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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)

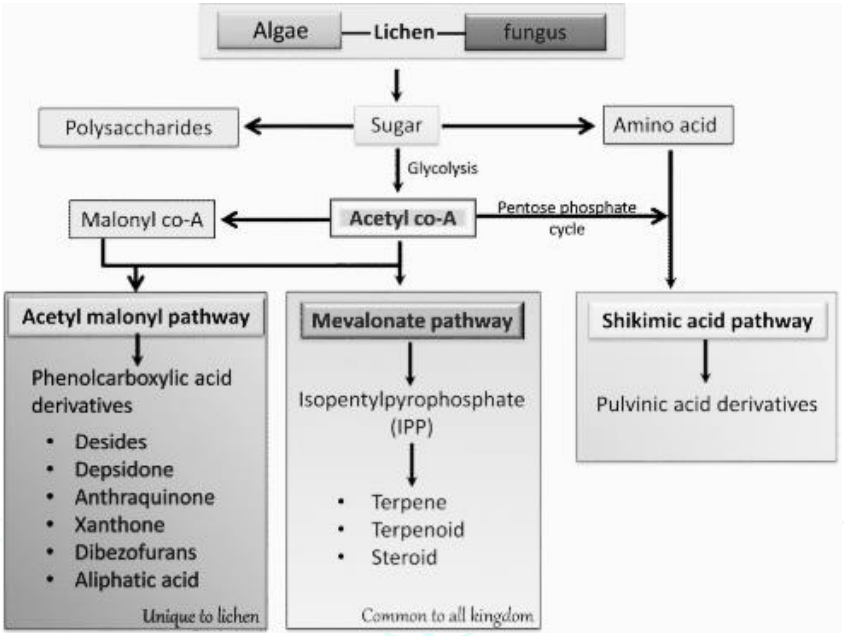

Figure 2: Metabolic pathways involved in the synthesis of lichen metabolites[21]

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.

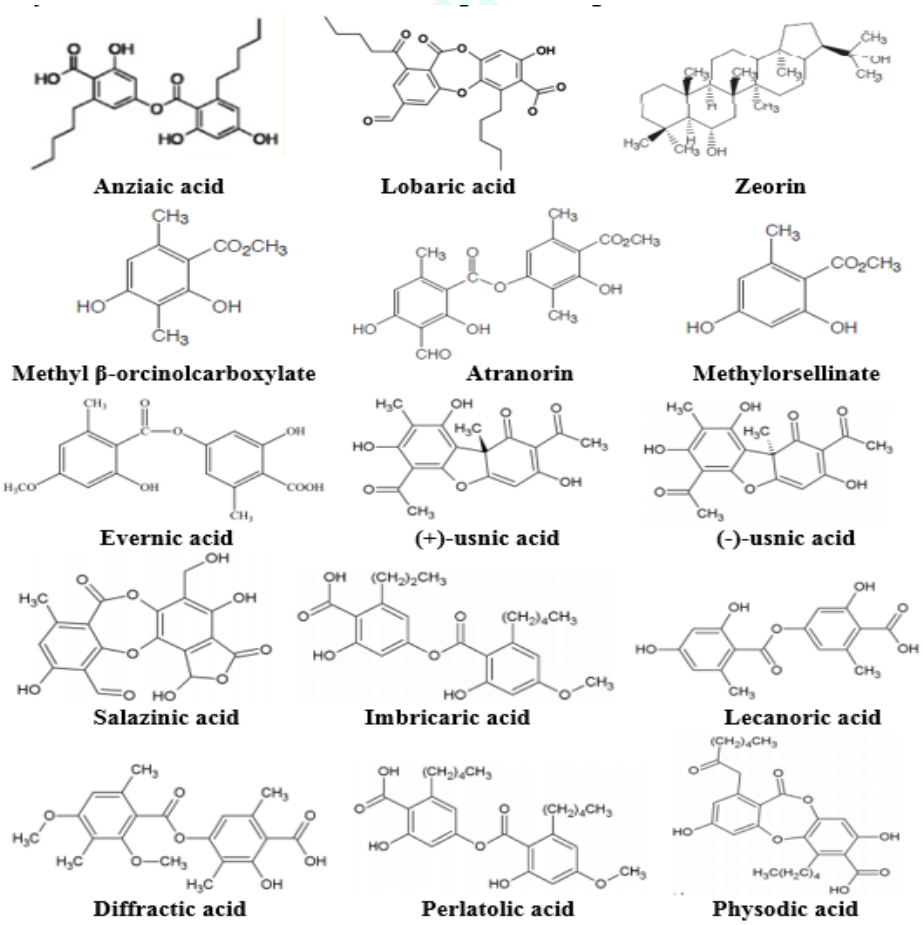

Figure 3: Structures of some lichen metabolites having enzyme inhibitory activity

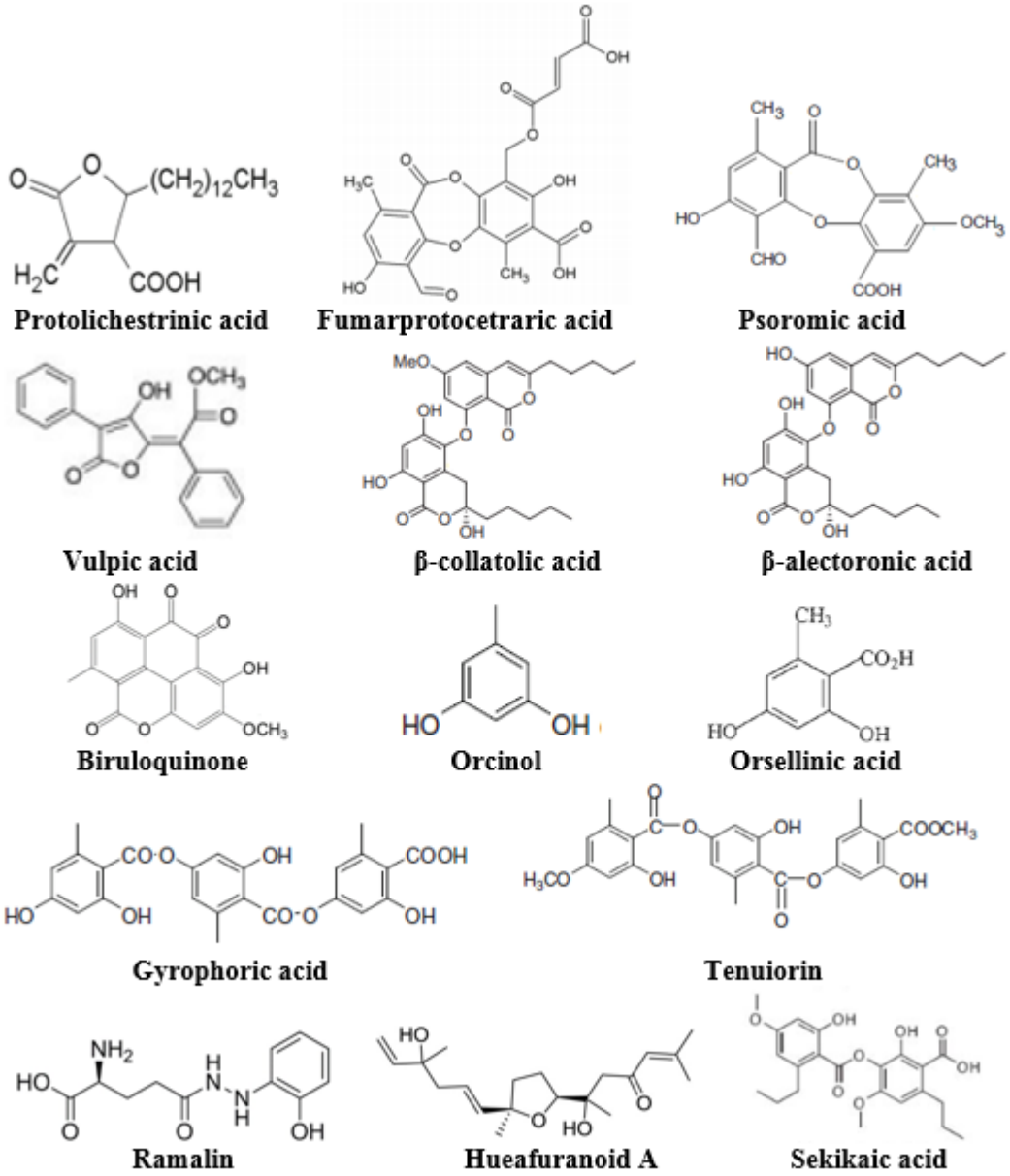

Figure 4: Structures of some lichen metabolites having enzyme inhibitory activity

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

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