extract of *S. microcarpum* (32.4% inhibition) and *C. dimorphoclada* (16.1% inhibition), respectively. Kim and Cho[107] evaluated tyrosinase inhibitory activity of methanolic extracts of *Umbilicaria esculenta* and *Usnea longissima*. The inhibitory activity of *U. esculenta* and *U. longissima* was shown to be 67.4% and 84.8%, respectively. The study revealed that the extracts showed the activity via the inhibition of tyrosinase glycosylation. The study of Matsubara *et al.*[108] showed anti-tyrosinase activity of lichen metabolite resorcinol and its synthetic analogues. One of the analogues, 4-alkylresorcinols, displayed strong inhibitory activity.

Xanthine oxidase inhibitory activity

Methanol extract from the lichen *Caloplaca biatorina* was tested for inhibitory activity against xanthine oxidase. The lichen extract exhibited a concentration dependent inhibition of the enzyme[83]. The methanolic extracts obtained from some Graphidaceae members were inhibitory against xanthine oxidase with an IC_{50} value ranging from 2.0 to 5.26μg/ml[109]. Methanolic extract of some graphidaceous lichens viz. *Graphina glaucorufa*, *G. multistriata*, *G. salacinilabiata*, *Graphis assamensis*, *G. nakanishiana* and *Phaeographopsis indica* were shown to display inhibitory activity against xanthine oxidase with an IC_{50} value of 3.4, 4.8, 2.9, 6.8, 8.6 and 3.6μg/ml, respectively[99]. Behera *et al.*[101] showed inhibitory activity of methanol extract of natural thalli and in vitro grown cultures of *Graphis guimarana, G. nakanishiana* and *G. schizograpta* against xanthine oxidase.

Behera and Makhija[105] screened xanthine oxidase inhibitory activity of extracts obtained from natural thallus and *in vitro* grown cultures of the lichen *Bulbothrix setschwanensis*. Extracts were effective in causing inhibition of enzyme with IC_{50} values of >40%. Extract from natural thallus inhibited xanthine oxidase with an IC_{50} value of 52.1µg/ml. Xu *et al.*[110] isolated a new pheophytin, (132S, 17S, 18S)-132-hydroxy-20-chloro-ethylpheophorbide together with two known analogues from *Usnea diffracta* and evaluated their inhibitory activity against xanthine oxidase. The compounds showed significant inhibitory activity against xanthine oxidase.

Inhibition of fatty acid synthase activity

The study of Bessadottir *et al.*[111] showed that the treatment with (+)-protolichesterinic acid in SK-BR-3 cells results in overexpression of fatty acid synthase indicating the primary effect of the compound on the activity of fatty acid synthase. Lauinger *et al.*[77] studied the potential of four lichen compounds namely evernic acid, vulpic acid, (+)-usnic acid and psoromic acid to inhibit the enzymes involved in fatty acid biosynthesis pathway. Compounds viz. vulpic acid, evernic acid, (+)-usnic acid displayed inhibition of one or more enzymes of fatty acid biosynthesis pathway.

Cholinesterase inhibitory activity

A mixture of acetylated depsidones with moderate inhibitory activity against acetylcholinesterase were isolated from a foliose lichen by Pejin *et al.*[112]. Perlatolic acid, a lichen derived compound, is shown to exhibit promising acetylcholine esterase inhibition activity[113]. A depsidone compound isolated from the foliose lichen *Lobaria pulmonaria* was shown to exert moderate inhibitory activity against acetylcholinesterase[114]. Lobaric acid, isolated from *Heterodermia* sp. was shown to exhibit inhibitory activity against acetyl-cholinesterase with an IC_{50} value of 26.86µM and butyryl-cholinesterase with an IC_{50} value of 36.76µM[79]. Biruloquinone, a compound isolated from the lichen forming fungus *Cladonia mucilenta*, was screened for acetylcholinesterase inhibitory activity. The compound exhibited dose dependent inhibitory activity against the enzyme with an IC_{50} value of 27.1µg/ml[115].

Lipoxygenase inhibitory activity

Ingolfsdottir *et al.*[116] isolated protolichesterinic acid from *Cetraria islandica* and screened its activity against 5-lipoxygenase in vitro. The compound was shown to exhibit inhibitory activity against the enzyme 5-lipoxygenase. Two isomeric compounds namely (+)-lichesterinic acid and (-)-lichesterinic acid, synthesized from (+)-protolichesterinic- and (-)-allo-protolichesterinic acids, respectively, were also effective against 5-lipoxygenase activity. Ingolfsdottir *et al.*[117] recovered a lichen substance from *Stereocaulon alpinum* and screened for enzyme inhibitory activity. The compound was identified as lobaric acid and was shown to display concentration dependent inhibitory activity with an IC_{50} value of 7.3µM. Ingolfsdottir *et al.*[118] isolated Baeomycesic acid from *Thamnolia subuliformis* and found its potent concentration dependent inhibitory activity against 5-lipoxygenase with an IC_{50} value of 8.3 µM. An alkamide designated as 9-cis-octa-decenamide was isolated from the lichen *Stereocaulon alpinum*. The compound was shown to display only slight activity against 5-lipoxygenase[119]. The lichen compounds imbricaric acid and perlatolic acid, isolated from the lichen *Cetrelia monachorum*, were effective against 5-lipoxygenase with and IC_{50} value of 5.3 and 1.8µM, respectively[120].

Two orcinol derivatives viz. tenuiorin and methyl orsellinate, isolated from the lichen *Peltigera leucophlebia* were shown to exhibit inhibitory activity against 15-lipoxygenase from soybeans *in vitro*. Tenuiorin and methyl orsellinate were also moderately effective against 5-lipoxygenase (from porcine leucocytes) with IC_{50} values of 41.6µM and 59.6µM, respectively[121]. Lichen compounds viz. protolichesterinic acid, lobaric acid and baeomycesic acid exhibit inhibitory activity against 5-lipoxygenase. Protolichesterinic acid and lobaric acid also exhibit 12-lipoxygenase activity[122]. Lichen metabolites viz. lobaric acid, (+)-protolichesterinic acid and baeomycesic acid, isolated from *Stereocaulon* alpinum, *Cetraria islandica* and *Thamnolia vermicularis*, respectively were screened for inhibitory activity on platelet-type 12(S)-lipoxygenase. The compounds lobaric acid and (+)-protolichesterinic acid showed pronounced inhibitory activity against the enzyme while baeomycesic acid caused slight activity[123]. Behera *et al.*[124] determined anti-lipoxygenase activity of ethyl acetate extract of 8 *Heterodermia* sp. Extracts were effective in causing dose dependent inhibition of lipoxygenase with IC_{50} value of 0.123, 0.187, 0.187, 0.153, 0.160, 0.229, 0.150 and 0.232mg/ml in case of *H. diademata*, *H. angustiloba*, *H. albicans*, *H. flabellata*, *H. antillarum*, *H. isidiophora*, *H. incana* and *H. pseudospeciosa*, respectively.

Cyclooxygenase (COX) inhibitory activity

Two compounds viz. atranorin and chloroatranorin, isolated from hexane extract of *Parmotrema saccatilobum* inhibited COX-1 and COX-2 enzymes in a dose dependent manner[125]. Lobaric acid and atranorin, isolated from *Stereocaulon alpinum*, were screened for inhibitory activity against cyclooxygenase. Lobaric acid showed inhibitory activity (IC_{50} value 29.2µM) while atranorin was found to be inactive[117]. An alkamide designated as 9-cis-octa-decenamide, isolated from the lichen *Stereocaulon alpinum*, was shown to display inhibitory activity against cyclooxygenase from sheep seminal vesicle microsomes with an IC_{50} value of 64.3µM[119]. Jager *et al.*[126] evaluated inhibitory potential of extracts of some lichens against prostaglandin-synthesis through inhibitory activity against cyclooxygenase. Ethanol extract of *Pseudocyphellaria aurata* caused highest inhibition of 96%. Extracts of *Parmelia autrosinensis*, *P. reticulata*, *P. soredians*, *Heterodermia speciosa*, *Usnea undulata* and *Ramalina celastri* also revealed promising inhibitory activity. Through in silico molecular docking studies, Khan *et al.*[127] highlighted the possible inhibitory role of lichen metabolites such as atranorin, lecanoric acid, and diffractic acid against cyclooxygenase-2 enzyme. The study of Engel *et al.*[128] revealed anti-inflammatory properties of *U. barbata* in an ultraviolet-B model with HaCaT keratinocytes. Extract inhibited prostaglandin E2 synthesis through an effect on COX-2 activity rather than on protein expression.

Prolyl endopeptidase inhibitory activity

Extract of a Himalayan lichen *Cetrelia olivetorum* was screened for inhibitory activity against Prolyl endopeptidase. The extract caused inhibition of the enzyme with an IC_{50} value of 144-288 µg/ml[129].

Inhibitory activity against Phospholipase A_2

Two depside compounds viz. orcinol and methyl orsellinic acid, isolated from the methanol extract of *Umbilicaria esculenta*, were shown to inhibit human synovial fluid Phospholipase A_2[130].

Inhibition of Prostaglandin E_2 synthase-1 activity

Oettl *et al.*[120] isolated two compounds viz. imbricaric acid and perlatolic acid from the lichen *Cetrelia monachorum* and

screened them for inhibitory activity against Prostaglandin E_2 synthase-1. Both imbricaric acid and perlatolic acid were effective and showed inhibition of the enzyme with an IC_{50} value of 1.9 and 0.4µM, respectively. Through validated pharmacophore models (cell free assays), Bauer *et al.*[131] revealed physodic acid and perlatolic acid as potent inhibitors of Prostaglandin E_2 synthase-1 with IC_{50} values of 0.4 and 0.43µM, respectively.

Aldehyde oxidase inhibitory activity

Valadbeigi[83] screened methanol extract obtained from *Caloplaca biatorina* for inhibitory activity against aldehyde oxidase enzyme. The extract was shown to exhibit concentration dependent inhibition of aldehyde oxidase.

Aldose reductase inhibitory activity

Ethyl acetate extract of a macrolichen *Parmotrema tinctorum* was found to exhibit inhibitory activity against aldose reductase with an IC_{50} value of 139.28±2.6µg/ml[87].

Inhibition of DNA polymerases

Le *et al.*[132] isolated eight new alkylated decalin-type polyketides from the mycobiont of a crustose lichen *Pyrenula* sp. The polyketide compounds (1 and 7) showed inhibitory activities against mammalian DNA polymerases α and β with IC_{50} values ranging from 8.1 to 19.5µM.

Pancreatic lipase inhibitory activity

Kumar *et al.*[28] investigated anti-obesity activity of methanol extract of *Everniastrum cirrhatum* in terms of inhibition of chicken pancreatic lipase. The extract was effective and was shown to inhibit lipase activity in a concentration dependent manner. Shivanna *et al.*[133] screened ethyl acetate and methanol extracts of two lichens viz. *Heterodermia leucomelos* and *Ramalina celastri* against chicken pancreatic lipase activity. Extracts were effective against enzyme activity in a concentration dependent manner. Methanol extracts were effective to more extent than ethyl acetate extracts.

Plk1 inhibitory activity

Williams *et al.*[75] isolated a new depside and two known depsides from *Parmotrema* sp. and subjected these compounds for their inhibitory efficacy against Plk1 (polo-like kinase-1). The new depside, β-collatolic acid and β-alectoronic acid showed inhibitory effect against Plk1 with IC_{50} value of 2.8, 0.7, and 1.7µM, respectively.

Topoisomerase inhibitory activity

A depside compound Anziaic acid was isolated from *Hypotrachyna* sp. and evaluated for its topoisomerase inhibitory activity. The compound was effective in causing inhibition of *E. coli* and *Y. pestis* Topo 1with IC_{50} value 14-19µM. Anziaic acid was also effective against human topoisomerase II but had little effect on human topoisomerase I[40].

β-glucuronidase inhibitory activity

Lobaric acid, isolated from *Heterodermia* sp. was shown to exhibit inhibitory activity against β-glucuronidase with an IC_{50} value of 3.28±0.05µM[79].

Inhibitory activity against phosphodiesterase

Lobaric acid, isolated from *Heterodermia* sp., caused significant inhibition of phosphodiesterase enzyme with an IC_{50} value 313.7±2.2µM[79].

Urease inhibitory activity

Metabolites namely (S)-(−)-usnic acid and fumarprotocetraric acid, isolated from *Cladonia rappii* were shown to be active against jack bean urease. The compounds were effective in their interaction with the urease[134]. Compounds viz. ethyl heamatomate, atraric acid, ethyl orsellinate, lecanoric acid, gyrophoric acid, and licanorin isolated from *Parmotrema cooperi* were shown to exhibit inhibitory activitiy against urease with IC_{50} value of 42.13, 16.50, 50.83, 67.20, 52.53 and 34.06µM, respectively. Orsellinic acid was not effective in causing inhibition of urease[17]. Thadhani *et al.*[79] isolated lobaric acid from *Heterodermia* sp. and evaluated its inhibitory activity against urease. The metabolites was not effective in causing inhibition of urease. The study of Aydin *et al.*[135] revealed dose dependent inhibition of urease enzyme by ethanol and ethyl acetate extracts of the lichen *Usnea longissima*. Ethanol extract was more effective than ethyl acetate extract.

Inhibitory activity against Trypsin

Proksa *et al.*[136] isolated compounds viz. atranorin, physodic acid, oxyphysodic acid and virensic acid from a lichen species *Pseudevernia furfuracea*. The compound atranorin was shown to be the strongest inhibitor of trypsin.

Thioredoxin reductase inhibitory activity

The inhibitory effect of some lichen acids including diffractaic acid, evernic acid, lobaric acid, lecanoric acid, and vulpinic acid against the activity of thioredoxin reductase purified from rat lung was investigated[137]. All the tested compounds displayed marked effect on enzyme activity with stronger inhibitory activity displayed by lecanoric acid and vulpinic acid.

Elastase inhibitory activity

Atranorin, isolated from the lichen *Pseudevernia furfuracea* was shown to exhibit strong inhibitory activity against porcine pancreatic elastase[136]. Aydin *et al.*[135] showed concentration dependent inhibition of elastase enzyme by ethanol and ethyl acetate extracts of *Usnea longissima*. Ethanol extract caused marked inhibitory activity than ethyl acetae extract.

Inhibition of hydroxy-3-methyl-glutaryl-CoA reductase (HMGR)

Behera *et al.*[38] screened extracts of *Usnea complanata* and isolated compounds viz. usnic acid and psoromic acid for inhibitory activity against HMGR. Ethyl acetate and methanol extracts of the lichen were shown to display 74.81% and 65.18% inhibition of HMGR. Usnic acid and psoromic acid were also effective in causing inhibition of HMGR in noncompetitive and competitive type. Mahadik *et al.*[138] showed dose dependent inhibition of HMGR by solvent extracts of *U. complanata*. At 200µg/ml concentration, the enzyme inhibition by extracts was in the order: ethyl acetate > methanol > ethanol > acetone extract.

Inhibition of angiotensin converting enzyme (ACE)

In a study, methanol, acetone, and ethanol extracts of *Usnea complanata* were shown to inhibit ACE by 43.47%, 23.18% and 21.73% respectively. Two compounds viz. usnic acid and psoromic acid, isolated from *U. complanata*, were effective in causing inhibition of ACE in uncompetitive and mixed type[38]. At 200µg/ml concentration, an inhibition of 46.4%, 44.3%, 23.2% and 16% of ACE was produced by ethanol, ethyl acetate, methanol and acetone extract of *U. complanata*[138].

Tyrosyl-DNA Phosphodiesterase 1 (Tdp1) inhibitory activity

Usnic acid derivatives were shown to exhibit Tdp1 inhibitory potential. Zakharenko *et al.*[139] **(2016)** synthesized and tested novel usnic acid derivatives with an enamine moiety for inhibitory activity against Tdp1 enzyme. The enamines were effective with IC_{50} values in the range 0.16-2.0µM. Zakharova *et al.*[140] screened 29 derivatives of (+)-usnic acid against Tdp1 inhibitory activity using a fluorescent-based assay. One of the derivatives i.e. 6m showed activity the lowest IC_{50} value of 25nM. Dyrkheeva *et al.*[141] synthesized a series of usnic acid derivatives comprising a terpenoid moiety and subjected them for activity against Tdp1 enzyme. Compounds viz. 15A, 15B, 15G, 16A, 16B, and 16G were effective with IC_{50} values in the range 0.33-2.7µM. The inhibitory activities were shown to be dependent on the length and flexibility of the terpenoid moiety.

Inhibition of sulfatase and aromatase activity

Ingólfsdóttir *et al.*[142] evaluated inhibition of estrogen formation through inhibition of two enzymes sulfatase and aromatase. An inhibitory activity of 83%, 95% and 90% against sulfatase was observed in case of extracts of *Cladonia gracilis*, *Sphaerophorus fragilis* and *S. globosus*, respectively. Extracts of *Cetrariella delisei*, *Melanelia hepatizon* and *S. globosus* caused 82%, 73% and 74% inhibition of aromatase, respectively.

Telomerase inhibitory activity

In a study, ethyl acetate, hexane and aqueous extracts obtained from the lichen *Umbilicaria esculenta* displayed strong inhibitory activity against telomerase[143].

Inhibition of Rab geranylgeranyl transferase activity

The study carried out by Deraeve *et al.*[144] revealed the potential of psoromic acid to inhibit the enzyme Rab geranylgeranyl transferase. The compound was effective and selectively inhibited the activity of the enzyme with an IC_{50} of 1.3µM.

Anti-UGM activity

Psoromic acid, a lichen derived compound, was shown to exhibit marked inhibitory activity against UDP-galactopyranose mutase (UGM) associated with *Mycobacterium tuberculosis*. An inhibition of 85.8% of UGM was observed[145].

Arylamine-N-acetyltransferase inhibitory activity

Psoromic acid, a lichen derived compound, was shown to exhibit marked inhibitory activity against Arylamine-N-acetyltransferase associated with *Mycobacterium tuberculosis*. The compound caused an inhibition of 77.4% of the enzyme with an IC_{50} value of 8.7µM[145].

Inhibition of HIV-1 reverse transcriptase

In a study by Pengsuparp *et al.*[146], protolichesterinic acid from the lichen *Cetraria islandica*, was shown to inhibit the activity of HIV-1 reverse transcriptase with an IC_{50} value of 24µM.

Monoamine oxidase inhibitory activity

Okuyama *et al.*[147] evaluated the inhibitory potential of three anthraquinones viz. averantin 6-monomethyl ether, solorinic acid, and 4,4'-bissolorinic acid, and two depsides namely methyl gyrophorate and gyrophoric acid, isolated from a lichen, *Solorina crocea*, against monoamine oxidase. Only anthraquinones were shown to display inhibition of monoamine oxidase enzyme. Kinoshita *et al.*[148] revealed the monoamine oxidase inhibitory activity of lichen metabolites and their synthetic analogues. One compound designated as 4-acylresorcinol displayed potent inhibitory activity with IC_{50} value $4.27x10^{-6}$M.

p-hydroxyphenylpyruvate dioxygenase inhibitory activity

Romagni *et al.*[14] showed phytotoxic activity of usnic acid isolated from *Alectoria sarmentosa* (Ach.) in terms of irreversible inhibition of activity of p-hydroxyphenylpyruvate dioxygenase (with an apparent IC_{50} value of 70nM). Treatment with the compound (-)-usnic acid resulted in a concentration dependent bleaching of the cotyledonary tissues together with a decrease of chlorophylls as well as carotenoids. However, least bleaching effect was observed in case of (+) enantiomer of usnic acid.

CONCLUSIONS

Natural products have been extensively screened for enzyme inhibition studies. Extensive literature survey carried out in this study revealed the potential of lichen extracts and purified metabolites from lichens to inhibit a range of enzymes such as lipase, amylase, glucosidase, urease, tyrosinase, xanthine oxidase, sulfatase, aromatase, elastase, monoamine oxidase, lipoxygenase, ACE, Tdp1, UDP-galactopyranose mutase, thioredoxin reductase, HIV-1 reverse transcriptase, trypsin, phosphodiesterase, telomerase, and topoisomerase. Lichens appears to be promising candidates for development of novel enzyme inhibitors which can be utilized as a remedy against various diseases and disorders. Studies concerning in vitro propagation of lichen symbionts for isolation of bioactive components with enzyme inhibitory activity may be undertaken.

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CONFLICTS OF INTEREST

None declared

REFERENCES

1. Huneck S. The significance of lichens and their metabolites. Naturwissenschaften 1999; 86(12): 559-570.
2. Molnár K, Farkas E. Current results on biological activities of lichen secondary metabolites: a review. Z Naturforsch C, 2010; 65(3-4):157-173.
3. Boustie J, Tomasi S, Grube M. Bioactive lichen metabolites: alpine habitats as an untapped source. Phytochem Rev 2011; 10:287-307.
4. Jagtap V, Tripathi M, Joshi Y. First report on the occurrence of plasticolous lichens from Uttarakhand, India. J Appl Nat Sci 2013; 5(2):342-344.
5. Rogers RD. Medicinal lichens. Fungi 2014; 7(2-3):56-58.
6. Kusmoro J, Noer IS, Jatnika MF, Permatasari RE, Partasasmita R. Lichen diversity in geothermal area of Kamojang, Bandung, West Java, Indonesia and its potential for medicines and dyes. Biodiversitas 2018; 19(6):2335-2343.
7. Soundararajan S, Shanmugam P, Nagarajan N, Palanisamy D, Ponnusamy P. In vitro study on screening antimicrobial and anti-oxidant potential of *Ramalina fastigiata*. J Drug Delivery Ther 2019; 9(1):216-219.
8. Upreti DK, Divakar PK, Nayaka S. Commercial and ethnic use of lichens in India. Econ Bot 2005; 59(3): 269-273.

9. Shukla P, Upreti DK, Nayaka S, Tiwari P. Natural dyes from Himalayan lichens. Indian J Tradit Know 2014; 13(1):195-201.
10. Singh S, Upreti DK, Lehri A, Paliwal AK. Quantification of lichens commercially used in traditional perfumery industries of Uttar Pradesh, India. Indian J Plant Sci 2015; 4(1):29-33.
11. Weissbuch BK. Medicinal lichens: the final frontier. Journal of the American Herbalists Guild 2016; 12(2):23-28.
12. Londoño-Castañeda PA, Buril MLL, Rego-Cunha IP, Silva NH, Honda NK, Pereira EC, Andrade LHC. Lichens used in the traditional medicine by the Pankararu Indigenous Community, Pernambuco-Brazil. Global Journal of Science Frontier Research: C Biological Science 2017; 17(4): 15-22.
13. Ogmundsdóttir HM, Zoëga GM, Gissurarson SR, Ingólfsdóttir K. Anti-proliferative effects of lichen-derived inhibitors of 5-lipoxygenase on malignant cell-lines and mitogen-stimulated lymphocytes. J Pharm Pharmacol 1998; 50(1):107-115.
14. Romagni JG, Meazza G, Nanayakkara DNP, Dayan FE. The phytotoxic lichen metabolite, usnic acid, is a potent inhibitor of plant p-hydroxyphenylpyruvate dioxygenase. FEBS Lett 2000; 480: 301-305.
15. Karunaratne V, Bombuwela K, Kathirgamanathar S, Thadhani VM. Lichens: A chemically important biota. J Natn Sci Foundation Sri Lanka 2005; 33(3):169-186.
16. Turk H, Yılmaz M, Tay T, Turk AO, Kıvanc M. antimicrobial activity of extracts and chemical races of the lichen *Pseudevernia furfuracea* and their physodic acid, chloroatranorin, atranorin, and olivetoric acid constituents. Z Naturforsch 2006; 61c: 499-507.
17. Choudhary IM, Ali M, Atia-tul-Wahab, Khan A, Rasheed S, Shyaula SL, Attar-ur-Rahman. New antiglycation and enzyme inhibitors from *Parmotrema cooperi*. Sci China Chem 2011; 54(12): 1926-1931.
18. Mitrovic T, Stamenkovic S, Cvetkovic V, Radulovic N, Mladenovic M, Stankovic M, Topuzovic M, Radojevic I, Stefanovic O, Vasic S, Comic L. *Platismatia glauca* and *Pseudevernia furfuracea* lichens as sources of antioxidant, antimicrobial and antibiofilm agents. EXCLI Journal 2014; 13:938-953.
19. Varol M. Natural small-molecules obtained from lichens as a novel source of anti-angiogenic agents. J Appl Pharm 2015; 8: 1.
20. Thorsteinsdottir UA, Thorsteinsdottir M, Lambert IH. Protolichesterinic acid, isolated from the lichen *Cetraria islandica*, reduces LRRC8A expression and volume-sensitive release of organic osmolytes in human lung epithelial cancer cells. Phytother Res 2016; 30(1):97-104.
21. Prateeksha, Paliya BS, Bajpai R, Jadaun V, Kumar J, Kumar S, Upreti DK, Singh BR, Nayaka S, Joshi Y, Singh BN. The genus *Usnea*: a potent phytomedicine with multifarious ethnobotany, phytochemistry and pharmacology. RSC Adv 2016; 6:21672.
22. Tomović J, Kosanić M, Ristić S, Ranković B, Stanojković T, Manojlović N. Chemical composition and bioactive properties of the lichen, *Pleurosticta acetabulum*. Trop J Pharm Res 2017; 16(12):2977-2984.
23. Castro ON, Benites J, Rodilla J, Santiago JC, Simirgiotis M, Sepulveda B, Areche C. Metabolomic analysis of the lichen *Everniopsis trulla* using Ultra High Performance Liquid Chromatography-Quadrupole-Orbitrap Mass Spectrometry (UHPLC-Q-OT-MS). Chromatographia 2017; 80:967–973.
24. Cardile V, Graziano ACE, Avola R, Piovano M, Russo A. Potential anticancer activity of lichen secondary metabolite physodic acid. Chem Biol Interact 2017; 263:36-45.
25. Kekuda PTR, Vinayaka KS, Sachin MB. Chemistry, ethnobotanical uses and biological activities of the lichen genus *Heterodermia* Trevis. (Physciaceae; Lecanorales; Ascomycota): A comprehensive review. J Appl Pharm Sci 2018; 8(5):148-155.
26. Steckelings UM, Artuc M, Wollschlager T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. Acta Derm Venereol 2001; 81:321-325.
27. Balbaa M, El Ashry ESH. Enzyme inhibitors as therapeutic tools. Biochem Physiol 2012; 1(2):1000103.
28. Kumar AHS, Kekuda PTR, Vinayaka KS, Swathi D, Venugopal TM. Anti-obesity (pancreatic lipase inhibitory) activity of *Everniastrum cirrhatum* (Fr.) Hale (Parmeliaceae). Phcog J 2011; 3(19):65-68.
29. Lunagariya NA, Patel NK, Jagtap SC, Bhutani KK. Inhibitors of pancreatic lipase: state of the art and clinical perspectives. EXCLI Journal 2014; 13:897-921.
30. Awllia JAJ, Sara A, Atia-tul-Wahab, AL-Ghamdi M, Rasheed S, Huwait E, Choudhary IM. Discovery of new inhibitors of urease enzyme: A study using STD-NMR Spectroscopy. Lett Drug Des Discovery 2015; 12: 819-827.
31. Satish BNVS, Kumar P, Avanti SM, Singh S. Salivary amylase as potential biochemical marker in diabetes mellitus. International Journal of Recent Surgical and Medical Sciences 2016; 2(1): 19-22.
32. Buitrago E, Hardre R, Haudecoeur R, Jamet H, Belle C, Boumendjel A, Bubacco L, Reglier M. Are human tyrosinase and related proteins suitable targets for melanoma therapy?. Curr Top Med Chem 2016; 16: 3033-3047.
33. Ramsay RR, Tipton KF. Assessment of enzyme inhibition: a review with examples from the development of monoamine oxidase and cholinesterase inhibitory drugs. Molecules 2017; 22: 1192.
34. Shivaraj B, Pattabiraman TN. Natural plant enzyme inhibitors. Characterization of an unusual alpha-amylase/trypsin inhibitor from ragi (*Eleusine coracana* Geartn.). Biochem J 1981; 193(1):29-36.
35. Schneider I, Bucar F. Lipoxygenase inhibitors from natural plant sources. Part 1: Medicinal plants with inhibitory activity on arachidonate 5-lipoxygenase and 5-lipoxygenase[sol]cyclooxygenase. Phytother Res 2005; 19(2):81-102.
36. Subramanian R, Asmawi ZM, Sadikun A. *In vitro* α-glucosidase and α-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. Acta Biochim Pol 2008; 55(2):391-398.
37. Jiang C, Liang L, Guo Y. Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades. Acta Pharmacol Sin 2012; 33:1217-1245.
38. Behera BC, Mahadik N, Morey M. Antioxidative and cardiovascular-protective activities of metabolite usnic acid and psoromic acid produced by lichen species *Usnea complanata* under submerged fermentation. Pharm Biol 2012; 50(8):968-979.
39. Kumar S, Kumar V, Rana M, Kumar D. Enzyme inhibitors from plats: An alternate approach to treat diabetes. Pharmacogn Commun 2012; 2(2):18-33.
40. Cheng B, Cao S, Vasquez V, Annamalai T, Tamayo-Castillo G, Clady J, Tse-Dinh Y. Identification of Anziaic acid, a lichen depside from *Hypotrachyna* sp., as a new topoisomerase poison inhibitor. PLoS ONE 2013; 8(4): e60770.
41. Revathy T, Jayasri MA, Suthindhiran K. Anti-oxidant and enzyme-inhibitory potential of marine Streptomyces. Am J Biochem Biotechnol 2013; 9(3):282-290.
42. Ramanjooloo A, Cresteil T, Lebrasse C, Beedessee G, Oogarah P, van Soest RWM, Marie DEP. α-Glucosidase inhibitory activity of marine sponges collected in Mauritius waters. Nat Prod Res 2015; 29(4):383-387.
43. Jayaraj S, Suresh S, Kadeppagari R. Amylase inhibitors and their biomedical applications. Starch 2013; 65(7-8):535-542.
44. van de Laar FA. Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes. Vasc Health Risk Manag 2008; 4(6):1189-95.
45. Taylor SD, Hill B. Recent advances in protein tyrosine phosphatase 1B inhibitors. Expert Opin Investig Drugs 2004; 13(3):199-1214.
46. Verma N, Behera BC, Sonone A, Makhija U. Lipid peroxidation and tyrosinase inhibition by lichen symbionts grown in vitro. Afr J Biochem Res 2008; 2(12):225-231.
47. Pacher P, Nivorozhkin A, Szabó C. Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol. Pharmacol Rev 2006; 58(1):87-114.
48. Follmer C. Ureases as a target for the treatment of gastric and urinary infections. J Clin Pathol 2010; 63(5): 424-430.
49. Steinhilber D, Hofmann B. Recent advances in the search for novel 5-Lipoxygenase inhibitors. Basic Clin Pharmacol Toxicol 2014; 114:70–77.
50. Harris RC, Breyer MD. Update on cyclooxygenase-2 inhibitors. Clin J Am Soc Nephrol 2006; 1: 236-245.
51. Psarra A, Nikolaou A, Kokotou MG, Limnios D, Kokotos G. Microsomal prostaglandin E2 synthase-1 inhibitors: a patent review. Expert Opin Ther Pat 2017; 27(9):1047-1059.
52. Dastidar SG, Rajagopal D, Ray A. Therapeutic benefit of PDE4 inhibitors in inflammatory diseases. Curr Opin Investig Drugs 2007; 8(5):364-372.

53. Kelland LR. Overcoming the immortality of tumour cells by telomere and telomerase based cancer therapeutics--current status and future prospects. Eur J Cancer 2005; 41(7):971-979.
54. Zhang JS, Lei JP, Wei GQ, Chen H, Ma CY, Jiang HZ. Natural fatty acid synthase inhibitors as potent therapeutic agents for cancers: A review. Pharm Biol 2016; 54(9):1919-1925.
55. Dexheimer TS, Antony S, Marchand C, Pommier Y. Tyrosyl-DNA phosphodiesterase as a target for anticancer therapy. Anticancer Agents Med Chem 2008; 8(4):381-389.
56. Berdis AJ. DNA polymerases as therapeutic targets. Biochemistry 2008; 47(32):8253-8260.
57. Liu X. Targeting Polo-like kinases: A promising therapeutic approach for cancer treatment. Transl Oncol 2015; 8(3): 185-195.
58. Sinha BK. Topoisomerase inhibitors. A review of their therapeutic potential in cancer. Drugs 1995; 49(1): 11-19.
59. Sane KM, Mynderse M, Lalonde DT, Dean IS, Wojtkowiak JW, Fouad F, Borch RF, Reiners JJ, Gibbs RA, Mattingly RR. A novel geranylgeranyl transferase inhibitor in combination with lovastatin inhibits proliferation and induces autophagy in STS-26T MPNST cells. J Pharmacol Exp Ther 2010; 333(1): 23-33.
60. Lampe JW, Li SS, Potter JD, King IB. Serum β-glucuronidase activity is inversely associated with plant-food intakes in humans. J Nutr 2002; 132(6): 1341-1344.
61. Fabian CJ. The what, why and how of aromatase inhibitors: hormonal agents for treatment and prevention of breast cancer. Int J Clin Pract 2007; 61(12): 2051-2063.
62. Shah R, Singh J, Singh D, Jaggi AS, Singh N. Sulfatase inhibitors for recidivist breast cancer treatment: A chemical review. Eur J Med Chem 2016; 114: 170-190.
63. Grossberg GT. Cholinesterase inhibitors for the treatment of Alzheimer's disease: getting on and staying on. Curr Ther Res Clin Exp 2003; 64(4): 216-235.
64. Männisto PT, Venäläinen J, Jalkanen A, García-Horsman JA. Prolyl oligopeptidase: a potential target for the treatment of cognitive disorders. Drug News Perspect 2007; 20(5): 293-305.
65. Rosenson RS, Hurt-Camejo E. Phospholipase A2 enzymes and the risk of atherosclerosis. Eur Heart J 2012; 33(23): 2899-2909.
66. Schemmel KE, Padiyara RS, D'Souza JJ. Aldose reductase inhibitors in the treatment of diabetic peripheral neuropathy: a review. J Diabetes Complications 2010; 24(5): 354-360.
67. White WB. Angiotensin-converting enzyme inhibitors in the treatment of hypertension: an update. J Clin Hypertens (Greenwich) 2007; 9(11): 876-882.
68. Pazzucconi F, Dorigotti F, Gianfranceschi G, Campagnoli G, Sirtori M, Franceschini G, Sirtori CR. Therapy with HMG CoA reductase inhibitors: characteristics of the long-term permanence of hypocholesterolemic activity. Atherosclerosis 1995; 117(2): 189-198.
69. Entzeroth M, Ratty AK. Monoamine Oxidase Inhibitors—Revisiting a Therapeutic Principle. Open Journal of Depression 2017; 6: 31-68.
70. Castro HC, Loureiro NI, Pujol-Luz M, Souza AM, Albuquerque MG, Santos DO, Cabral LM, Frugulhetti IC, Rodrigues CR. HIV-1 reverse transcriptase: a therapeutical target in the spotlight. Curr Med Chem 2006; 13(3): 313-324.
71. Brandl T, Simic O, Skaanderup PR, Namoto K, Berst F, Ehrhardt C, Schiering N, Mueller I, Woelcke J. Trypsin inhibitors for the treatment of pancreatitis. Bioorg Med Chem Lett 2016; 26(17): 4340-4304.
72. Westwood IM, Bhakta S, Russell AJ, Fullam E, Anderton MC, Kawamura A, Mulvaney AW, Vickers RJ, Bhowruth V, Besra GS, Lalvani A, Davies SG, Sim E. Identification of arylamine N-acetyltransferase inhibitors as an approach towards novel anti-tuberculars. Protein Cell 2010; 1(1): 82-95.
73. Soltero-Higgin M1, Carlson EE, Phillips JH, Kiessling LL. Identification of inhibitors for UDP-galactopyranose mutase. J Am Chem Soc 2004; 126(34): 10532-10533.
74. Saccoccia F, Angelucci F, Boumis G, Carotti D, Desiato G, Miele AE, Bellelli A. Thioredoxin reductase and its inhibitors. Curr Protein Pept Sci 2014; 15: 621-646.
75. Williams DE, Loganzo F, Whitney L, Togias J, Harrison R, Singh MP, McDonald LA, Kathirgamanathar S, Karunaratne V, Andersen RJ. Depsides isolated from the Sri Lankan lichen *Parmotrema* sp. exhibit selective Plk1 inhibitory activity. Pharm Biol 2011; 49(3): 296–301.
76. Cui Y, Yim JH, Lee DS, Kim YC, Oh H. New diterpene furanoids from the Antarctic lichen *Huea* sp. Bioorg Med Chem Lett 2012; 22(24): 7393-7396.
77. Lauinger IL, Vivas L, Perozzo R, Stairiker C, Tarun A, Zloh M, Zhang X, Xu H, Tonge PJ, Franzblau SG, Pham DH, Esguerra CV, Crawford AD, Maes L, Tasdemir D. Potential of lichen secondary metabolites against Plasmodium liver stage parasites with FAS-II as the potential target. J Nat Prod 2013; 76(6): 1064-1070.
78. Karunaratne V, Thadhani VM, Khan SN, Choudhary IM. Potent α-glucosidase inhibitors from the lichen *Cladonia* species from Sri Lanka. J Natn Sci Foundation Sri Lanka 2014; 42(1): 95-98.
79. Thadhani VM, Naaz Q, Choudhary IM, Mesaik AM, Karunaratne V. Enzyme inhibitory and immunomodulatory activities of the depsidone lobaric acid extracted from the lichen *Heterodermia* sp. J Natn Sci Foundation Sri Lanka 2014; 42(2): 193-196.
80. Yusof H, Azahar H, Din LB, Ibrahim N. Chemical constituents of the lichens *Cladonia multiformis* and *Cryptothecia* sp. Malaysian J Anal Sci 2015; 19(5): 930-934.
81. Honda NK, Lopes TIB, Costa RCS, Coelho RG, Yoshida NC, Rivarola CRV, Marcelli MP, Spielmann AA. Radical-scavenging potential of phenolic compounds from Brazilian lichen. Orbital: Electronic J Chem 2015; 7(2): 99-107.
82. Studzińska-Sroka E, Dubino A. Lichens as a source of chemical compounds with antiinflammatory activity. Herba Pol 2018; 64(1): 56-64.
83. Valadbeigi T. Chemical composition and enzymes inhibitory, brine shrimp larvae toxicity, antimicrobial and antioxidant activities of *Caloplaca biatorina*. Zahedan J Res Med Sci 2016; 18(11): e4267.
84. Hengameh P, Rashmi S, Rajkumar HG. In vitro inhibitory activity of some lichen extracts against α-amylase enzyme. European Journal of Biomedical and Pharmaceutical Sciences 2016; 3(5): 315-318.
85. Tekale SS. The A-amylase inhibitory and dye degradation potential of the lichen (*parmelia perlata*). International Journal of Basic and Applied Research 2018; 8(8): 256-260.
86. Shivanna R, Parizadeh H, Garampalli RH. Screening of lichen extracts for in vitro antidiabetic activity using alpha amylase inhibitory assay. International Journal of Biological and Pharmaceutical Research 2015; 6(5): 364-367.
87. Raj PS, Prathapan A, Sebastian J, Antony AK, Riya MP, Rani MR, Biju H, Priya S, Raghu KG. *Parmotrema tinctorum* exhibits antioxidant, antiglycation and inhibitory activities against aldose reductase and carbohydrate digestive enzymes: an in vitro study. Nat Prod Res 2014; 28(18): 1480-1484.
88. Vinayaka KS, Karthik S, Nandini KC, Kekuda PTR. Amylase inhibitory activity of some macrolichens of Western Ghats, Karnataka, India. Indian Journal of Novel Drug Delivery 2013; 5(4): 225-228.
89. Valadbeigi T, Shaddel M. Amylase inhibitory activity of some macrolichens in Mazandaran province, Iran. Physiol Pharmacol 2016; 20: 215-219.
90. Karthik S, Nandini KC, Kekuda PTR, Vinayaka KS, Mukunda S. Total phenol content, insecticidal and amylase inhibitory efficacy of *Heterodermia leucomela* (L). Ann Biol Res 2011; 2(4): 38-43.
91. Parizadeh H, Garampalli RH. Evaluation of some lichen extracts for β-glucosidase inhibitory as a possible source of herbal anti-diabetic drugs. Am J Biochem 2016; 6(2): 46-50.
92. Verma N, Behera BC, Sharma BO. Glucosidase inhibitory and radical scavenging properties of lichen metabolites salazinic acid, sekikaic acid and usnic acid. Hacettepe J Biol Chem 2012; 40(1): 7-21.
93. Lee KA, Kim MS. Glucosidase inhibitor from *Umbilicaria esculenta*. Can J Microbiol 2000; 46(11): 1077-1081.
94. Seo C, Sohn JH, Park SM, Yim JH, Lee HK, Oh H. Usimines A-C, bioactive usnic acid derivatives from the Antarctic lichen *Stereocaulon alpinum*. J Nat Prod 2008; 71(4): 710-712.
95. Seo C, Choi YH, Ahn JS, Yim JH, Lee HK, Oh H. PTP1B inhibitory effects of tridepside and related metabolites isolated from the Antarctic lichen *Umbilicaria antarctica*. J Enzyme Inhib Med Chem 2009; 24(5): 1133-1137.
96. Seo C, Sohn JH, Ahn JS, Yim JH, Lee HK, Oh H. Protein tyrosine phosphatase 1B inhibitory effects of depsidone and pseudodepsidone metabolites from the Antarctic lichen *Stereocaulon alpinum*. Bioorg Med Chem Lett 2009; 19(10): 2801-2803.

97. Seo C, Yim JH, Lee HK, Oh H. PTP1B inhibitory secondary metabolites from the Antarctic lichen *Lecidella carpathica*. Mycology 2011; 2(1): 18-23.
98. Higuchi M, Miura Y, Boohene J, Kinoshita Y, Yamamoto Y, Yoshimura I, Yamada Y. Inhibition of tyrosine activity by cultured lichen tissues and bionts. Planta Med 1993; 59(3): 253-255.
99. Behera BC, Adawadkar B, Makhija U. Capacity of some Graphidaceous lichens to scavenge superoxide and inhibition of tyrosinase and xanthine oxidase activities. Curr Sci 2004; 87(1): 83-87.
100. Behera BC, Adawadkar B, Makhija U. Tyrosinase-inhibitory activity in some species of the lichen family Graphidaceae. J Herb Pharmacother 2006; 6(1): 55-69.
101. Behera BC, Adawadkar B, Makhija U. Tissue-culture of selected species of the Graphis lichen and their biological activities. Fitoterapia 2006; 77(3): 208-215.
102. Paudel B, Bhattarai HD, Koh HY, Lee SG, Han SJ, Lee HK, Oh H, Shin HW, Yim JH. Ramalin, a novel nontoxic antioxidant compound from the Antarctic lichen *Ramalina terebrata*. Phytomedicine 2011; 18(14): 1285-1290.
103. Chang Y, Ryu J, Lee S, Park SG, Bhattarai HD, Yim JH, Jin MH. Inhibition of melanogenesis by Ramalin from the Antarctic lichen *Ramalina terebrata*. J Soc Cosmet Scientists Korea 2012; 38(3): 247-254.
104. Lopes TIB, Coelho RG, Honda NK. Inhibition of mushroom tyrosinase activity by orsellinates. Chem Pharm Bull (Tokyo) 2018; 66(1): 61-64.
105. Behera BC, Makhija U. Inhibition of tyrosinase and xanthine oxidase by lichen species *Bulbothrix setschwanensis*. Curr Sci 2002; 82(1): 61-66.
106. Honda NK, Goncalves K, Brandao LFG, Coelho RG, Micheletti AC, Spielmann AA, Canez LS. Screening of lichen extracts using tyrosinase inhibition and toxicity against *Artemia salina*. Orbital: Electronic J Chem 2016; 8(3): 181-188.
107. Kim MS, Cho HB. Melanogenesis inhibitory effects of methanolic extracts of *Umbilicaria esculenta* and *Usnea longissima*. J Microbiol 2007; 45(6): 578-582.
108. Matsubara H, Kinoshita K, Koyama K, Ye Y, Takahashi K, Yoshimura I, Yamamoto Y, Miura Y, Kinoshita Y. Anti-tyrosinase activity of lichen metabolites and their synthetic analogues. J Hattori Bot Lab 1997; 83: 179-185.
109. Behera BC, Adawadkar B, Makhija U. Inhibitory activity of xanthine oxidase and superoxide-scavenging activity in some taxa of the lichen family Graphidaceae. Phytomedicine 2003; 10(6-7): 536-543.
110. Xu HB, Yang TH, Xie P, Liu SJ, Liang YN, Zhang Y, Song ZX, Tang ZS. Pheophytin analogues from the medicinal lichen *Usnea diffracta*. Nat Prod Res 2018; 32(9): 1088-1094.
111. Bessadóttir M, Skúladóttir EÁ, Gowan S, Eccles S, Ögmundsdóttir S, Ogmundsdóttir HM. Effects of anti-proliferative lichen metabolite, protolichesterinic acid on fatty acid synthase, cell signalling and drug response in breast cancer cells. Phytomedicine 2014; 21(12): 1717-1724.
112. Pejin B, Tommonaro G, Iodice C, Tesevic V, Vajs V. Acetylcholinesterase inhibition activity of acetylated depsidones from *Lobaria pulmonaria*. Nat Prod Res 2012; 26(17): 1634-1637.
113. Reddy RG, Veeraval L, Maitra S, Chollet-Krugler M, Tomasi S, Dévéhat FL, Boustie J, Chakravarty S. Lichen-derived compounds show potential for central nervous system therapeutics. Phytomedicine 2016; 23(12): 1527-1534.
114. Pejin B, Tommonaro G, Iodice C, Tesevic V, Vajs V, De Rosa S. A new depsidone of *Lobaria pulmonaria* with acetylcholinesterase inhibition activity. J Enzyme Inhib Med Chem 2013; 28(4): 876-878.
115. Heng L, Li C, Kim JC, Liu Y, Jung JS, Koh YJ, Hur J. Biruloquinone, an acetylcholinesterase inhibitor produced by lichen-forming fungus *Cladonia macilenta*. J Microbiol Biotechnol 2013; 23(2): 161-166.
116. Ingolfsdottir K, Breu W, Huneck S, Gudjonsdottir GA, Müller-Jakic B, Wagner H. In vitro inhibition of 5-lipoxygenase by protolichesterinic acid from *Cetraria islandica*. Phytomedicine 1994; 1: 187–191.
117. Ingolfsdottir K, Gissurarson SR, Müller-Jakic B, Breu W, Wagner H. Inhibitory effects of the lichen metabolite lobaric acid on arachidonate metabolism in vitro. Phytomedicine 1996; 2: 243–246.
118. Ingólfsdóttir K, Wiedemann B, Birgisdóttir M, Nenninger A, Jónsdóttir S, Wagner H. Inhibitory effects of baeomycesic acid from the lichen *Thamnolia subuliformis* on 5-lipoxygenase in vitro. Phytomedicine 1997; 4(2): 125-128.
119. Ingólfsdóttir K, Gissurarson SR, Nenninger A, Neszmelyi A, Wiedemann B, Wagner H. Biologically active alkamide from the lichen *Stereocaulon alpinum*. Phytomedicine 1997; 4(4): 331-334.
120. Oettl SK, Gerstmeier J, Khan SY, Wiechmann K, Bauer J, Atanasov AG, Malainer C, Awad EM, Uhrin P, Heiss EH, Waltenberger B, Remias D, Breuss JM, Boustie J, Dirsch VM, Stuppner H, Werz O, Rollinger JM. Imbricaric acid and perlatolic acid: Multi-targeting anti-inflammatory depsides from *Cetrelia monachorum*. PLoS ONE 2013; 8(10): e76929.
121. Ingolfsdottir K, Gudmundsdottir GF, Ogmundsdottir HM, Paulus K, Haraldsdottir S, Kristinsson H, Bauer R. Effects of tenuiorin and methyl orsellinate from the lichen *Peltigera leucophlebia* on 5-/15-lipoxygenases and proliferation of malignant cell lines in vitro. Phytomedicine 2002; 9(7): 654-658.
122. Haraldsdóttir S, Guolaugsdóttir E, Ingólfsdóttir K, Ogmundsdóttir HM. Anti-proliferative effects of lichen-derived lipoxygenase inhibitors on twelve human cancer cell lines of different tissue origin in vitro. Planta Med 2004; 70(11): 1098-1100.
123. Bucar F, Schneider I, Ogmundsdóttir H, Ingólfsdóttir K. Anti-proliferative lichen compounds with inhibitory activity on 12(S)-HETE production in human platelets. Phytomedicine 2004; 11(7-8): 602-606.
124. Behera BC, Morey MV, Gaikwad SB. Anti-lipoxygenase, radical scavenging and antimicrobial activities of lichen species of genus *Heterodermia* (Physciaceae). Botanica Pacifica 2016; 5(1): 79-85.
125. Bugni TS, Andjelic CD, Pole AR, Rai P, Ireland CM, Barrows LR. Biologically active components of a Papua New Guinea analgesic and anti-inflammatory lichen preparation. Fitoterapia 2009; 80(5): 270-273.
126. Jager AK, Weber DJ, van Staden J. Screening of South African lichens for prostaglandin-synthesis inhibitors. S Afr J Bot 1997; 63(5): 300-302.
127. Khan MF, Nabila SA, Rashid RB, Rahman MS, Chowdhury AA, Rashid MA. In silico molecular docking studies of lichen metabolites against cyclooxygenase-2 enzyme. Bangladesh Pharm J 2015; 18(2): 90-96.
128. Engel K, Schmidt U, Reuter J, Weckesser S, Simon-Haarhaus B, Schempp CM. *Usnea barbata* extract prevents ultraviolet-B induced prostaglandin E2 synthesis and COX-2 expression in HaCaT keratinocytes. J Photochem Photobiol B. 2007; 89(1): 9-14.
129. Savale SA, Pol CS, Khare R, Verma N, Gaikwad S, Mandal B, Behera BC. Radical scavenging, prolyl endopeptidase inhibitory, and antimicrobial potential of a cultured Himalayan lichen *Cetrelia olivetorum*. Pharm Biol 2016; 54(4): 692-700.
130. Kim J, Song K, Yoo I, Chang H, Yu S, Bae K, Min T. Two phenolic compounds isolated from *Umbilicaria esculenta* as Phospholipase A_2 inhibitors. Korean J Mycol 1996; 24(3): 237-242.
131. Bauer J, Waltenberger B, Noha SM, Schuster D, Rollinger JM, Boustie J, Chollet M, Stuppner H, Werz O. Discovery of depsides and depsidones from lichen as potent inhibitors of microsomal Prostaglandin E2 synthase-1 using pharmacophore models. ChemMedChem 2012; 7(12): 2077-2081.
132. Le DH, Takenaka Y, Hamada N, Mizushina Y, Tanahashi T. Polyketides from the cultured lichen mycobiont of a Vietnamese *Pyrenula* sp. J Nat Prod 2014; 77(6): 1404-1412.
133. Shivanna R, Parizadeh H, Garampalli RH. In vitro anti-obesity effect of macrolichens *Heterodermia leucomelos* and *Ramalina celastri* by pancreatic lipase inhibitory assay. Int J Pharm Pharm Sci 2017; 9(5): 137-140.
134. Lage TCA, Maciel TMS, Mota YCC, Sisto F, Sabino JR, Santos JCC, Figueiredo IM, Masia C, Fatima A, Fernandes SA, Modolo LV. In vitro inhibition of *Helicobacter pylori* and interaction studies of lichen natural products with jack bean urease. New J Chem 2018; 42: 5356-5366.
135. Aydin S, Kinalioglu K, Sokmen BB. Antioxidant, anti-urease and anti-elastase activities of *Usnea longissima* Ach. Bangladesh J Bot 2018; 47(3): 429-435.

136. Proksa B, Adamcová J, Sturdíková M, Fuska J. Metabolites of *Pseudevernia furfuracea* (L.) Zopf. and their inhibition potential of proteolytic enzymes. Pharmazie 1994; 49(4): 282-283.
137. Ozgencli I, Budak H, Ciftci M, Anar M. Lichen acids may be used as a potential drug for cancer therapy; by inhibiting mitochondrial thioredoxin reductase purified from rat lung. Anticancer Agents Med Chem 2018; 18(11): 1599.
138. Mahadik ND, Morey MV, Behera BC, Makhija UV, Naik DG. Cardiovascular-protective, antioxidative, and antimicrobial properties of natural thallus of lichen *Usnea complanata*. Lat Am J Pharm 2011; 30(2): 220-228.
139. Zakharenko A, Luzina O, Koval O, Nilov D, Gushchina I, Dyrkheeva N, Švedas V, Salakhutdinov N, Lavrik O. Tyrosyl-DNA Phosphodiesterase 1 inhibitors: Usnic acid enamines enhance the cytotoxic effect of camptothecin. J Nat Prod 2016; 79(11): 2961-2967.
140. Zakharova O, Luzina O, Zakharenko A, Sokolov D, Filimonov A, Dyrkheeva N, Chepanova A, Ilina E, Ilyina A, Klabenkova K, Chelobanov B, Stetsenko D, Zafar A, Eurtivong C, Reynisson J, Volcho K, Salakhutdinov N, Lavrik O. Synthesis and evaluation of aryliden- and hetarylidenfuranone derivatives of usnic acid as highly potent Tdp1 inhibitors. Bioorg Med Chem 2018; 26(15): 4470-4480.
141. Dyrkheeva N, Luzina O, Filimonov A, Zakharova O, Ilina E, Zakharenko A, Kuprushkin M, Nilov D, Gushchina I, Švedas V, Salakhutdinov N, Lavrik O. Inhibitory effect of new semisynthetic usnic acid derivatives on human Tyrosyl-DNA Phosphodiesterase 1. Planta Med 2019; 85(2): 103-111.
142. Ingólfsdóttir K, Lee SK, Bhat KPL, Lee K, Chai H, Kristinsson H, Song LL, Gills J, Gudmundsdottir JT, Mata-Greenwood E, Jang M, Pezzuto JM. Evaluation of selected lichens from Iceland for cancer chemopreventive and cytotoxic activity. Pharm Biol 2000; 38(4): 313-317.
143. Xu B, Li C, Sung C. Telomerase inhibitory effects of medicinal mushrooms and lichens, and their anticancer activity. Int J Med Mushrooms 2014; 16(1): 17-28.
144. Deraeve C, Guo Z, Bon RS, Blankenfeldt W, DiLucrezia R, Wolf A, Menninger S, Stigter AE, Wetzel S, Choidas A, Alexandrov K, Waldmann H, Goody RS, Wu Y. Psoromic acid is a selective and covalent rab-prenylation inhibitor targeting autoinhibited RabGGTase. J Am Chem Soc 2012; 134(17):7384-7391.
145. Hassan STS, Sudomova M, Berchova-Bimova K, Gowrishankar S, Rengasamy KRR. Antimycobacterial, enzyme inhibition, and molecular interaction studies of psoromic acid in *Mycobacterium tuberculosis*: Efficacy and safety investigations. J Clin Med 2018; 7:226.
146. Pengsuparp T, Cai L, Constant H, Fong HHS, Lin L, Kinghorn DA, Pezzuto JM, Cordell GA. Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. J Nat Prod 1995; 58(7):1024-1031.
147. Okuyama E, Hossain CF, Yamazaki M. Monoamine oxidase inhibitors from a lichen, *Solorina crocea* (1.) ACH. Jpn J Pharmacogn 1991; 45(2):159-162.
148. Kinoshita K, Saito D, Koyama K, Takahashi K, Sato Y, Okuyama E, Fujimoto H, Yamazaki M. Monoamine oxidase inhibitory effects of some lichen compounds and their synthetic analogues. J Hattori Bot Lab 2002; 92:277-284.

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