Occurrence of terpenes, polyketides, and tannins in some Japanese lichens and green mosses

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Terpenes, polyketides, and tannins are valuable chemical classes that are famous for their varied biological activities such as being antioxidant, anticancer, antibiotic, and immunosuppressant agents. On the other hand, lichens and mosses are rich sources of biologically active compounds. However, rare studies have described neither the chemical analyses nor the biological activities of such samples. In this review, the chemical constitutions of five Japanese originated lichens and moss samples belonging to the species Candelariella vitellina, Lepraria incana, Dirinaria applanata, Brachythecium velutinum, and Brachythecium rutabulum were described with focus on three chemical classes which are terpenes such as Dechloromycorrhizin A, Hericenone A, demethoxyviridin, Scytalidic acid, Ovellin B, Ceriporic acid B, Ganodermatriol, Fomefficinic acid A, Ganoderol A, Ganoderol F; polyketides such as Chaetoquadrin A, Comazaphilone C, Hormothamnione, Arnottianamide, Avermutin, 4′-Hydroxyphlebiarubrone, 4′-Hydroxyphlebiarubrone, Citropone A, Atrovenetin; and finally secondary metabolites (tannins) such as 5′ methoxydehydrodiconiferyl alcohol, ellagic acid 3,3′-di-O-methyl ether, 5,5′-dehydrodiferulic acid, 3,3′,4-tri-O-methylellagic acid, and 5′-methoxydehydrodiconiferyl alcohol.

Keywords:
Brachythecium velutinum, *Candelariella vitellina*, *Dirinaria applanata*, *Lepraria incana*, *Brachythecium rutabulum*, terpenes, polyketides, tannins, biological activities

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Introduction

Lichens are symbiotic associations of fungi with microalgae and/or cyanobacteria, which are considered among the slowest growing organisms, with strong tolerance to adverse environmental conditions [1]. Lichens are a valuable source of many natural classes with varying biological potentials including antiviral, antifungal, analgesic, antipyretic, antioxidant, and anticancer effects [2,3]. The potential of lichens for the monitoring of radionuclides has been well documented [4,5]. Lichens can grow on rocks and exist as epiphytes on trees and leaves [6]. Most of the lichens are terrestrial and few are marine with the ability to adapt water and saline stress, extreme temperature, and air pollutants [7] Lichens produce a wide array of biologically active primary (intracellular) and secondary (extracellular) metabolites (Fig. 1). More than1000 metabolites were extracted from lichens, some of these compounds are exclusively produced by lichens, while others were commonly observed in fungal extracts and those of higher plants [3,5]. In recent times, lichens and their secondary metabolites have been getting increased attention due to their nutritional value and pharmaceutical potential; lichens are used in medicine for many purposes such as for treating bronchitis, spleen enlargement, asthma, heart and stomach disorders, vomiting, treating wounds, and skin disorders [1,8,9]. Lichens metabolites (also known as lichen substances) are either primary or secondary metabolites [8,9]. Primary metabolites are required for the growth and maintenance of cells, and those metabolites include amino acids, proteins, polyols, polysaccharides, vitamins, and carotenoids. On the other hand, lichen secondary metabolites do not contribute in growth, development, or reproduction but they are usually derived from primary metabolism [2,5,8].

Candelariella

Candelariella (known as crustose lichen) is a well-known and commonly occurring genus, growing on many types of substrates, particularly in exposed and nitrogen-enriched regions. The most prominent components of the lichen flora are from species belonging to the genus *Candelariella* on road-side trees, limestone rocks, and in alpine, terricolous habitats. However, the knowledge of the distribution and ecology of individual species is still poor for many

Figure 1

Candelariella vitellina (Photographs taken by Waill A. Elkhateeb, Locality: Hakozaki Higashi-ku Fukuoka-shi Japan).

Figure 2

Lepraria incana (Photographs taken by Waill A. Elkhateeb, Locality: Hakozaki Higashi-ku Fukuoka-shi Japan).

species. Few lichenologists collect and study *Candelariella*, possibly because of the presumed difficulties in correctly identifying the species [10]. *Candelariella vitellina* (also known as egg yolk lichen) is a common and widespread crustose lichen. It is characterized by its green-yellow to orange-yellow colors, and it grows on the bark, rock, and wood all over the world (Fig. 2). *C. vitellina* belongs to the kingdom Fungi, class lecanoromycetes, order *Candelariales,* and family *Candelariaceae.* This promising lichen is a rich source of antioxidants and anticancer compounds. *C. vitellina* is a common green-yellow lichen found on the barks, woods, and rocks in Japanese forests. High-performance liquid chromatography and –high-resolution electrospray ionization mass spectrometry analyses revealed seven new compounds and 11 natural compounds of terpenes and polyketides [11,12].

Lepraria

The genus *Lepraria* Ach., with a worldwide distribution, comprises morphologically simple lichen-forming fungi that never develop fruiting bodies. Thallus crustose to sub-foliose or squamulose, with a powdery, granular, cottony, membranous or sub-squamulose to sub-foliose appearance; variously colored, but not very bright, grayish, greenish and creamy hues prevalent; thin to thick, soft or hard [13]. The lichen *Lepraria incana* (also known as dust lichen) belongs to the kingdom Fungi, class lecanoromycetes, order: Lecanorales, Family: Stereocaulaceae (Fig. 3). It is a common lichen that grows on many substrates in the pattern of granulated patches or dust-like form. Rare studies have been conducted describing the chemical analysis and biological activities of this lichen. Previous chemical investigation showed that *L. incana* contained

Figure 3

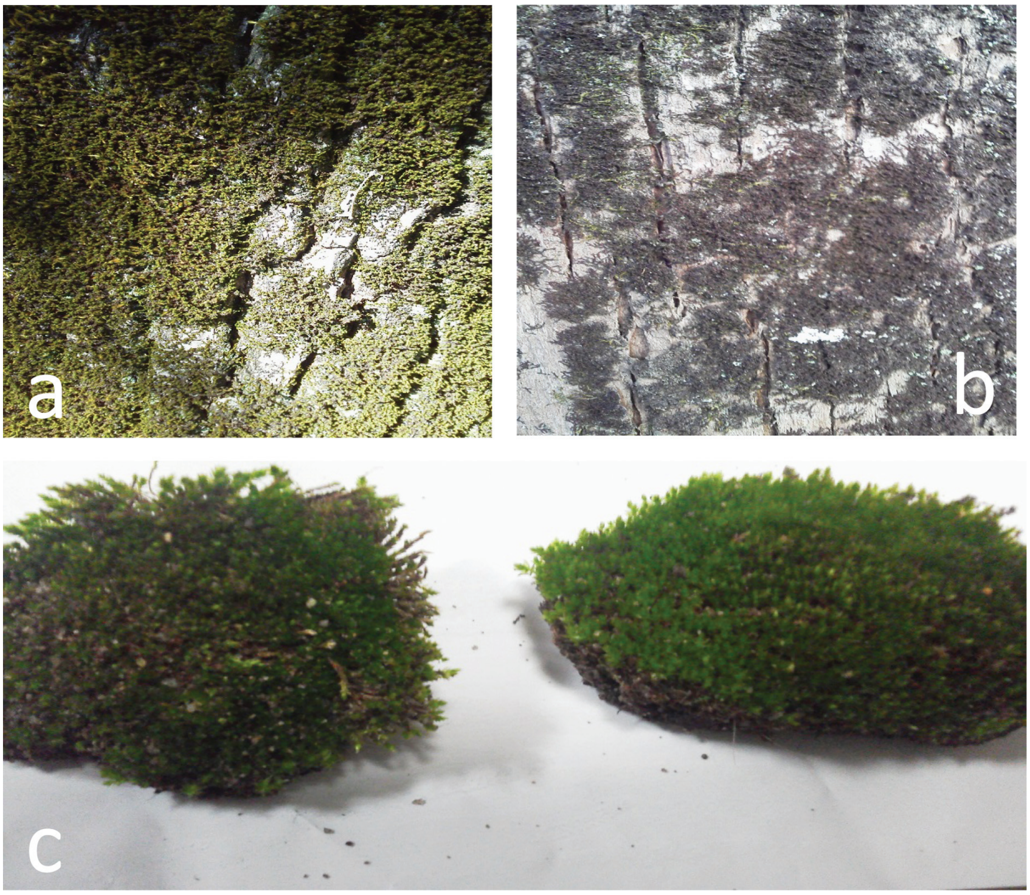
Dirinaria applanata (Photographs taken by Waill A. Elkhateeb, Locality: Hakozaki Higashi-ku Fukuoka-shi Japan).

Divaricatic acid, nordivaricatic acid, zeorin [13], and atranorin; anthraquinones in addition to parietin, fallacinal, parietinic acid and citreorosein [14], gyrophoric acid, lecanoric acid, thamnolic acid, and an unknown terpenoid [15].

Dirinaria

Dirinaria genus is widely distributed in the tropical and subtropical areas that comprised approximately 36 species worldwide [16]. *Dirinaria applanata* is a worldwide spreading lichen that belongs to the kingdom Fungi, class lecanoromycetes, order: Teloschistales, Family: Caliciaceae. Chemical analyses conducted on this lichen are described in few studies [17,18]. *D. applanata* is a foliose lichen, which is widely distributed in tropical areas (Fig. 4). Previous chemical investigations showed that *D. applanata* contained atranorin, carotenoids divaricatinic acid and its ester derivatives, methyl hematommate, methyl β- orcinolcarboxylate, ramalinic acid, lichenxanthones, tannins, and terpenes such as the novel hopane 1β-acetoxy-21α-hopane-3β,22-diol [17–21].

Figure 4



Green moss: (a) *Brachythecium velutinum* (green), (b) *Brachythecium velutinum* (brown), and (c) *Brachythecium rutabulum* (photographs taken by Waill A. Elkhateeb, locality: Hakozaki Higashi-ku Fukuoka-shi, Japan).

Green moss

Brachytheciaceae is a family of mosses, class Hypnales from the order Hypnales. The family includes more than 40 genera and 250 species. The most common genus is *Brachythecium* and the most common species are *Brachythecium rutabulum* and *Brachythecium velutinum*. *B. rutabulum* and *B. velutinum* (also known as Velvet Feather-moss) is a common moss which was previously classified as lichen. It occurs on the wood, including the branches, base and roots of trees, and on dead wood, as well as stones and compacted soil. *B. rutabulum* and *B. velutinum* were a large moss, growing in lax, glossy, bright green, or yellowish green tufts or patches. It is common in Europe and Asia and occurs in many habitats, such as soil (both in woodland and non-forest vegetation), tree boles, logs, stones, and walls [22]. These species are frequently found in man-made habitats such as lawns in gardens, where it is regarded as an unwanted plant. Antibacterial properties of *B. rutabulum* extracts have been recently reported by Singh *et al.* [23], and their use has been reported in the Himalayas [24]. Some mosses have recently been confirmed as sources of antibacterial substances. *B. rutabulum* extract shows antibacterial activity against, for example, *Bacillus subtilis, Escherichia coli*, and *Staphylococcus aureus*, and antifungal activity against, for example, *Aspergillus flavus, Candida albicans*, and *Trichophyton rubrum* [23], and acts as an antioxidant [25]. Rare studies were conducted describing the chemical analysis and biological activities of this moss. It should be noted that all lichens mentioned in this review are Japanese originated (Fig. 4) [17], .

Chemical constitution of some Japanese lichens and green mosses

Terpenes are a chemical class of compounds that represent a major section of secondary metabolites [26]. *Terpenes* basically consist of five-carbon isoprene units, which are assembled to each other as many isoprene units in numerous ways. Terpenoids are modified terpenes with different functional groups with oxidized methyl group removed or located at different positions [27]. According to the number of these isoprene units, terpenes are generally classified into monoterpenes (having two isoprene units, 10 carbon atoms), sesquiterpenes (having three isoprene units, 15 carbon atoms), diterpenes (having four isoprene units, 20 carbon atoms), triterpenes (having six isoprene units, 30 carbon atoms), and tetraterpenes (carrying eight isoprene units, 40 carbon atoms). Among various biological activities, many members of terpenes are specifically potent anticancer agents, exhibit antimalarial activity [27].

As shown in Table 1, *C. vitellina* is rich in various bioactive organic compounds belonging to terpenes such as dechloromycorrhizin A, hericenone A, demethoxyviridin, scytalidic acid, ovellin B, ceriporic acid B, ganodermatriol, fomefficinic acid A, ganoderol A, and ganoderol F. Majority of these compounds exhibit well-known biological activities. *B. velutinum* chemical analysis revealed the presence of many terpenes compounds such as bufotalin, dantaxusin A, moreollic acid, dihydroisomorellin, suberixanthin, taxuspine B, and taxuspine C, while only the terpenes tetrahydroxyoleanenoic-acid 28-O-β-D-glucopyranosyl ester, taxuspine B, and taxuspine C were detected in the extract of the lichen *B. rutabulum*. The lichen *L. incana* showed variety of terpenes including pavoninin-2, terpecurcumin Q, ergosterol acetate, taxuspine C, and lantadene A methyl ester (Table 1). Finally, Gaigrandin, terpecurcumin Q, ergosterol acetate, taxuspine C, and dichrostachine F are the only terpenes detected in the extract of the lichen *D. applanata.*

On the other hand, polyketides represent a huge group of secondary metabolites [26]. Many polyketides have antimicrobial, immunomodulatory, and immunosuppressive properties. Moreover, polyketides include the main chemical structure of different parasiticides, anticancer, and hypocholesterolemic compounds. Polyketide pharmaceutical market has recorded annual sales of as high as 20 billion dollars in the first decade of the 21st century [53]. *C. vitellina* sample from Japan was also a rich source of polyketides such as chaetoquadrin A, comazaphilone C, hormothamnione, arnottianamide, avermutin, 4′-hydroxyphlebiarubrone, 4′-hydroxyphlebiarubrone, citropone A, and atrovenetin (Table 1). Among the remaining listed lichens, polyketides were represented by schisantherin I which was detected in the *B. rutabulum* extract.

Tannins are a class of water-soluble polyphenolic biomolecules that bind to and precipitate proteins and various other organic compounds including amino acids and alkaloids. Some members of tannins are among the famous plant growth regulators and pesticides. They have many biological activities as antioxidants, metal chelators, anti-inflammatory, and anticancer agents [54]. Among the described lichens and mosses tannins detected include 5′ methoxydehydrodiconiferyl alcohol in the extract of *B. velutinum. L. incana* extract was rich in tannins such as ellagic acid 3,3′-di-O-methyl ether, 5,5′-dehydrodiferulic acid, 3,3′,4-tri-O-methylellagic acid, and 5′-methoxydehydrodiconiferyl alcohol.

Table 1 LC-HRESIMS analysis of the methanolic extract of some Japanese lichens and green mosses

No.	*m/z* experimental	Formula	Suggested compound	Chemical class	Activity	References
Candelariella vitellina						
1	331.15442	$C_{19}H_{22}O_5$	Hericenone A	Terpenes	Cytotoxic	Rama Rao and Reddy [28]
2	361.16473	$C_{20}H_{24}O_6$	Chaetoquadrin A	Polyketide	Inhibit mouse liver monoamine oxidase	Kim *et al.* [29]
3	417.15454	$C_{22}H_{24}O_8$	Comazaphilone C	Polyketide	Antibacterial, cytotoxic	Gao *et al.* [30]
4	401.12302	$C_{21}H_{20}O_8$	Hormothamnione	Polyketide	Cytotoxic	Gerwick *et al.* [31]
5	382.12869	$C_{21}H_{19}NO_6$	Arnottianamide	Polyketide	Cytotoxic	Yang *et al.* [32]
6	371.11279	$C_{20}H_{18}O_7$	Avermutin	Polyketide	Cytotoxic	Engström *et al.* [33]
7	323.09152	$C_{19}H_{14}O_5$	Demethoxyviridin	Terpenes	Antioxidant	Wang *et al.* [34]
8	405.19070	$C_{22}H_{28}O_7$	Scytalidic acid	Terpenes	No reported activity	
9	416.17020	$C_{22}H_{25}NO_7$	Ovellin B	Terpenes	Cytotoxic	Belofsky *et al.* [35]
10	321.07587	$C_{19}H_{12}O_5$	4′-Ydroxyphlebiarubrone	Polyketide	No reported activity	
11	311.09174	$C_{18}H_{14}O_5$	Ligustrone B	Polyketide	No reported activity	
12	343.11789	$C_{19}H_{18}O_6$	Atrovenetin	Polyketide	Antioxidant	Ishikawa *et al.* [36]
13	355.28442	$C_{21}H_{38}O_4$	Ceriporic acid B	Terpenes	Antioxidant	Rahmawati *et al.* [37]
14	439.35672	$C_{30}H_{46}O_2$	Ganoderol A	Terpenes	Cytotoxic	Chen *et al.* [38]
15	455.35144	$C_{30}H_{46}O_3$	Ganoderiol F	Terpenes	Cytotoxic	Chen *et al.* [38]
16	457.36728	$C_{30}H_{48}O_3$	Ganodermatriol	Terpenes	Cytotoxic	Liu *et al.* [39]
17	469.36700	$C_{31}H_{48}O_3$	Fomefficinic acid A	Terpenes	Cytotoxic	Shen *et al.* [40]
18	394.12833	$C_{22}H_{19}NO_6$	Citropone A	Polyketide	No reported activity	
19	502.32721	$C_{28}H_{43}N_3O_5$	Beauverolide D	Cyclic peptide	No reported activity	
20	516.34253	$C_{29}H_{45}N_3O_5$	Beauverolide E	Cyclic peptide	No reported activity	
21	564.34235	$C_{33}H_{45}N_3O_5$	Beauverolide F	Cyclic peptide	No reported activity	
Brachythecium velutinum (Brown)						
1	465.1016	$C_{21}H_{20}O_{12}$	Hyperoside	Flavonoid glycoside	Antidepressant, antioxidant	Park *et al.* [41]
2	303.0488	$C1_5H_{10}O_7$	Robinetin	Flavonoid aglycone	multidrug resistance proteins inhibitor	van Zanden *et al.* [42]
3	287.0542	$C_{15}H_{10}O_6$	Scutellarein	Flavonoid aglycone	Anticancer	Shi *et al.* [43]
4	445.2548	$C_{26}H_{36}O_6$	Bufotalin	Terpenes	Anticancer	Zhang *et al.* [44]
5	621.2695	$C_{35}H_{40}O_{10}$	Dantaxusin A	Terpenes	No reported activity	
6	593.2745	$C_{34}H_{40}O_9$	Moreollic acid	Terpenes	Cytotoxic	Asano *et al.* [45]
7	623.2853	$C_{35}H_{42}O_{10}$	Taxuspine B	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
8	607.2901	$C_{35}H_{42}O_9$	Taxuspine C	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
9	547.2692	$C_{33}H_{38}O_7$	Dihydroisomorellin	Terpenes	Anticancer	Kobayashi *et al.* [46]
Brachythecium velutinum (Green)						

(*Continued*)

Table 1 (***Continued***)

No.	*m/z* experimental	Formula	Suggested compound	Chemical class	Activity	References
1	365.2061	$C_{24}H_{28}O_3$	Ugonstilbene A	Phenols	Anti-inflammatory	Asano *et al.* [45]
2	366.1903	$C_{19}H_{27}NO_6$	Harzianic acid	Alkaloid	Antibiotic, Plant growth promoting	Asano *et al.* [45]
3	389.1587	$C_{21}H_{24}O_7$	5′-Methoxydehydrodiconiferyl alcohol	Tannin	No reported activity	
4	593.2745	$C_{34}H_{40}O_9$	Moreollic acid	Terpenes	Cytotoxic	Asano *et al.* [45]
5	623.2853	$C_{35}H_{42}O_{10}$	Taxuspine B	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
6	607.2903	$C_{35}H_{42}O_9$	Taxuspine C	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
7	593.4369	$C_{42}H_{56}O_2$	Suberixanthin	Terpenes	No reported activity	
Brachythecium rutabulum						
1	325.0698	$C_{18}H_{12}O_6$	Sterigmatocystine	Xanthene	Cytotoxic	Kobayashi *et al.* [46]
2	639.2798	$C_{35}H_{42}O_{11}$	Propinquanin B	Polyketide	Cytotoxic	Kobayashi *et al.* [46]
3	623.2853	$C_{35}H_{42}O_{10}$	Taxuspine B	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
4	607.2901	$C_{35}H_{42}O_9$	Taxuspine C	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
5	653.2955	$C_{36}H_{44}O_{11}$	Schisantherin I	Polyketide	Anti-inflammatory	Ci *et al.* [47]
6	661.4631	$C_{39}H_{64}O_8$	Tetrahydroxyoleanenoic-acid 28-O-β-D-glucopyranosyl ester	Terpenes	No reported activity	
Lepraria incana						
1	331.0438	$C_{16}H_{10}O_8$	Ellagic acid 3,3′-di-O-methyl ether	Tannin	Antitumor	Zhang *et al.* [48]
2	387.1065	$C_{20}H_{18}O_8$	5,5′-Dehydrodiferulic acid	Tannin	No reported activity	
3	345.0596	$C_{17}H_{12}O_8$	3,3′,4-Tri-O-methylellagic acid	Tannin	Antitumor	Alam and Tsuboi [49]
4	389.1587	$C_{21}H_{24}O_7$	5′-Methoxydehydrodiconiferyl alcohol	Tannin	No reported activity	
5	620.4150	$C_{35}H_{57}NO_8$	Pavoninin-2	Terpenes	No reported activity	
6	571.3073	$C_{36}H_{42}O_6$	Terpecurcumin Q	Terpenes	Anticancer	Lim. [50]
7	439.3565	$C_{30}H_{46}O_2$	Ergosteryl acetate	Terpenes	No reported activity	
8	607.2903	$C_{35}H_{42}O_9$	Taxuspine C	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
9	567.4009	$C_{36}H_{54}O_5$	Lantadene A methyl ester	Terpenes	Antitumor	Sharma *et al.* [51]
Dirinaria applanata						
1	331.0438	$C_{16}H_{10}O_8$	Ellagic acid 3,3′-di-O-methyl ether	Tannin	Antitumor	Zhang *et al.* [48]
2	387.1065	$C_{20}H_{18}O_8$	5,5′-Dehydrodiferulic acid	Tannin	No reported activity	
3	345.0596	$C_{17}H_{12}O_8$	3,3′,4-Tri-O-methylellagic acid	Tannin	Antitumor	Alam and Tsuboi [49]
4	389.1587	$C_{21}H_{24}O_7$	5′-Methoxydehydrodiconiferyl alcohol	Tannin	No reported activity	
5	425.2134	$C_{22}H_{32}O_8$	Gaigrandin	Terpenes	No reported activity	
6	571.3073	$C_{36}H_{42}O_6$	Terpecurcumin Q	Terpenes	Anticancer	Lim. [50]
7	439.3565	$C_{30}H_{46}O_2$	Ergosteryl acetate	Terpenes	No reported activity	
8	607.2903	$C_{35}H_{42}O_9$	Taxuspine C	Terpenes	*Inhibit drug transport activity* of *P-glycoprotein* in *multidrug-resistant cells*	Kobayashi *et al.* [46]
9	621.3057	$C_{36}H_{44}O_9$	Dichrostachine F	Terpenes	Anticancer	Long *et al.* [52]

Also, same tannins (ellagic acid 3,3′-di-O-methyl ether, 5,5′-dehydrodiferulic acid, 3,3′,4-tri-O-methylellagic acid, 5′-methoxydehydrodiconiferyl alcohol) were detected in the extract of *D. applanata*.

Conclusion

Screening for novel compounds are extremely important nowadays due to the emergence of new fatal diseases especially cancers, infections caused by drug-resistant microbes, or the currently spreading Corona virus disease caused by COVID-19 virus. Lichens are generous source of novel compounds that can be investigated for their potential biological activities. In this review, the chemical composition of some lichens originated in Japan and green mosses is described showing their richness in bioactive compounds especially from the chemical classes of terpenes, polyketides, and tannins. Majority of members of such chemical classes are known as promising antiviral, anticancer, antioxidant, antimicrobial, immunomodulatory, and immunosuppressive agents. Further studies on those marvelous group can contribute in discovering potent and/or novel compounds capable of competing with currently used drugs or even replace such drugs.

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Conflicts of interest

There are no conflicts of interest.

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