Review of Literature

REVIEW OF LITERATURE

Lichen

The lichen thallus primarily occupies 90% volume of mycobiont and partial contribution of algae for lichen colour. From outside, visible part of lichen body is the fungal part which holds the algae within. So, lichens are placed in kingdom Mycota (fungus). During the last five decades, ethnobotanical work on lichens have been carried out in different parts ofthe world by several researchers. Since the time of Chinese and Egyptian civilizations, lichens have been used in traditional medicine system. In various pharmacopoeias, the use of lichen as medicine has been quoted (Nayaka *et al*., 2010). Lichens were used by the medicinal practitioners throughout the world as herbs in the middle era (Hale, 1983). Lichens consist of medicinal properties against various diseases and are often used in folk medicines (Rankovic *et al*., 2008).

The spot test of *Ramalia sp., Usnea complanata, Usnea fischeri, Physcia dilatata, Parmotrema austrosinensis, Parmelia andinum* and *Parmelia sucata* were documentated by Ramya and Thirunalasundari (2014).

Phytochemical analysis

The phytochemical screening would play an important role in the exploration of the raw materials and their properties to invent its application in pharmaceutical industry and for the beneficiary establishment of chemical elements which had basis of pharmacologically effective principles.

Anupama *et al*. (2017) evaluated the phytochemical analysis of methanol, ethyl acetate,acetone and petroleum ether extracts of the lichen *Parmotrema tinctorum.* This lichen showed the presence of carbohydrates, phenols, tannins, coumarins, flavonoids, saponins and terpenoids. Gupta *et al*. (2015) found flavonoids as the major secondary metabolites in acetone extract of *Parmotrema reticulatum*.

Revathi *et al*. (2014) performed the phytochemical analysis of ethanol and methanol extracts of *Parmotrema perlatum* and confirmed the presence of alkaloids, phytosterols, tannins and phenolic compounds. The presence of various phytochemicals such as flavonoids, saponins, alkaloids, tannins, phlobotannins, steroids and glycosides were evaluated in the lichens *Ramalina sp., Usnea complanata, Usnea fischeri, Physcia dilatata, Parmotrema austrosinensis, Parmelia andium* and *Parmelia sulcata* (Ramya and Thirunalasundari, 2014).

Rashmi and Rajkumar (2014) reported the presence of secondary metabolites such as alkaloids, tannins, saponins, glycosides, flavonoids, proteins, triterpenes, carbohydrates and steroids of nine lichen species using different solvents such as petroleum ether, ethyl acetate, chloroform, acetoneand methanol. The species analyzed were *Flavoparmelia caperata, Roccella montagnei, Teloschistes flavicans, Physcia aipolia, Parmotrema austrosinensis, Parmotrema grayanum, Parmotrema tinctorum, Parmotrema reticulatum* and *Usnea subflorida.*

Kosanic *et al*. (2014) studied the phytochemical analysis, antioxidant, antimicrobial and anticancer activities of acetone extracts of *Acarospora fuscata* and *Parmelia arseneana*. Sibi *et al*. (2013) evaluated the three phytochemical compositions such as glycosides, steroids and terpenoids in the methanol extract *of Parmelia perlata*. Dzomba *et al*. (2012) discovered the presence of phytochemical constitutents such as alkaloids, tannins, saponins, cardiac glycosides, flavonoids, anthraquinones and steroidal terpenes in ethanol extract of *Cladonia digitata*.

Manojlovic *et al*. (2012) analysed the phytochemicals of methanol and chloroform extracts of *Umbilicaria cylindrica* by using HPLC-UV method. Baral and Maharjan (2021) studied the phytochemical constituents such as volatile oil, saponins, coumarins, quinones, flavonoids, glycosides and carotenoids in four populated lichen species *Usnea cetraria, Parmelia reticulum, Cetraria sp.,* and *Evernastrium nepalense*.

Lichen in folk medicine:

Since ancient times, lichens have been used as household item in India (Wang *et al*., 2001). The economic uses of lichens growing in different parts of India with their constituents was first time described by Chopra *et al.* (1958). 'Pathar Phool', 'Daggar Phool', 'Chadila' were the different trade names of lichens. They were collected from various parts of the country and used for various purposes (Shah, 2014). Lichens are used as ingredient for making perfumes known as 'Athar' for the past 800 years at Kannauj, Uttar Pradesh. They are also used as one of the main ingredients in the preparation of powdered spices like ‘Garam Masala’. In traditional method of medicine preparation, they are blended with aromatic herbs including flavoring and curing tobacco (Shah, 2014). *Parmelia chinense* is used as liniment for headache and diuretic and to help wounds heal (Malhotra *et al.*, 2008).

Table 1: Lichens and their uses in folk medicines

S. No	Lichen	Country	Uses	Reference
1.	*Evernia furfuracea*	Egypt	Embalming mummies	Llano (1948)
2.	*Cetraria islandica*	Europe	Tonic	Schneider (1904)
		France	Pectoral and emollient	Novaretti and Lemordant 1990
		Spain	Asthma and anti-inflammatory	Upreti and Chatterrjee (2007)
		Sweden	Asthma, diabetes, nephritis, Lung disease, Whooping cough and cold	Airaksinen *et al.* (1986)
3.	*Cladonia sp.,*	-	Diarrhoea and internal chest pains	Smith (1983), Kari (1987)
4.	*Lobaria pulmonaria*	Canada	Coughing	Hu *et al*. (1980)
5.	*Lobaria retigera and Parmelia saxatilis*	China	Chinese medicine	
6.	*Usnea longissimi*	China	Chinese medicine and Ulcers	Chopra *et al* (1934)
		India	Treating bone fraction	Brij LaL (1988)
7.	*Usnea filipendula*	Russia	Treat wounds and prevent bacterial infections	Moskalenko (1986)
8.	*Usnea africana*	East africa	Stomach ache	Kokwaro (1976)
9.	*Usnea articulata*	Auckland	Treat wounds and skin bruises	Brooker *et al*. (1987)
10.	*Lobaria pulmonaria*	Sikkim, India	Eczema, lung trobles, haemorrhages and asthma	Biswas (1956)
11.	*Heterodermia diademata*	Sikkim, India	Protect wounds and acts from infection	Saklani and Upreti (1992)
12.	*Lecanora muralis*	USA	Treat colic	Powers (1877)
13.	*Cladonia fruticulosa kremp*	China	Bacterial infection of skin	Wang and Qian (2013)
14.	*Rhizoplaca chrysoleuca* (Sm.) Zopf	China	Tuberculosis, intestinal obstructions, trauma with pus formation, burns, Scalds, Skin infection, Cancer, Pain relief	Wang and Qian (2013)

Richardson reported the use of lichens as food, medicine, in dyes and perfumes. Crude drug of 'Chharila' were sold in Indian markets which comprises of three species of *Parmelia* (Chandra and Singh, 1971). The smoke of Chharila was trusted to relieve headache. It is used for wound treatment in powdered form. Some of the lichen have ethno pharmacological properties. Certainly, these organisms are a soure of original compounds (e.g depsides and depsidones) that have been poorly explored for their biological activities (Muller, 2001).

GC-MS analysis

Studies have revealed that the slow-growing organism lichen, produce a diverse array of secondary metabolites, with different biological activities.The natural bioactive compounds originated from lichens are used in many research. They possess beneficial role without causing side effects and are known to produce more than 800 secondary metabolites (Huneck and Yoshimura, 1996).

The major components in *Parmelia reticulatum* were identified by Adesalu and Agadagba (2016) using Gas Chromatography-Mass spectrometry analysis. Depending on the species of lichen, concentration of the extract, type of the solvent used and the tested organisms, lichen compounds have been shown to have a range of activities including antifungal (Halama and van Haluwyn, 2004; Schmeda-Hirschmann *et al*., 2008), antioxidant (Odabaso glu *et al*., 2006, Luo *et al*., 2009; Rankovic *et al*., 2010), antiviral, antimicrobial (Yilmaz *et al*., 2004) as well as cytotoxic and anti-inflammatory (Suleyman *et al*., 2003) effects.

pratibha *et al.*, (2016) examined the GC-MS analysis of *Parmelia perlata* in three different solvents such as Petroleum ether, chloroform and acetone.

Table 2: Biological targets of lichen and their compounds

S. No.	References	Source	Host Lichen	Compounds	Biological targets
1	Basnet *et al*. (2019a)	*Myrothecium inundatum*	*Ramalina* sp.	Myrotheol A (1), B (2), myrotheside D (4), sphaeropsidin A (5), hymatoxin L (6), 16-α-D-mannopyranosyloxyisopimar-7-en-19-oic acid (7),16- α-D-glucopyranosyloxyisopimar-7-en-19-oic-acid (8)	RKO cell lines
				Compounds (1-2), and (4-7)	K562 Cell line
2	Basnet *et al*. (2019)	*Hypoxylon fuscum*	*Usnea* sp.	5,6-Epoxy-phomol (9), Hypoxyolide A (10), phomol (12)	K562, SW480, AND HepG2 cell Lines
				Hypoxyside A (11)	K562 Cell line
				Cisplatin (Positive control)	K562, SW480, and Hep G2 cell Lines
3	Chen *et al*. (2019)	*Aspergillus* sp.	*Cetrelia* sp.	Isocoumarindole A (13), Gemcitabine	-
4	Yuan *et al*. (2018b)	*Talaromyces* sp.	*Xanthoparmelia angustiphylla*	Talaromycin A (14), clearanol A (15),6-	MDA-MB-231 cells

				methylbiphenyl (19), palmitic acid (20)	
				Compounds (16), (17), (19), (20)	HBE cells
				Compounds (14-17), (20)	THLE cells
5	Xu *et al*. *(*2018b)	*Floricola striata*	*Umbillicaria* sp.	Floricolin K (21), L (22), M (23), N (24)	A2780, MCF-7 cell line
				Floricolin N (24)	A549
				Floricolin O (24)	A2780, MCF-7
				Adriamycin (Positive control)	A2780, MCF-7 and A549 cell lines
6	Wang *et al*. (2017)	*Apiospora montagnei*	*Cladonia* sp.	Myrocin A (28), libertellenone G (29), N-hydroxyapiosporamide (30), apiosporamide (31), acremonone G (32), bostrycin (33)	L5178 murine lymphoma cell
				Kahalalide Fa (Positive control)	
7	Li *et al*. (2015a)	*Tolypocladium cylindrosporum*	*Lethariella zahlbruckneri*	Pyridoxatin (34), terpendole E (35)	MDA-MB-231, A2780, K562 and A549 cell lines
8	Li *et al*. (2015b)	*Aapergillus versicolor*	*Lobaria quercizans*	Diorcinol G (36), Diorcinol I (48),	PC3, A549, A2780, MDA-MB-

					231, and HEPG2 cell lines
				Diorcinol H (37),	MDA-MB-231 cell lines
				Diorcinol D (39),	PC3 and HEPG2 cell lines
				3,7-dihydroxy-1,9-dimethyldibenzofuran (40)	PC3c, MDA-MB231 and HEPG2 cell lines
9	Samanthi *et al*. (2015a)	*Curvularia trifolii*	*Usnea sp.*	(1,14-dihydroxy6-methyl-6,7,8,9,10,10α,14,14 α-octahydro-1H-benzo[f][1] oxacyclododecin-4(13H)-one (41)	PC3M, NCI-H460, SF-268, MCF-7, and MDA-MA-231 cell lines
10	Chen *et al*. (2014)	*Eurotium sp.*	*Cladina grisea*	7-O-methylvariecolortide A (42), variecolortide B (43), variecolortide C (44)	Caspase-3 inhibitory activity
11	Dou *et al*. (2014)	*Aspergillus versicolor*	*Lobaria retigera*	8-O-methylversicolorin B (45), 8-O-methylversicolorin A (46)	Pc-3 cells, H460
12	Zhang *et al*. (2012)	*Chaetomium globosum*	*Everniastrum nepalense*	Chaetoglobosin E (47), Isochaetoglobosin D (48), Chaetoglobosin G (49), Cytoglobosin C (50)	HCT-116 cell lines

13	Wang *et al*. (2013a)	*Ulocladium sp.*	*Everniastrum sp.*	Ophiobolins P-T (51-55), (6-epi-21,21-O-dihy-droophiobolin G (56),6-epi-ophiobolin G (57), and 6-epi- ophiobolin G (57)	KB and HepG2 cell lines
				Ophiobolin T (55) and 6-epi- ophiobolin G (57)	HepG2
14	Wang *et al*. (2013b)	*Ulocladium sp.*	*Everniastrum sp.*	TCA 9b (59	HeLa cell line
15	Yuan *et al*. (2013)	*Myxotrichum sp.*	*Cetraria islandica*	Myxotrichin A (60), maxotrichin D (61)	K562 cell
16	Ye *et al*. (2013)	*Phialophora sp.*	*Cladonia ochrochlora*	Altenusin (62)	HL-60 and A-549
17	Chen *et al*. (2013)	*Chaetomium elatum*	*Everniastrum cirrhatum*	Xanthoquinodin A4	SMMC-7721, A-549MCF-7, SW480 cell lines
				Xanthoquinodin A5 (63), Xanthoquinodin A1 (68), Xanthoquinodin A3(70)	HL-60, SMMC7721, A-549, MCF-7, SW480 cell lines
				Xanthoquinodin A6 (65)	HL-60, SMMC7721, A-549, MCF-7, SW480 cell lines

				Xanthoquinodin B4 (66), Xanthoquinodin B5 (67), Xanthoquinodin A2 (69)	HL-60, SMMC7721, A-549, MCF-7 cell lines
				Positive control cisplatin	HL-60, MMC7721, A-549, MCF-7, SW480 cell lines
18	Li *et al*. (2012)	*Phaeosphaeria sp.*	*Heterodermia obscurata*	Phaeosphaerins A-F (71-76)	PU3, DU145 and LNCaP cell lines
				Phaeosphaerin C (73)	K562 Cells
				Hypocrellin A (77)	K562 Cells
19	Zhang *et al*. (2012)	*Preussia Africana*	*Ramalin calicaris*	Preusschromone A (78),	A549, HeLa, HCT116 cell lines
				Preusschromone A (79),	A549, MCF, HeLa, HCT116 cell lines
				Positive control cisplatin	A549, MCF, HeLa, HCT116 cell lines
20	Wijieratne *et al*. (2012)	*Geopyxis majalis*	*Pseudevernia intense*	Geopyxin B (80)	NCI-H460, SF-268, MCF-7, PC-3 M and MB-231 cell lines
21		*Coniochaeta sp.*	*Xanthoria mandschurica*	Conioxepinol B (81)	HeLa cells

	Wang *et al*. (2010a)			Conioxepinol D (82)	A549 and MDA-MB-231 cell lines
22	Zhang *et al*. (2009)	*Neurospors terricola Antibacterials*	*Everniastrum cirrhatum*	Terricollene A (83), C (84),1-O-methylterricolyne (85)	HeLa cells
				Terricollene A (83)	MCF-7 cells
23	Basnet *et al*. (2019b)	*Hypoxylon fuscum*	*Usnea* sp.	Phomol (12),16-α-D-mannopyranosyloxyisopimar-7-en-19-oic acid (86), and 8-methoxy-1-naphthyl-β-glucoppyranoside (87)	*Staphylococcus aureus*
24	Padhi *et al*. (2019a)	*Talaromyces funiculosus*	*Diorygma hieroglyphicum*	Funiculosone (88), mangrovamide J (89) and ravenelin (90)	*Staphylococcus aureus, Escherichia coli*
25	Padhi *et al*. (2019b)	*Aspergillus niger*	*Parmotrema ravum*	Aurasperone A (91),	*Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli*
				Asperpyrone A (92),	*Staphylococcus aureus and Escherichia coli*

				Fonsecinone A (93)	*Pseudomonas syringae* pv. *maculicola*
				Carbonarone A (94),	*Dickeya solani*
				And pyrophen (95)	*Micrococcus luteus* *Aeromonas hydrophilla* *Listeria innocua*
26	Wang *et al*. (2012)	*Ulocaldium sp.*	*Everniastrum* sp.	6-O-methylnorlichexanthone (96), norlichexanthone (97), griseoxanthone C (98),	*Bacillus subtilis*
				Norlichexanthone (97)	Methicillin-resistantt *Staphylococcus aureus* (MRSA)
27	Kim *et al*. (2014)	Endolichenic fungus *CR1546C*		®-4,6,8-trihydroxy-3,4-dihydro-1(2H)-naphthalenone(99),6,8-dihydroxy-(3R)- (2-oxopropyl),3,4-dihydroisocoumarin (100)	*Bacillus subtilis*

28	Wang *et al*. (2013b)	*Ulocaldium sp.*	*Everniastrum* sp.	Ophiobolin P (51)	MRSA, *Bacillus subtilis*
				Ophiobolin T (55)	MRSA, *Bacillus subtilis* and Bacille Calmette-Guerin (BCG) strain
29	Wang *et al*. (2013a)	*Ulocaldium sp.*	*Everniastrum* sp.	TCA 1b (101)	Bacille Calmette - Guerin strain
30	Wang *et al*. (2010b)	*Coniochaeta sp.*		Coniothiepinol A (102)	*Enterococcus faecium* and *E. faecalis*
				Coniothienol A (103)	*E. faecium* and *E. faecalis*
31	Ding *et al*. (2009)	*Pestalotiopsis sp.*	*Clavaroids* sp.	Ambuic acid (104), its derivative (105)	*Staphylococcus aureus* (ATCC 6538)
32	Padhi *et al*. (2019b)	*Aspergillus niger*	*Parmotrema ravum*	Aspergyllone (106)	*C. parapsilosis*
				Aurasperone A (91)	*C. krusei*
				Carbonarone A (94)	*C.albicans* and *C. krusei*
				Pyrophen (95)	*C.parapsilosis Candida utilis*
33	Chen *et al*. (2019)	*Aspergillus sp.*	*Cetrelia* sp.	Isocoumarindole A (13), positive control caspofungin	*C. albicans*

34	Padhi *et al*. (2019a)	*Talaromyces funiculosus*	*Diorygma hieroglyphicum*	Funiculosone (88)	*C. albicans*
35	Yuan *et al*. (2017)	*Pestalotiopsis sp.*	*Cetraria islandica*	Two ambuic acid derivative (polyketide-terpene hybrid metabolite) (107), (108)	*Fusarium oxysporum*
				Compound (108), (109)	*Fusarium gramineum*
36	Hu *et al*. (2017)	*Tolypocladium sp.*	*Pemelia* sp.	Pyridoxatin (34)	*C. albicans*
37	Chang *et al*. (2015)	*Tolypocladium sp. Cylindrosporum*	*Lethariella zahlbruckner*	Pyridoxatin (34)	Antifungal against both fluconazole-susceptible and fluconazole-resistant isolates of *C. tropicalis*
38	Xie *et al*. (2016)	*Phialocephala fortinii*		Palmarumycin P3(110), phialocephalarin B (111)	*C. albicans*
39	Li *et al*. (2016) Zhang *et al*. (2018)	*Floricola striata*	*Umbilicaria* sp.	Floricolins A, (112), B (113), C (114)	*C. albicans*
				Floricolin C (114)	*Candida albicans*
40	Zhou *et al*. (2016)	*Biatriospora sp.*	*Pseudosyphellara* sp.	Biatriosporin D (115), K(116),6-deoxy7-O-demrthyl-3,4-	*Fluconazole resitance Candida albicans*

				anhydrofusarubin(117),2-acetonyl-3-methyl-5-7-mrthoxynaphthazarin(118)	
				Biatriosporin D (115)	-
41	Wu *et al*. (2015a)	*Periconia sp.*	*Parmelia* sp.	Pericoterpenoid A (119)	*Aspergillus niger*
42	Zhao *et al*. (2015a)	*Nodulisporium sp.*	*Everniastrum* sp.	Nodulisporipyrones A-D (120-123),	*Aspergillus niger*
43	Li *et al*. (2015b)	*Aspergilus versicolor*	-	Diorcinol D (39)	*Candida sp.*
44	Li *et al*. (2015c)	*Aspergilus versicolor*	*Lobaria quercizans*	Diorcinol D (39), mixture of violaceol I (124),/violaceol II (126),Cordyol C (125)	*Candida albicans*
				Diorcinol I (38),3,7-dihydroxy-1,9-dimethyldi-benzofuran (40)	*Candida albicans*
45	Wu *et al*. (2015b)	*Periconia sp.*	*Parmelia* sp.	Pericocin A (127), pericocin B (128),pericocins C (129) and D (130),3-(2-oxo-2H-pyran-6-yl) propanoic acid (131)	*Aspergillus niger*

				Cycloheximide	
46	Kim *et al*. (2014)	Endolichenic fungus CR1546C	-	®-4,6,8-trihydroxy-3,4-dihydro-1(2H)-naphthalenone(99),6,8-dihydroxy-(3R)-(2-oxopropyl)-3,4-dihydroisocoumarin (100),6,8-dihydroxy-(3)-(2-oxopropyl)isocoumarin (132),6,8-dihydroxy-3-[(2S)-2-hydroxypropyl]isocoumarin (133),2,4-dihydroxy -6-(2-oxopropyl)-benzoic acid (134),6,8-dihydroxy 3®-methyl-3,4-dihydroisocoumarin (136),6,8-dihydroxy-3®-methyl-s,4-dihydroisocoumarin (137),(3R,4S)-3,4,8-trihydroxy-3,4-dihydro-1(2H)-naphthalenone (138), and (3S,4S)-3,4,6,8-trtrahydroxy-3,4-	*Candida albicans*

				dihydro-1(2H)-naphthalenone (139)	
47	Yuan *et al*. (2013)	*Myxotrichum sp.*	*Cetraria islandica*	Myxodial A (140)	*Candida albicans* (s.c.5314)
48	Wang *et al*. (2012)	*Ulocladium* sp.	-	7-hydroxy-3,5-dimethyl-isochromen-1-one (141)	*Candida albicans* (s.c.5314)
49	Wu *et al*. (2011)	*Xylaria* sp.	*Leptogium saturninum*	(cyclo(N-methyl-L-Phe-L-Val-D-Ile-L-Leu-L-Pro) (142)	*Candida albicans*
50	Wang *et al*. (2010b)	*Coniochaeta* sp.	-	Coniothiepinol A (102)	*Fusarium oxysporum* (CGMCC 3.2830)
51	Kim *et al*. (2018b)	*Phoma* sp.	-	Phomalichenone A (143), (E)-1-(2,4-dihydroxy-3-(2-hydroxyethyl)-6-methoxyphenyl) but-2-en1-one (144)	Inhibition of nitric oxide (NO) production
				Phomalichenone A (143)	
52	Kim *et al*. (2018a)	*Dothideomyces* sp.	-	Dothideopyrone F (145)	Inhibition of NO production
				Dothideopyrone F (145)	
53	Samanthi *et al*. (2015a)	*Curvulsris trifolii*	*Usnea* sp.	5-methoxy4,8,15-trimethyl-3,7-dioxo-1,3,7,8,9,10,11,12,13,14,15α-dodechydro-cyclododeca[*de*]isochrom	-

				ene-15-carboxylic acid (146)	
54	Wang *et al*. (2012)	*Ulocladium* sp.	*Everniastrum* sp.	Altenusin (62), alterlactone (147)	-
55	Samanthi *et al*. (2015a)	*Curvulsris trifolii*	*Usnea* sp.	(1,14-dihydroxy6-methyl-6,7,8,9,10,10 α-octahydro-1H-benzo[*f*][1] oxacylododecin-4 (13H)-one (41) and 5-methoxy4,8,15-trimethyl-3,7-dioxo-1,3,7,8,9,10,11,12,13,14,15,15 α-dodecahydrocyclododeca[*de*]isochromene-15-carboxylic acid (146)	-
56	Samanthi *et al*. (2015b)	*Penicillium citrinum*	*Parmotrema* sp.	5-acetyl-3,5,7'-tri,ethoxy-3'H-spiro[cyclohexa[2,4]diene-1,1'-isobenzofuran]-3,6'-dione (148) and 4-acetyl-2'-hydroxy-3',5',6-trimethoxy biphenyl-2-carboxylic acid (149)	-

57	Zhao *et al*. (2016)	Endolichenic fungus ELF000039	*Parmotrma austrosinense* (KoLRI no.009,806)	(3R)-5-hydroxymellein (150)	DPPH assay
				(3R)-5-hydroxymellein (150)	Reducing power
				(3R)-5-hydroxymellein (150)	Superoxide anion scavenging activity
					Inhibition of linoleic acid peroxidation
					Mouse melanoma cell lines, B16F1 and B16F10 or the normal cell line
58	Kawakami *et al*. (2019)	*Dothideomyces* sp.	*Pertusaria laeviganda*	Norlichexanthone (97) Ascorbic acid	ORAC
59	He *et al*. (2012)	*Nigrospora sphaerica*	*Parmelinella wallichiana*	Alternariol (151), alternariol-9-Me ether (152)	Herbes Simplex virus – *in vitro*
60	Zhao *et al*. (2014)	Endolichenic fungus ELF000039	*Parmotrma austrosinense* (KoLRI no.009,806)	(3R)-5-hydroxymellein (150)	-
61	Yuan *et al*. (2016)	*Myxotrichum* sp.	*C.islandica*	Myxotritones A and C (156,157),7,8-dihydro-7R,8S-dihydroxy-3,7-dimethyl-2-benzopyran-6-one (158)	-

62	Zheng *et al*. (2013)	*Nodulisporium* sp. (No.65-17-2-1)	*Everniastrum* sp.	Demethoxyviridin (167)	Aβ42 aggregation inhibitory activity
63	Li *et al*. (2018)	*Ophiosphserells korrae*		Ophiosphaerellin C (168), (1S,5S,6R)-5-hydroxy-3,5-dimethyl-1-((Z)-2-methylbut-2-enoyl) bicycle [4.1.0] hept-3-en2-one (169), Ophiosphaerekorrin A (170)	AChE inhibitory activity
64	Kim *et al*. (2018c)	*Xylaria grammica*	*Menegszzia* sp.	Grammicin (171)	Nematicidal activity against *Meloidogyne incognita*
				Grammicin (171)	Inhibitory activity against *Meloidogyne incognita* egg hatching
65	Wijeratne *et al*. (2016)	*Lecythophora* sp., Parmotrema tinctorum and *Lecythophora* sp.	*Cladonia evansii*	Oxaspirol B (172	-

Antimicrobial activity

Lichens have economic benefits to human beings due to their antibiotic properties that are important for biomedical applications. Lichens and their metabolites yield incredible bioactive substances for the treatment of various human diseases caused by different pathogenic microorganisms. There are almost 2040 species of lichens present in India (Awasthi, 2007).

In the beginning of the antibiotic era in 1950s numerous lichens were screened for antibacterial activity (Klosa, 1953). Various lichen metabolites were discovered to be active against Gram positive organisms (Lauterwein, 1995). *Dermatocarpon miniatum* was reported to have antimicrobial properties (Burkholder *et al*., 1944). This lichen also used in China for lowering high blood pressure, as a diuretic for expelling parasites, to treat dysentery, malnutrition in children, for improving digestion and for abdominal distention. Other than this, it is taken as drink decoction or even eaten as soup (Wang and Qian, 2013).

Aoussar *et al*. (2020) investigated the antibacterial activity of acetone extract of *Evernia prunasstri, Ramalina farinacea and Pseudevernia furfuracea* against the Gram-positive and Gram-negative bacteria such as *Staphylococcus aureus*, five clinical Methicillin- Resistant *Staphylococcus aureus* (MRSA) isolates from burn wounds of patients at IbnRochd University Hospital of Casablanca (Morocco), *Listeria innocua, Bacillus subtilis and Escherichia coli, Pseudomonas aeruginosa* and *Proteus mirabilis.*

Dixit *et al*. (2018) investigated the antibacterial and antifungal properties of acetone and methanol extracts of *Usnea* sp., and *Parmotrema* sp., against seven bacteria and fungal pathogens such as *Staphylococcus aureus, Staphylococcus sp., Escherichia coli, Aspergillus niger, Aspergillus flavus, Candida albicans and Trycophyton sp.,* Antimicrobial activity of *Parmelia perlata* was studied by pratibha and mahesh (2017) for different pathogenic bacteria (*Bacillus subtilis*, *Escherichia coli*, *Streptomyces grieveces* and *Staphylococcus aureus*) and fungi (*Penicillium funiculosam*, *Aspergillus niger* and *Fusarium oxysporium*).

Hassabo (2016) focused the traditional uses of Sudanese *Parmelia perlata* (shaibah) and studied antimicrobial activity against the pathogenic bacteria (*Staphylococcus aureus, Bacillus subtilus, Escherichia coli* and *Pseudomonas aeruginosa*) and the fungus (*Candida albicans*). Ganesan *et al*. (2015) evaluated the petroleum ether, ethyl acetate, acetone, ethanol and water extracts of *Parmotrema austrosinense, Parmotrema hababianum and Parmotrema tinctorum* for antibacterial activity against *Proteus vulgaris, Bacillus cereus, Staphylococcus aureus, Klebsiella pneumonia, Pseudomonas aeruginosa, Escherichia coli* and *Salmonella typhimurium.*

Antibacterial activity of various solvent extracts of Parmeloid lichens was discovered by Ayyappadasan *et al*. (2015). The antimicrobial activity of methanolic extract of *Ramalina* lichen species was reported (Sahin *et al*., 2015). Anjali *et al*. (2015) reported the antimicrobial activity of 2-propanol extract of *Parmotrema tinctorum* against ten bacteria (*Escherichia coli, Bacillus subtilis, Salmonella abony, Klebsiella pneumonia, Coynebacterium rubrum, Staphylococcus aureus, Salmonella typhimurium, Pseudomonas aeruginosa, Streptococcus pyogenes* and *Bacillus cereus*) and two fungi (*Aspergillus flavus* and *Aspergillus niger*).

Srivastava (2013) screened some Indian lichens for their antibacterial properties against six human pathogens such as *Staphylococcus aureus, Streptococcus faecalis, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa* and *Salmonella typhimurium*. Dzomba *et al*. (2012) investigated the antibacterial activity of the ethanol extract of *Cladonia digitata* against *Escherichia coli, Clostridium perfringens* and *Staphylococcus aureus.*

Devi *et al*. (2011) evaluated the antimicrobial activity of different solvent extracts of *Roccella belangeriana* (Tiwari *et al.*, 2011) investigated antifungal activity of four foliose lichens viz., *Bulbothirx setschwanensis, Everniastrum nepalense, Heterodermia diademata* and *Parmelaria thomsonii* against seven plant pathogenic fungi such as *Aspergillus flavus, Aspergillus fumigatus, Alternaria alternata, Fusarium oxysporum, Fusarium solani, Fusarium roseum and Penicillium citrinum*.

Ali *et al*. (2009) studied the antibacterial activity of the aqueous and ethanol extracts of *Anaptychia ciiaris, Cetrelia olivetonum, Lecanora muralis, Peltigera poydactyla, Peltigera praetextata, Ramalina farinacea, Rhizoplaca melanophthalma, Umbilicaria vellea, Xanthoria elegans, Xanthoria parietina, Xanthoparmelia tinctio* against six pathogens (*Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Klebsiella pneumoniae, Staphylococcus aureus and Staphylococcus epidermidis*).

kekuda *et al*. (2009) studied three lichen species namely *Parmotrema pseudotinctorum* and *Ramalina hossei* collected from the forest area of Bhadra Wildlife sanctuary. He revealed from this study that, Atranorin and Lecanoric acid were present in *Parmotrema pseudotinctorum* and Usnic acid and sekikaic acid detected in *Ramalina hossei.* For the antibacterial activities lichen extracts, honey and their combination were used against tested bacteria (*Escherichia* coli, *Staphylococcus aureus* and *Pseudomonas aeruginosa*).

Various lichenic compounds such as lobar acid, physodic acid, rhizocarpic acid, 3- hydroxyphysodic acid, hybocarpone, and (R)-(+)-usnic acid were isolated, from *Sterocaulon dactylophyllum, Hypogymnia physodes, Psilolechia lucida, Hypogymnia physodes, Lecanora conizaeoides,* and *Lecanora albescens* lichen species respectively (Kokubun *et al*., 2007).

The antibacterial activity of *Ramalina farinacea*, *Parmelia furfuracea,* and *Evernia prunastri* extracts were evaluated by the micro dilution method against bacterial strains including clinical isolates of methicillin-resistant *Staphylococcus aureus* (Tay *et al.,* 2004)

Pavithra *et al* (2013) analyzed the extract of *Usnea pictoides* for its antimicrobial activity against the bacteria *Staphylococcus aureus* and *Pseudomonas aerugionsa* and the fungi *Candida albicans* and *Cryptococcus neoformaus*. From the lichen *Parmelia perlata*, about 19 phytochemicals such as Glycosides, cardiac glycosides, alkaloids, tannins, phenols, flavonoids, steroids, phytosterols, diterpens, terpenoids, saponins, resins, quinines, phlobotannins, carbohydrates, proteins, amino acids, lipids and volatile oil were identified (Leela and Devi, 2017)

Antioxidant activity

Hyperlipidemia is caused by a diet high in fat, mainly saturated fat and Cholesterol. Natural antioxidants comprise of antifungal, antibacterial, anti-inflammatory, antiviral and antiallergic properties.However very limited researchers proved that lichens have antioxidant activity (Rankovic *et al*., 2010; Silva *et al*., 2010). Lichens have been involved in several studies looking for new natural antioxidants and their potential protective effects vs. chronic diseases (Fernández-Moriano *et al*., 2015; Nguyen *et al*., 2019).

Aoussar *et al*. (2020) studied the antioxidant activity of acetone extract of *Evernia prunasstri, Ramalina farinacea and Pseudevernia furfuracea* by DPPH and FRAP methods. Fernandez-moriano *et al*. (2016) evaluated the antioxidant activity of ten Parmeliaceae lichens such as *Bulbothrix setschwanensis, Flavoparmelia caperata,* *Flavoparmelia euplecta,Flavoparmelia haysomii, Hypotrachyna cirrhata, Lethariella canariensis, Myelochroa irrugans, Parmelia omphalodes, Usnea aurantiacoatra, Usnea contextmotyka* using three assays (oxygen radical absorbance capacity (ORAC) 1,1- diphenyl -2- picrylhydrazyl radical scavenging activities (DPPH) and ferric reducing antioxidant power (FRAP).

Marijana *et al*. (2015) evaluated the antioxidant activity of *Evernia prunasti* and *Pseudoevernia furfuraceae* by free radical scavenging, superoxide anion radical scavenging, reducing power and determination of total phenolic compounds. The antioxidant activity of methanol and ethyl acetate extracts of the lichen *Cetraria aculeate* was studied by Tomovic *et al* (2015).

Kosanic *et al*. (2014) studied the antioxidant activity of acetone extracts of the lichens *Parmelia arseneana* and *Acarospora fuscata*. Antioxidant activity was evaluated by DPPH radical scavenging activity, superoxide anion radical scavenging activity, reducing power activity and determination of total phenolic compounds.

Vivek *et al*. (2014) studied the scavenging of DPPH free radicals by the extracts of three *Parmotrema* species such as *Parmotrema grayanum, Parmotrema praesorediosum* and *Parmotrema tinctorum.* Dzomba *et al*. (2012) studied the antioxidant activity of ethanol extract of the lichen *Cladonia digitata* using the free radical scavenging activity of DPPH and reducing power assay.

Behera *et al.* (2005) examined the antioxidant activity of *Usnea ghattensis, Heterodemia podocarpa, Arthothelium awasthi* and *P. tinctorum* by culturing the mycobionts *in vitro*. Among the lichens tested, the extracts of *Arthothelium awasthi* and *Usnea ghattensis* exhibited more antioxidant activity compared to the *Heterodemia podocarpa* which propose that the extract of a mycobiont cultures have more antioxidant property and lichens can be used as an edible source as they have natural antioxidant property against the oxidative stress.

Molecular docking

Joshi *et al*. (2019) studied the non-steroidal anti-inflammatory drugs targeting Cyclooxygenase-2 by molecular docking. Further, he also performed screening of 412 lichen compounds virtually that are of natural origin. The screening was done using molecular docking against human Cox2 enzyme. The results were validated by X-scorePrediction followed by ADMET and Drug-likeness analysis.

Mishra *et al*. (2017) isolated two compounds namely roccellic acid and everninic acid from the lichen *Roccella montagnei*. These two compounds were tested for *in silico* molecular docking against Cyclin Dependent kinase enzyme isomer to support the cytotoxic activity.

Khan *et al*. (2015) evaluated binding mode of five lichen metabolites namely Diffractic acid, Lecanoric acid, Atranorin (3a), Usnic acid, Salazinic acid with cyclo-oxygenase-2 enzyme using AutoDock vina.

Acetylcholinesterase (ACHE) inhibitors are yet the best drugs presently available for control of Alzheimers's disease. Ece and Pejin (2015) discovered depsidone molecules (1-7) that interact with active site Acetylcholinesterase (ACHE).

Anti-inflammatory

Some lichens have various biological activities such as antimicrobial, anti-tumor, anti-inflammatory, analgesic, antiviral, antiprotozoal, antipyretic, and antiproliferative (Lawrey, 1989; Huneck, 1999; Halama and van Haluwin, 2004; Rankovic *et al*., 2010). Cotton pellet-induced granuloma, xylene induced ear swelling, Carragennan inducededema, histamine induced and Carboxymethyl cellulose sodium-induced leukocyte emigration in mice models were used to quantify the anti-inflammatory activity (Jain *et al.,* 2016).

Cancer and inflammation activities of six lichen extracts such as *Evernia prunastri, Pseudevernia furfuracea, Umbilicaria pustulata, Umbilicaria crustose, Flavoparmelia caperata*, *Platesmania glauca* were studied (Ingelfinger *et al*., 2020).

Guvenc *et al*. (2012) studied the methanolic extract of *Pseudevernia furfuracea* and its fraction and isolates for the anti-inflammatory activity. The anti-inflammatory activity of the lichen *Rhizophora mucronata* by three different assays such as membrane stabilization assay, protein denaturation assay and albumin denaturation assay were documentated (kaur *et al.,* 2018).

Guniz *et al*. (2010) reported the anti-inflammatory effect of the methanolic extract of *Peltigera rufescens* on acute and chronic phases of inflammation.

Bionanoparticles

Alqahtani *et al*. (2020) first reported the biosynthesis and characterization of biogenic AgNPs using UV-Vis spectroscopy, Transmission electron microscopy (TEM), Dynamic Light Scattering (DLS) and Zeta potential, Fourier-transform infrared spectroscopy (FTIR) from the extracts of the lichens *Xanthoria parietina* and *Flavopunctelia flaventior.*

Antiproliferative activity

Cancer is one of the main causes of death all over the world. The health organization(WHO) estimates that 84 million people would die of cancer between 2005 and 2015 (Dahier, 2010)

Aoussar *et al*. (2020) assessed the cytotoxity of the acetone extracts of *Evernia prunasstri, Ramalina farinacea and Pseudevernia furfuracea* against the human prostate cancer (22RVI), Human colon carcinoma (HT-29), human hepato cellular carcinoma (Hep G2) and Hamster ovarian cancer (CHO) cell lines by WSTF assay. Ristic *et al*. (2016) studied the cytotoxic activity of *Ramalina fastigiata* and *Ramalina fraxinea* using MTT assay on the human epithelial carcinoma (HeLa), human lung carcinoma (A549) and human colon carcinoma (LS14).

Fernandez-moriano *et al.* (2016) aimed to investigate the cytotoxic activity of methanol extracts of ten Parmeliaceae species such *as Bulbothrix setschwanensis, Flavoparmelia caperata, Flavoparmelia euplecta, Flavoparmelia haysomii, Hypotrachyna cirrhata, Lethariella canariensis, Myelochroa irrugans, Parmelia omphalodes, Usnea aurantiacoatra, Usnea context motyka* collected in different continents.

Ari *et al*. (2015) tested the antigrowth effect of *Hypogymnia physodes* in human breast cancer cell lines (MCF-7 & MDA-MB-231) by MTT and ATP viability assays. Anticancer activity of *Parmelia* species against human melanoma, colon carcinoma and breast cancer cell lines were reported in previous studies (*Manojlovic et al*., 2012; Ari *et al*., 2015).

Kosanic *et al*. (2014) investigated the anticancer activity of acetone extract of *Parmelia arseneana* and *Acarospora fuscata* against LS174 (human colon carcinoma cell line),A549 (human lung carcinoma cell line), Fem-X (malignant melanoma cell line) and a chronicmyelogeneous leukaemia K562 cell line using MTT assay.

Kosanic *et al*. (2013) studied the anticancer activity of *Evernia prunasti* and *Pseudoevernia furfuraceae* against Fex X (human melanoma) and LS174 (human colon carcinoma) cell lines using MTT assay.

Backorova *et al*. (2011) reported the sensitivity of nine human cancer cell lines (A2780, Hela, MCF -7, SK-BR-3, HT-29, MCT-116 P53^{+}/$^{+}$HCT-116 P53$^{-/-}$, HL-60 and Jurkat) towards four typical secondary metabolites of lichens (parietin, atranorin, usnic acid, gyrophoric acid). Ali (2009) examined the cytotoxicity activity of the aqueous and ethanol extract of *Anaptychia ciiaris, Cetrelia olivetonum, Lecanora muralis, Peltigera poydactyla, Peltigera praetextata, Ramalina farinacea, Rhizoplaca melanophthalma, Umbilicaria vellea, Xanthoria elegans, Xanthoria parietina* and *Xanthoparmelia tinctio.*

The anticancer activity of lecanoric acid, a secondary metabolite of the lichen *Parmotrema tinctorum* and its derivatives orsellinates obtained by structural modification was carried out *in vitro* (Bogo *et al*. 2010) with sulforhodamine B using HEP-2 larynx carcinoma, MCF7 breast carcinoma ,786-0 kidney carcinoma and B16-F10 murine melanoma cell lines in addition to a normal (vero) cell line in order to calculate the selectivity index of the compounds.

The cytotoxic activity of n- hexane, diethyl ether and methanol extracts of *Cladonia convoluta, Cladonia rangiformis, Evernia prunastri, Flavoparmelia caperata* (as *Parmelia caperata*), *Plastismatia glauca, Ramalina cuspidata* and *Usnea rubicunda* on two murine and four human cancer cell lines was tested (Bezivin *et al*., 2003).

Isolation

Gerson and Seaward (1997) stated that lichens are not merely a combination of one fungus and one alga, but also harbor other organisms. Hawksworth (1988) declared fungal – algal symbioses involving different numbers of bionts (i) **Two –biont symbioses** is Mycobiontas inhabitant (Mycophycobiosis, Fungal parasites of algae) and Mycobiont asexhabitant (lichens) (ii) **Three-biont symbioses** is Two photobionts: one mycobiont (Cephalodia, Blue-green/green morphotypes, Algicolous lichens, Bryophyllous lichens) and Two mycobionts: one photobiont (Lichenicolous fungi, Mechanical hybrids) (iii) Four-biont symbioses is Three photobionts: one mycobiont (Cephalodia); Two photobionts: two mycobionts (Lichenicolous lichens) and three mycobionts: one photobiont (Fungi on lichenicolous fungi). (iv)Five or more biont symbioses (Mechanical Hybrids).

According to the Dual theory of lichens proposed by Simon Schwendener "Lichens are a combination of fungi with algae or cyanobacteria, whereby the true nature of the lichen association began to emerge" (Honegger, 2000). Lichen is a composite organism (symbiotic) of algae and/or cyanobacteria living among filaments (hyphae) of a fungus in a mutually beneficial relationship (Brodo, 2001). Hawksworth (1988) interpreted lichen as a stable self-supporting association of a mycobiont and a photobiont in which the mycobiont is the exhabitant.

Lichens are relatively 'self-contained miniature ecosystems' in and of themselves, likely with more microorganisms living with the fungi, algae, and/or cyanobacteria, implementing other functions as partners in a system that evolves as an even more complex composite organism - holobiont (Gerson and Seaward, 1977; Honegger, 1991; Barreno *et al.,* 2008; Grube *et al.,* 2009;).

Lichen thallus can be considered as a ‘functional organismic community’ or as a microhabitat with a large variety of coexisting fungal, algal and bacterial genotypes (Boonpragob *et al.*, 2013). Goward stated that "Lichens are fungi that have discovered agriculture" The lichen fungi(Kingdom Fungi) manufacture food by photosynthesis using cultivate partners. Sometimes the partners are algae and other times partner is cyanobacteria (Kingdom Monera), some capable fungi both, at once.

Lichens are classified based on the fungal species and not the species of the algae orcyanobacteria. Lichens as well the fungi within them are assigned with the same binomial names, which may cause some confusion. The alga bears its own scientific name, (Kirk *et al*., 2008). Since lichens do not follow article 13.2 of ICN, hence it’s relevant to call them as Lichenized fungi.

Girlanda *et al*. (1997) isolated several endolichenic fungi from the lichen *Parmelia taractica* collected from Italy. The isolated endolichenic fungi were *Acremonium butyri, Alternaria alternata, Alternaria* sp.*, Arthrinium phaeopermum, Cladosporium cladosporioides, Drechslera* sp.*, Epicoccum purpurascens, Fusarium* *solani, Fusarium sp. 1, Geomyces pannorum var.asperulants, Heteroconium chaetospira, Karsteniomyces* sp., *Mucor hiemalis, Paecilomyces farinosus, Paecilomyces lilacinus, Penicillium griseofulvum, Penicillium melini, Penicillium purpurogenum, Penicillium raciborskii, Penicillium verruculosum, Penicillium viridicatum, Phoma sp.1, Tolypocladium geodes, Tolypocladium* sp., *Trichoderma harzianum, Trichoderma polysporum, Trichoderma viride, Ulocladium aternariae, Myceliumsterilia dematiaceum* 1, 2, 3, 4, 5, 6, 7 *Mycelium sterilia moniliaceum* 1, 2, 3, 4, 5, 6

Girlanda *et al.* (1997b) isolated several endolichenic fungi from the lichen *Peltigera praetextata* collected from Italy. They were *Alternaria alternata, Alternaria sp., Cylindrocarpon gracile, Cylindrocarpon heteronema, Epicoccum purpurascens, Fusarium solani, Fusarium* sp.1, *Fusarium* sp. 2, *Geomyces pannorum var. asperulants, Mucor hiemalis, Penicillium griseofulvum, Penicillium melinii, Penicillium purpurogenum, Phoma putaminum, Phoma* sp. 1, *Phoma* sp. 2, *Tolypocladium geodes, Tolypocladium niveum, Trichoderma harzianuma, Trichoderma polysporum, Trichoderma viride, Mycelium sterilia dematiaceum* 2, 5, 6, 3, 4.

Jayakumar *et al* (2016) isolated the endolichenic fungi (*Talaromyces tratensis*) from the lichen *Lecanora sp.* collected from India. From Hakgala Montane Forest in Sri Lanka, 28 endolichenic fungal strains have been isolated from the lichen *Parmotreama* sp., *Usnea* sp. and *Pseudocyphellaria* sp., (Kannangara *et al.*, 2009). Suryanarayanan *et al*. (2005) isolated many endolichenic fungi from the following different lichen species.

Suryanarayanan *et al*. (2005) isolated many endolichenic fungi from the following different lichens species in India:

S. No.	Lichen	Endolichenic fungi
1.	*Dirinaria picta*	*Botrytis* sp., *Chaetomium sp., Cladosporium* sp., *Lasiodiplodia theobromae, Paecilomyces sp., Pestalotiopsis* sp., *Sporormiella intermedia, Nigrospora oryzae, Xylariaceous form 1.*
2.	*Heterodermia diademata*	*Chaetomium* sp., *Cladosporium sp., Humicola* sp., *Nigrospora oryzae, Paecilomyces* sp., *Sporormiella intermedia, Xylariaceous* form 1

3.	*Physcia aipolia*	*Botrytis sp., Chaetomium sp., Cladospori sp. Glomerella cingulata, Huicola sp., Lasiodiplodia theobromae, Phomopsis sp., Nigrospora oryzae, Sporormiella intermedia, Xylariaceous* form 1
4.	*Pyxine cocoes*	*Botrytis* sp., *Chaetomium* sp., *Cladosporium* sp., *Humicola* sp., *Lasiodiplodia theobromae, Paecilomyces* sp., *Phomopsis* sp., *Xylariaceous* form 1
5.	*Roccella montagnei*	*Botrytis* sp., *Chaetomium* sp., *Cladosporium* sp., *Paecilomyces* sp., *Phyllosticta capitalensis, Rhizopus* sp., *Sporormiella intermeia, Xylariaceous* form 1

Li *et al*. (2007) isolated many endolichenic fungi from the following different lichens species in China:

S.No.	**Lichen**	**Endolichenic fungi**
1.	*Cladonia coniocraea*	*Chaetomium globosum, Scopulariopsis sp., Trichoderma sp.*
2.	*Dermatocarpon miniatum*	*Acremonium sp. 1, Coniochaeta sp., Geniculosporium serpens, Nodulisporium sp., Phialophora bubakii, Phialophora sp., Scopulariopsis sp.*
3.	*Melanelia sorediata*	*Acremonium sp.2, Chaetomium elatum, Chaetomium globosum, Nodulisporium sylviforme, Nodulisporium sp., Phialophra bubakii, Scopulariopsis sp., Trichoderma sp. Thielavia sp.6, Trichobotrys sp., Mycelia sterilia*
4.	*Parmelia* sp.,	*Geniculosporium serpens, Coniochaeta sp., Sporothrix sp., Scopulariopsis sp., Hyphomycetes sp.3, Thielavia sp, Mycelia sterilia*
5.	*Punctelia borreri*	*Nodulisporium hyalosporum, Chaetomium globosum, Chaetomium sp., Nodulisporium sp., Hypoxylon fuscum, Phoma sp., Scopulariopsis sp., Sporothrix sp., Thielavia sp.1, Thielavia sp.2, Thielavia sp.*3, *Thielavia sp. 4, Thielavia sp.5*
6.	*Ramalina sinensis*	*Phialophora bubakii, Mycelia sterilia, Sporothrix sp.*

7.	*Xanthoria mandschurica*	*Sporormiella minima, Coniochaeta sp., S. muskokensis, Mycelia sterilia, Scopulariopsis sp., Sporormiella sp.1, Sporormiella sp.2*

Kannangara *et al.* (2009) studied several endolichenic fungi from three lichens in Sri Lanka.

S. No.	Lichen	Endolichenic fungi
1.	*Pseudocyphellarria sp.*	*Chrysosporium sp. 2, Phoma sp., Penicillium sp., Aspergillus sp.1, Aspergillus sp.2., Mycelia sterilia sp. 8,9,10*
2.	*Parmotrema sp.*	*Chrysosporium sp. 1, Chrysosporium sp. 2, Cladosporium sp., Curvularia sp., Aspergillus sp.1, Aspergillus sp. 2, Nigrospora sp., Fusarium sp., Broomella sp., Periconia sp., Phoma sp., Acremonium sp., Mycelia sterilia sp.1,2,3,4,5,6,7,8,9,10.*
3.	*Usnea sp.*	*Curvularia sp., Fusarium sp., Nigrospora sp., Chrysosporium sp. 1, Chrysosporium sp. 2, Cladosporium sp., Mycelia sterilia sp.1,2,3,4,5*

Vinayaka *et al.* (2016) using a number of foliose and fruticose lichens, isolated the following endolichenic fungi from India:

S. No.	Lichen	Endolichenic fungi
1.	*Cladonia fruticulosa*	*Chaetomium globosum, Alternaria alternata, Hypoxylon sp., Phoma leveillei, Fusarium heterosporum, Trichoderma viride, Xylaria sp., Mycelia sterilia sp.2,5*
2.	*Heterodermia dendritica*	*Fusarium lateritium, Chaetomium globosum, Colletotrichum dematium, Curvularia lunata, Phoma leveillei, Penicillium chrysogenum, Thielavia sp., Thielavia basicola, Xylaria sp., Xylaria vaporaria, Mycelia sterilia sp.1,2,3,4,*
3.	*Heterodermia incana*	*Cladosporium cladosporioides, Chaetomium sp., Fusarium lateritium, Phialophora verrucosa, Phoma sp., Rhizoctonia solani, Thielavia sp., Mycelia sterilia sp 1,4,5*
4.	*Parmotrema cristiferum*	*Chaetomium globosum, Aspergillus niger, Fusarium solani, Chaetomium sp., Fusarium heterosporum, Rhizoctonia solani, Xylaria vaporaria, Xylaria sp., Mycelia sterilia sp. 1*

5.	*Parmotrema reticulatum*	*Chaetomium globosum, C. elatum, Chaetomium sp., Alternaria alternata, Fusarium solani, Hypoxylon sp., Penicillium chrysogenum, Phoma leveillei, Thielavia basicola, Pestalotiopsis hypodermia, Xylaria sp.,*
6.	*Parmotrema tinctorum*	*Alternaria alternata, Chaetomium globosum, Chaetomium sp., Colletotrichum dematium, Phoma sp., Pestalotiopsis hypodermia, Trichoderma viride, Mycelia sterilia sp.1*
7.	*Ramalina pacifica*	*Curvularia lunata, Chaetomium globosum, Chaetomium sp., Colletotrichum dematium, Fusarium heterosporum, Fusarium solani, Phialophora verrucosa, Xylaria vaporaria, Mycelia sterilia sp. 2,5,6*
8.	*Ramalina arabum*	*Aspergillus niger, Chaetomium elatum, Chaetomium sp., Colletotrichum dematium, Cladosporium cladosporioides, Chalara sp., Fusarium lateritium, Phoma leveillei, Trichoderma viride, Thielavia basicola, Xylaria sp., Xylaria vaporaria, Mycelia sterilia sp. 1*
9.	*Teloschistes flavicans*	*Aspergillus niger, Chaetomium globosum, Cladosporium cladosporioides, Fusarium lateritium, Phoma sp., Pestalotiopsis hypodermia, Xylaria sp., Mycelia sterilia sp. 3,4,6*
10.	*Usnea galbinifera*	*Aspergillus niger, Chaetomium elatum, Cladosporium cladosporioides, Fusarium heterosporum, Phialophora verrucosa, Thielavia basicola, Xylaria sp., Mycelia sterilia sp. 1,6*
11.	*Usnea stigmatoides*	*Colletotrichum dematium, Cladosporium cladosporioides, Curvularia lunata, Chaetomium globosum, Chalara sp., Fusarium lateritium, Rhizoctonia solani, Fusarium solani, Penicillium chrysogenum, Trichoderma viride, Mycelia sterilia sp. 3,4*

Table 3: Natural product and biological activity of endolichenic fungi isolated from lichen

Lichen Host	Endolichenic Fungal Strain	Natural Product	Biological Activity	References
Clavaroids sp.	*Pestalotiopsis* sp.	Ambuic acid derivative	Antibacterial	Ding *et al*. (2009)
Everniastrum cirrhatum	*Neurospora terricola*	Myxotrichin A (64) Myxotrichin D (67) Terricollene A (93)	Cytotoxic	Zhang *et al*. (2009)
Xanthoria mandschurica	*Coniochaeta* sp.	Conioxepinol B (76)	Cytotoxic	Wang *et al*. (2010b)
		Conioxepinol D (76)	Cytotoxic	
Leptogium saturninum	*Xylaria* sp.	Cyclo (N-methyl-L-Phe-L-Val-D-Ile-Leu-L-Pro	Antifungal synergist	Wu *et al*. (2011)
Heterodermia obscurata	*Phaeosphaeria* sp.	Phaeosphaerin A (27)	Cytotoxic	Li *et al*. (2012)
Ramalina calicaris	*Preussia africana*	Phaeosphaerin C (69)	Cytotoxic	Zhang *et al*. (2012)
Pseudevemia intensa	*Geopyxis majalis*	Geopyxin A (111), acetate and diester derivatives	Cytotoxic	Wijeratne *et al*. (2012)
		Geopyxin B (112)		
		Geopyxin C (113), acetate and diester derivatives		

Everniastrum sp.	*Ulocadium* sp.	7-hydroxy-3,5-dimethhyl-isochromen-1-one (52)	Antifungal	Wang *et al*. (2012)
Everniastrum cirrhatum	Chaetomium elatum (No.63-10-3-1)	Xanthoquinodin A4 (10); Xanthoquinodin A5 (11); Xanthoquinodin A6 (12); Xanthoquinodin B4 (13a); Xanthoquinodin A5 (13b)	Cytotoxic	Chen *et al*. (2013)
Cetraria islandica	*Myxotrichum* sp.	Myxodiol A (62); Myxotrichin A (64); Myxotrichin D (67)	Cytotoxic	Yuan *et al*. (2013)
Everniastrum sp.	*Ulocadium* sp.	Ophiobolin P (117) Ophiobolin P (121)	Antibacterial Cytotoxic Antibacterial	Wang *et al*. (2013b)
Lobaria retigera	*Aspergillus versicolor*	8-O-methylversicolorin A (6) 8-O-methylversicolorin A (7)	Cytotoxic	Dou *et al*. (2014)
Sticta fuliginosa	CR1546C	(R)-4,6,8-Trihydroxy-3,4-dihydro-1(2H)-naphthalenone (38)	Antifungal	Kim *et al*. (2014)
Peltigera elisabethae var. mauritzii	*Aspergillus* sp (No.16-20-8-1)	9-acetyldiorcinol B (90)	$A\beta_{42}$ aggregation	Zhao *et al*. (2014)
Lobaria quercizans	*Aspergillus versicolor* (125a)	Diorcinol G (87)	*Lobaria retigera*	Zhao *et al*. (2014)

Everniastrum sp.	*Nodulisporium sp.* (No.65-17-2-1)	Nodulisporiviridin A (122)	$A\beta_{42}$ aggregation	Zhao *et al*. (2015a)
		Nodulisporiviridin B (123)		
		Nodulisporiviridin C (124)		
		Nodulisporiviridin D (125)		
		Nodulisporiviridin E (126)		
		Nodulisporiviridin F (127)		
		Nodulisporiviridin G (128)		
		Nodulisporiviridin H (129)		
Parmotrema sp.	*Penicillium citrinum*	5’-acetyl-3,5,7’-trimethoxy-3’H-spiro [cyclohexa [2,4] diene-1,1’-isobenzofuran]-3’,6-dione (58)	Antioxidant	Samanthi *et al*. (2015)
		4’-acetyl-2’’-hydroxy -3’,5’,6- trimethoxy biphenyl-2-carboxylicacid (85)	Antioxidant	

Preliminary phytochemical studies

Qualitative analysis

Isolation and identification of secondary metabolites from an endolichenic fungus was first reported by Paranagama *et al* (2007). Isolation of bioactive natural products from endolichenic fungi have been gradually increased and have special attention for their potential to produce bioactive metabolites possessing new structure and representing different structural classes including terpenoids, steroids, peptides, quinones, xanthones, sulphurcontaining chromenones, etc. Nevertheless, chemistry and bioactivity of these phytochemical compounds have not yet been investigated thoroughly which still remain to be unexplored. Because of the reason that most of the endolichenic fungi are not fully collected from all over the world (Kellogg and Raja, 2017).

Quantitative analysis

In natural products research, endolichenic fungi have, of late, become a new avenue for evaluation of bioactive secondary metabolite chemistry. Last 10 years of research have revealed potential new structures, and interest in the production of bioactive natural products from the culture of endolichenic fungi which has increased substantially, since first report of metabolites from endolichenic fungi was done 9 years ago, research into endolichenic fungal natural products has steadily increased, representing small but growing body of literature.

Santiago *et al*. (2021) studied total phenol and flavonoid content of three lichens (*Usnea baileyi, Usnea bismolliuscula* and *Usnea pectinata*) and 5 endolichenic fungi (*Astrocystisbambusae, Annulohypoxylon albidiscum, Daldinia eschacholtzii, Nemania bipapillata* and *Xylaria venustula*).

Antimicrobial activity

Many Natural products obtained from microbes are likely to be useful in numerous fields which include agriculture, industry, and medicine (Demain, 2014). In the medical point of view, microbial metabolites have been the prime source of most antibiotics presently accessible in the market (Imhoff, 2011).

Newly, in Europe *Sclerotium rolfsii* has also been found on different hosts, including juglans and sunflowers (Belisario and Corazza, 1996; Infantino *et al*., 1997). Plant diseases caused by *Sclerotium rolfsii* have been potentially controlled by mycoparasitic fungi.

Blackwell (2011) stated fungi represent an interesting group known to produce a wide range of bioactive compounds and their metabolites are diverse in terms of structures and functions. Kaul *et al.* (2012) declared the fungal metabolites are broadly known to exhibit a wide range of biological properties including antimicrobial, antioxidant, and anticancer.

Pathi *et al*. (2015) studied the antimicrobial activity of isolated 19 distinct endolichenic fungi from the lichen *Parmelia* sp., against the pathogenic bacteria (*Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Proteus vulgaris, Shigella flexneri* and *Klebsiella pneumonia*) and fungi (*Candida albicans, Candida krusei* and *Trichophyton mentagrophytes*).

Poornima *et al*. (2018) studied the antimicrobial activity of isolated 10 endolichenic fungi from the lichens *Parmotrema tinctorum, Parmotrema grayanam, Parmotrema reticulatum, Parmotrema austrosinense, Heterodermia speciosa, Pyxiene petricola* against pathogenic bacteria *Escherichia coli, Staphylococcus aureus, Streptococcus sp.,* and fungi (*Aspergillus niger, Candida albicans*).

Santiago *et al*. (2021) assessed the antimicrobial activity of three lichens (*Usnea baileyi, Usnea bismolliuscula, Usnea pectinata*) and 5 endolichenic fungi (*Astrocystis bambusae, Annulohypoxylon albidiscum, Daldinia eschacholtzii, Nemania bipapillata, Xylaria venustula*) against gram positive bacterium *Staphylococcus aureus*, gram negative bacterium *Escherichia coli* and yeast *Candida albicans*.

The antibacterial activity of nine endolichenic fungi isolated from the foliose lichen *Parmotrema rampoddense* against *Enterococcus faecalis, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, Enterobacter agglomerans* was reported (Tan *et al*., 2020). The antimicrobial activity of 19 compounds isolated from the endolichenic fungus *Hypoxylon fuscum* against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli* and *Candida albicans* was studied (Basnet *et al*., 2019).

Antioxidant activity

Secondary metabolites derived from the endolichenic fungi comprise different classes of compounds such as steroids, quinones, terpenoids, peptides, xanthones, and sulfur- containing chromenones, which possess various biological activities like anticancer, antiviral, antibacterial, antifungal, and anti-Alzheimer's activities (Biosca *et al*., 2016; Muggia *et al*., 2016; Suryanarayanan and Thirunavukkarasu, 2017).

Endolichenic fungi derived compounds like quinones, phenolic and heterocyclic compounds showed strong cytotoxic, antimicrobial activity and antioxidant activity. Other pharmacological activities of these ELF include antiviral, anti-inflammatory, UV protectant, Ab42 (small peptide Ab42) aggregation inhibition and anti-Alzheimer's properties (Singh *et al*., 2017; Cimmino *et al*., 2019). During the period from 2008 to 2019 (up to March) provides a comprehensive overview of the bioactive metabolites identified from endolichenic fungi, which includes ninety-nine novel compounds from a total of 172 compounds reported. Novel molecules isolated from endolichenic fungi are depicted in Table 4.

Table 4: Compounds of endolichenic fungi and their biological activity

Lichen	Endolichenic Fungi	Compounds	Biological Activity	References
Usnea cavernosa	*Corynespora sp.*	Corynesporol hydroxydehydroherbarin	Cytotoxicity	Paranagama *et al*., 2007
Pseudocyphellaria sp.,	*Broomella sp.,*	Crude extract	Antifungal	Kannanagara *et al*., 2009
Parmelinella wallichiana	*Alternaria sp., Nigrospora sp.and Phialophora sp.*	Heptaketides	Antifungal	He *et al.*, 2012
Everniastrum sp.	Unidentified fungus	Polyketides	Antimicrobial	Wang *et al*., 2012
Cladonia gracilis	*Scopulariopsis sp.*	1-(40-hydroxy-30,50-dimethoxyphenyl)-1,8-dimethoxynaphthalen-2-ol	-	Yang *et al.*, 2012
Ramalina calicris	*Preussia africana*	Thiopyranchromenone and other chromone Derivatives	Cytotoxicity	Zhang *et al.*, 2012
Everniastrum cirrhatum	*Chaetomium elatum*	*Xanthoquinodins*	Cytotoxicity	Chen *et al*., 2013
Everniastrum sp.	*Ulocladium sp.*	*Ophiobolins P, Q, R, S, T*	Cytotoxicity and antibacterial	Wang *et al.*, 2013
Everniastrum sp.	*Ulocladium* sp.	*Tricyloalternarenes F, G, H*	Cytotoxicity	Wang *et al.*, 2013
Cladina grisea	*Eurotium* sp.	*7-O-Methylvariecolortide Variecolortide B, Variecolortide C,*	*Caspase-3 inhibitory activity*	Chen *et al.*, 2014
Lobaria zahlbruckneri	*Tolypocladium cylidrosporum*	*Tetramic acids and pyridine alkaloids*	Cytotoxicity	Li *et al.*, 2014
Xanthoparmelia sp.	*Peziza* sp.	*Mono- and bis-furanone derivatives*	Antimicrobial Cytotoxicity	Zhang *et al.*, 2014
Peltigera elisabethae var mauritzii	*Aspergillus niger*	*Diphenyl ethers*	Anti-Aß42 aggregation activity	Zhao *et al.*, 2014

Everniastrum nepalense	*Chaetomium globosum*	*Chactoglobosin y*	Cytotoxicity	Zheng *et al.*, 2014
Lethariella sp.	*Tolypocladium cylidrosporum*	*Pyridoxatin*	Candida growth inhibition	Chang *et al.*, 2015
Unknown lichen species	*Pleosorales* sp.	*Cucurbitarins A, B, C, D, E; 3,10-dihydroxyl -4,8-dimethoxy-6 methylbenzocoumarin; 3,8,10 trihydroxy-4-methoxy-6-methylbenzocoumarin, (5R)-5-hydroxy-2,3 dimethylcyclohex-2-en-1-one*	-	Jiaoa *et al.*, 2015
Lobaria quercizans	*Aspergillus versicolor*	*Diorcinols F, G, H; 3-methoxyviolaceol –II; Bisabolane sesquiterpenoids; Sydowiols D, E*	Cytotoxicity	Li *et al.*, 2015b
Parmotrema sp.	*Pencillium citrinum*	*Polyketides*	Antioxidant activity	Samanthi *et al.*, 2015
Parmelia sp.	*Periconia* sp.	*Pericoterpenoid A*	Antimicrobial	Wu *et al*,.2015

GC-MS ANALYSIS

Some novel metabolites including cucurbitarins, chaetoglobosin, terpenoids, naphthalene derivatives, heptaketides, diphenylethers, polyketides, alkaloids, pyridoxatin,variecolortide, tricycloalternarenes, thiopyranchromenone and chromone derivatives exhibiting interesting bioactivities have been synthesized form endolichenic fungi (Kannangara *et al*. 2009; He *et al*. 2012; Yang *et al*., 2012; Zhang *et al*., 2012; Wang *et al*., 2012, 2013a,b; Chen *et al*., 2013, 2014; Zhang *et al*., 2014; Zheng *et al*., 2014; Zhao *et al*., 2014; Li *et al*., 2014, 2015; Chang *et al.*, 2015; Jiaoa *et al.*, 2015; Samanthi *et al*., 2015; Wu *et al*., 2015) and can serve as ultimate, readily renewable, and inexhaustible source of novelnatural products displaying broad spectrum of biological activities.

Molecular docking

In-silico methods were used with the main goal to contribute to the understanding of the mechanisms underlying the interaction of biomolecules isolated from thefungus *Phomopsis* species and eight different types of receptors that belongs to usually multidrug resistant bacterial pathogens (Ignjatovic *et al*., 2021).

Anti-inflammatory

The regulation of an inflammatory response can be attained by strenghtening the lysosomal membrane which otherwise would release the compounds to trigger inflammation. Since the lysosomal membrane is similar to the erythrocyte membrane in humans, this activityprovides the technique to assess antiinflammatory activity of the extracts using the heat- induced hemolysis principle (Leelaprakash and Doss, 2011).

In China, the endolichenic fungus *Nodulisporium sp*. isolated from the lichen lichen *Everniastrum sp.,* was reported to contain compounds belonging to the viridian family, which are known to possess anti-inflammatory activity (Zheng, 2013).

Cell line

Yang *et al*. (2018) discovered the cytotoxicity activity of acetonic extracts of endolichenic fungus isolated from the lichen *Endocarpon pusillum* against human gastric cancer cells and CT 26 mouse colon cancer cells.

Basnet *et al*. (2019) studied the cytotoxic effects of isolated 19 compounds from the endolichenic fungus *Hypoxylon fuscuna* against on K562, SW480 and Hep G2 cell lines.

Bionanoparticles

Bharathidasan *et al*. (2012) investigated the biosynthesis of silver nanoparticles using *Aspergillus conicus*, *Penicillium janthinellum* and *Phomosis* sp. and was monitored by UV- Vis spectrophotometer.Verma *et al.* (2010) studied the silver nanoparticles via UV-Vis spectrophotometer for *Aspergillus clavatus* isolated from the stem of *Azadirachta indica.*

The mycelia free filtrates of three endophytic fungal isolates such as *Aspergilus tamarii*, *Aspergillus niger* and *Penicillium ochrochloron* were discovered by UV-Visible spectrophotometer (Devi *et al*., 2017).

Abdel-Hafez *et al*. (2016) studied that 5mM concentration of $AgNO_3$ solution was optimum for the synthesis of AgNPs through *Penicillium* sp. and *Cladosporium sphaerospermum* respectively.

Singh *et al*. (2017) discovered the biological synthesis of silver nanoparticles (AgNPs) from supernatant of endophytic fungus *Aternaria* sp., isolated from the leaves of *Raphamus sativus*. The synthesized AgNPs were characterized by UV-Vis spectroscopy, Fourier transform intrared spectroscopy (FTIR) and Transmission electron microscopy (TEM) for observed size and shape of AgNPs.