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Application of Bryophytes to Foods, Food Additives and Phytomedicines

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ABSTRACT

Little attention has been paid to the bryophytes for application on the human diet, despite the presence of 23,000 species worldwide. Some mosses and liverworts produce significant levels of terpenoids and polyphenolic compounds possessing characteristic odors and tastes, and cytotoxic antimicrobial, antifungal, anti-oxidant, diuretic, anti-obesity, and many others and they contain significant nutrients such as lipids including highly unsaturated fatty acids and vitamins. Since Asakawa and his coworkers reported the original papers, review articles, and books concerning the isolation and structure elucidation as well as their bio- and pharmacological activity, and chemosystematics of bryophytes, many reviews on phytochemicals and their potential pharmaceutical application have been published. Herein, the distribution of several representative terpenoids, polyphenolic compounds and polyketides, having biological and pharmacological activity in bryophytes and application of bryophytes to foods and food additives are surveyed.

1 | Introduction

The bryophytes are found everywhere in the world, except in the sea. They grow on wet soil or rocks (Figure 1a), the trunks of trees (Figure 1b), in lakes, rivers, and even in Antarctica. The bryophytes are placed taxonomically between the algae and the pteridophytes. There are about more than 23,000 species in the world and they are further divided into three phyla, the Bryophyta (mosses 15,000 species) (Figure 2), the Anthoceratophyta (hornworts 300 species) (Figure 3), and the Marchantiophyta (liverworts 8000 species) (Figure 4a and 4b, Figure 5). They are considered to be the oldest terrestrial plants, although no strong scientific evidence for this has appeared in the literature.

Glime also summarized medicinal uses of bryophytes, including herbal medicines; liver, lung, skin, eye, and ear ailments, stones, ringworm, heart, and cardiovascular medicine, nose bleeds, neurological conditions, inflammation, fever, urinary and bowel treatments, gym ecology, disinfectant and infections, nose and throat, burns, hair treatments, sedatives, antidotes, filters, surgical and larger wounds and so on. Although bryophytes have been used as the medicinal plants as mentioned above, these plant groups have not yet been used as foods, food additives and beverages. In fact, neither literatures nor prescription how to use bryophytes as foods has not yet been reported although a few Japanese bryologists took some liverworts, such as *Bazzania pompeana* as flied foods (Tempura in Japanese cuisine) and said that taste possessed mossy smell and no side effect (Inoue, private communication). However, now some liverworts have been recognized to be edible and used as the foods and food additives in Japan, as discussed later.

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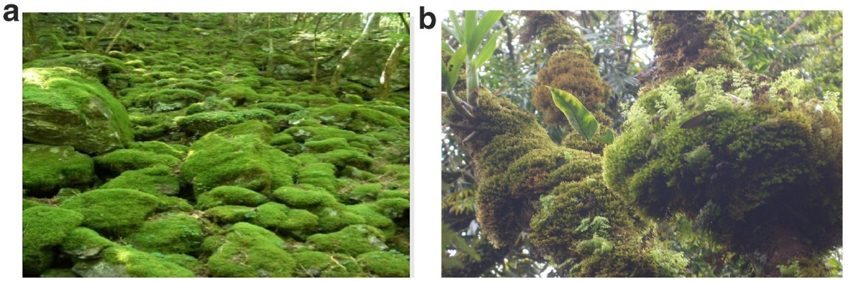


FIGURE 1 | (a) Mosses on wet rocks (Tokushima) (b) Liverworts on trunks of trees.

FIGURE 2 | *Sphagnum* species (moss).

FIGURE 3 | *Phaeceros carolinianus* (hornwort).

Many species of liverworts possess characteristic fragrant odors and an intense pungent, sweet, or bitter taste. Generally, bryophytes are not damaged by bacteria and fungi, insect larvae and adults, snails, slugs, and other small mammals. Furthermore, some liverworts cause intense allergenic contact dermatitis and allelopathy (Asakawa 1982; Asakawa et al. 1995, 2013).

Although liverworts possess such bioactive interesting substances, their isolation was neglected for almost a century. We have been interested in isolation and structural elucidation of bioactive substances from bryophytes and their biological assay. Since 1972, more than 1000 species of bryophytes collected worldwide have been chemically analyzed for their chemistry, pharmacology, and application as sources of cosmetics, foods, medicinal or agricultural agents. The bioactivities of bryophytes are mainly due to the terpenoids and phenolic compounds (Ding 1982; Glime 2017; Asakawa 1990a, 1990b, 1993, 1994, 2001, 2004, 2007a, 2007b, 2008a, 2008b; Asakawa and Ludwiczuk 2009; Asakawa 2015; Asakawa et al. 2009, 2000; Asakawa et al. 2014).

Since Asakawa and his coworkers reported the original papers, review articles, and books concerning the isolation and structure elucidation as well as their bio- and pharmacological activity, and chemosystematics of bryophytes (Asakawa 1982; Asakawa et al. 1995, 2013; Asakawa et al. 1976; Takemoto and Asakawa 1977), many review articles of phytochemicals and their potential pharmaceutical application have been published (Zinsmeister et al. 1991; Harris 2008; Azuelo et al. 2011; Nandy and Dey 2012; Singh and Srivastava 2013; Dziwak et al. 2022; Dey and Mukerjee 2015; Chandra et al. 2017; Cianciulllo et al. 2022; Cianciullo et al. 2022). Here, the bio- and chemical diversity of bryophytes and the chemical structures of the several representative terpenoids, polyphenols, and polyketides found in bryophytes and their bioactivities, as well as the application of bryophytes to "foods and food additives beverages" are surveyed.

2 | Biodiversity of Bryophytes

In the literature of Chinese medicinal spore-forming plants, 24 lichens, 74 sea-algae, 22 mosses, 5 liverworts, 112 fungi, and 329 ferns have been listed with their Latin names, morphological characteristics, distribution locations, pharmacological activity and effects, and their prescription uses in detail (Ding 1982). There are 54 endemic genera of bryophytes in the southern hemispheric countries, except Africa (Inoue 1988). In Far East and South Asia, a relatively large number of endemic genera has been recorded, however, North America, and Europe are impoverished regions of endemic genera (Mohamed et al. 2008). The Marchantiophyta (liverworts) includes two subclasses, the Jungermanniidae and Marchantiidae, and six orders, 49 families, 130 genera, and 8000 species.

This hypothesis was mainly based on the resemblance of the present-day liverworts to the first land plant fossils, the spores of which date back almost 350–400 million years. Among the bryophytes, almost all liverworts possess beautiful cellular oil bodies which are peculiar, membrane-bound cell organelles that consist of ethereal terpenoids and aromatic oils suspended in a carbohydrate- or protein-rich matrix, while the other two phyla do not. These oil bodies are very important biological markers for the taxonomy of the Marchantiophyta and contain various bio active secondary metabolites, such as bibenzyls, bis-bibenzyls, vitamins, highly unsaturated fatty acids, and terpenoids.

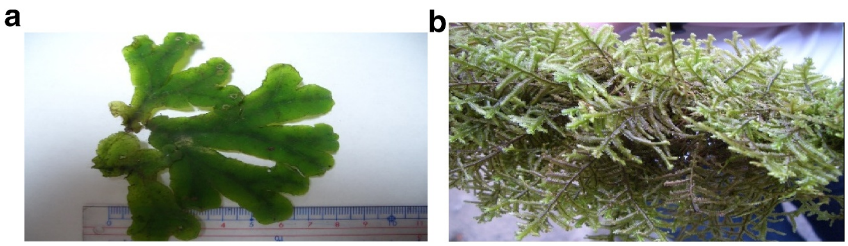
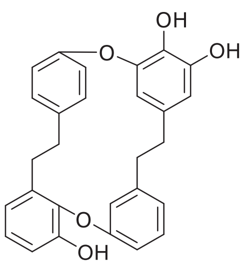


FIGURE 4 | (a) *Dumortiera hirsuta* (liverwort) (b) *Ptychanthus striatus* (liverwort).

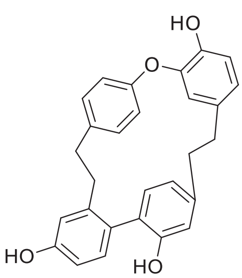
FIGURE 5 | *Marchantia polymorpha* (♀) (liverwort).

3 | Chemical Diversity of Bryophytes

Several hundred new compounds have been isolated from the liverworts and more than 40 new carbon skeletal terpenoids and aromatic compounds such as very characteristic bisbibenzyls, marchantin [marchantin A (1)], riccardin [riccardin C (2)], isoriccardin, plagiochin, isoplagiochin, neomarchantin, perrottetin, paleatin and pusilatin series were found (Asakawa 1982; Asakawa et al. 1995, 2013).

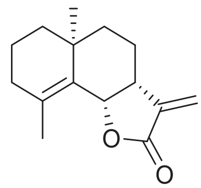


(**1**) marchantin A

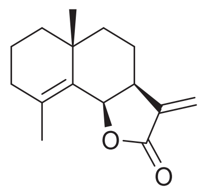


(**2**) riccardin C

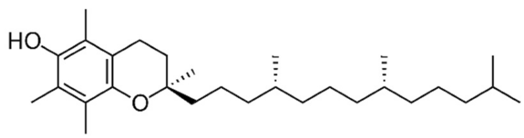
The most characteristic chemical phenomenon of the liverworts is that most of the sesqui- and diterpenoids are enantiomers to those found in higher plants. It is very noteworthy that different liverwort species of the same genus like *Frullania tamarisci* and *F. dilatata* (Frullaniaceae) each produces sesquiterpene lactone enantiomers, (+)-frullanolide (3) and (−)-frullanolide (4) (Asakawa 1982; Asakawa et al. 1995, 2013).



(**3**) (+)-frullanolide



(**4**) (-)-frullanolide



(**5**) α-tocopherol

Almost all liverworts elaborate α-tocopherol (5) and squalene. The characteristic components of the Bryophyta (mosses) are highly unsaturated fatty acids, and alkanones, such as 5,8,11,14,17-eicosapentaenoic acid, 7,10,13,16,19-docosapentaenoic acid and 10,13,16-nonadecatrien-7-yn-2-one. The presence of hydrophobic terpenoids is very rare in the Marchantiophyta. A few bitter kaurene diterpene glycosides were found in *Jungermannia* species and a number of flavonoid glycosides and their aglycones were isolated from or detected in liverworts and mosses (Asakawa 1982; Asakawa et al. 1995, 2013). The distribution of secondary metabolites in Anthoceratophyta (hornwort) is very poor. Some cinnamic acid and its derivatives as well as simple lignanes have been found in several species (Asakawa et al. 1995, 2013).

4 | Bioactivity of Secondary Metabolites Obtained From Bryophytes

The bryophytes could be explored as medicinal plants (Table 1) rather than in the human diet since they elaborate a number of

TABLE 1 | The representative bryophytes used as medicinal plants.

Species name [M: moss] [L: liverwort]	Biological activity, effects, applications
[M] *Aerobryum lanosum* (Asakawa 1982)	Antibacterial, antidotal, antirhinitis, antipyretic, For adenopharyngitis, bacteriosis, body aches Diarrhea, menstrual pain, healing wound To treat bruise, burns, fever, fractures, intermittent fever Used as medicinal plant (herbal medicine)
[L] *Conocephalum conicum* (Asakawa 1982; Asakawa et al. 1995)	Antidotal, antifungal (*Candida albicans*), antimicrobial, antipyretic For cuts, burns, fractures, gallstones, poisonous snake bites, scalds To treat boils, eczema, wounds
[M] *Funaria hygrometrica* (Asakawa 1982; Asakawa et al. 1995)	Hemostasis For athlete's foot dermatophytosis (dermatomycosis, dermomycosis), bruises, pulmonary tuberculosis, skin infection, vomitus cruentus (hepatemesis)
[L] *Marchantia polymorpha* (Asakawa 1982; Asakawa et al. 1995)	Antidotal, antifungal, antihepatic, antimicrobial, antipyretic, diuretic For cuts, fractures, open wounds, scalds, swollen tissue To treat abscesses, boils, burns, cut, eczema, jaundice of hepatitis, pulmonary tuberculosis, snake bites, wounds and external cure to reduce inflammation, reputation of cooling and cleansing the liver
[M] *Polytrichum commune* (Asakawa 1982; Asakawa et al. 1995)	Antidotal, antipyretic, diuretic, hemostasis, ldxative, For bleeding from gingivae, common cold, gynecological aid, hair growth cuts, hematemesis, inflammation, night sweats, pulmonary tuberculosis, speed up labor process during child birth, uterine prolapse To treat fever To dissolve kidney and gall bladder stones, Used as herbal tea
[M] *Rhodobryum giganteum* (Asakawa et al. 1995)	Sedative To cure angina To treat cardiovascular diseases, fever, hypertension, nervous prostration To reduce oxygen resistance by increasing the rate of flow in the aorta by over 30% to cuts Used as herbal tea
[M] *Sphagnum* species (Asakawa et al. 1995)	To relieve the itch of mosquito bite. To treat skin problems (acne, chilblain dandruff, eczema, insect bites, painful inflammation of small blood vessels in the skin, ringworm)

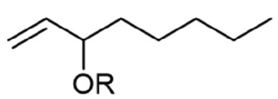
bioactive secondary metabolites. The bioactivities of the secondary metabolites obtained from bryophytes: (1) psychological, (2) diuretic, (3) allergenic contact dermatitis, (4) cytotoxic, (5) antimicrobial, (6) antifungal, (7) antiviral, (8) insect antifeedant, mortality and nematocidal, (9) antitrypanosomal, anti-leishmanial and antitrichomonal, (10) brine shrimp lethal, (11) piscicidal, (12) α-amylase and α-glucosidase inhibitory, (13) melanin production inhibitory and sedative effect, (14) antidiabetic nephropathy, (15) superoxide release inhibitory, (16) antioxidant, (17) anti-inflammatory, (18) acetylcholinesterase and tyrosinase inhibitory, (19) neurotrophic activity, (20) muscle relaxing and calcium inhibitory activity, (21) cardiotonic and vasopressin (VP) antagonist, (22) liver X-receptor (LXR) agonist, (23) cathepsins B and L inhibitory, (24) antiplatelet, antithrombin and thromboxane synthase inhibitory, (25) farnesoid X-receptor (FXR) activation, (26) vasorelaxation, (27) irritancy and tumor promoting, (28) sex pheromones of brown algae from liverworts and (29) plant growth regulating activities.

5 | Characteristic Odor

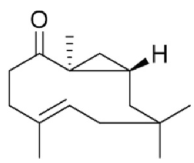
Almost all liverworts emit a characteristic odor when crushed. Lipophilic terpenoids and aromatic compounds constituted in the oil bodies are responsible for the intense sweet-woody, turpentine, sweet-mossy, fungal- and carrot-like, mushroom, or seaweed-like odor (Asakawa 1990b; Mizutani 1975; Hayashi et al. 1977). Almost all liverworts that emit a mushroom odor contain 1-octen-3-ol (6) and its acetate (7). The significant scent components potentially used as food additives are listed in Table 2.

TABLE 2 | Sent compounds from liverworts.

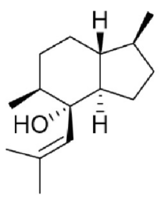
Species name	Compounds	Odor property
Cheilolejeunea imbricata (Toyota et al. 1997)	(*R*)-dodec-2-en-1,5-olide (*R*)-tetradec-2-en-1,5-olide	Milky
Colura leratii (=*Leptolejeunea leratii*) (Sakurai et al. 2020)	4-methoxystyrene	Myrrh like
Conocephalum conicum (Toyota, Saito, et al. 1997; Ghani et al. 2016)	1-octen-3-ol (6) 1-octen-3-yl acetate (7), methyl cinnamate (13)	Strong mushroomy Strong mushroomy Medicinal
Cyathodium foetidissimum (Sakurai et al. 2018; Salazar Allen et al. 2017)	4-methoxystyrene 2-aminoacetophenone	Myrrh like
Fossombronia angulosa (Ludwiczuk et al. 2008)	Dictyotene (20) Multifidene (21) dictyopterene (22)	Ocean smell
Frullania tamarisci subsp. *tamarisci*, *F. tamarisci* subsp. *obscura* (Asakawa et al. 1991; Sono 1991)	tamariscol (9)	Carnation
Leptolejeunea elliptica (Toyota et al. 1997; Sakurai et al. 2020)	5-vinylguiaoacol 4-vinylphenol *p*-cresol *m*-cresol Methyl-cinnamate (13)	Grocery Acid Green, floral Sweaty Waxy, clay
Mannia fragrans (Huneck et al. 1988)	Grimaldone (15)	Strong mossy
Marchantia paleacea subsp. *diptera* *M. paleacea* subsp. *paleacea* (Sakurai et al. 2016)	(*S*)-(−)-Perillaldehyde (14)	*Perilla frutescens* smell
Metzgeria species *Pallavicinia* sp. *Pellia endiviifolia* *Riccardia* sp. (Asakawa et al. 1995)	dimethyl sulfide (19)	Algae
Plagiochila sciophila (Asakawa et al. 1995)	Bicyclohumulenone (8)	Strong mossy
Wiesnerella denudata (Asakawa et al. 1995)	1-octen-3-ol (6), 1-octen-3-yl acetate (7), nerol (16), neryl acetate (17), linalyl acetate (18)	Sweet citrus



(6) 1-octen-3-ol, R=H
(7) 1-octen-3-yl, acetate R=Ac



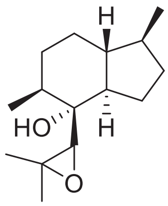
(8) (+)-bicyclohumulenone



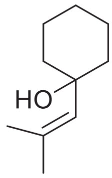
(9) (-)-tamariscol

Plagiochila sciophila elaborates (+)-bicyclohumulenone (8), which possesses an aroma reminiscent of a variety of scents based on a strong woody note, resembling the odor of patchouli, vetiver, cedar wood, irises, moss, and carnations (Asakawa et al. 1995). There are about 300–375 species of *Frullania* species belonging to the Frullaniaceae, which are epiphytic liverworts. (−)-Tamariscol (9) isolated from *Frullania tamarisci* subsp. *tamarisci, F. tamarisci* subsp. *obscura*, *F. nepalensis,* and *F. asagrayana* similarly possesses a remarkable aroma reminiscent of the woody and powdery green notes of mosses, hay, costus, violet leaves, and seaweeds. Both compounds are important in commerce, where they are used as perfumes as such, and as fragrance components in the powdery floral-, oriental bouquet-, fantastic chypre-, fancy violet- and white rose-types in various cosmetics. The synthetic epoxytamariscol (10) also emit the same odor as the original tamariscol. It is noteworthy that the *Frullania* species that produce tamariscol only grow in high mountains (Asakawa et al. 1991; Sono 1991). The total synthesis of (−)-tamariscol (9) was accomplished using commercially available 4-methoxyacetophenone in 13 steps (Tori et al. 1991). A synthetic minitamariscol,1-hydroxy-1-(2-methyl-1-propenyl)-cyclohexane (11) had a sweet mossy aroma, similar to that of tamariscol itself (Sono 1991).

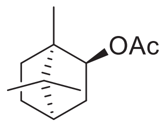
Japanese mushroom, *Tricholoma matsutake*, which has been used in Japanese cuisine, for example, consommé soup. Thus, the significant flavor of *T. matsutake* is created limitless in the whole year from this large thalloid liverwort.



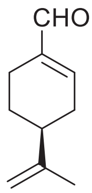
(10) epoxy tamariscol



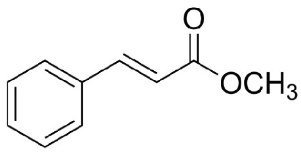
(11) mini-tamariscol



(12) (+)-bornyl acetate



(14) (*S*)-(-)-perill-aldehyde



(13) methyl cinnamate

6 | Highly Efficient Production of Mushroomy Components of *Tricholoma matsutake* From the Liverwort *Conocephalum conicum*

There are three chemotypes of the liverwort, *Conocephalum conicum*. Types 1, 2, and 3 emit (−)-sabinene, (+)-bornyl acetate (12), and methyl cinnamate (13) as the major components, respectively, and are responsible for the characteristic odors of each type (Toyota, Saito, et al. 1997). When *C. conicum* (Type 2) (Figure 6a) was stored in a glass vessel or plastic box for 1 to 9 months, the liverwort dramatically changed morphologically to form fine, and thin gametophytes as shown in Figure 6b and 6c, which appeared to be totally different plant from the original one. The stressed *C. conicum* also drastically changed its chemical composition. The chemical marker, bornylacetate, of this type gradually decreased and then methyl cinnamate (13) (35.3%, 50.0% and 50.2%) was newly produced after 3, 6, and 9 months, respectively (Ghani et al. 2016). The chemical profile of the volatile components after 6 to 9-month cultivation of *C. conicum* was almost the same as that of the most expensive

7 | Highly Efficient Production of (*S*)-(−)-perillaldehyde From the Liverwort *Marchantia paleacea* subsp. *diptera*

When the large thalloid liverwort *Marchantia paleacea* subsp. *diptera* (Figure 7a) was cultured on Nipp soil or half strength of Gamborg's B5 medium including 2% sucrose in an artificially growth cabinet at 24°C for 16 h (light) and 22°C for 8 h (dark), (*S*)-(−)-perillaldehyde (14) which is the most important aroma of *Perilla frutescens* (Lamiaceae) was elaborated in 50% yield, along 1-perillyl alcohol, shisool, limonene-10-ol, and *p*-menthen-10-al. Considering the biosynthetic pathway, only (*S*)-(−)-limonene-7-hydroxygenase may play an important role in the formation of perillaldehyde (Sakurai et al. 2016). When we cultured the same species in the same manner as mentioned earlier without any media, like sucrose, (*S*)-(−)-perillaldehyde (14) was created although it took a few months. *M. paleacea* subsp. *paleacea* also produces the same aldehyde when it was cultured in the sealed plastic box (Figure 7b). Thus (*S*)-(−)-perillaldehyde can be created limitless for a year in this simple

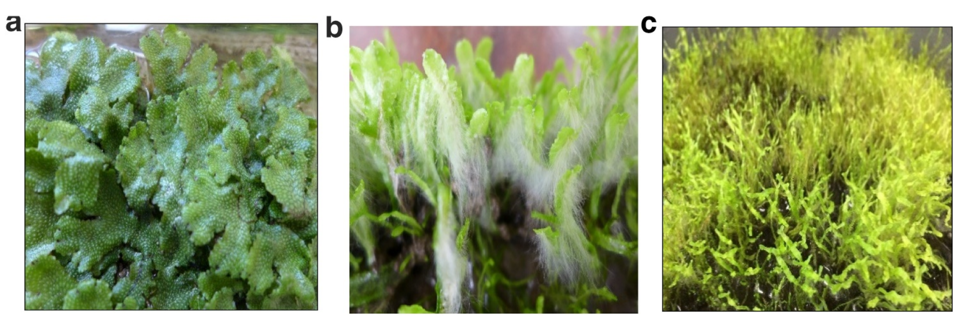


FIGURE 6 | (a) *Conocephalum conicum* (Type 2) (b) *C. conicum* (cultured for 6 months) (c) *C. conicum* (cultured for 9 months) (liverwort).

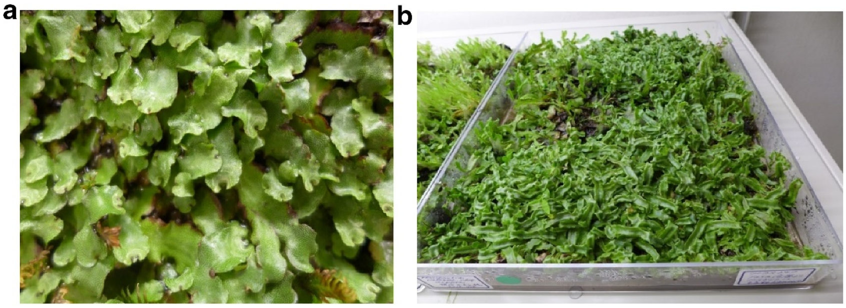
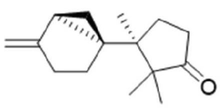


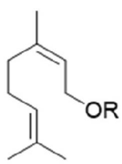
FIGURE 7 | (a) *Marchantia paleacea* subsp. *diptera* (liverwort) (b) *M. paleacea* subsp. *diptera* (cultured for 3 months).

manner (Asakawa et al. 2022) and thus both *M. paleacea* can be applied as food additive as some soup.

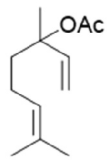
The strong, sweet mossy note of *Mannia fragrans* is attributable to grimaldone (15) (Huneck et al. 1988). The strong sweet-mushroomy scent of the ether extract of *Wiesnerella denudata* is due to (+)-bornyl acetate (12) and to a mixture of the monoterpene hydrocarbons, α-terpinene, β-phellandrene, terpinolene, α-pinene, β-pinene, and camphene. The odor of the steam distillate of *W. denudata* is weaker than that of its ether extract. The steam distillate contains α-terpinene (31%), nerol (16, 14%), neryl acetate (17, 27%), and linalyl acetate (18) but the contents of 1-octen-3-ol (6, 7%) and its acetate (7%, 2%) are lower than that of *Conocephalum conicum* (Asakawa et al. 1995).



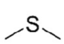
(15) grimaldone



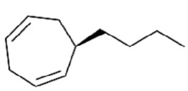
(16) nerol, R=H
(17) neryl acetate, R=Ac



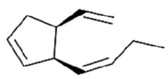
(18) linalyl acetate



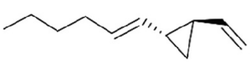
(19) dimethyl sulfide



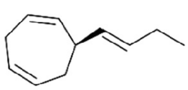
(20) dictyotene



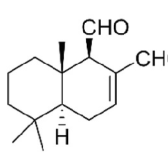
(21) multifidene



(22) dictyopterene



(23) ectocarpene



(24) polygodial

Liverworts belonging to the Metzgeriales emit ocean or marine algal like smell. When they are dried, immediately one feels this characteristic smell. The GC/MS analysis indicated that *Blasia, Metzgeria, Pallavicinia* and *Riccardia* contain dimethyl sulfide (19), which is important odor of some sea algae used in Japanese cuisine (Asakawa et al. 1995). The Greek *Fossombronia angulosa* is chemically very characteristic since it elaborates dictyotene (20), multifidene (21) and dictyopterene (22) which were all previously isolated from a brown algal source (Ludwiczuk et al. 2008). The French Polynesian liverwort, *Chandonanthus hirtellus* also produced dictyotene (20) and ectocarpene (23) (Ludwiczuk et al. 2009). Dictyotene is responsible for the ocean smell. These hydrocarbons are significant sex pheromones of marine brown algae, such as *Dictyota* species.

8 | Pungency, Bitterness and Sweet-Tasting

Some genera of liverworts, such as the *Hymenophyton*, *Lobatiriccardia, Pallavicinia*, *Pellia*, *Porella*, *Trichocoleopsis,* and *Wiesnerella* species elaborate potent pungent constituents (Asakawa et al. 1995; Asakawa 2012, 2014), which exhibit interesting biological activities, such as antibacterial, antifungal, antiviral, insecticidal, insect antifeedant and many others. Species in the genera *Anastrepta, Lophozia,* and *Scapania,* and many other stem-leafy liverworts produce intense bitter principles (Asakawa et al. 1995, 2013). In Table 3, the significant pungent, bitter and sweet bryophytes and their active compounds which possess the properties against food protection and additives are shown, *Porella vernicosa* complex (*P. arboris-vitae, P. fauriei, P. gracillima, P. obtusata* subsp. *macroloba, P. roellii* and *P. vernicosa*) contain surprisingly intense pungent substances (Asakawa 1982; Asakawa et al. 1995, 2013). *Jamesoniella autumnalis* contains an intense bitter principle whose taste resembles that of the leaf of lilac or *Swertia japonica,* or the root of *Gentiana scabra* var. *orientalis*. The strong hot taste of *Porella vernicosa* complex is due to the drimane sesquiterpene dialdehyde, (−)-polygodial (24) (Asakawa 1982; Asakawa and Aratani 1976; Asakawa et al. 2012), which is the major component of the Japanese medicinal plant, *Polygonum hydropiper,* the Malaysian *P. minus,* and the Argentinean *P. punctatum* var. *punctatum* (Polygonaceae) (Asakawa et al. 2012). The Malaysian *Polygonum minutum* and Japanese *P. hydropiper* have been used as the vegetable. Polygodial (24) is found not only in higher and liverwort plants, but also some ferns, the

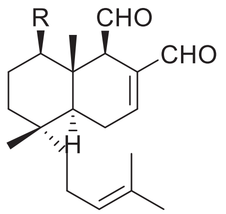
TABLE 3 | Pungent, bitter and sweet tasting substances from bryophytes.

Species name	Compound or solvent extract	Hot taste
Lobatiriccardia yakushimensis (Asakawa et al. 1985) *Pallavicinia levieri* (Asakawa et al. 1995) *Pellia epiphylla* (Asakawa et al. 2013) *Trichocoleopsis sacculata* *Pellia endiviifolia* (Asakawa et al. 1995; Hashimoto et al. 1995; Ono et al. 1996)	Sacculatal (25) 1β-hydroxysacculatal (26) 19-hydroxysacculatal (82)	Persistent hot taste
Plagiochila adiantoides *P. fruticosa,* *P. hattoriana* *P. ovalifolia* *P. pulcherima* *P. yokogurensis* and many other pungent *Plagiochila* sp. (Asakawa 1982; Asakawa et al. 1995, 2013; Hashimoto et al. 1994)	Plagiochiline A (32) Plagiochilal B (34) Furanoplagiochilal (35)	Persistent hot taste Persistent hot taste Persistent hot taste
Plagiochila yokogurensis (Asakawa et al. 1995)	Plagiochiline I (33)	Persistent hot taste
P. arboris-vitae *P. canariensis* *P. fauriei* *P. gracillima* *P. obtusata* subsp. *macroloba* *P. roellii* (Asakawa et al. 1995; Asakawa et al. 2012) *P. vernicosa* (Asakawa et al. 1995; Asakawa and Aratani 1976; Asakawa et al. 2012; Ono et al. 1992)	(−)-polygodial (24)	Persistent hot taste
Wiesnerella denudata (Asakawa et al. 1995)	tulipinolide (31)	Weak hot taste
		Bitter taste
Anastrepta orcadensis (Connolly 1990; Rycroft 1990)	Anastreptin A (48)	Potent bitter taste
Barbilophozia attenuata *B. barbata* *B. floerkei* (Connolly 1990; Rycroft 1990)	Barbilycopodin (49)	Potent bitter taste
B. floerkei (Connolly 1990; Rycroft 1990)	10-deacetoxybarbilycopodin (51)	Moderate bitter taste
Gymnocolea inflata (Huneck et al. 1983)	Gymnocolin (42)	Potent and persistent bitter taste
Jamesoniella autumnalis (Asakawa et al. 1995, 2013; Asakawa and Ludwiczuk 2018)	Jamesoniellide A (36) Jamesoniellide C (37) Jamesoniellide E (38) Jamesoniellide F (39) Jamesoniellide H (40) Jamesoniellide I (41)	Potent and persistent bitter taste
Jungermannia infusca (Nagashima et al. 1990)	Infuscaside A (43) Infuscaside B (44) Infuscaside C (45) Infuscaside D (46) Infuscaside E (47)	Potent persistent bitter taste
Scapania undulata (Rycroft 1990)	Scapanin A(50)	Potent bitter taste
[Moss]		**Sweet taste**
Fissidens species (Asakawa and Ludwiczuk 2018)	Ethanol	Strong sweet
Rhodobryum giganteum (Asakawa and Ludwiczuk 2018)	Ethanol	Moderate sweet

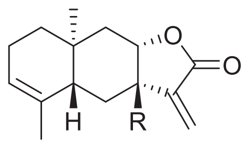
Argentinean *Thelypteris hispidula* and the New Zealand *Blechnum fluviatile* as major components (Asakawa et al. 1995).

The sacculatane diterpene dialdehyde, sacculatal (25), 1β-hydroxysacculatal (26), together with several sacculatane-type diterpenoids, 18- (27) and 19-hydroxysacculatals (28), and two eudesmanolides, diplophyllolide (29) and *ent*-7-hydroxydiplophyllolide (30), and a germacranolide, tulipinolide (31), which possess potent pungency were isolated from *Pellia endiviifolia* (Figure 8) and *Trichocoleopsis sacculata, Chiloscyphus polyanthos,* and *Wiesnerella denudata,* respectively (Asakawa 1982; Asakawa et al. 1995, 2013; Hashimoto et al. 1995).

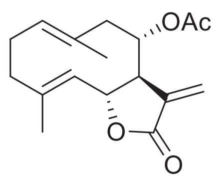
When one chews a whole plant of the stem-leafy liverworts, *Plagiochila asplenioides, P. fruticosa, Plagiochila ovalifolia* (Figure 9), and *Plagiochila yokogurensis* which contain plagiochiline A (32) and plagiochiline I (33), a potent pungent taste slowly develops. It is suggested that both compounds might be converted into the pungent unsaturated dialdehyde by human saliva. In fact, as shown in Chart 1, treatment of plagiochiline A (32) with amylase in phosphate buffer or with human saliva produces two strong pungent components, plagiochilal B (34) whose partial structure is similar to that of the pungent drimane-type sesquiterpene dialdehyde, polygodial (24), and furanoplagiochilal (35) (Hashimoto et al. 1994).



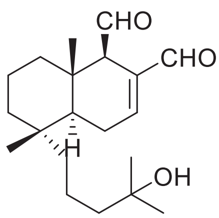
(**25**) sacculatal, R=H
(**26**) 1β-hydroxy-sacculatal, R=OH



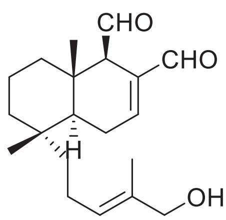
(**29**) diplophyllolide, R=H
(**30**) *ent*-7 -hydroxy-diplophyllolide, R=OH



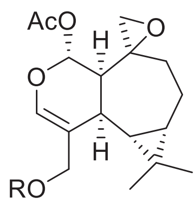
(**31**) tulipinolide



(**27**) 18-hydroxy-sacculatal



(**28**) 19-hydroxy-sacculatal



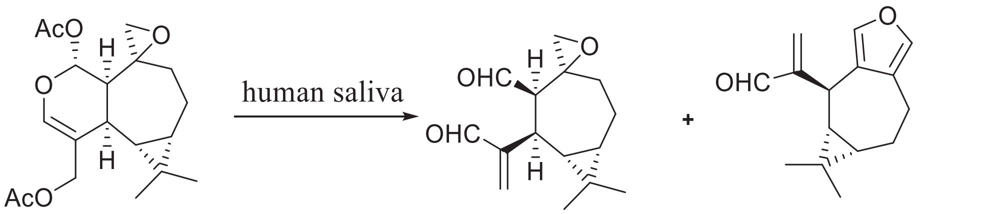
(**32**) plagiochiline A, R=Ac
(**33**) plagiochiline I, R=H

The hot taste of *Pallavicinia levieri* and *Lobatiriccardia yakushimensis* (=*Riccardia robata* var. *yakushimensis*) which belong to the Metzgeriales, is also due to sacculatal (25) (Asakawa et al. 1985). Polygodial (24) and sacculatal (25) have been obtained from cell suspension cultures of *Porella vernicosa* and *Pellia endiviifolia*, respectively (Ono et al. 1992; Ono et al. 1996).

Most of the species belonging to the Lophoziaceae produce bitter substances. *Jamesoniella autumnalis* is the king of bitter tasting liverwort, since one chews it, the bitter taste intensely remains on tongue for at least 5 h. This taste is due to a complex mixture of clerodane diterpenoids, such as furanoclerodane lactones (36–41) (Asakawa et al. 1995, 2013; Asakawa and Ludwiczuk 2018).

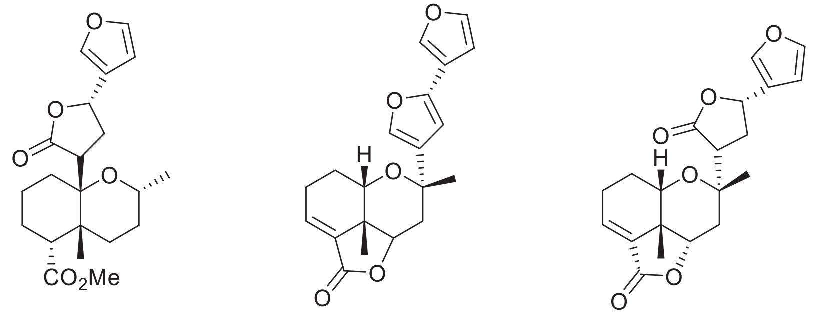
FIGURE 8 | *Pellia endiviifolia* (liverwort).

FIGURE 9 | *Plagiochila ovalifolia* (liverwort).

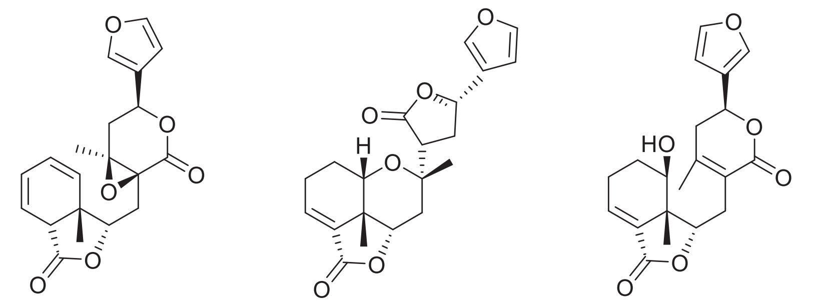


(**32**) plagiochiline A (**34**) plagiochilal B (**35**) furanoplagiochilal

CHART 1 | Formation of two pungent 2,3-secoaromadendranes, plagiochilal B (34) and furanoplagiochilal (35) from plagiochiline A (32) by human saliva.

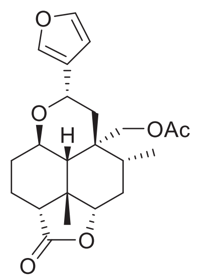


(**36**) jamesoniellide A (**37**) jamesoniellide D (**38**) jamesoniellide E

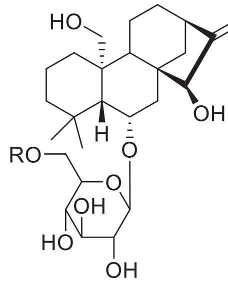


(**39**) jamesoniellide F (**40**) jamesoniellide H (**41**) jamesoniellide I

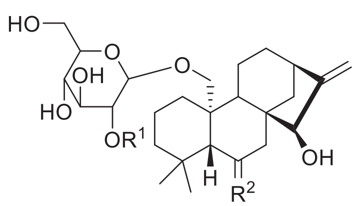
Gymnocolea inflata is persistently bitter, and induces vomiting when one chews a few leaves for several seconds. This surprisingly intense bitterness is due to the clerodane diterpene lactone, gymnocolin A (42) (Huneck et al. 1983). *Jungermannia infusca* has an intense bitter taste which is due to the presence of the infuscasides A-E (43–47) (Nagashima et al. 1990). These metabolites were the first diterpene glycosides isolated from liverworts. *Anastrepta orcadensis*, *Barbilophozia lycopodioides,* and *Scapania undulata* are also bitter liverworts from which highly oxygenated, bitter diterpenoids, anastreptin A (48), barbilycopodin (49) (Connolly 1990; Rycroft 1990), and scapanin A (50) (Nishiki et al. 2007) were isolated, respectively. 10-Deacetoxybarbilycopodin (51) from *Barbilophozia floerkei* also showed moderate bitter taste (Connolly 1990; Rycroft 1990).



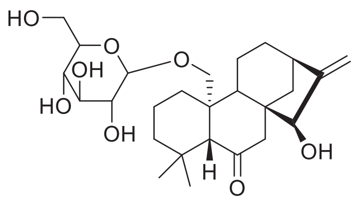
(**42**) gymnocolin A



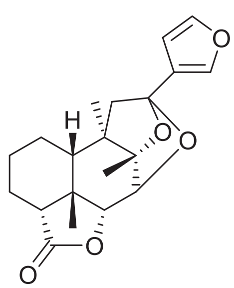
(**43**) infuscaside A, R=Ac
(**47**) infuscaside E, R=H



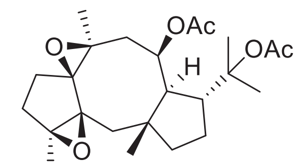
(**44**) infuscaside B, R^1=Ac, R^2=O
(**45**) infuscaside C, R^1= Ac, R^2=H_2



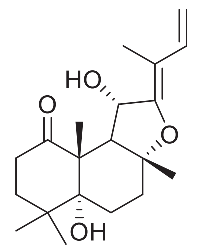
(**46**) infuscaside D



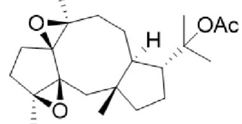
(**48**) anastreptin A



(**49**) barbilycopodin



(**50**) scapanin



(**51**) 10-deacetoxy-barbilycopodin

9 | Application of Bryophytes to Foods, Food Additives and Beverages

A large number of bryophyte were chemically analyzed and more than 1000 of phytochemicals found. Especially bisbibenzyls such as marchantin series possessing multi-biological activity, potent antibacterial and antifungal as well as cytotoxic, antioxidant activity were obtained from *Marchantia* species. As a large amount of marchantin A can be obtained from the cultured *Marchantia polymorpha* and *M. paleacea* subsp. *diptera* or the powdered *Marchantia* species be used as food additives directly because marchantin A are not toxic against mammals. *Marchantia polymorpha* has been used for a long time as one of medicinal liverworts in Far East because it contained multiple bio- and pharmacological activity.

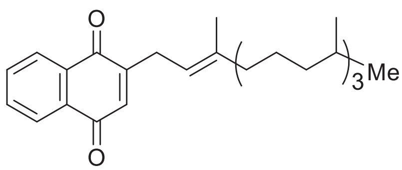
Tempura made of the fresh thallus of *M. polymorpha* prepared in the Japanese restaurant showed a good taste like sea-algae. Thus *M. polymorpha* used in China as the medicinal plant will be widely used as human food materials. The powder of *M. polymorpha* and *M. paleacea* subsp. diptera is used as herbal tea. Our success of highly efficient production of mushroomy fragrant components of the most expensive Japanese mushroom, *Tricholoma matsutake*, from the large thalloid liverwort, *Conocephalum conicum*, and of perillaldehyde from *Marchantia paleacea* subsp *diptera*, using plant engineering system now link as the sources of food additives for consome soup and the fresh thallus of the former liverwort has been used directly for Hamburger and Tempura cuisine in Japanese restaurants. As mentioned above, many liverworts produce hot-tasting substances which could be used as spices for foods and as food preservatives effect because they also possess potent antimicrobial and antifungal activities.

There are several sweet mosses, such as *Fissidens* and *Rhodobryum* species. Almost all *Fissidens* species produce a potent sweet taste. However, the true sweet principles have not yet been isolated from or detected in these special mosses. The isolated products from these mosses could become the potentially new non-calorie sweet principle for the human diet (Asakawa and Ludwiczuk 2018).

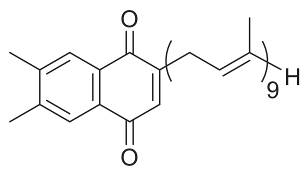
As mentioned earlier, several components isolated from liverworts, possessed commercially significant value in cosmetic fields. Bicyclohumulenone (8) and tamariscol (9) are such examples; they can apply as fragrant components itself, and as foods additives as well as inner sprays and deodorants. Steam vapor spread from humidifiers including essential oils of the above-mentioned liverworts may play important role in decrease the patients infected by COVID-19 virus to cover its spike protein and the other viruses.

As feeds for livestocks and foods for humans, bryophytes are very useful because they contain some vitamins, and minerals and fibers. The mosses, *Barbella pendula*, *B. enervis*, *Floribundaria nipponica*, *Hypnum plumaeforme*, and *Neckeropsis nitidula,* and some of the liverworts, contain quantitatively much vitamin B_2. Chickens and puppies fed a diet including these powered bryophytes gained more weight than did control animals. The supplement did not cause any sickness or distaste. Since there are more than 14,000 species of mosses, more species possessing vitamin B_2 will be undoubtedly discovered.

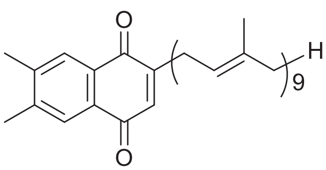
Nishiki et al. analyzed 700 liverworts chemically, and found that almost all of them contained α-tocopherol (5) and squalene (Nishiki et al. 2007). The mosses *Atrichum undulatum* and *Mnium hornum,* produce α-tocopherol. The liverworts, *Marchantia polymorpha* and *Pellia endiviifolia,* and the above two mosses produce vitamin K (52), plastoquinone (53), plastohydroquinone (54), and α-tocoquinone (55) (Asakawa 1990b).



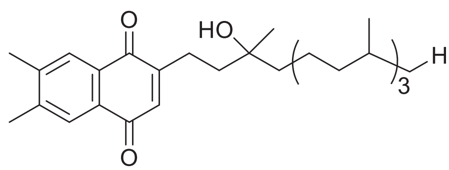
(**52**) vitamin K



(**53**) plastoquinone



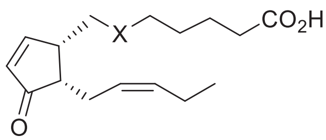
(**54**) plastohydoquinone



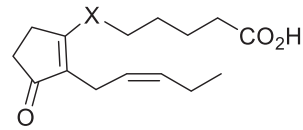
(**55**) α-tocoquinone

compound flavor to perfumes and the other cosmetics as well as deodorant spray (Asakawa et al. 1995). To refer the pleasant odor of each species of liverworts we tried to obtain their essential oils and solvent extracts. The essential oils, and solvent extracts from many liverworts, for example, *Marchantia polymorpha*, *Pellia endiviifolia*, *Plagiochila* and *Porella* species indicated the strong antimicrobial and antifungal properties. Not only the isolated compounds but also essential oils and solvent extracts could be used as preservation of foods and

Prostaglandin-like fatty acids (56–61) have been found in some mosses, such as *Dicranum scoparium*, *Dicranum japonicum* and *Leucobryum* species (Ichikawa et al. 1983, 1984). These, and other highly unsaturated fatty acids from bryophytes are viscous liquids, and it is thought that they are instrumental protecting herbivorous animals living in very cold places from the cold (Prins 1981). Such unsaturated fatty acids from many mosses (Lu et al. 2019), like those obtained from fish oils, play an important role as antioxidants in human bodies.



(**58**) 4-cyclopentenone-(2*S*),(2'*Z*)-pentenyl-(3*S*)-octanoic acid, X= $-(CH_2)_2-$



(**59**) 2-cyclopentenone-2-[(2'*Z*)-pentenyl]-3-(2''-octynoic acid), X= $-CH_2-C\equiv C-$

(**60**) 2-cyclopentenone-2-[(2'*Z*)-pentenyl]-3-(2''-octenoic acid, X= $-CH_2CH{=}CH-$

(**61**) 2-cyclopentenone-2-[(2'*Z*)-pentenyl]-3-octanoic acid, X= $-(CH_2)_3-$

10 | Application of Bryophytes to the Phytomedicines

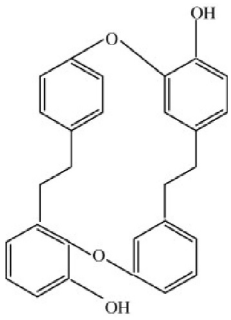
The mosses, *Rhodobryum giganteum* and *R roseum* are charming species because the crude extracts process neuro and cardiovascular protect effects. *Polytrichum* species are also beneficial species because of the presence of anticancer products. There are many other species which have been used as the traditional crude drugs in each country although their bioactive compounds are unknown. A number of the crude extracts and isolated compounds from bryophytes have been screened against various human cancer cell lines. Several of them possess powerful cytotoxicity against such cancer cell lines (Asakawa 2020).

One of the most important bryophytes is the liverwort, *Marchantia polymorpha* which contains structurally stable marchantin A (1) as a large amount in the crystal state and it shows multiple bio- and pharmacological activity, like cytotoxicity as discussed earlier. Marchantin A (1) and C (62) display tubulin polymerization inhibitory activity and the former bis-bibenzyl possesses potent antitrypanosomal, antiinfluenza and muscle relaxation activity. Generally, liverworts are tiny plant group, however, *M. polymorpha* is very easily to collect in field and culture in the green house and can obtain 500–1000 kg of the fresh material (Figures 10 and 11) (Asakawa et al. 2022).

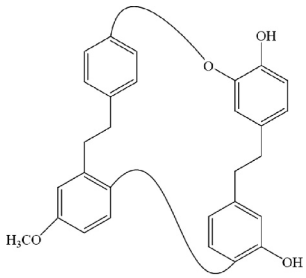
The major component of *M. paleacea* subsp. *diptera* is also marchantin A, whose content is much higher than *M. polymorpha* and one can easily collect it in the mountain. As a large amount of marchantins was obtained from these thalloid liverworts, it is very easy to modify their original structures chemically or enzymatically to give the different types of bioactive compounds from the original ones. Such application was carried out to the different marchantins, riccardins, and plagiochins series by Asakawa's and Lou's groups. These macrocyclic bis-bibenzyls possess the same tubulin polymerization inhibitory activity as that of paclitaxel, clinically used as anticancer drug and antimalarial drugs because marchantin A showed strong antitrypanosomal activity. Although active compounds have not yet been isolated, biocream prepared from *n*-hexane crude extract of the African liverwort *Marchantia debilis* cured the bacterial infected skin disease completely after 2 weeks of treatment of that ointment (Yongabi et al. 2016), In Africa, there are still many bacterial and fungal infected skin disease, therefore the further investigation of the isolation of active compounds from *M. debilis* and activity mechanisms are necessary.

FIGURE 10 | *Marchantia polymorpha*.

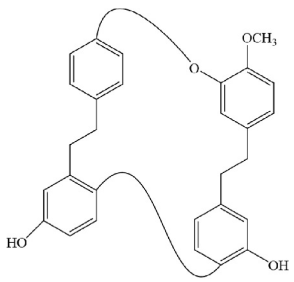
FIGURE 11 | *Marchantia polymorpha* (♀) (liverwort) (huge habitat on wet soil).



(**62**) Marchantin C



(**63**) riccardin A



(**64**) riccardin F

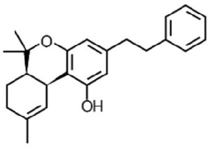
Furthermore, riccardin C (2) obtained from the liverworts, *Reboulia hemisphaerica* (Figure 12) (Asakawa and Matsuda 1982) and *Blasia pusilla* which showed LXRα agonist and LXRβ antagonist effects, possessed the property of elevation of high-density lipoprotein cholesterol and decreased triglycerides in vitro product for human body, and in vivo using mouse (Tamehiro et al. 2005). From 1.25 kg of the dried liverwort *R. hemispaherica*, 1 g of pure riccardin C (2) was obtained (Asakawa and Ludwiczuk 2018). Riccardin C (2) also enhances cholesterol efflux from THP-1. Riccardin C (2) and its seven *O*-methyl derivatives, including riccardin A (63) and riccardin F (64), were synthesized. According to a preliminary structure-activity relationship study of these seven *O*-methylated riccardins, the three phenolic hydroxy groups of riccardin C (2) were determined as being indispensable for binding to the LXR receptor (Hioki et al. 2009). Thus *R. hemisphaerica* could be also used as some food additives or beverage materials since riccardin C does not show any side effect against mammals.

FIGURE 12 | *Reboulia hemisphaerica* (liverwort).

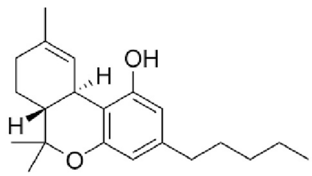
FIGURE 13 | *Radula perrottetii* (liverwort).

Another promising clinically used compound is perrottetinene (65) which has been isolated from the Japanese and New Zealand liverworts, *Radula* species initially (Figure 13). The structure of perrottetinene (65) resembles tetrahydrocannabinoid (66) obtained from *Cannabis sativa.* Not surprisingly PET showed the same psychoactivity and powerful antiinflammatory activity. It is very easy to cultivate the *Radula* species for a whole year, thus PET is one of the potentially important clinical drugs.

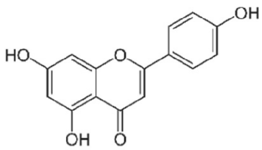
Diuretic activity of the Chinese *M. polymorpha* was suggested by Ding (Ding 1982). Xiao et al. [247] described that 80% ethanol extract containing flavones, apigenin (67), and luteolin (68) which is seen as yellow pigment of sporophytes in Figure 4c, and their glucuronides, and quercetin (69) showed significant increase of the volume of urine of rats.



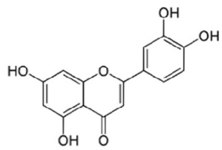
perrottetinene (**65**)



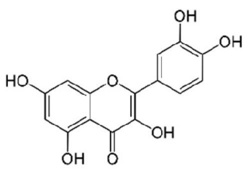
tetrahydrocannabinoid (**66**)



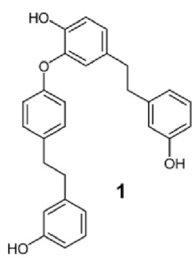
(**67**) apigenin



(**68**) luteolin



(**69**) quercetin



(**70**) perrottetin E

11 | Conclusion

The bryophytes are terrestrial green spore-forming plant and there are 23,000 species in the world. They are divided to three classes, the Bryophyta (mosses), Marchantiophyta (liverworts) and Anthocerotophyta (hornworts) among which the Marchantiophyta species have chemically been studied widely because they contain cellular oil bodies which are easily extracted with organic solvents to obtain a large number of secondary metabolites. Since 1903, about one thousand references concerning phytochemicals of bryophytes are available [1,2.7] and more than two thousand of secondary metabolites many of which show various biological activity were isolated from or detected in bryophytes and their structures elucidated as mentioned earlier.

FIGURE 14 | Culture room of liverworts.

The crude extracts and essential oils from liverworts are chemically complex since they contain various lipophilic terpenoids, aromatic compounds and polyketides, which are used as the chemical markers of each genus and family of liverworts. Among the secondary metabolites, bis-bibenzyls and bibenzyls are the most characteristic chemical components of liverworts although only two bis-bibenzyls, riccardin C (2) and perrottetin E (70) have been found in the fern and higher plants, *Primula* species. Bis-bibenzyls possess not only characteristic structures but also various bio- and pharmacological activity, such as muscle relaxant, antioxidant, tubulin polymerization and NO production inhibition, antiviral, antimicrobial, antifungal, anti-trypanosomal and among others. Only a few percents of bryophytes have chemically been studied since 1903, because bryophytes are very tiny, difficult to identify, and thought to be useless as human diet. However, the recent plant engineering technique, some liverworts, such as the thalloid liverworts, *Conocephalum conicum*, *Marchantia paleacea* subsp. *diptera* and *M. polymorpha* and the stem-leafy ones, *Bazzania japonica* and *Radula perrottetii*, are very easily to cultivate for the production of a large number of secondary metabolites containing cytotoxic bis-bibenzyls and characteristic sent substances (Figure 14). Now the fresh thallus of *C. conicum* have been used as foods for hamburger and consommé soup in Japan although bryophytes have been neglected for a long time as the food materials.

Some mosses produce vitamin B_2 and many kinds of highly unsaturated fatty acids and lipid (triglycerides) containing highly unsaturated alkane moiety. Thus, further strategy is to focus on secondary metabolites which could be applied as some diets to cattles and cultured fishes. The metabolites of liverworts should be applied to create clinical drugs because they possess some potentially important several metabolites in various liverworts, particularly bis-bibenzyls such as marchantin and isoplagiochin series, which possess potent cytotoxicity against numerous human cancer cell lines and involves interference with the normal break down of microtubules during cell division of cancer cells, like clinical anticancer drug, paclitaxel (taxol) and docetaxel. A bibenzyl cannabinoid, perrottetinene (70) from the peculiar liverwort, *Radula* species possesses the potential drug used clinically since it shows the exactly same psycho- and anti-inflammatory activity as those of well-known drug, tetrahydrocannabinoid (THC).

Author Contributions

Yoshinori Asakawa, investigation and wrote the original draft of the manuscript. Jianbo Xiao, reviewed and revised the manuscript.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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