



## Bryophytes as a source of bioactive volatile terpenoids – A review

Agnieszka Ludwiczuk<sup>a,\*</sup>, Yoshinori Asakawa<sup>b</sup>

<sup>a</sup> Department of Pharmacognosy with Medicinal Plant Unit, Medical University of Lublin, 1 Chodzki Str., 20-093, Lublin, Poland

<sup>b</sup> Institute of Pharmacognosy, Tokushima Bunri University, 180 Yamashiro-cho, Tokushima, 770-8514, Japan



### ARTICLE INFO

#### Keywords:

Bryophytes  
Liverworts  
Terpenoids  
Cytotoxicity  
Phytotoxicity  
Antifungal

### ABSTRACT

Bryophytes, phylogenetically placed between the algae and pteridophytes, are divided into three classes: mosses, liverworts, and hornworts. Traditional system of medicine throughout the world has been utilizing this group of plants to treat various ailments. One of the outstanding features of these spore forming plants is their chemistry, especially that of the liverworts. Liverworts have yielded a rich array of terpenoids, especially sesqui- and di-terpenoids. Many of these compounds are characterized by unprecedented structures, and some have not been found in any other plants, fungi or marine organisms. Among the bryophytes, the chemical constituents of liverworts and their biological activity have been studied in the most detail. In this review the chemistry of the terpenoids found in bryophytes have been presented, and their phytotoxic, antimicrobial, antifungal, cytotoxic, anti-inflammatory, piscicidal, insect repellent, antileishmanial and antitrypanosomal activities.

### 1. Introduction

The plants known as 'bryophytes' comprise the second largest group of plants after angiosperms. These are divided into three classes, mosses (Bryophyta), liverworts (Marchantiophyta), and hornworts (Anthocerotophyta) (Asakawa et al., 2013a). Bryophytes are considered to be the oldest terrestrial plants, and among them it has been suggested that the liverworts are the earliest embryophyte lineage, and are the sister of all other land plants (Wellman et al., 2003; Qiu et al., 2006). As the first inhabitants of terrestrial habitats they were frequently exposed to adverse environmental conditions, such as pathogen attack, insect predation, and UV injury (Xie and Lou, 2009; Whitehead et al., 2018). In general, bryophytes display a low morphological complexity, but a high degree of chemical diversification (Asakawa et al., 2013a, 2013b; Ludwiczuk and Asakawa, 2014), suggesting that secondary metabolites, and especially terpenoids, may play an important role in bryophyte-environment interactions (Whitehead et al., 2018; Chen et al., 2018). Such 'chemical weapons' are necessary for these small plants, since they lack mechanical protection like higher vascular plants. Bryophytes are colonial organisms, that are usually grown in humid locations where they form mats and cushions over soil, rocks, or on the trunks and leaves of vascular plants. Many kinds of invertebrates inhabit such bryophyte colonies. Despite this, there is little evidence of feedant activity on the bryophytes. These small, ubiquitous plants are also not infected by either bacteria or fungi (Asakawa, 2008; Chen et al., 2018). Bryophytes are considered to be nutritionally useless to humans. In fact,

no references concerning their use as foods for humans have been seen. However, a number of bryophytes have been widely used as medicinal plants in China and North America as decoctions or crushed, and the resulting powder mixed with oil has been used to cure burns, bruises, external wounds, fractures, snake bites, convulsions, uropathy, pneumonia, neurasthenia, etc. (Glime, 2007; Harris, 2008; Asakawa, 2008; Asakawa et al., 2013c).

Terpenoids have been reported to be involved in many biological and ecological processes (Cheng et al., 2007; Holopainen et al., 2013). Among the bryophytes, the liverworts are extremely rich source of terpenoids, however, a few mosses and hornworts are also known to produce such kind of components. Several substances isolated from bryophytes were shown to be phytotoxic, inhibiting germination and growth of vascular plants in standard lab tests. This toxicity inspired the search of other valuable compounds with antibacterial, antifungal, anti-inflammatory, cytotoxic, or insect repellent activities (Asakawa, 1982, 1995, 2008; Asakawa et al., 2013a; Chen et al., 2018).

### 2. Chemical diversity of terpenoids present in bryophytes

#### 2.1. Terpenoids in liverworts

Liverworts (Marchantiophyta) are plants that produce a wide array of biologically active secondary metabolites, and among them terpenoids are the most abundant. These compounds are accumulated in the oil bodies, which are a prominent and highly distinctive organelle

\* Corresponding author. Department of Pharmacognosy with Medicinal Plant Unit, Medical University of Lublin, 1 Chodzki Str, 20-093, Lublin, Poland.  
E-mail address: [aludwiczuk@pharmacognosy.org](mailto:aludwiczuk@pharmacognosy.org) (A. Ludwiczuk).

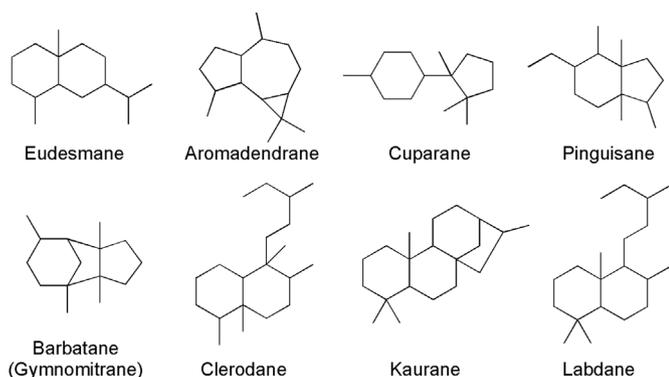


Fig. 1. Common sesquiterpene and diterpene skeletons found in the liverworts.

uniquely found in liverworts. Over the last 40 years, more than 1600 compounds belonging to the terpenoids have been reported from this plant group (Asakawa, 1982, 1995; Asakawa et al., 2013a).

The most diverse and biggest groups are sesquiterpenoids. These belongs to more than 60 different skeletal groups, among which the eudesmane and aromadendrane skeletons are most prevalent. Others, like cuparane, pinguisane and barbatane are also quite common (Fig. 1). Liverworts are plants in which one can find relatively rare groups of naturally occurring compounds. These are *seco*-africanes (1, 2), noraristolanes (3, 4), 1,10-*seco*- (5, 6) and 2,3-*seco*-aromadendranes (7, 8), *seco*-cuparanes (9), tridensanes (10), pinguisanes (11, 12), ricciocarpanes (13, 14), neotrifaranes (15), chenopodanes (16, 17), and riccardiphanes (18, 19), among others (Fig. 2) (Asakawa et al., 2013a,b; Ludwiczuk and Asakawa, 2014). Many of the sesquiterpenoids

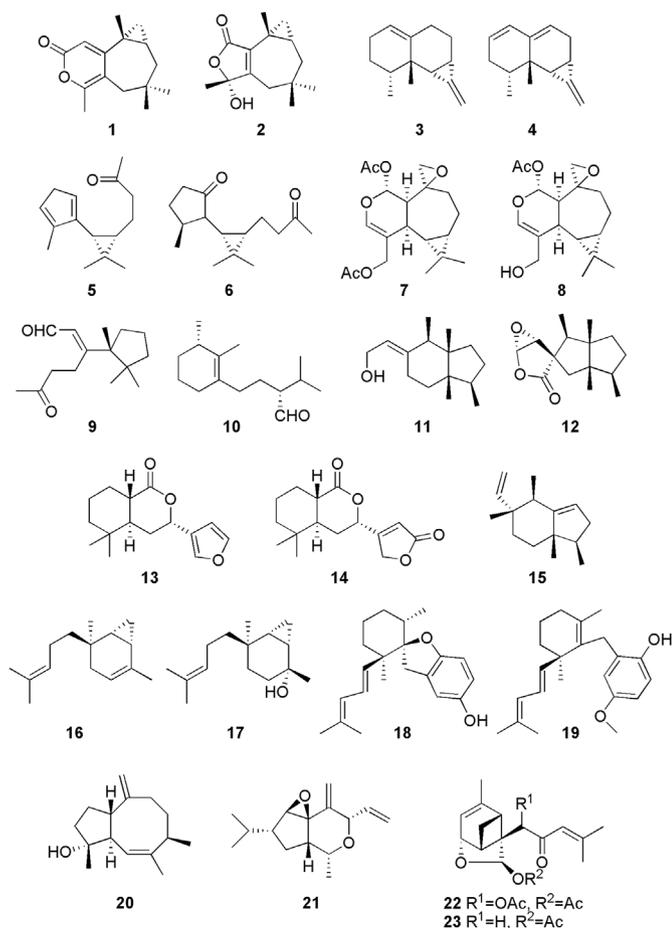


Fig. 2. Rare naturally occurring sesquiterpenoids found in the liverworts.

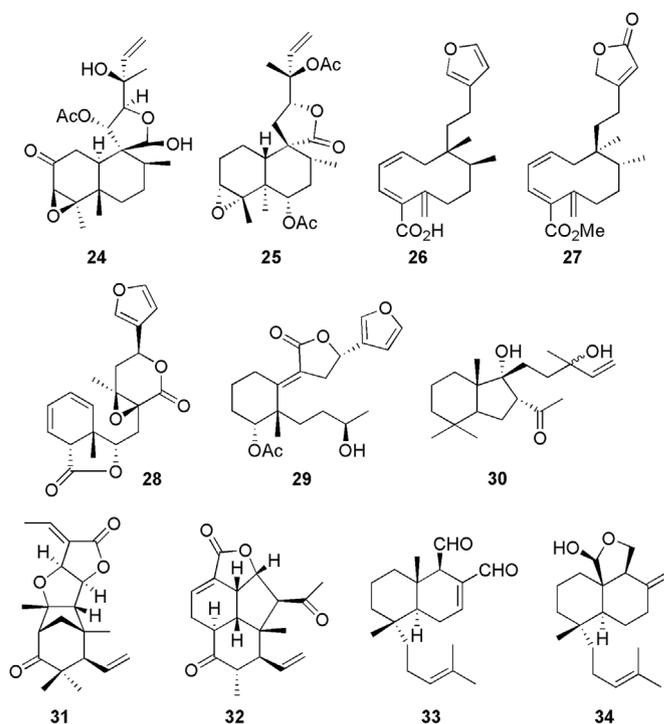


Fig. 3. Representatives of diterpenoids found only in the liverworts.

occurring in the liverworts are species specific. An interesting example is the occurrence of dumortane-type compounds (e.g. 20) in *Dumortiera hirsuta* in Argentinean, South African and Indonesian specimens or hodgsonoxanes (e.g. 21) in *Lepidolaena hodgsoniae* characteristic for New Zealand and unusual bergamotanes, clavigerins (e.g. 22, 23) occurring only in the New Zealand *Lepidolaena clavigera* (Fig. 2) (Chen et al., 2018).

Liverworts are also rich sources of a number of different skeletal diterpenoids. The most prevalent are clerodane, kaurane and labdane skeletons (Fig. 1). Compounds of spiroclerodane (24, 25), 5,10-*seco*-clerodane (26, 27), 9,10-*seco*-clerodane (28, 29), infuscane (30), *abeo*-labdane (31, 32), and sacculatane (33, 34) types are representatives of diterpenoids found only in the liverworts (Fig. 3). Among rare naturally occurring diterpenoids, the liverworts biosynthesize dolabellanes (35, 36), fuscocanones (37), cembranes (38), vibsanes (39), neodenduranones (40), visciccanes (41), and prenyl guaianes (42) (Fig. 4) (Asakawa et al., 2013a,b; Ludwiczuk and Asakawa, 2014).

A characteristic structural phenomenon of liverwort constituents is that most sesqui- and diterpenoids are enantiomers of those found in higher plants, although there are a few exceptions such as compounds in the germacrane and guaiane classes. The liverwort, *Reboulia hemisphaerica* produces (+)-thujopsene (43), while (–)-enantiomer (44) is a major component of cedar wood essential oil. *ent*-Verticillanes, e.g. (–)-verticillol (45) are characteristic components of the liverwort *Jackiella javanica*. The enantiomer (46) of compound 45 was found as a constituent of conifer tree. (+)-Verticillanes are also present in the higher plant belonging to genus *Bursera* (Fig. 5) (Asakawa et al., 2013a).

Some liverwort species emit intense fragrant odor on being crushed. Such a fragrance is generally due to monoterpenoids. Our previous study showed that these are usually present in liverworts belonging to order Marchantiales (complex thalloid liverworts). The most characteristic fragrant compounds are  $\alpha$ - (47) and  $\beta$ -pinene (48), limonene (49), and bornyl acetate (50) (Fig. 5) (Ludwiczuk et al., 2008; Ludwiczuk and Asakawa, 2015).

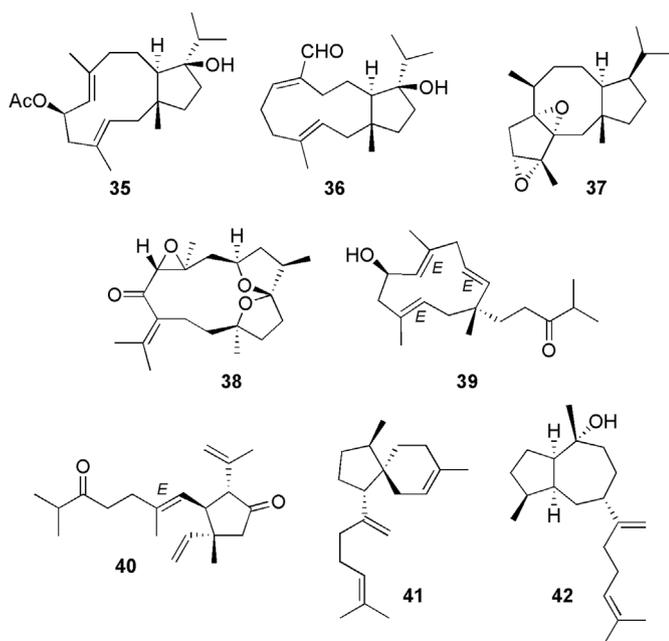


Fig. 4. Rare naturally occurring diterpenoids found in the liverworts.

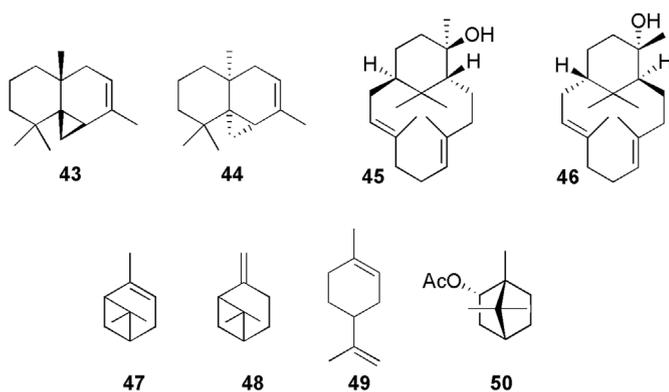


Fig. 5. Examples of enantiomers found in the liverworts and vascular plants (43–46) and most frequently occurring monoterpenoids (47–50).

## 2.2. Terpenoids in mosses and hornworts

It has been considered for a very long time that liverworts are not chemically related to mosses and hornworts because of the absence of oil bodies. However, there is some scientific evidence on the presence of terpenoids in these two bryophyte groups. The volatile terpenoids were detected in mosses including *Mnium*, *Plagiomnium*, *Homalia*, *Plagiothecium* and *Taxiphyllum* species (Asakawa, 1995; Asakawa et al., 2013a), and in the hornworts from *Anthoceros* species (Sonwa and König, 2003; Xiong et al., 2018).

The most common monoterpene detected in mosses is  $\beta$ -cyclocitral (51). The other compounds, e.g.  $\alpha$ - (47) and  $\beta$ -pinene (48), limonene (49), and camphor (52) were also detected as frequent constituents (Saritas et al., 2001). The Japanese *Plagiomnium acutum* produces *ent*-sesquiterpene hydrocarbons,  $\beta$ -cedrene (53),  $\alpha$ -cedrene (54),  $\alpha$ -acoradiene (55) and dolabellane diterpenoid, (+)-dolabella-3,7-dien-18-ol (59), which have also been found in liverworts (Toyota et al., 1998a). The three new sesquiterpene hydrocarbons, (+)-10-*epi*-muurolo-4,11-diene (56), (–)-1,2-dihydro- $\alpha$ -cuparenone (57), and (+)-dauca-8,11-diene (58), were isolated as major components from the essential oil of *Mnium hornum* and *Plagiomnium undulatum* by preparative GC (Saritas et al., 2001). Two pimarane-type diterpenoids, momilactones A (60) and B (61) were isolated from the moss *Hypnum*

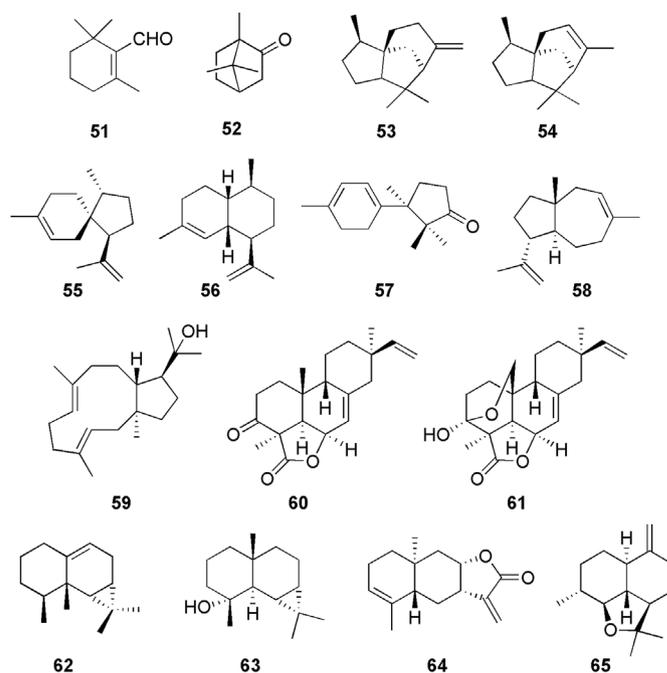


Fig. 6. Selected mono-, sesqui-, and diterpenoids found in mosses and hornworts.

*plumaeforme*. Both components were previously identified as phytoalexins in rice (Fig. 6) (Nozaki et al., 2007).

There is almost no data concerning the occurrence of terpenoids in hornworts. Sonwa and König (2003) identified several kinds of common mono-, sesqui-, and diterpenoids in the essential oil of the hornwort *Anthoceros caucasicus*. The GC/MS analysis showed that limonene (49) was the major component among monoterpenoids. In the analyzed essential oil sesquiterpenoids, e.g. aristolene (62), maaliol (63), diplophyllolide (64) and veticadinoxide (65) were detected (Fig. 6) (Sonwa and König, 2003). Xiong and coworkers (2018) also showed the presence of common mono- and sesquiterpenoids in another two *Anthoceros* species, *A. punctatus* and *A. agrestis*.

## 3. Bioactivity of volatile terpenoids present in the bryophytes

The development of land plants is dependent on interactions with other organisms, including microbes, fungi, herbivores, but also with the other plants with which they are competing for space and nutrients. The secondary metabolites, and especially terpenoids pay an important role in plant evolution and ecology. These components also show a wide array of biological activities. This section provides data concerning toxicity of terpenoids isolated from bryophytes, with particular emphasis to their phytotoxicity, antimicrobial and antifungal activity, activities on insects and molluscs, piscicidal activity, antileishmanial and antitrypanosomal activity, as well as cytotoxicity, anti-inflammatory, and CNS activity. The summary of bioactive terpenoids occurring in bryophytes (liverworts, mosses) is presented in Table 1.

### 3.1. Plant growth inhibitory activity

It is well known that higher plants do not want to grow around bryophytes. It has been demonstrated that bryophyte carpets showed inhibitory effects on the emergence of seedlings of other plants (Zamfir, 2000). van Tooren (1990) found that the numbers of emerging seedlings of angiosperms were reduced up to 30% in the presence of a bryophyte layer. Asakawa (1982) reported that most crude extracts of bryophytes, especially those containing pungent substances, show inhibitory activity against germination and root elongation. Several plant

**Table 1**  
Bioactive volatile terpenoids isolated from liverworts and mosses.

Activity	Terpenoids	Species	References	
Phytotoxicity	(–)-Polygodial (66)	<i>Porella</i> spp.	Asakawa, 1982	
	(–)-Isobicyclogermacrene (67)	<i>Lepidozia vitrea</i>	Matsuo et al., 1984a	
	(–)-Lepidozenal (68)	<i>Lepidozia vitrea</i>	Matsuo et al., 1984a	
	(+)-Vitrenal (69)	<i>Lepidozia vitrea</i>	Matsuo et al., 1984b Kodama et al., 1986	
Insect antifeedant	3-Hydroxy- $\beta$ -ionone (70)	<i>Rhynchostegium pallidifolium</i>	Kato-Noguchi and Seki, 2010	
	Plagiochiline A (7)	<i>Plagiochila</i> spp.	Asakawa et al., 1980	
	Plagiochilide (71)	<i>Plagiochila</i> spp.	Asakawa, 1995	
	(–)-Polygodial (66)	<i>Porella</i> spp.	Asakawa et al., 1988	
	Hodgsonox (21)	<i>Lepidoleana hodgsoniae</i>	Ainge et al., 2001	
	Clavigerin B (23)	<i>Lepidoleana clavigera</i>	Perry et al., 2003	
	Clavigerin C (72)	<i>Lepidoleana clavigera</i>	Perry et al., 2003	
Molluscicidal activity	Dehydrocostus lactone (82)	<i>Targionia lorbeeriana</i>	Neves et al., 1999	
	Riccioleone A (13)	<i>Riccioleone natans</i>	Wurzel et al., 1990	
	Riccioleone B (14)	<i>Riccioleone natans</i>	Wurzel et al., 1990	
Piscicidal activity	Cuparenone (73)	<i>Riccioleone natans</i>	Wurzel et al., 1990	
	(–)-Polygodial (66)	<i>Porella</i> spp.	Asakawa, 1982	
	Sacculal (33)	<i>Pellia endiviifolia</i>	Asakawa, 1982	
Antitrypanosomal activity	$\alpha$ -Eudesmol (76)	<i>Trichocoleopsis sacculata</i>	Asakawa, 1982	
	Plagiochiline A (7)	<i>Porella stephaniana</i>	Otoguro et al., 2011	
	Plagiochiline A (7)	<i>Plagiochila</i> spp.	Aponte et al., 2010	
Antileishmanial activity	Plagiochiline A (7)	<i>Plagiochila</i> spp.	Aponte et al., 2010	
Antimicrobial activity	Diplophyllin (86)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
	(–)-Diplophyllolide (87)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
	(–)- $\alpha$ -Herbertenol (88)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
	(–)-Herbertene-1,2-diol (89)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
	Sacculal (33)	<i>Pellia endiviifolia</i>	Asakawa, 2008	
	ent-Trachyloban-17-al (85)	<i>Jungermannia exsertifolia</i> subsp. <i>cordifolia</i>	Scher et al., 2010	
	Antifungal activity	Gymnomitrol (77)	<i>Bazzania trilobata</i>	Scher et al., 2004
		5-Hydroxycalamenene (78)	<i>Bazzania trilobata</i>	Scher et al., 2004
		7-Hydroxycalamenene (79)	<i>Bazzania trilobata</i>	Scher et al., 2004
		Drimenol (80)	<i>Bazzania trilobata</i>	Scher et al., 2004
Drimenol (81)		<i>Bazzania trilobata</i>	Scher et al., 2004	
Dehydrocostus lactone (82)		<i>Targionia lorbeeriana</i>	Neves et al., 1999	
Acetyltriflocosolide lactone (83)		<i>Targionia lorbeeriana</i>	Neves et al., 1999	
11- <i>aH</i> -Dihydrodehydrocostus lactone (84)		<i>Targionia lorbeeriana</i>	Neves et al., 1999	
Plagiochiline A (7)		<i>Plagiochila ovalifolia</i>	Toyota et al., 1998b	
		<i>Plagiochila disticha</i>	Asakawa, 1990	
Cytotoxicity	Plagiochiline I (8)	<i>Plagiochila disticha</i>	Aponte et al., 2010	
	Polygodial (66)	<i>Porella</i> spp.	Asakawa, 2008	
	Sacculal (33)	<i>Pellia endiviifolia</i>	Asakawa, 2008	
	Lepidozenolide (90)	<i>Lepidozia fauriana</i>	Shu et al., 1994	
	Marsupellone (91)	<i>Marsupella emarginata</i>	Nagashima et al., 1993	
	Acetoxymarsupellone (92)	<i>Marsupella emarginata</i>	Nagashima et al., 1993	
	Chandolide (93)	<i>Chandonanthus hirtellus</i>	Komala et al., 2010b	
	13-Hydroxychiloscyphone (94)	<i>Chiloscyphus rivularis</i>	Wu et al., 1997	
	(–)-ent-Arbusculin B (95)	<i>Hepatostolonophora paucistipula</i>	Baek et al., 2003	
	(–)-ent-Costunolide (96)	<i>Hepatostolonophora paucistipula</i>	Baek et al., 2003	
	(–)-Diplophyllolide (87)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
		<i>Clasmatocolea vermicularis</i>	Lorimer et al., 1997	
		<i>Chiloscyphus subporosa</i>	Lorimer et al., 1997	
	(–)- $\alpha$ -Herbertenol (88)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
	(–)-Herbertene-1,2-diol (89)	<i>Mastigophora diclados</i>	Komala et al., 2010a	
	Tulipinolide (97)	<i>Frullania</i> sp.	Komala et al., 2011	
	4 $\alpha$ ,5 $\beta$ -Epoxy-8- <i>epi</i> -inunolide (98)	<i>Porella perrottetiana</i>	Komala et al., 2011	
	Glaucescenolide (99)	<i>Schistochila glaucescens</i>	Scher et al., 2002	
	Rabdombrosanin (100)	<i>Lepidolaena taylorii</i>	Perry et al., 1996	
	8,14-Epoxyabdombrosanin (101)	<i>Lepidolaena taylorii</i>	Perry et al., 1996	
	16,17-Dihydroabdombrosanin (102)	<i>Lepidolaena taylorii</i>	Perry et al., 1996	
	ent-11 $\alpha$ -Hydroxy-16-kauren-15-one (103)	<i>Jungermannia</i> sp.	Nagashima et al., 2003	
	ent-1 $\beta$ -Hydroxy-9(11),16-kauradien-15-one (104)	<i>Jungermannia</i> sp.	Nagashima et al., 2003	
	ent-9(11),16-Kauradiene-12,15-dione (105)	<i>Jungermannia</i> sp.	Nagashima et al., 2003	
	ent-6 $\beta$ -Hydroxy-16-kauren-15-one (106)	<i>Jungermannia</i> sp.	Nagashima et al., 2005	
	Jungermannenone A (107)	<i>Jungermannia</i> sp.	Nagashima et al., 2003	
	Jungermannenone B (108)	<i>Jungermannia</i> sp.	Nagashima et al., 2005	
	Jungermannenone C (109)	<i>Jungermannia</i> sp.	Nagashima et al., 2005	
	Jungermannenone D (110)	<i>Jungermannia</i> sp.	Nagashima et al., 2005	
	Momilactone B (112)	<i>Hypnum plumaeforme</i>	Kim et al., 2007	

(continued on next page)

Table 1 (continued)

Activity	Terpenoids	Species	References
Immunomodulatory, anti-inflammatory, and CNS activity	Furanopinguisanol (113)	<i>Porella cordaena</i>	Radulovic et al., 2016
	Furanopinguisanone (114)	<i>Porella cordaena</i>	Radulovic et al., 2016
	Norpinguisone (115)	<i>Porella densifolia</i>	Quang and Asakawa, 2010
	Norpinguisome methyl ester (116)	<i>Porella densifolia</i>	Quang and Asakawa, 2010
	$\alpha$ -Herbertenol (88)	<i>Mastigophora diclados</i>	Harinantenaina et al., 2007
	Herbertene-1,2-diol (89)	<i>Mastigophora diclados</i>	Harinantenaina et al., 2007
	$\beta$ -Herbertenol (117)	<i>Mastigophora diclados</i>	Harinantenaina et al., 2007
	Herbertenol (118)	<i>Herbertus sakurai</i>	Harinantenaina et al., 2007
	Cuparenediol (119)	<i>Lejeunea aquatica</i>	Harinantenaina et al., 2007
	2-Hydroxy-4-methoxycuparene (120)	<i>Bazzania decrescens</i>	Harinantenaina et al., 2007
	12-Hydroxydolabella-3(E),7(E)-dien-6-one (121)	<i>Lepidozia reptans</i>	Li et al., 2018
	6,12-Dihydroxydolabella-3(E),7(E)-diene (122)	<i>Lepidozia reptans</i>	Li et al., 2018
	12-Hydroxydolabella-3(E),7(Z)-dien-6-one (123)	<i>Lepidozia reptans</i>	Li et al., 2018
	13-Hydroxy- <i>ent</i> -kaura-3,15-dione (124)	<i>Lepidozia reptans</i>	Li et al., 2018
	3-Hydroxy- <i>ent</i> -kaura-15-one (125)	<i>Lepidozia reptans</i>	Li et al., 2018

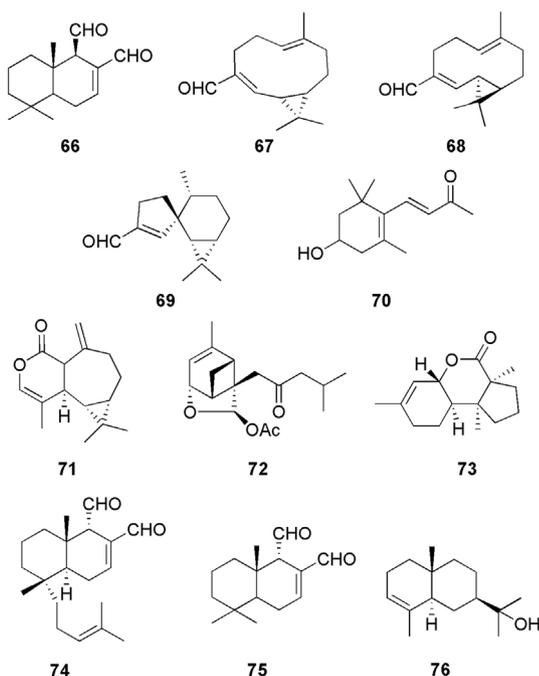


Fig. 7. Compounds with phytotoxicity, insect antifeedant, piscicidal and anti-trypansomal activity.

growth regulatory terpenoids have been isolated from liverworts. One of them is the pungent sesquiterpene dialdehyde, (–)-polygodial (66), which inhibits the germination and root elongation of rice in the husk at 100 ppm. At a concentration of less than 25 ppm, it dramatically promotes root elongation of rice (Asakawa, 1982). (–)-Isobicyclgermacrenal (67) and (–)-lepidozenal (68) from *Lepidozia vitrea* were tested against rice seedlings. Both compounds completely inhibited the growth of leaves and roots at a concentration of 50 and 250 ppm, respectively. The 50% growth inhibition ( $I_{50}$ ) of leaves and roots was observed for isobicyclgermacrenal (67) at 7 ppm (Matsuo et al., 1984a). The enantiomeric pair, (+)-vitrenal (69) isolated from *L. vitrea*, and synthetic (–)-vitrenal were tested for growth regulatory activity using rice seedlings and lettuce hypocotyls. The natural (+)-isomer showed strong inhibition ( $I_{50}$  = 18 ppm), while the (–)-isomer exhibited weak stimulatory activity (Matsuo et al., 1984b; Kodama et al., 1986). Kato-Noguchi and Seki (2010) showed that the intact stems of the moss *Rhynchosstegium pallidifolium* and its secondary metabolite, 3-hydroxy- $\beta$ -ionone (70) inhibit the hypocotyl and root growth of cress (*Lepidium sativum*) (Fig. 7).

### 3.2. Insect antifeedant and molluscicidal activity

The predation resistance of bryophytes comes from their effective performance in chemical defense. Long before the discovery of secondary metabolites in bryophytes, Himalayans used them as insects' repellents when storing food (Glime, 2007). The phytochemical studies on *Plagiochila* species showed that plagiochiline A (7), a representative of 2,3-seco-aromadendranes widely occurring in these liverworts, is a strong antifeedant against the African armyworm, *Spodoptera exempta* at 1–10 ng/cm<sup>2</sup> in a choice leaf disk test for 2 h (Asakawa et al., 1980). Another compound isolated from *Plagiochila* species, plagiochilide (71), killed brown planthopper, *Nilaparvata lugens* (Delphacidae) at 100  $\mu$ g/mL (Asakawa, 1995).

Polygodial (66) from the *Porella vernicosa* complex was the most active metabolites among all drimanes tested for antifeedant activity against aphids. Natural (–)-polygodial (66) and the synthetic (+)-enantiomer showed similar levels of activity as aphid antifeedants (Asakawa et al., 1988). (–)-Polygodial killed mosquito larvae at a concentration of 40 ppm, and had mosquito repellent activity which was stronger than the commercially available DEET. (Asakawa, 1995; Asakawa and Ludwiczuk, 2018).

Hodgsonox (21), isolated from the New Zealand liverwort *Lepidolaena hodgsoniae* is toxic to larvae of the blowfly *Lucilia cuprina* with a  $LC_{50}$  value of 0.27 mg/mL (Ainge et al., 2001). Clavigerins B (23) and C (72), compounds occurring in another *Lepidolaena* species, *L. clavigera* have significant antifeedant activities against *Anthrenocerus australis* (0.026% for 23 and 0.052 for 72) and *Tineola bisselliella* (0.1% for both compounds). They showed similar efficiency as the well-known insect antifeedant, azadirachtin (Perry et al., 2003).

Cuparane- and monocyclofarnesane-type sesquiterpenoids occurring in the liverwort, *Ricciocarpos natans* have been tested against *Biomphalaria glabrata*. Among tested compounds, ricciocarpin A (13) was the most toxic with an  $LC_{100}$  of 11 ppm, while ricciocarpin B (14) with a  $\gamma$ -lactone moiety caused a significant reduction of the activity to an  $LC_{100}$  of 43 ppm. Cuparenolide (73) showed molluscicidal activity with  $LC_{100}$  at 32 ppm (Wurzel et al., 1990) (Fig. 7).

### 3.3. Piscicidal activity

The strongest piscicide from bryophytes is the pungent sesquiterpene dialdehyde, (–)-polygodial (66) occurring in some of the *Porella* species, as well as sacculatal (33), diterpene dialdehyde present in *Pellia endiviifolia* and *Trichocoleopsis sacculata*, among others. Japanese killifish (*Oryzias latipes*) are killed within 2 h by a 0.4 ppm solution of 66 (Asakawa, 1982). Killifish are also killed within 2 h by a 0.4 ppm solution of synthetic (+)-polygodial. Hence, piscicidal activity is not affected by the chirality of polygodial. The natural polygodial and its enantiomer are also very toxic to fresh water bitterlings, which are

killed within 3 min by a 0.4 ppm solution. Sacculatal (**33**) was lethal to killifish within 20 min at a concentration of 1 ppm. On the other hand, isosacculatal (**74**) and isopolygodial (**75**) show neither piscicidal nor molluscicidal activity, even at 10,000 ppm (Asakawa, 1982, 1995; Asakawa and Ludwiczuk, 2018) (Fig. 7).

### 3.4. Antitrypanosomal and antileishmanial activity

Antitrypanosomal activity of 24 terpenoids from liverworts and higher plants was evaluated against *Trypanosoma brucei* strain GUTat 3.1. Among them,  $\alpha$ -eudesmol (**76**) isolated from *Porella stephaniana* showed highly-promising antitrypanosomal activity, with an ED<sub>50</sub> value of 0.10  $\mu$ g/mL (Fig. 7). This activity was stronger than that of commercially used antitrypanosomal drugs, eflornithine and suramin (ED<sub>50</sub> 2.27 and 1.5  $\mu$ g/mL, respectively) (Otoguro et al., 2011).

Plagiochiline A (**7**) showed antileishmanial activity against *Leishmania amazonensis* axenic amastigotes with an IC<sub>50</sub> of 7.1  $\mu$ M and trypanocidal activity against *Trypanosoma cruzi* trypomastigotes at an MIC 14.5  $\mu$ M (Aponte et al., 2010).

### 3.5. Antimicrobial and antifungal activity

An interesting feature of bryophytes is that they are not infected by bacteria or fungi. It suggests that they have defenses against such infections. Numerous studies have demonstrated that terpenoids present in liverworts and in other bryophytes have antibiotic effects. In particular lipophilic extracts of several liverworts like *Bazzania*, *Frullania*, *Marchantia*, *Conocephalum*, *Porella*, *Plagiochila* spp. show antibacterial and antifungal activity (Asakawa, 1982, 1995, 2008; Asakawa and Ludwiczuk, 2018). Liverwort extract with antimicrobial effect was even sold in Germany (Frahm, 2004). Several antimicrobials have been isolated from the liverworts. *Bazzania trilobata* contained five antifungal active sesquiterpenoids, gymnomitrol (**77**), 5-hydroxycalamenene (**78**), 7-hydroxycalamenene (**79**), drimenol (**80**), and drimenal (**81**) against a range of phytopathogenic fungi, including *Botrytis cinerea*, *Cladosporium cucumerinum*, *Pyricularia oryzae*, *Phytophthora infestans*, and *Septoria tritici*. Gymnomitrol (**77**) showed inhibition against *P. infestans* at IC<sub>50</sub> 0.1  $\mu$ g/mL. 5-Hydroxycalamenene (**78**) showed inhibitory activity against *P. oryzae* at IC<sub>50</sub> 1.7  $\mu$ g/mL while 7-hydroxycalamenene (**79**) had antifungal activity against *P. oryzae*, *C. cucumerinum*, and *S. tritici* at IC<sub>50</sub> 4.1, 10.0, and 11.8  $\mu$ g/mL, respectively. Compound **79** was also tested for *in vivo* activity against *Plasmopara viticola* on grape vine leaves and showed inhibitory activity at a concentration of 250 ppm. The infection was reduced from 100% in the control to 30% in the treated plants in a greenhouse. Drimenol (**80**) inhibited the growth of *C. cucumerinum* at concentrations of 6.6  $\mu$ g/mL. Drimenal (**81**) exhibited potent activity against *P. infestans* and *S. tritici* with an IC<sub>50</sub> value of < 0.3 and 17.6  $\mu$ g/mL (Scher et al., 2004).

Dehydrocostus lactone (**82**), acetyltrifolucosolide lactone (**83**), and 11-*aH*-dihydrodehydrocostus lactone (**84**) from *Targionia lorbeeriana* showed antifungal activity against *Cladosporium cucumerinum* with MIC values of 0.5, 10, and 3  $\mu$ g/mL, respectively. Compound **82** also showed larvicidal activity against *Aedes aegypti*, with an LC<sub>100</sub> value of 12.5 ppm and antifungal activity against *C. albicans* (MIC 5  $\mu$ g/mL) using a bioautographic TLC method (Neves et al., 1999).

The crude ether and methanol extracts of the Tahitian *Mastigophora diclados* showed antimicrobial activity against *B. subtilis* and *S. aureus* (MIC 16  $\mu$ g/mL). Bioactivity-guided fractionation of both extracts gave diplophyllin (**86**), (-)-diplophyllolide (**87**), (-)- $\alpha$ -herbertenol (**88**), and (-)-herbertene-1,2-diol (**89**), among which compounds **88** and **89** showed moderate antimicrobial activity against *B. subtilis* at MIC values of 8  $\mu$ g/mL (Komala et al., 2010a).

Sacculatal (**33**), isolated from *Pellia endiviifolia*, showed potent antibacterial activity against *Streptococcus mutans* (a causative organism of dental caries), exhibiting a LD<sub>50</sub> value of 8  $\mu$ g/mL (Asakawa, 2008).

In the search for new antituberculosis lead compounds from

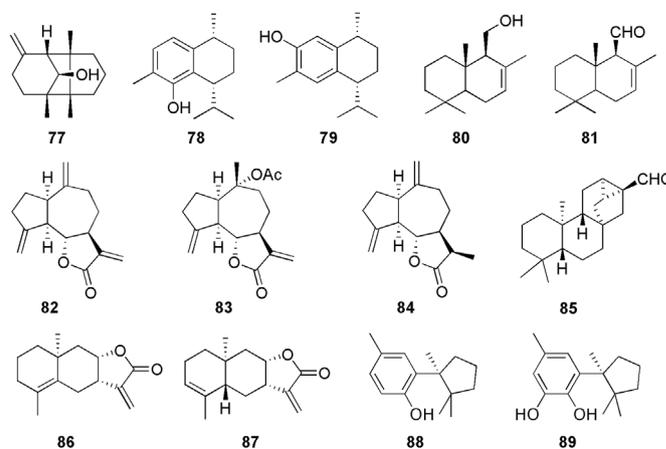


Fig. 8. Terpenoids with antibacterial and antifungal activity.

bryophytes, Scher et al. (2010) isolated 14 trachylobane diterpenoids from the liverwort *Jungermannia exsertifolia* subsp. *cordifolia*, among which *ent*-trachyloban-17-al (**85**) showed the most significant activity against the virulent *Mycobacterium tuberculosis* H37Rv strain, with a MIC<sub>90</sub> value of 24  $\mu$ g/mL (Fig. 8).

### 3.6. Cytotoxicity

Several bryophytes have been screened for cytotoxic activity. Spjut et al. (1986) tested 184 species of mosses and 23 species of liverworts and one hornwort for cytotoxicity and *in vivo* antitumor activity. They found that ethanol extracts of 43 species were active, while those of 75 species were toxic to the mice. The most promising moss species were *Tetraphis pellucida*, *Plagiomnium cuspidatum*, *Metaneckera mendesii*, *Bryoandersonia illecebra*, *Dicranella heteromalla*, *Racomitrium sudeticum*, *Polytrichum ohioense* and *Anomodon attenuatus*. Among liverworts the most active were *Dumortiera hirsuta* and *Bazzania trilobata*. The only hornwort tested was inactive (Spjut et al., 1986). The diethyl ether extracts of the liverworts *Bazzania pompeana*, *Kurzia makinoana*, *Lophocolea heterophylla*, *Makinoa crispata*, *Marsupella emarginata*, *Pellia endiviifolia*, *Plagiochila fruticosa*, *P. ovalifolia*, *Porella caespitans*, *P. japonica*, *P. perrottetiana*, *P. vernicosa*, and *Radula perrottetii* showed cytotoxicity against P-388 cells (IC<sub>50</sub> value range 4–20  $\mu$ g/mL). In contrast, the crude extracts of *Frullania diversitexta*, *F. ericoides*, *F. muscicola*, *F. tamarisci* subsp. *obscura*, *Lepidozia vitrea*, *Pallavicinia subciliata*, *Plagiochila sciophila*, *Spruceanthus semirepandus*, and *Trocholejeunea sandvicensis* were inactive against this same cell line (IC<sub>50</sub> values > 20  $\mu$ g/mL) (Asakawa, 1982, 1995; 2008).

Detailed phytochemical analysis of bryophytes, especially liverworts, led to the isolation of many terpenoids with cytotoxic activity. The ether extract of *Plagiochila ovalifolia* showed inhibitory activity against P-388 murine leukemia cells, and its major constituent, plagiochiline A (**7**) exhibited IC<sub>50</sub> values of 3.0  $\mu$ g/mL (Toyota et al., 1998b). This compound also showed cytotoxicity to KB cells with IC<sub>50</sub> 0.28  $\mu$ g/mL (Asakawa, 1990). Aponte et al. (2010) also reported that plagiochiline A (**7**) and I (**8**) isolated from the Peruvian *Plagiochila disticha* showed cytotoxic activity against a panel of human tumor cell lines, 3T3, H460, DU145, MCF-7, M-14, HT-29, K562, and VERO. Among them, compound **7** exhibited the strongest activity against all of cell lines at a concentration between GI<sub>50</sub> 1.4–6.8  $\mu$ M. Polygodial (**66**) widely occurring in *Porella vernicosa* complex, as well as sacculatal (**33**) isolated from *Pellia endiviifolia*, showed cytotoxic activity against a human melanoma cell line (IC<sub>50</sub> value range 2–4  $\mu$ g/mL). Compound **33** was also weakly cytotoxic for Lu1 (IC<sub>50</sub> 5.7  $\mu$ g/mL), KB (3.2  $\mu$ g/mL), LNCaP (7.6  $\mu$ g/mL), and ZR-75-1 cells (7.6  $\mu$ g/mL) (Asakawa, 2008). Lepidozenolide (**90**) from the Taiwanese *Lepidozia fauriana* showed potent cytotoxicity when evaluated in the P-388 murine leukemia cell

line ( $IC_{50}$  2.1  $\mu\text{g}/\text{mL}$ ) (Shu et al., 1994). Marsupellone (91) and acetoxymarsupellone (92), from the German *Marsupella emarginata* showed cytotoxicity ( $ID_{50}$  1  $\mu\text{g}/\text{mL}$ ) against P388 (Nagashima et al., 1993).

The Tahitian liverwort *Chandonanthus hirtellus* produced a new sesquiterpene lactone, chandolide (93) which were evaluated for cytotoxic activity against the HL-60 leukemia cell line, and exhibited  $IC_{50}$  value of 5.3  $\mu\text{g}/\text{mL}$  (Komala et al., 2010b). 13-Hydroxychiloscyphone (94) obtained from *Chiloscyphus rivularis* collected in Oregon showed cytotoxic activity against A-549 lung carcinoma cells ( $IC_{50}$  value 2.0  $\mu\text{g}/\text{mL}$ ) (Wu et al., 1997). (–)-*ent*-Arbusculin B (95) and (–)-*ent*-costunolide (96), from *Hepatosolonophora paucistipula*, showed cytotoxic activity against P388 murine leukemia cells, with  $IC_{50}$  values of 1.1 and 0.7  $\mu\text{g}/\text{mL}$ , respectively (Baek et al., 2003).

The ether and methanol extracts of the Tahitian *Mastigophora di-clados* showed cytotoxic activity against HL-60 cells at  $IC_{50}$  2.4 and 13.1  $\mu\text{g}/\text{mL}$  and KB cells at 14.6 and 32.5  $\mu\text{g}/\text{mL}$ , respectively. (–)-Diplophyllolide (87), (–)- $\alpha$ -herbertenol (88), (–)-herbertene-1,2-diol (89), isolated from both extracts were cytotoxic against HL-60 cells with  $IC_{50}$  values of 2.5, 1.4, and 12.8,  $\mu\text{g}/\text{mL}$ , respectively. They also showed cytotoxicity against KB cells ( $IC_{50}$  values of 14.2, 3.3, and 12.5) (Komala et al., 2010a). Biologically-directed isolation of the ethanol extract from the New Zealand liverworts *Clasmatocolea vermicularis* and *Chiloscyphus subporosa* led to the isolation of (–)-diplophyllolide (87), as the major cytotoxic component. This compound showed activity against P388 murine leukemia cells, with  $IC_{50}$  value of 0.4  $\mu\text{g}/\text{mL}$  (Lorimer et al., 1997). From the Tahitian *Frullania* species, tulipinolide (97) was obtained. This compound showed cytotoxicity against the HL-60 cell line at  $IC_{50}$  4.6  $\mu\text{M}$ . The Japanese liverwort, *Porella perrottetiana* produces cytotoxic lactone, 4 $\alpha$ ,5 $\beta$ -epoxy-8-*epi*-inunolide (98), which exhibited activity against HL-60 cells ( $IC_{50}$  8.5  $\mu\text{M}$ ) (Komala et al., 2011). Glaucescenolide (99) from the New Zealand *Schistochila glaucescens* showed cytotoxic activity against P-388 murine leukemia cells ( $IC_{50}$  2.3  $\mu\text{g}/\text{mL}$ ) (Scher et al., 2002) (Fig. 9).

The ethanol-soluble extract of *Lepidolaena taylorii*, which showed cytotoxicity against the P-388 cell line ( $IC_{50}$  1.3  $\mu\text{g}/\text{mL}$ ), was purified to give *ent*-8,9-secokaurane diterpenoids. Rabdumbrosanin (100) and 8,14-epoxyrabdumbrosanin (101) showed the most potent cytotoxic activities ( $IC_{50}$  values of 0.06 and 0.27  $\mu\text{g}/\text{mL}$ , respectively). 16,17-Dihydro-rabdumbrosanin (102) also showed cytotoxicity against P-388 cells at 0.80  $\mu\text{g}/\text{mL}$  (Perry et al., 1996). The *ent*-16-kauren-15-one derivatives (103–106) together with rearranged kaurenes, jungermannones A-D (107–110), isolated from the New Zealand *Jungermannia* species showed cytotoxic activity against HL-60 cells at  $IC_{50}$  values from 0.4 to 7.0  $\mu\text{M}$  (Nagashima et al., 2003, 2005).

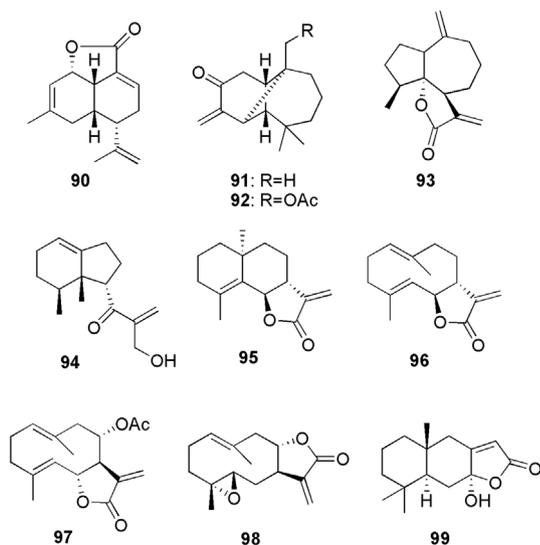


Fig. 9. Cytotoxic sesquiterpenoids

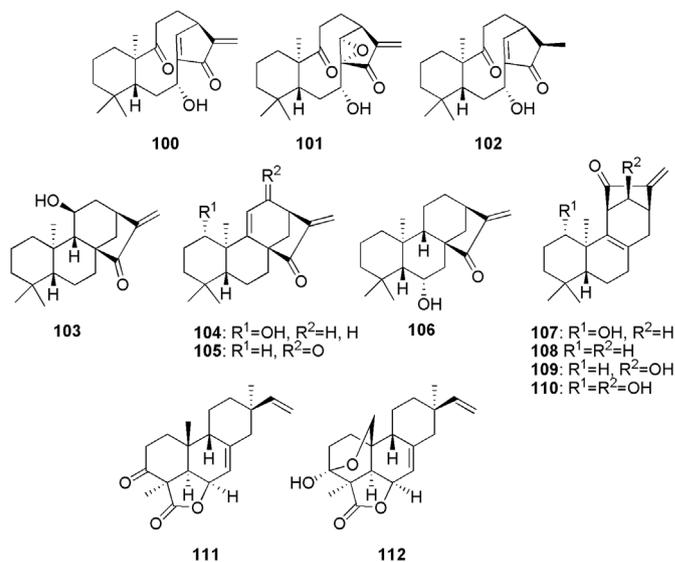


Fig. 10. Cytotoxic diterpenoids.

The two pimarane diterpenoids, momilactones A (111) and B (112), which were identified as phytoalexins in rice, were isolated from the moss *Hypnum plumaeforme* (Nozaki et al., 2007). Momilactone B (112) was shown to be cytotoxic against human colon cancer HT-29 and SW620 cells at 1  $\mu\text{M}$  (Kim et al., 2007) (Fig. 10).

### 3.7. Anti-inflammatory, immunomodulatory and central nervous system activity

Inflammation is a biological response of the immune system that can be triggered by a variety of factors, for example toxic compounds. It could be responsible for numerous acute and chronic diseases, including cancer. Augmentation of the immune response is desirable to prevent infection in states of immunodeficiency, to fight established infections and cancer (Shukla et al., 2012; Radulovic et al., 2016). There are some literature data that indicate the occurrence of anti-inflammatory and immunomodulatory tepenoids among liverwort species.

From the Serbian *Porella cordaeana* essential oil two pinguisane-type sesquiterpenoids,  $\alpha$ -furanopinguisanol (113) and furanopinguisanone (114) were isolated (Radulovic et al., 2016). The authors studied the effects of these two compounds on the viability of splenocytes, as a possible mode of regulation of innate and immune inflammatory responses. It was shown that  $\alpha$ -furanopinguisanol (113) induces a blast-like transformation of splenocytes in higher concentration ( $10^{-4}$  M), while in lower ones ( $10^{-8}$  to  $10^{-6}$  M) it acted as a cytotoxic agent. Furanopinguisanone (114) exerted prominent cytotoxicity in all tested concentrations (Radulovic et al., 2016).

Two other pinguisane sesquiterpenoids, norpinguisone (115) and norpinguisone methyl ester (116), isolated from *Porella densifolia* were screened for anti-inflammatory activities by the model of lipopolysaccharide (LPS)-induced nitric oxide (NO) production with RAW264.7 cells. Both compounds showed the inhibition at  $IC_{50}$  = 1.7  $\mu\text{M}$  and  $IC_{50}$  = 45.5  $\mu\text{M}$ , respectively (Quang and Asakawa, 2010).

Harinantenaina and coworkers (2007) showed that herbertane sesquiterpenoids (88, 89, 117, 118) isolated from *Mastigophora di-clados* and *Herbertus sakuraii* as well as cuparenoids (119, 120) from *Lejeunea aquatica* and *Bazzania decrescens*, showed inhibition of lipopolysaccharide (LPS)-induced production of NO. The highest inhibition was attributed to 2-hydroxy-4-methoxycuparene (120,  $IC_{50}$  = 4.1  $\mu\text{M}$ ) and the lowest to  $\alpha$ -herbertenol (88,  $IC_{50}$  = 76  $\mu\text{M}$ ). It is interesting to note that the only difference between compounds 88 and 117 is the *ortho* or

*para* position of the hydroxyl group regarding the aromatic methyl. From the *ortho* (**88**, IC<sub>50</sub> = 76 μM) to a *para* (**117**, IC<sub>50</sub> = 12 μM) position the activity increases 6 times. Comparing the activity of compounds **89** (IC<sub>50</sub> = 8 μM) and **119** (IC<sub>50</sub> = 9 μM) with compound **118** (IC<sub>50</sub> = 34 μM), it seems that an aromatic methyl group is important for this type of inhibition, while oxidation of this group to a formyl one decreased the inhibition of NO production. The strong inhibitory activity of compound **120** was related to the inhibition of LPS-induced iNOS mRNA (Harinantenaina et al., 2007).

Also diterpenoids isolated from the liverwort species were reported to show anti-inflammatory activity. The Chinese liverwort, *Lepidozia reptans*, produces dollabellane- and *ent*-kaurane-type diterpenoids (Li et al., 2018). The authors detected NO level in LPS-stimulated RAW264.7 macrophages to evaluate anti-inflammatory function of five compounds (**121**–**125**). Among them, compounds **121** and **123** moderately suppressed the production of NO in a dose dependent manner. The results showed that compound **123** (IC<sub>50</sub> = 34.9 μM), which has a *Z* geometry of the C-7/8 double bond, exhibited higher inhibitory activity than that of compound **121** (IC<sub>50</sub> = 46.8 μM), which bearing an *E* geometry of the C-7/8 double bond. It indicated that the geometry of double bond on the dollabellane-type skeleton may effect the anti-inflammatory activity. In addition, they effectively diminished mRNA levels of IL-6, IL-β, IL-α, TNF-α and protein expression of COX-2 (Li et al., 2018) (Fig. 11).

Secondary metabolites found in the liverwort species can also affect the central nervous system and alter activity in the brain. These are bibenzyl cannabinoids belonging to the tetrahydrocannabinol type, perrottetinene (**126**) and perrottetinic acid (**127**). Both compounds could be detected in the volatile extracts of some *Radula* species. Compound **126** was isolated in 1994 from *Radula perrottetii* (Toyota et al., 1994). After this finding, the same compound has been detected also in *R. campanigera*, *R. chinensis*, *R. laximera* and *R. marginata* (Asakawa et al., 2013a). The last species also produces perrottetinic acid (**127**). Perrottetinene (PET, **126**) structurally resembles Δ<sup>9</sup>-tetrahydrocannabinol (Δ<sup>9</sup>-THC, **128**) from *Cannabis sativa*, but the liverwort compound has *cis* configuration in the cyclohexene ring (*cis*-PET) compared with *trans*-THC. Chicca and coworkers (2018) demonstrated

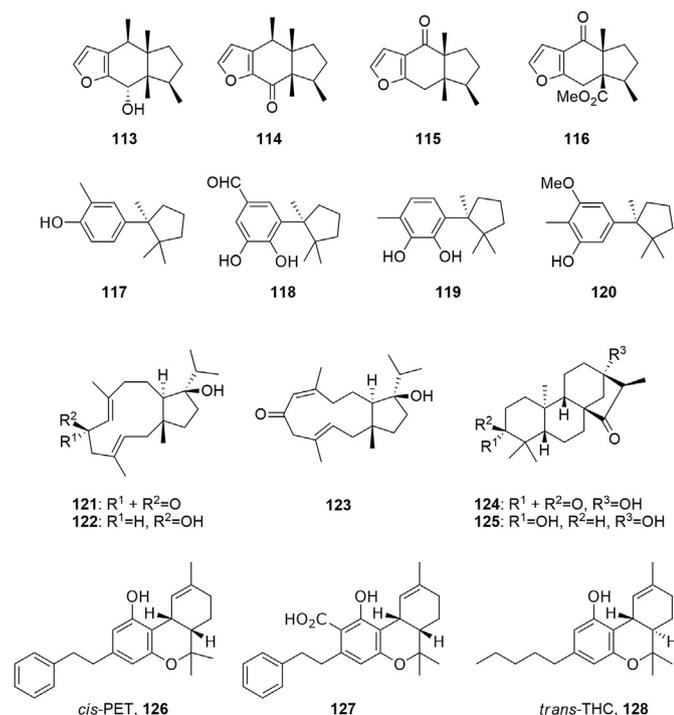


Fig. 11. Anti-inflammatory, immunomodulatory, and CNS active compounds from liverworts.

that *cis*-PET (**126**) and its *trans*-diastereoisomer readily penetrate the brain and induce hypothermia, catalepsy, hypolocomotion and analgesia in a CB1 receptor-dependent manner in mice, similarly to Δ<sup>9</sup>-*trans*-THC. The *cis*-PET isomer was less potent CB1R partial agonist than the *trans*-PET. Unexpectedly, the perrottetinene diastereoisomers differed pharmacologically from Δ<sup>9</sup>-*trans*-THC as it significantly reduced basal PGD<sub>2</sub> and E<sub>2</sub> levels in the brain in a CB1R-dependent manner, potentially limiting its adverse effects and reducing neuroinflammation. *cis*-PET (**126**) from *Radula* species could be an interesting lead for drug development as it might have fewer side effects than Δ<sup>9</sup>-*trans*-THC from *Cannabis sativa* and reduces prostaglandins (Chicca et al., 2018) (Fig. 11).

#### 4. Comparison of biological properties of the bryophyte volatile terpenoids with those present in higher plants

In contrast to the spore-forming plants, such as bryophytes, essential oils and volatile extracts from higher plants, as well as their secondary metabolites are widely utilized as a source of substances useful for human beings. Especially, essential oils (EOs) have a great commercial value and are widely used in traditional medicine, by phytotherapy practitioners, and in public health services for the treatment of several diseases (Edris, 2007). EOs are frequently studied for their antimicrobial, antifungal, antioxidant, repellent, insecticidal, antifeedant, larvicidal, and cytotoxic properties, as well as for their use as food preservatives (Pandey et al., 2017). Addition of EOs to edible products, either by direct mixing or in active packaging and edible coatings, represent a valid alternative to prevent autoxidation and prolong shelf life (Amorati et al., 2013; Pandey et al., 2017).

The ability to accumulate EOs is not omnipresent in plants but scattered throughout the plant kingdom. From the taxonomical and systematic point of view, not the production of essential oils is the distinctive feature since this is a quite heterogeneous group of substances, but either the type of secretory containers (trichomes, oil glands, lysogenic cavities, or schizogenic oil ducts) or the biosynthetically specific group of substances, for example, mono- or sesquiterpenes, phenylpropenes, and so on (Franz and Novak, 2010). Among bryophytes, only liverworts are plants with enormous chemical diversity of the volatiles. These spore-forming plants are characterized by the presence of oil bodies, unique organelles in which terpenoids and aromatic compounds are accumulated (Asakawa et al., 2013a). In comparison to the higher plants, there is still, not enough data on the biological activity of these plants and their compounds. On the other hand many of the compounds present in the liverworts species are characterized by unprecedented structures, and some, including the pinguisane-type sesquiterpenoids and sacculatane-type diterpenoids, have not been found in any other plants, fungi or marine organisms (Asakawa et al., 2013a,b). A review of the literature shows that there are some components which are common for liverworts and higher plants. These include drimane sesquiterpenoids, compounds that do not occur widely in Nature. Drimanic components, especially polygodial (**66**) can be found within Cannellaceae, Winteraceae and Polygonaceae families of higher plants, in liverworts belonging to the *Porella vernicosa* complex, as well as in some ferns (Jansen and de Groot, 2004; Asakawa et al., 2012). Polygodial (**66**) was reported as promising antifungal agent against yeast-like and filamentous fungi because of its effectiveness compared to potent antibiotics such as actinomycin D, rifampicin and amphotericin B (MIC's < 25 μg/mL) (Jansen and de Groot, 2004). Moreover, the combination of polygodial with very weak antifungal compounds, including anethole, safrole, methyleugenol and sorbic acid enhanced the activity significantly, sometimes up to 64-fold (Kubo and Himejima, 1991; Himejima and Kubo, 1992; Kubo and Lee, 1998). The primary antifungal action of polygodial comes in part from its ability to function as a nonionic surfactant. More specifically, it inhibits the plasma membrane H<sup>+</sup>-ATPase by disrupting and disorganizing the hydrogen bonds at the lipid bilayer-protein interface. However,

polygodial does not act by a single defined process, but, rather, has multiple functions by which it exerts its potent fungicidal action (Kubo et al., 2001). As it was shown in Table 1, in addition to the antifungal activity, polygodial (66) also exhibited piscicidal, plant-growth, insect antifeedant and cytotoxic activity. Correa et al. (2011) also showed that the hexane extracts and polygodial isolated from stem barks of *Drimys brasiliensis* (Winteraceae) exhibited activity against *Leishmania* ssp. and *Trypanosoma cruzi*.

Another group of sesquiterpenoids that are present in liverworts and higher plants are calamenanes. It was shown that 5- (78) and 7-hydroxycalamenene (79) isolated from liverwort *Bazzania trilobata* have antifungal activity (Scher et al., 2004). 7-Hydroxycalamenene-rich essential oil from *Croton cajucara*, a very important medicinal plant in Brazil, showed the antibacterial activity against *Staphylococcus aureus* (MRSA), *Mycobacterium tuberculosis* and *M. smegmatis*, and also antifungal activity against *Mucor circinelloides* and *Rhizopus oryzae*. The most active compound was 7-hydroxycalamenene (79) (Azevedo et al., 2013). Another studies showed that this compound was active against the main agent of zygomycosis. All species tested were sensitive to compound 79 at concentrations ranging from 19.53 to 2500 µg/mL. The highest activity was observed against *Absidia cylindrospora*, *Cunninghamella elegans*, *Mucor circinelloides*, *M. plumbeus*, *Rhizopus oryzae* and *R. microsporus* (Azevedo et al., 2014).

Sesquiterpene lactones are very popular compounds present in liverworts and higher plants. Costunolide (96) and dehydrocostus lactone (82) isolated from the liverwort species are also derived from many species of higher plants, such as *Inula helenium*, *Saussurea lappa* and *Laurus nobilis*. They have been reported for their wide spectrum of biological effects, including anti-inflammatory, anticancer, antiviral, antimicrobial, antifungal, antioxidant, antidiabetic, antiulcer, and anthelmintic activities. In recent years, they have caused extensive interest due to their potential anti-cancer activities for various types of cancer (Lin et al., 2015; Wang et al., 2017). Costunolide (96) and dehydrocostus lactone (82) usually coexist in medicinal plants, and they have similar chemical as well as anti-cancer properties. A great number of research results supported that both compounds can exert their anti-cancer activities by various pathways, mainly manifested in inhibition of cancer cell proliferation, induction of cancer cell apoptosis and differentiation, inhibition of metastasis and invasion, reversal of multidrug resistance, and inhibition of angiogenesis (Lin et al., 2015). The study conducted by Wang et al. (2017) showed also that after treatment with dehydrocostus lactone (82), the glioblastoma (U118, U251 or U87) cells were significantly inhibited in their viability, proliferation and migration. The obtained results indicated that the anti-cancer properties of the dehydrocostus lactone in glioma may be mediated, at least in part, through inhibition of the NF-κB/COX-2 signaling pathway by targeting IKKβ in vitro and in vivo (Wang et al., 2017).

Table 1 contains the data about bioactive diterpenoids found in liverworts and mosses. These components mainly belong to kaurane-, trachylobane- and pimarane-type of diterpenoids, and show cytotoxic activity. Such a compounds have been reported in several families of higher plants, especially in species belonging to the Asteraceae, Euphorbiaceae and Lamiaceae families (Garcia et al., 2007; Uchoa et al., 2013; Revegilia et al., 2018). Kauranes and pimaranes have been largely cited as cytotoxic, anti-inflammatory, antibacterial, antifungal, antiviral and phytotoxic (Garcia et al., 2007; Revegilia et al., 2018). On the other hand, the biological activities of trachylobane compounds are poorly investigated, they are cited to possess vasorelaxant and cytotoxic properties (Uchoa et al., 2013).

The comparison of the bioactive terpenoids present in bryophytes and higher plants shows that they are similar. Because of this it is possible to use both group of terrestrial plants as a source of substances useful for human beings, depending on availability. On the other hand, the liverworts, as a source of compounds that are not found in higher plants, may become an origin of new plant medicines or plant protection products.

## 5. Conclusions and perspectives

Bryophytes are considered to be the oldest terrestrial plants. As such, they are the first land plants to synthesize terpenoids. Although morphologically simple, they are characterized by enormous diversity of such kind of compounds. Terpenoid secondary metabolites play an important role as defenses against biotic stresses such as insects and microbial pathogens. Among bryophytes, liverworts are the most studied for terpenoid chemistry. It is also well known that liverworts often have distinctive aroma and some of them have very pungent or bitter taste. The combination of odor and taste, in addition to the cytotoxicity and other activities of some compounds, clearly act as a deterrents to herbivory (Asakawa et al., 2013a; Chen et al., 2018).

It should be also mentioned that endophytes associated with bryophytes species are also able to synthesize bioactive compounds, and they contribute, in part, to the control of microbial or herbivore attack. Opelt and Berg (2004) have stated that bryophytes are a reservoir for a broad range of hitherto largely unknown microbial population. Further research is needed to determine the relationship between the chemical diversification of bryophytes and their symbiotic fungi.

Terpenoids and other compounds occurring in the bryophytes, also in the bryophyte endophytes, can be important for human health, but much work remains to link medical effects with specific bryophyte species or compound. As it was shown, the bryophyte chemistry is very interesting and many of the isolated secondary metabolites showed interesting biological activity.

## Conflicts of interest

The authors confirm that this article content has no conflict of interest.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Transparency document

Transparency document related to this article can be found online at <https://doi.org/10.1016/j.fct.2019.110649>.

## References

- Ainge, G.D., Gerard, P.J., Hinkley, S.F.R., Lorimer, S.D., Weavers, R.T., 2001. Hodgsonox, a new class of sesquiterpene from the liverwort *Lepidolaena hodgsoniae*. Isolation directed by insecticidal activity. *J. Org. Chem.* 66, 2818–2821.
- Amorati, R., Foti, M.C., Valgimigli, L., 2013. Antioxidant activity of essential oils. *J. Agric. Food Chem.* 61, 10835–10847.
- Aponte, J.C., Yang, H., Vaisberg, A.J., Castillo, D., Malaga, E., Verastegui, M., Cason, L.K., Stivers, N., Bates, P.J., Rojas, R., Fernandez, I., Lewis, W.H., Sarasara, C., Sauvain, M., Gilman, R.H., Hammond, G.B., 2010. Cytotoxic and anti-infective sesquiterpenes present in *Plagiochila disticha* (Plagiochilaceae) and *Ambrosia peruviana* (Asteraceae). *Planta Med.* 76, 705–707.
- Asakawa, Y., 1982. Chemical constituents of the hepaticae. In: Herz, W., Grisebach, H., Kirby, G.W. (Eds.), *Progress in the Chemistry of Organic Natural Products*, vol 42 Springer, Vienna 1-285.
- Asakawa, Y., 1990. Biologically active substances from bryophytes. In: Chopra, R.N., Bhatla, S.C. (Eds.), *Bryophyte Development: Physiology and Biochemistry*. CRC Press, Boca Raton, pp. 259–287.
- Asakawa, Y., 1995. Chemical constituents of the bryophytes. In: Herz, W., Kirby, G.W., Moore, R.E., Steglich, W., Tamm, Ch (Eds.), *Progress in the Chemistry of Organic Natural Products*, vol 65 Springer, Vienna 1-618.
- Asakawa, Y., 2008. Liverworts – potential source of medicinal compounds. *Curr. Pharmaceut. Des.* 14, 3067–3088.
- Asakawa, Y., Ludwiczuk, A., 2018. Chemical constituents of bryophytes: structures and biological activity. *J. Nat. Prod.* 81, 641–660.
- Asakawa, Y., Toyota, M., Takemoto, T., Kubo, I., Nakanishi, K., 1980. Insect antifeedant secoaromadendrane-type sesquiterpenes from *Plagiochila* species. *Phytochemistry* 19, 2147–2154.
- Asakawa, Y., Dawson, G.W., Griffiths, D.C., Lallemand, J.-Y., Ley, S.V., Mori, K., Mudd,

- A., Pezechk-Leclaire, M., Pickett, J.A., Watanabe, H., Woodcock, C.M., Zong-Ning, Z., 1988. Activity of drimane antifeedants and related compounds against aphids and comparative biological effects and chemical reactivity of (-) and (+)-polygodial. *J. Chem. Ecol.* 14, 1845–1855.
- Asakawa, Y., Ludwiczuk, A., Harinantenaina, L., Toyota, M., Nishiki, M., Bardon, A., Nii, K., 2012. Distribution of drimane sesquiterpenoids and tocopherols in liverworts, ferns and higher plants: Polygonaceae, Canellaceae and Winteraceae species. *Nat. Prod. Commun.* 7, 685–692.
- Asakawa, Y., Ludwiczuk, A., Nagashima, F., 2013a. Chemical constituents of bryophytes: bio- and chemical diversity, biological activity, and chemosystematics. In: In: Kinghorn, A.D., Falk, H., Kobayashi, J. (Eds.), *Progress in the Chemistry of Organic Natural Products*, vol 95 Springer-Verlag, Vienna 1-796.
- Asakawa, Y., Ludwiczuk, A., Nagashima, F., 2013b. Phytochemical and biological studies of bryophytes. *Phytochemistry* 91, 52–80.
- Asakawa, Y., Ludwiczuk, A., Hashimoto, T., 2013c. Cytotoxic and antiviral compounds from bryophytes and inedible fungi. *J. Pre-Clin. Clin. Res.* 7, 73–85.
- Azevedo, M.M.B., Chaves, F.C.M., Almeida, C.A., Bizzo, H.R., Duarte, R.S., Campos-Takaki, G.M., Alviano, C.S., Alviano, D.S., 2013. Antioxidant and antimicrobial activities of 7-hydroxycalamenene-rich essential oils from *Croton cajucara* Benth. *Molecules* 18, 1128–1137.
- Azevedo, M.M.B., Almeida, C.A., Chaves, F.C.M., Campos-Takaki, G.M., Rozental, S., Bizzo, H.R., Alviano, C.S., Alviano, D.S., 2014. Effects of 7-hydroxycalamenene isolated from *Croton cajucara* essential oil on growth, lipid content and ultrastructural aspects of *Rhizopus oryzae*. *Planta Med.* 80, 550–556.
- Baek, S.-H., Perry, N.B., Lorimer, S.D., 2003. *ent*-Costunolide from the liverwort *Hepatostolophora paucistipula*. *J. Chem. Res. (Synop.)* 14–15.
- Chen, F., Ludwiczuk, A., Wei, G., Chen, X., Crandall-Stotler, B., Bowman, J.L., 2018. Terpenoid secondary metabolites in bryophytes: chemical diversity, biosynthesis and biological functions. *Crit. Rev. Plant Sci.* 37, 210–231. <https://doi.org/10.1080/07352689.2018.1482397>.
- Cheng, A.-X., Lou, Y.-G., Mao, Y.-B., Lu, S., Wang, L.-J., Chen, X.-Y., 2007. Plant terpenoids: biosynthesis and ecological functions. *J. Integr. Plant Biol.* 49, 179–186.
- Chicca, A., Schafroth, M.A., Reynoso-Moreno, I., Erni, R., Petrucci, V., Carreira, E.M., Gertsch, J., 2018. Uncovering the psychoactivity of a cannabinoid from liverworts associated with a legal high. *Sci. Adv.* 4, eaat2166. <https://doi.org/10.1126/sciadv.aat2166>.
- Correa, D.S., Tempone, A.G., Reimao, J.Q., Taniwaki, N.N., Romoff, P., Favero, O.A., Sartorelli, P., Mecchi, M.C., Lago, J.H.G., 2011. Anti-leishmanial and anti-trypanosomal potential of polygodial isolated from steam barks of *Drimys brasiliensis* Miers (Winteraceae). *Parasitol. Res.* 109, 231–236.
- Edris, A.E., 2007. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: a review. *Phytother. Res.* 21, 308–323.
- Frahm, J.-P., 2004. Recent developments of commercial products from bryophytes. *Bryologist* 107, 277–283.
- Franz, Ch, Novak, J., 2010. Sources of essential oils. In: Baser, H.C., Buchbauer, G. (Eds.), *Handbook of Essential Oils. Science, Technology, and Applications*. CRC Press, Taylor & Francis Group, London, New York, pp. 39–81.
- Garcia, P.A., de Oliveira, A.B., Batista, R., 2007. Occurrence, biological activities and synthesis of kaurane diterpenes and their glycosides. *Molecules* 12, 455–483.
- Glime, J.M., 2007. Economic and ethnic uses of bryophytes. In: In: Zander, R.H. (Ed.), *Flora of North America North of Mexico*, vol 27. Oxford University Press, New York, Oxford, pp. 14–41.
- Harinantenaina, L., Quang, D.N., Nishizawa, T., Hashimoto, T., Kohichi, C., Soma, G.-I., Asakawa, Y., 2007. Bioactive compounds from liverworts: inhibition of lipopolysaccharide-induced inducible NOS mRNA in RAW 264.7 cells by herbiterpenoids and cuparenoids. *Phytomedicine* 14, 486–491.
- Harris, E.S.J., 2008. Ethnobotany: traditional uses and folk classification of bryophytes. *Bryologist* 111, 169–218.
- Himejima, M., Kubo, I., 1992. Antimicrobial agents from *Licaria puchuri-major* and their synergistic effect with polygodial. *J. Nat. Prod.* 55, 620–625.
- Holopainen, J.K., Himanen, S.J., Yuan, J.S., Chen, F., Stewart, C.N., 2013. Ecological functions of terpenoids in changing climates. In: Ramawat, K.G., Merillon, J.M. (Eds.), *Natural Products*. Springer-Verlag, Berlin Heidelberg, pp. 2913–2940. [https://doi.org/10.1007/978-3-642-22144-6\\_129](https://doi.org/10.1007/978-3-642-22144-6_129).
- Jansen, B.J.M., de Groot, A., 2004. Occurrence, biological activity and synthesis of drimane sesquiterpenoids. *Nat. Prod. Rep.* 21, 449–477.
- Kato-Noguchi, H., Seki, T., 2010. Allelopathy of the moss *Rhynchostegium pallidifolium* and 3-hydroxy- $\beta$ -ionone. *Plant Signal. Behav.* 5, 702–704.
- Kim, S.J., Park, H.R., Park, E., Lee, S.C., 2007. Cytotoxic and antitumor activity of momilactone B from rice hulls. *J. Agric. Food Chem.* 77, 1702–1706.
- Kodama, M., Tambunan, U.S.F., Tsunoda, T., 1986. Total synthesis of (-)-vitrenal and its biological activity. *Tetrahedron Lett.* 27, 1197–1200.
- Komala, I., Ito, T., Nagashima, F., Yagi, Y., Asakawa, Y., 2010a. Cytotoxic, radical scavenging and antimicrobial activities of sesquiterpenoids from the Tahitian liverwort *Mastigophora diclados* (Brid.) Nees (Mastigophoraceae). *J. Nat. Med.* 64, 417–422.
- Komala, I., Ito, T., Nagashima, F., Yagi, Y., Kawahata, M., Yamaguchi, K., Asakawa, Y., 2010b. Zierane sesquiterpene lactone, cembrane and fusicoccane diterpenoids from the Tahitian liverwort *Chandonanthus hirtellus*. *Phytochemistry* 71, 1387–1394.
- Komala, I., Ito, T., Nagashima, F., Yagi, Y., Asakawa, Y., 2011. Cytotoxic bisbenzyls, germacrane- and pinguisane-type sesquiterpenoids from the Indonesian, Tahitian and Japanese liverworts. *Nat. Prod. Commun.* 6, 303–309.
- Kubo, I., Himejima, M., 1991. Anethole, a synergists of polygodial against filamentous microorganisms. *J. Agric. Food Chem.* 39, 2290–2292.
- Kubo, I., Lee, S.H., 1998. Potentiation of antifungal activity of sorbic acid. *J. Agric. Food Chem.* 46, 4052–4055.
- Kubo, I., Fujita, K., Lee, S.H., 2001. Antifungal mechanism of polygodial. *J. Agric. Food Chem.* 49, 1607–1611.
- Li, S., Niu, H., Qiao, Y., Zhu, R., Sun, Y., Ren, Z., Yuan, H., Gao, Y., Li, Y., Chen, W., Zhou, J., Lou, H., 2018. Terpenoids isolated from Chinese liverworts *Lepidozia reptans* and their anti-inflammatory activity. *Bioorg. Med. Chem.* 26, 2392–2400.
- Lin, X., Peng, Z., Su, Ch, 2015. Potential anti-cancer activities and mechanisms of costunolide and dehydrocostunolactone. *Int. J. Mol. Sci.* 16, 10888–10906.
- Lorimer, S.D., Burges, E.J., Perry, N.B., 1997. Diplophyllolide: a cytotoxic sesquiterpene lactone from the liverworts *Clasmatocolea vermicularis* and *Chiloscyphus subporosa*. *Phytomedicine* 4, 261–263.
- Ludwiczuk, A., Asakawa, Y., 2014. Fingerprinting of secondary metabolites of liverworts: chemosystematic approach. *J. AOAC Int.* 97, 1234–1243.
- Ludwiczuk, A., Asakawa, Y., 2015. Chemotaxonomic value of essential oil components in liverwort species. A review. *Flavour Fragrance J.* 30, 189–196.
- Ludwiczuk, A., Nagashima, F., Gradstein, S.R., Asakawa, Y., 2008. Volatile components from selected Mexican, Ecuadorian, Greek, German, and Japanese liverworts. *Nat. Prod. Commun.* 3, 133–140.
- Matsuo, A., Nakayama, N., Nakayama, M., 1984a. Structures and conformations of (-)-isobicyclergmacrenal and (-)-lepidozenal, two key sesquiterpenoids of the *cis*- and *trans*-10,3-bicyclic ring system from the liverwort *Lepidozia vitrea*: X-ray crystal structure analysis of the hydroxyl derivative of (-)-isobicyclergmacrenal. *J. Chem. Soc. Perkin Trans. 1*, 203–214.
- Matsuo, A., Uto, S., Nozaki, H., Nakayama, M., 1984b. Structure and absolute configuration of (+)-vitrenal, a novel carbon skeletal sesquiterpenoid having plant-growth-inhibitory activity from the liverwort *Lepidozia vitrea*. *J. Chem. Soc. Perkin Trans. 1*, 215–221.
- Nagashima, F., Ohi, Y., Nagai, T., Tori, M., Asakawa, Y., Huneck, S., 1993. Terpenoids from the German and Russian liverworts. *Phytochemistry* 33, 1445–1448.
- Nagashima, F., Kasai, W., Kondoh, M., Fujii, M., Watanabe, Y., Braggins, J.E., Asakawa, Y., 2003. New *ent*-kaurene-type diterpenoids possessing cytotoxicity from the New Zealand liverwort *Jungermannia* species. *Chem. Pharm. Bull.* 51, 1189–1192.
- Nagashima, F., Kondoh, M., Fujii, M., Takaoka, S., Watanabe, Y., Asakawa, Y., 2005. Novel cytotoxic kaurane-type diterpenoids from the New Zealand liverwort *Jungermannia* species. *Tetrahedron* 61, 4531–4544.
- Neves, M., Morais, R., Gafner, S., Stoekli-Evans, H., Hostettmann, K., 1999. New sesquiterpene lactones from the Portuguese liverwort *Targionia lorbeeriana*. *Phytochemistry* 50, 967–972.
- Nozaki, H., Hayashi, K.-I., Nishimura, N., Kawaide, H., Matsuo, A., Takaoka, D., 2007. Momilactone A and B as allelochemicals from moss *Hypnum plumaeforme*: first occurrence in Bryophytes. *Biosci. Biotechnol. Biochem.* 71, 3127–3130.
- Opelt, K., Berg, G., 2004. Diversity and antagonistic potential of bacteria associated with bryophytes from nutrient-poor habitats of the Baltic sea coast. *Appl. Environ. Microbiol.* 70, 6569–6579.
- Otoguro, K., Iwatsuki, M., Ishiyama, M., Namatame, M., Nishihara-Tukashima, A., Kiyohara, H., Hashimoto, T., Asakawa, Y., Omura, S., Yamada, H., 2011. In vitro antitrypanosomal activity of plant terpenes against *Trypanosoma brucei*. *Phytochemistry* 72, 2024–2030.
- Pandey, A.K., Kumar, P., Singh, P., Tripathi, N.N., Bajpai, V.K., 2017. Essential oils: sources of antimicrobials and food preservatives. *Front. Microbiol.* 7, 1–13. <https://doi.org/10.3389/fmicb.2016.02161>.
- Perry, N.B., Burgess, E.J., Tangney, R.S., 1996. Cytotoxic 8,9-secokaurane diterpenes from a New Zealand liverwort, *Lepidolaena taylorii*. *Tetrahedron Lett.* 37, 9387–9390.
- Perry, N.P., Burges, E.J., Foster, L.M., Gerard, P.J., 2003. Insect antifeedant sesquiterpene acetals from the liverwort *Lepidolaena clavifera*. *Tetrahedron Lett.* 44, 1651–1653.
- Qiu, Y.-L., Li, L., Wang, B., Chen, Z., Knoop, V., Groth-Maloney, M., Dombrowska, O., Lee, J., Kent, L., Rest, J., Estabrook, G.F., Hendry, T.A., Taylor, D.W., Testa, C.M., Ambros, M., Crandall-Stotler, B., Duff, R.J., Stech, M., Frey, W., Quandt, D., Davis, C.C., 2006. The deepest divergences in land plants inferred from phylogenomic evidence. *Proc. Natl. Acad. Sci. U.S.A.* 103, 15511–15516.
- Quang, D.N., Asakawa, Y., 2010. Chemical constituents of the Vietnamese liverwort *Porella densifolia*. *Fitoterapia* 81, 659–661.
- Radulovic, N.S., Filipovic, S.I., Zlatkovic, D.B., Dordevic, M.R., Stojanovic, N.M., Randjelovic, P.J., Mitic, K.V., Jevtic-Stoimenov, T.M., Radelovic, V.N., 2016. Immunomodulatory pinguisane-type sesquiterpenes from the liverwort *Porella cordaena* (Porellaceae): the “new old” furanopunginanol and its oxidation product exert mutually different effects on rat splenocytes. *RSC Adv.* 6, 41847–41860.
- Reveglia, P., Cimmino, A., Masi, M., Nocera, P., Berova, N., Ellestad, G., Evidente, A., 2018. Pimarane diterpenes: natural source, stereochemical configuration, and biological activity. *Chirality* 30, 1115–1134.
- Saritas, Y., Mekem Sonwa, M., Iznaguen, H., König, W.A., Muhle, H., Mues, R., 2001. Volatile constituents in mosses (Musci). *Phytochemistry* 57, 443–457.
- Scher, J.M., Burgess, E.J., Lorimer, S.D., Perry, N.B., 2002. A cytotoxic sesquiterpene and unprecedented sesquiterpene-bisbenzyl compounds from the liverwort *Schistochila glaucescens*. *Tetrahedron* 58, 7875–7882.
- Scher, J.M., Speakman, J.B., Zapp, J., Becker, H., 2004. Bioactivity guided isolation of antifungal compounds from the liverwort *Bazzania trilobata* (L.) S.F. Gray. *Phytochemistry* 65, 2583–2588.
- Scher, J.M., Schinkovitz, A., Zapp, J., Wang, Y., Franzblau, S.G., Beker, H., 2010. Structure and anti-TB activity of trachylobanes from the liverwort *Jungermannia exsertifolia* ssp. *cordifolia*. *J. Nat. Prod.* 73, 656–663.
- Shu, Y.-F., Wei, H.-C., Wu, C.-L., 1994. Sesquiterpenoids from the liverworts *Lepidozia vitrea* and *L. fauriana*. *Phytochemistry* 37, 773–776.
- Shukla, S., Bajpai, V.K., Kim, M., 2012. Plants as potential sources of natural immunomodulators. *Rev. Environ. Sci. Biotechnol.* 13, 17–33.
- Sonwa, M., König, W.A., 2003. Chemical constituents of the essential oil of the hornwort *Anthoceros caucasicus*. *Flavour Fragrance J.* 18, 286–289.

- Spjut, R.W., Suffness, M., Cragg, G.M., Norris, D.M., 1986. Mosses, liverworts, and hornworts screening for antitumor agents. *Econ. Bot.* 40, 310–338.
- Toyota, M., Kinugawa, T., Asakawa, Y., 1994. Bibenzyl cannabinoid and bisbibenzyl derivative from the liverwort *Radula perrottetii*. *Phytochemistry* 37, 859–862.
- Toyota, M., Kimura, K., Asakawa, Y., 1998a. Occurrence of *ent*-sesquiterpene in the Japanese moss – *Plagiomnium acutum*: first isolation and identification of *ent*-sesqui- and dolabellane-type diterpenoids from the Musci. *Chem. Pharm. Bull.* 46, 1488–1489.
- Toyota, M., Tanimura, K., Asakawa, Y., 1998b. Cytotoxic 2,3-secoaromadendrane-type sesquiterpenoids from the liverwort *Plagiochila ovalifolia*. *Planta Med.* 64, 462–464.
- Uchoa, P.K.S., da Silva Jr., J.N., Silveira, E.R., Lima, M.A.S., Braz-Filho, R., Costa-Lotufo, L.V., Araujo, A.J., de Moraes, M.O., do O Pessoa, C., 2013. Trachylobane and kaurane diterpenes from *Croton floribundus* Spreng. *Quim. Nova* 36, 778–782.
- van Tooren, B.F., 1990. Effects of a bryophyte layer on the emergence of chalk grassland species. *Acta Oecol.* 11, 155–163.
- Wang, J., Yu, Z., Wang, Ch, Tian, X., Huo, X., Wang, Y., Sun, Ch, Feng, L., Ma, J., Zhang, B., Yang, Q., Ma, X., Xu, Y., 2017. Dehydrocostus lactone, a natural sesquiterpene lactone, suppresses the biological characteristics of glioma, through inhibition of the NF- $\kappa$ B/COX-2 signaling pathway by targeting IKK $\beta$ . *Am. J. Cancer Res.* 7, 1270–1284.
- Wellman, C.H., Osterloff, P.L., Mohluddln, U., 2003. Fragments of the earliest land plants. *Nature* 425, 282–285.
- Whitehead, J., Wittemann, M., Cronberg, N., 2018. Allelopathy in bryophytes – a review. *Lindbergia* 41. <https://doi.org/10.25227/linbg.01097>.
- Wu, C., Gunatilaka, A.A.L., McCabe, F.L., Johnson, R.K., Spjut, R.W., Kingston, D.G.I., 1997. Bioactive and other sesquiterpenes from *Chiloscyphus rivularis*. *J. Nat. Prod.* 60, 1281–1286.
- Wurzel, G., Becker, H., Eicher, T., Tiefensee, K., 1990. Molluscicidal properties of constituents from the liverwort *Ricciocarpos natans* and of synthetic lunularic acid derivatives. *Planta Med.* 56, 444–445.
- Xie, C.-F., Lou, H.-X., 2009. Secondary metabolites in Bryophytes: an ecological aspect. *Chem. Biodivers.* 6, 303–312.
- Xiong, W., Fu, J., Kollner, T.G., Chen, X., Jia, Q., Guo, H., Qian, P., Guo, H., Wu, G., Chen, F., 2018. Biochemical characterization of microbial type terpene synthases in two closely related species of hornworts, *Anthoceros punctatus* and *Anthoceros agrestis*. *Phytochemistry* 149, 116–122.
- Zamfir, M., 2000. Effects of bryophytes and lichens on seedling emergence of alvar plants: evidence from greenhouse experiment. *Oikos* 88, 603–611.