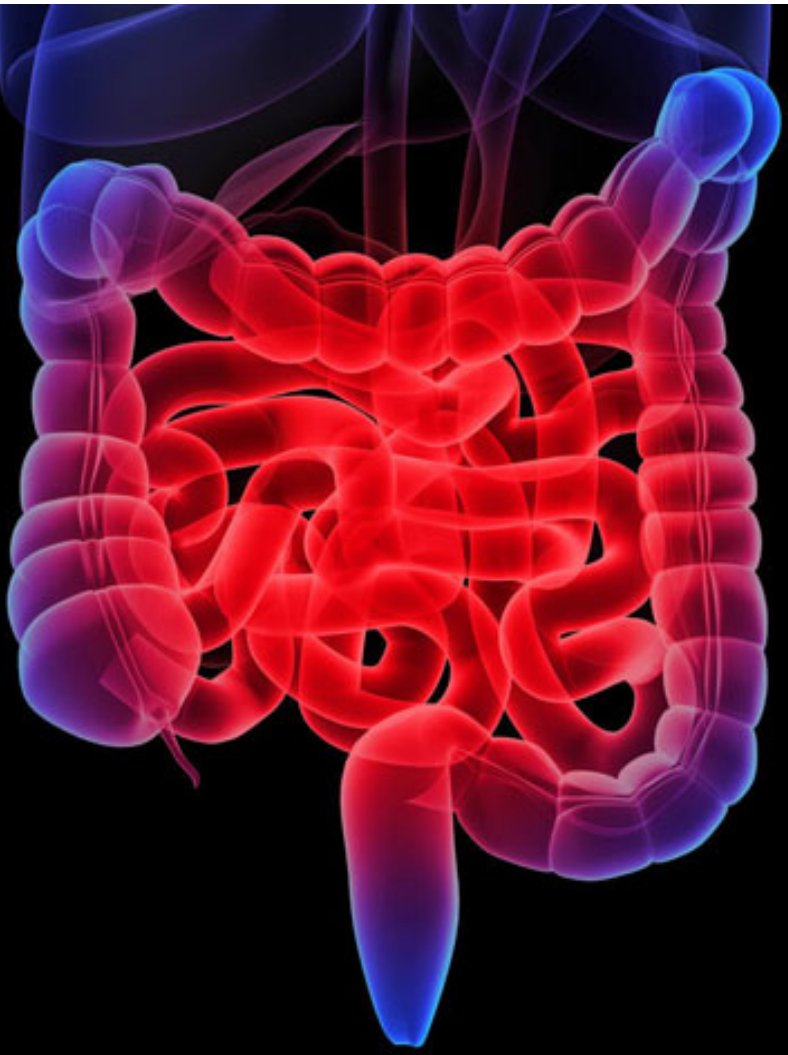

INFLAMMATORY BOWEL DISEASE

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Anti-Inflammatory Potential of Lichens and its Substances

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Abstract

Lichen is a symbiotic form of a mycobiont and a photobiont or a cyanobiont. In the folk medicine of different cultures, they are used to treat multiple conditions such as wounds, skin disorders, respiratory and digestive problems, inflammation and its complications. Medicinal applications of lichens are documented in Ayurveda, Unani, and Doctrine of Signature with the contribution of knowledge from traditional medicinal practitioners. In Asia and Europe, lichens are taken orally as a decoction to treat inflammation-related ailments. This review summarized the genera of lichens used in traditional medicine of different cultures across the world and also listed out the folk names of lichen species that have anti-inflammatory activity. In addition, the anti-inflammatory potential of lichen extracts and their substances are also discussed.

Introduction

Lichen (leikhēn means "what eats around itself"), is a symbiosis between a mycobiont (heterotropic fungi) and a photobiont (photosynthetic algae) or a cyanobiont (cyanobacteria) where the mycobiont involves in chemical signaling and provides shape and structure, while the photobiont/cyanobiont supply nutrient exchange, i.e., carbohydrates [1,2]. The taxonomy of lichens is defined based on mycobiont content since it proportionally accounts for 95-98% and plays a crucial role in the sexual reproduction of lichens. Lichens can be differentiated from fungi based on its photobiont content [3].

Generally, the growing rate of lichens is found to be less than 1 cm/year, which is the lowest among the plant kingdom [3,4]. It is interesting to note that lichens are epiphytes as they synthesize their food by photosynthesis using plants, asphalt, sand, leaf litter, roof materials, rocks, and dead logs as substrates. Mostly, lichens are deliberated as "pioneer" species and highly persist in terrestrial environments and rarely in freshwater or marine ecosystems [5]. As the lichens are generally termed as bio-monitors, they are very less resistant towards pollution and acid rains that contain high amounts of sulfur dioxide. Around

20,000 lichens have been identified across the world so far, containing mostly ascomycetes and basidiomycetes, and deuteromycetes to a much lesser extent. The thallus is an unique characteristic of lichens, which is usually a multicellular structure categorizing into crustose, leprose, foliose, filamentous, and fruticose [6].

Lichens are well-recognized for their medicinal applications. The majority of lichens are used in the traditional medicines of arctic and temperate areas and fewer in the tropics. About 60 genera of lichens are widely used in folk medicine by different cultures worldwide. Among all, the Usnea genus is the most widely used species [7]. As external agents, lichens have been widely used for dressing wounds, stopping bleeding, and topically for sores and skin infections [8–10]. In the form of extracts and decoction, lichens served to treat multiple ailments such as asthma, backache, bronchitis, colds, cough, diarrhea, eye infections, expel intestinal worms, fever, heartburn, inflammation associated with diabetes, intestinal problems, loss of appetite, lung diseases, neuralgia, malaria, respiratory problems, rheumatism, sickness, swelling, typhoid, vaginal discharge, etc [10-16]. In this book chapter, the roles of lichens in traditional medicine were discussed, followed by a discussion on the anti-inflammatory effects of lichens' extracts and compounds.

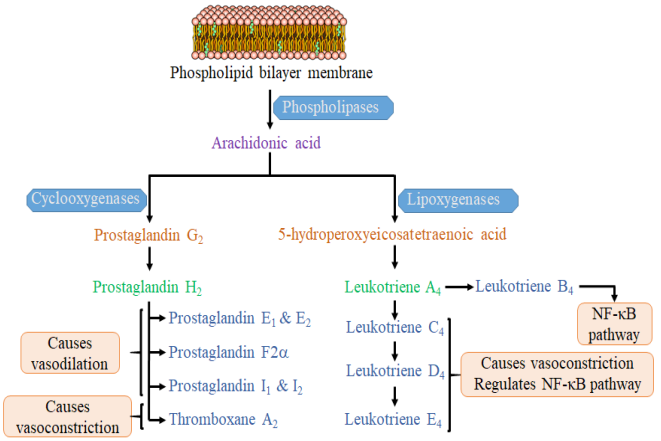


Figure 1: Metabolic pathway of arachidonic acid.

Inflammation

Inflammation is characterized by the stimulation of the host's non-immune and immune cells in response to infections and/or toxins in order to eradicate pathogens and stimulate tissue healing and recovery [17]. Based on the degree and extent of an inflammatory response, inflammation is classified into three subtypes, namely acute, sub-acute, and chronic inflammation. Acute inflammation is a short-term (1-3 days) illness or injury characterized by loss of function, heat, pain, redness, and swelling. Sub-acute inflammation can continue for 3-30 days, and if not resolved within 30 days, it develops into chronic inflammation that lasts for several months or years and is linked to many deadly diseases, such as allergies, cardiovascular diseases, cancer, diabetes, psoriasis, and rheumatoid arthritis [18].

Cytokines and autacoids play a key role in the inflammatory responses. Cytokines such as Interferon γ (INF-γ), Tumor Necrosis Factor α (TNF-α), and Interleukins (IL), have a complex role in inflammation [19,20]. Autacoids include eicosanoids (e.g. Leukotrienes (LTs), Prostaglandins (PGs), Phospholipids (PLs), Prostacyclins (PCs), and Thromboxanes (TXs)) and Platelet-Activating Factors (PAFs) [21]. Eicosanoids are synthesized from arachidonic acid (a 20-carbon polyunsaturated fatty acid) by activated leukocytes, platelets, and mast cells that are distributed widely in the human body. Additionally, eicosanoids are produced by bradykinin, TNF-α, and some hormones either indirectly by an accumulation of intracellular levels of Ca^{+2} ions or directly by activation of PLA2 that hydrolyzes arachidonic acid [22]. An increase in Ca^{+2} concentration is generally achieved by cell membrane damage, while activation of PLA2 is metabolized by two enzymatic pathways, such as Cyclooxygenase (COX) and Lipoxygenase (LOX) pathways [23].

Arachidonic acid is oxygenated into cyclic endoperoxide PGG2 in the presence of COX enzymes (prostaglandin-endoperoxide synthase), which is converted to the closely related PGH2. Due to their unstable nature, these byproducts are further converted into PGE1, PGE2, PGF2α, PGI1, and TXA2. Notably, PGE1, PGE2, and PGI1 are strong arteriolar dilators that increase the small-vein permeability, thereby enhance the effects of other pain-provoking mediators such as histamine and bradykinin. PGs and TXs can cause vasoconstriction and smooth muscle contraction, while TXA2 is an effective platelet-aggregating agent that is involved in the formation of thrombus [24-26] **(**Figure 1). On the other hand, LOX enzymes (5-LOX, 8-LOX, 12-LOX, and 15-LOX) oxidize arachidonic acid into 5-hydroperoxy eicosatetraenoic acid that, in turn, will be converted into leukotriene A4 (LTA4). LTA4 stimulates LTB4, LTC4, LTD4, and LTE4 cascade. Activated LTB4 binds to its receptors to activate phosphatidylinositol 3-kinase and Nuclear Factor kappa B (NF-κB) pathway, while LTC4, LTD4, and LTE4 bind to cysteinyl LT receptors, thereby regulate the NF-κB pathway. Particularly, LTC4 activates p50-65 complex by phosphorylating NF-κB p65 [27-29] (Figure 1).

Initially, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin, diclofenac, ibuprofen, and naproxen are widely used for inhibiting the COX-1/2 enzymes non-selectively [30]. These drugs, however, cause severe gastrointestinal problems. Later, selective COX-2 inhibitors, namely celecoxib and rofecoxib, with fewer side effects, are commonly used to treat inflammation and pain. Prolonged usage of selective COX-2 inhibitors, unfortunately, brings cardiovascular problems [31]. On the other hand, certain anti-asthmatic drugs are used as potential LOX inhibitors, such as marketed drugs, meclofenamate sodium, and zileuton [32,33].

Anti-inflammatory potential of lichens

Lichens species used for inflammation in traditional medicine

Lichen, in Greek "leprous," refers to a drug that treats skin diseases, especially skin peeling [34]. Since the 15th century, the usage of several lichen species such as Usnea, Cladonia, Evernia, Parmelia, Lobaria, Pertusaria, Peltigera, Rocella, Physica, and Xanthoria was documented in Ayurveda, Western Medical Herbalism, Traditional Chinese Medicine, Unani, Doctrine of Signature and Homeopathy. Remarkably, during the 18th dynasty Evernia furfuracea (L.) Mann belongs to the Parmeliaceae family was marketed as the first drug for treating microbial infections [35]. During middle age, medicinal practitioners prominently used lichens as herbs for inflammation, coughs, skin problems, and rabies [36]. The folk names of different lichen species used to treat inflammation-related conditions were listed in Table 1.

Table 1: The use of lichen species in traditional medicine for treating inflammation.

Species	Folk name	Culture (Location)	Ref
Cladina rangiferina (L.) Nyl.	Whapskumuk or epshatuk	Whapmagoostui Cree (Quebec, Canada)	[37]
Dendriscosticta wrightii (Tuck.) B. Moncada and Lücking	Shēn bēi niúpí yè or lǎo lóng pí or kuān yè niúpí yè	Ancient China	[7]
Evernia mesomorpha Nyl.	Biǎn zhī yī	Ancient China	[7]
Letharia vulpina (L.) Hue	Laxpt or maqa'hl Ōl-gät'-i	Umatilla and Cayuse (Oregon, USA) Yuki and Wailaki (CA, USA)	[38]
Lethariella cladonioides (Nyl.) Krog	Gangge Jīn shuā bǎ	Tibet Naki (China)	[7,39]
Lethariella sinensis Wei and Jiang	-	Naki (China)	[39]
Lobaria isidiosa (Müll. Arg.) Vain.	Lǎo lóng pí or shānhú yá fèi yī	Ancient China	[10]
Lobaria pulmonaria (L.) Hoffm.	Fèi yī or dōu yī or há mǎ qī or niúpí yè or shí lóng yī or shí lóng pí	Ancient China	[10]
Lobaria sublaevis (Nyl.) Yoshim.	Yà píng fèi yī or lǎo lóng pí	Ancient China	[7]
Masonhalea richardsonii (Hook.) Kärnefelt	Tlingit	Tlingit (Alaska, USA)	[40]
Ophioparma ventosa (L.) Norman	Hóng pán yī or shí shuāng or chì xīng yī	Ancient China	[7]
Parmelia omphalodes (L.) Ach.	Crottle, crotal, dark crottle, or fiasgag nancreag	Britain	[41]
Parmelioid lichens	Urth Lucca	Lëpushë (Albania) Lucca (Italy)	[42,43]
Parmotrema nilgherrense (Nyl.) Hale	Charila	Ayurvedic medicine (India)	[12]
Parmotrema saccatilobum (Taylor) Hale	-	Milne Bay (Papua New Guinea)	[44]
Parmotrema subtinctorium (Zahlbr.) Hale	Yà dà yè méi or yà ránliào méi yī	Ancient China	[7]
Parmotrema tinctorum (Nyl.) Hale	Dà yè méi or bái shí huā or shí Huā or méi yī or shí yī or há má pí	Ancient China	[7]
Punctelia borreri (Sm.) Krog	Fěn bān xīng diǎn méi or fěn bān méi yī	Ancient China	[7]
Ramalina conduplicans Vain.	Yìng zhī shù huā or shù huā or shù xū or shí huācài	Yi, Dai, and Han (s. Yunnan, China)	[7]
Ramalina roesleri (Hochst.) Hue	Ròucì shù huā	Ancient China	[7]
Ramalina spp. Ach.	Λειχήν or βρύον	Ancient Greece	[45]
Roccella sp.	Phŷkos thalássion or gnomeusilum	Ancient Greece	[7]
Stereocaulon paschale (L.) Hoffm.	Wapskirnok	Mistissini Cree (Quebec)	[37]
Sulcaria sulcata (Lév.) Bystrek ex Brodo and D. Hawksw.	Tóufǎ qī or gōu shù fā	Naki (China)	[7]
Thamnolia subuliformis (Ehrh.) W. Culb.	Xuě dǐ chá or tàibái chá or shí bái chá or tàibái zhēn or bái xuě chá or xuě chá	Nakhi (nw Yunnan, China)	[39]
Thamnolia vermicularis (Sw.) Ach. ex Schaerer	De chá or tàibái chá or shí bái chá or tàibái zhēn or tàibái cài or bái xuě chá or huí yàng dìyī	Nakhi (nw Yunnan, China)	[39]
Umbilicaria nanella Frey et Poelt	Xiǎo hēi fù shí ěr or hēi qí yī or hēi shí ěr zi or liè yè shí ěr or pán xíng shí ěr	Ancient China	[7]
Usnea aciculifera Vain.	Jiān cì sōng luó Sajasta	Ancient China Criollos (Dry Chaco, Argentina)	[7,46]
Usnea barbata (L.) Weber ex F.H. Wigg.	Tai angin	Karo (Indonesia)	[47]
Usnea ceratina Ach.	Jiǎo sōng luó or hóng suǐ sōng luó	Ancient China	[7]
Usnea densirostra Taylor	Yerba de la piedra, barba de piedra	Argentina	[48]
Usnea diffracta Vain.	Huán liè sōng luó or sōng jīn téng or sōng luó	Jianghua (China)	[10]
Usnea florida (L.) F. H. Wigg.	Huā sōng luó	Ancient China	[7]
Usnea longissima Ach.	Jianmingyan	Lisu (nw Yunnan, China)	[49]
Usnea pectinata Tayl.	Nǐ zhǎng sōng luó or dà péng cǎo or bìchǐ sōng luó	Ancient China	[7]

Usnea spp. Dill. ex Adans.	Ushna or shaibat-al-ajooz (Unani medicne) Sōng luó or nǔ luó Oak moss; tree moss	Muslim culture (India) Ancient China Europe	[50-52]
Usnea subfloridana Stirt.	Yà huā sōng luó	Ancient China	[7]
Usnea trichodeoides Vain.	Cūpí sōng luó or tiānpéng cǎo or biàn hóng zhǎng sōng luó or shù fā qī Liquen de bosc Islandski lišaj, islandska mahovina; mašina Tripoli	Ancient China Pallars (Spain) Lukomir (Bosnia and Herzegovina) Tripoli (Lebanon)	[7,9,53,54]
Varicellaria velata (Turner) Schmitt and Lumbsch	Bāo bèi jī píyī or shí xiāng	Ancient China	[7]
Xanthoparmelia conspersa (Ehrh. ex Ach.) Hale	Ubulembu belitye -	Xhosa (South Africa) Iroquois (Ontario, Canada)	[55,56]
Xanthoparmelia convoluta (Kremp.) Hale	-	Khoikhoi (Namibia)	[56]
Xanthoparmelia hottentotta (Ach.) A. Thell et al.	-	Khoikhoi (Namibia)	[56]
Xanthoparmelia spp. (Vain.) Hale	Tschétláat or nihaλá·d or céλá·d Owa'si or owa'huru'suki -	New Mexico Navajo (Arizona) Hopi (Arizona, USA)	[7,57]
Xanthoparmelia tinctina (Maheu and Gillet) Hale	Àn fù huáng méi or àn fù méi yī	Ancient China	[7]

Lichens extracts tested for anti-inflammatory activity

Lichens have long been considered as valuable sources to cure various conditions for humans and are also used as key ingredients in dyes and perfumes. Also, the medicinal properties of lichens are well-documented in Ayurveda, Unani, and Doctrine of Signature. Based on this evidence, scientists screened lichen extracts for various biological activities and determined their potentiality to treat various ailments. The studies on the anti-inflammatory potentiality of various lichen extracts are listed in Table 2.

The extracts of Cladonia clathrate, Lobaria pulmonaria, and Teloschistes flavicans were tested for anti-inflammatory activity using carrageenan-induced animal models [58-60]. The hydroalcoholic extract of C. clathrate was found to have significant inhibition in both rat paw edema and mice peritonitis induced by carrageenan [58]. Aqueous extract of L. pulmonaria showed moderate activity in paw edema and granuloma models as compared to standard drugs (nimesulide and indomethacin) [59]. Extracts of T. flavicans, on the other hand, were reported to have anti-edematogenic activity in the rat paw edema model but not effective on subchronic inflammation models [60].

Ingolfsdottir group (1994 & 1996) investigated the COX and 5-LOX inhibitory capacity of different extracts from Cetraria islandica and Stereocaulon alpinum and found that phenolic rich extract of S. alpinum has potent inhibition on both COX and 5-LOX, while petrolium ether and methanol extracts of C. islandica were selectively active against LOX enzymes [61,62]. The studies of COX inhibition of various extracts of Gyrophora exculenta presented their prominent inhibitory effects on PGH2 synthase [63].

Our group, over several years, has tested extracts of Dirinaria consimilis, Graphis ajarekarii, and Roccella montagnei against rat paw edema induced by formalin at two different doses. At both doses, the acetone extract of D. consimilis was reported to have more reduction in paw edema than chloroform extract of that species [64]. Hydroalcoholic extract of G. ajarekarii showed prominent activity than ethyl acetate extract from the same species [65]. On the other hand, acetone extract of R. montagnei was noticed to have a noticeable reduction in rat paw edema than standard [66]. Additionally, the investigation of extracts of D. consimilis and G. ajarekarii against protein denaturation found that only ethyl acetate and acetone extracts of both species were more active than chloroform and methanol extracts [67].

Also, other research group has investigated the anti-inflammatory activity of hydroalcoholic extract of Usnea barbata and Usnea hirta and revealed the equivalent activity of these extracts compared to that of the standard drugs phenylbutazone and hydrocortisone hemisuccinate [68].

Table 2: Lichen extracts with anti-inflammatory activities.

Lichen	Extract(s)	Bioassay	Pharmacological activity	Ref
Cladonia clathrata	Hydroalcoholic extract	Carrageenan-induced rat paw edema and peritonitis in mice	Significant activity in both bioassays.	[58]
Cetraria islandica	Petroleum ether, methanol and water extracts	5-LOX and COX inhibitory assay	Petroleum ether and methanol extracts exhibited pronounced activity in the 5-LOX assay and no activity on COX up to 50 µg/ml.	[61]
Dirinaria consimilis	Chloroform and acetone extracts	Formalin-induced rat paw edema	Acetone extract showed more reduction in paw edema than chloroform extract.	[64]
Dirinaria consimilis and Ramalina leiodea	Chloroform, ethyl acetate, acetone and methanol extracts	Protein denaturation	Ethyl acetate and acetone extracts of both species showed a prominent inhibitory profile against protein denaturation.	[67]

Graphis ajarekarii	Ethyl acetate hydroalcoholic extract	Protein denaturation and formalin-induced albino rat paw edema	In both bioassays, the hydroalcoholic extract showed prominent activity than ethyl acetate extract.	[65]
Gyrophora exculenta	Methylene chloride, ethyl acetate, and n-butanol extracts	COX activity (seminal sheep vesicle)	A prominent inhibitory effect on COX activity of prostaglandin H_2 synthase.	[63]
Lobaria pulmonaria	Aqueous extract	Carrageenan-induced paw edema, and cotton pellet granuloma	At tested doses, the aqueous extract of L. pulmonaria showed moderate activity compared to standard in both assays.	[59]
Roccella montagnei	Acetone extract	Formalin-induced rat paw edema	A prominent reduction in rat paw edema was observed.	[66]
Stereocaulon alpinum	-	5-LOX and COX inhibitory assay	Phenolic containing extract of S. alpinum showed potent activity on 5-LOX and COX.	[62]
Usnea barbata and Usnea hirta	Hydroalcoholic extract	Anti-inflammatory activity	The anti-inflammatory activity of both extracts was comparable with the standard.	[68]
Teloschistes flavicans	Diethyl ether, chloroform, and acetone extract	Carrageenan-induced rat paw edema and cotton pellet induced granulomatous lesion	The ethereal, chloroform and acetone extracts have anti-edematogenic activity but not effective on subchronic inflammation.	[60]

Lichen active substances against inflammation

Lichens produce unique substances, which may help them to survive in extreme environments. By using mevalonate, acetylpolymalonate, and shikimic acid pathways, lichens produce a diverse range of secondary metabolites, which are termed as "Lichen substances". All lichen substances are produced by mycobiont and accumulated in the hyphae, cortex or medullary layer to protect them from pathogens and external abiotic factors [59].

The systemic study of the chemistry of lichens and their substances was initiated in 1907 by a German scientist, Friedrich Wilhelm Zopf [69]. Later, several scientists applied chromatography techniques towards the lichen, which resulted in the isolation and elucidation of about 1050 unique substances [70]. Biosynthetically, lichen substances were divided into two groups: Primary (intracellular) and secondary (extracellular) metabolites. The primary metabolites include proteins, amino acids, carotenoids, polysaccharides, and vitamins found in the protoplasts and cell walls [69,71], while the secondary metabolites include phenolic compounds, terpenes, alkaloids. Chemically, lichen substances are categorized into two classes (a) aliphatic substances that contain mononuclear phenolic compounds, aliphatic and phenolic acids, and zeorin analogs and (b) aromatic substances that include depsides, depsidones, diketopiperazines, dibenzofurans, pulvic acids, quinones, and xanthones [59].

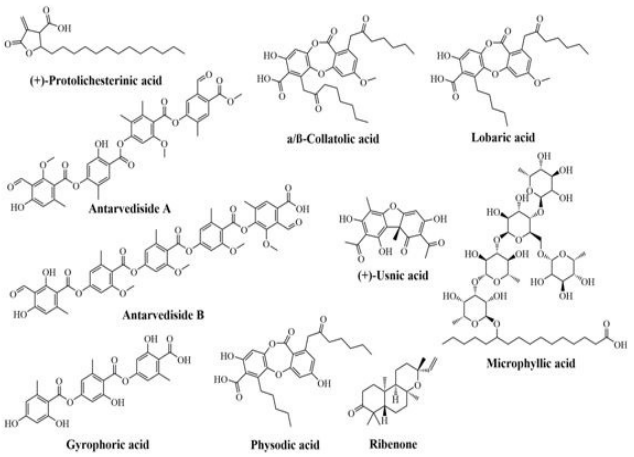


Figure 2: Chemical structure of lichen substances reported to have anti-inflammatory properties.

Lichen secondary metabolites exhibit antimicrobial [72,73], anti-tubercular [72], antioxidant [66], anti-inflammatory [74], fibrinolytic [65], cytotoxic [75], and antidiabetic [76] properties and could be used as sources of pharmaceutical chemicals. Lichen substances with anti-inflammatory activity are presented in Table 3, and their chemical structures are represented in Figure 2 and Table 4. Several groups investigated the potentiality of nearly 70 lichen substances against inflammation using protein denaturation, carrageen-induced models, immune enzyme assays, as well as COX, 5-LOX, LTB4 biosynthesis, and PG biosynthesis inhibitory activities [61,66,74,77-82]. Ingólfsdóttir and colleagues (1996 & 1997) tested two depsides (atranorin & baeomycesic acid) and a depsidone (lobaric acid) against 5-LOX and COX inhibitory assays and found that lobaric acid was active, while atranorin was inactive on both enzymes [62,81]. On the other hand, baeomycesic acid was specifically active against 5-LOX [81]. This group has also investigated the 5-LOX inhibitory property of (+)-protolichesterinic acid isolated from Cetraria islandica and revealed its dose-dependent inhibitory effects [61]. Sankawa group (1982) tested forty commercially available depsides and depsidones for their ability to inhibit PG biosynthesis using rabbit renal microsomes and reported that depside, 4-O-methylcryptochlorophaeic acid, was the most active one [78]. Additionally, the kinetic studies of this depside revealed its function as a competitive inhibitor of PG biosynthesis [77]. Later, seven lichen substances were isolated from Parmelia species and tested for LT B4 biosynthesis inhibitory activity [80]. Among those, only atranorin, diffractaic acid (+)-protolichesterinic acid showed significant inhibition of LT B4 biosynthesis in polymorphonuclear leukocytes, while other compounds were found to be either weak or inactive [80]. Gissurarson group (1997) isolated lobaric acid from Stereocaulon alpinum, evaluated its enzyme immunoassay using cysteinyl-LT and reported its effectiveness at 5.5 µM dose [82].

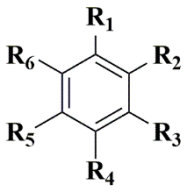
Tatipamula group isolated about fifteen lichen substances from Dirinaria consimilis [74], Graphis ajarekarii [65], Roccella montagnei [66], and Ramalina leiodea [83] and tested for protein denaturation inhibitory activity. All the tested metabolites showed moderate inhibitory activity against albumin protein denaturation with IC_{50} values ranging from 330-950 µg/mL as compared to the standard drug, indomethacin [65,74,84]. This group has also compared the potency of atranorin (a depside) with ribenone (a diterpene) in the formalin-induced albino rat paw edema model and found that atranorin showed prominent

activity than ribenone [65]. The anti-inflammatory potency of atranorin has also been tested by another group in carrageenan-induced rat models, which showed significant activity in paw edema, as well as leukocyte migration in rats as compared to standard [79].

Table 3: Lichen substances that possess anti-inflammatory activity.

Lichen substance	Source	Bioassay	Pharmacological activity	Ref
(+)-Protolichesterinic acid	Cetraria islandica	5-LOX inhibitory assay	Dose-dependent inhibitory effects	[61]
Forty depsides and depsidones	-	PG biosynthesis inhibitory assay	4-O-methylcryptochlorophaeic acid was the most active and competitive inhibitor.	[77,78]
Antarvediside A-B, sekikaic acid, atranorin, divaricatic acid and 2'-O-methyl divaricatic acid	Dirinaria consimilis	Protein denaturation inhibitory assay	Moderately active as compared to indomethacin	[74]
Atranorin	Cladina kalbii	Carrageenan-induced rat models	It showed significant inhibitory effect on carrageenan-induced rat paw edema and leukocyte migration.	[79]
Atranorin and lobaric acid	Stereocaulon alpinum	5-LOX and COX assays	Lobaric acid: IC_{50} values of 7.3 (5-LOX) and 29.2 (COX) µM Atranorin: Inactive on both enzymes	[62]
Atranorin and ribenone	Graphis ajarekarii	Protein denaturation assay and formalin-induced rat paw oedema	In both bioassays, atranorin showed prominent activity than ribenone	[65]
Atranorin, diffractaic acid, (+)-protolichesterinic acid, ethyl hematommate, (+)-usnic acid, methyl β-orcinolcarboxylate and gyrophoric acid	Parmelia nepalensis and Parmelia tinctorum	LT B4 biosynthesis inhibitory assay	Only atranorin, diffractaic acid, and (+)-protolichesterinic acid were active.	[80]
Baeomycesic acid	Thamnolia subuliformis	5-LOX and COX inhibitory assays	The IC_{50} value 8.3 µM on 5-LOX and inactive on COX	[81]
Divarinolmonomethylether, ethyl divaricatinate, divarinol, orcinol, methyl 2,6-dihydroxy-4-methylbenzoate, haematommic acid, atranol, ethyl haematommate and ethyl orsellinate	Roccella montagnei	Protein denaturation inhibitory assay	Moderately active as compared to indomethacin	[66]
Lobaric acid	Stereocaulon alpinum	Enzyme immunoassay	The ED_{50} of 5.5 µM on cysteinyl-leukotriene formation in the smooth muscle taenia coli from guinea pigs.	[82]
Methyl 2,6-dihydroxy-4-methyl benzoate, haematommic acid and ethyl haematommate	Ramalina leiodea	Protein denaturation inhibitory assay	Moderate active compared to indomethacin	[83]

Table 4: Mononuclear phenolic compounds from lichens possessing anti-inflammatory activity.



Lichen substance	R_1	R_2	R_3	R_4	R_5	R_6
2,4-Dihydroxy-6-pentylbenzoic acid	COOH	OH	H	OH	H	n-C_5H_{11}
2,4-Dimethoxy-6-pentylbenzoic acid	COOH	Me	H	Me	H	n-C_5H_{11}
2-Hydroxy-4-methoxy-6-pentylbenzoic acid	COOH	OH	H	Me	H	n-C_5H_{11}
2-Hydroxy-6-pentylbenzoic acid	COOH	OH	H	H	H	n-C_5H_{11}
Atranol	Me	H	OH	CHO	OH	H

Divarinol	n-C_3H_7	H	OH	H	OH	H
Divarinolmonomethylether	OH	H	OH	H	OMe	H
Ethyl divaricatinate	n-C_3H_7	$COOC_2H_5$	OH	H	OMe	H
Ethyl haematommate	Me	$COOC_2H_5$	OH	CHO	OH	H
Ethyl orsellinate	Me	$COOC_2H_5$	OH	H	OH	H
Haematommic acid	Me	COOH	OH	CHO	OH	H
Methyl-2,6-dihydroxy-4-methylbenzoate	Me	H	OH	COOMe	OH	H
Methyl-ß-orcinolcarboxylate	COOMe	OH	CHO	OH	H	Me
Orcinol	Me	H	OH	H	OH	H

Conclusions

The inflammation process, though a self-limiting process, can become chronic and can further lead to several other severe inflammatory conditions such as cancer, atherosclerosis, Alzheimer's, and rheumatoid arthritis. This review provided an overview on the effectiveness of lichens on anti-inflammation based on the current knowledge on traditional medicine as well as pharmacological studies. However, the available studies on this topic remain limited, which require a thorough chemical and pharmacological investigation of anti-inflammatory agents from lichens. The current review provides an overview on the topic to aid the investigators in designing and performing further pharmacological studies on lichens to fill these gaps.

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