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REVIEW

Phytochemicals from bryophytes: Structures and biological activity

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Abstract: Little attention has been paid to the bryophytes as sources for human diet despite the presence of 23,000 species in the world. Some mosses contain Vitamin B1, tocopherols, prostaglandin-like highly unsaturated fatty acids and phenolic compounds. On the other hand, liverworts contain enantiomeric mono-, sesqui- and diterpenoids similar to those found in vascular plants. Additionally, they possess bibenzyls, bis-bibenzyls and polyketides, many of them showing various bioactivity, such as antimicrobial, antiviral, anti-inflammatory, cytotoxicity against cancer cell lines, muscle relaxing, antioxidant and others. In this paper, the structures of phytochemicals from bryophytes and their biological activities are discussed.

Keywords: bryophytes; terpenoids; bibenzyls; bis-bibenzyls; antimicrobial; antiviral; anti-inflammatory; cytotoxic.

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1. INTRODUCTION

Bryophytes are found everywhere in the world except in the sea, on each continent including The Antarctic. They grow on wet soil or rocks in rivers, lakes and ponds, on the trunks of trees, even on the heads of some lizards. The bryophytes are placed taxonomically between algae and pteridophytes and there are about 23,000 species in the world. They are further divided into three phyla, Bryophyta (mosses 14,000 species), Marchantiophyta (liverworts 6,000 species) and Anthocerotophyta (hornworts 300 species). They are considered to be the oldest terrestrial plants, although no strong scientific evidence for this has appeared in the literature. This hypothesis is mainly based on the resemblance of the present-day liverworts to fossils of the first land plant, the spores of which date back almost 500 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 liverworts.[1–10]

The phytochemistry of bryophytes has been neglected for a long time because they are morphologically very small, difficult to collect in large amounts as pure samples, and their identification is very difficult even under the microscope. Despite of the existence of more than 20,000 species, they are considered to be nutritionally useless to humans because there are many other edible products from nature, such as vegetables, mushrooms, algae and even several ferns and lichens. In fact, no references concerning the use of liverworts as food for humans have been found.

However, some bryological researchers tried to eat some liverworts. *Bazzania pompeana* was prepared as Tempura (Japanese cuisine). Such fried material was edible although the strong mushroomy smell remained in the foods and nothing from sickness occurred (Inoue, private communication). *Marchantia polymorpha* was also fried with flour at 250 °C in a restaurant, and the author (YA), his wife and the chief of the restaurant ate it. The taste was very good like seagrass but the mossy note was retained in the food. Many liverworts produce hot-tasting substances, such capsaicin from paprika and compounds from pepper, that originated from some sesquiterpene and diterpene dialdehydes (see later). Some mosses, for example *Fissidens* and *Rhodobryum* species, elaborate strong sweet taste. These tasty liverworts could be useful as certain spices for foods or as food additives. Some liverworts and mosses produce high amounts of vitamins B_2 and E, and compounds related to them, as discussed later. Thus it is considered that the bryophytes have potentially important food properties.

On the other hand, many moss species have been used as medicinal plants. Most bryophytes used medicinally have been applied as decoctions. Additionally, bryophytes can be crushed and the resulting powder mixed with oil to make an ointment that reputedly heals cuts, burns and external wounds. North American Indians used *Bryum*, *Mnium*, *Philonotis* species and *Polytrichum juniperinum* as medicinal mosses to heal burns, bruises and wounds.[11] *M. polymorpha* has been used as a diuretic in Europe. French liverwort was soaked with a white liquor and the patients drank the resulting mixture of liquor and extracts.[12]

In the literature of the Chinese medicinal spore-forming plants, 24 lichens, 74 sea-algae, 22 mosses, 5 liverworts, 112 fungi and 329 ferns have been listed and their Latin names, morphological characteristics, distribution locations, pharmacological activities and effects, and their prescriptions given in detail.[13] Several mosses have been widely used medicinally in China, to heal burns, bruises, external wounds, snake bites, pulmonary tuberculosis, neurasthenia, fractures, convulsions, scald, uropathy, pneumonia, neurasthenia, *etc*.[7,8,14]

Many species of liverworts show 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, which indicated their potential bioactivity. Furthermore, some liverworts cause intense allergenic contact dermatitis and allelopathy. Although liverworts possess such pharmacologically interesting substances, their isolation and structural elucidation were neglected for almost a century. Then interest emerged for the application of bryophytes as foods for human or domestic animals and for the isolation and the structural elucidation of biologically active substances from bryophytes and their bioassay. Since 1972, more than 1,000 species of bryophytes collected in the world, especially Europe, South America, South–Eastern Asia, Japan, Madagascar and New Zealand, were chemically analyzed with respect to their chemistry, pharmacology, and application as sources of medicinal or agricultural drugs and cosmetic products. The biological activities of liverworts are due to terpenoids and aromatic compounds that are significant constituents of oil bodies in each species.[5,6,15–25]

In this paper, bio- and chemical diversity of the liverworts and the chemical structures of their bioactive compounds are surveyed. A few biosynthesis and hemi- and total synthesis of biologically active compounds are also discussed. Physical characteristics, such as odor and taste, and the possibility of use of bryophytes as foods are also discussed.

2. BIODIVERSITY OF BRYOPHYTES

The Marchantiophyta (liverworts) include two subclasses, the Jungermaniidae and Marchantiidae, 6 orders, 49 families, 130 genera and 6,000 species. There are 54 endemic genera in southern hemispheric countries, such as New

Zealand and Argentina.[24] In Asia, including Japan, a relatively large number of endemic genera has been recorded,[25] while South Africa, Madagascar and both North America and Europe are very poor regions of endemic genera.[26] The richness of endemic genera of bryophytes in the southern hemisphere suggests that the bryophytes might have originated from the past Antarctic islands since 350,000,000–400,000,000 years ago and developed to the northern hemisphere with a long range evolutionary process. In South–East Asia and South America, there are rain forests where many liverworts species still found, but many different species, such as the Lejeuneaceae species, are intermingled with them and their purification is time consuming work.

3. CHEMICAL DIVERSITY OF BRYOPHYTES

The extraction of oil bodies with *n*-hexane or diethyl ether, using ultrasonic apparatus, is very easy for stem-leafy liverworts giving a large amount of crude extract. In the case of thalloid liverworts, the specimens are ground mechanically and then extracted with non-polar solvents. At present, several hundred new compounds have been isolated from liverworts and more than 50 new carbon skeletal terpenoids and aromatic compounds have been found in this class. Most of the liverworts possess characteristic odiferous, pungent and bitter tasting compounds many of which show different activities: antimicrobial, antifungal, antiviral, allergenic contact dermatitis, cytotoxic, insecticidal, anti-HIV, superoxide anion radical release, plant growth regulatory, neurotrophic, NO production inhibitory, muscle relaxing, antiobesity, piscicidal and nematocidal activity. The biological activity ascribed to the liverworts is mainly due to lipophilic sesqui- and diterpenoids, phenolic compounds and polyketides, which are constituents of the oil bodies.

The most characteristic chemical phenomenon of liverworts is that most of sesqui- and diterpenoids are enantiomers of those found in higher plants, although there are a few exceptions, such as germacrane- and guaiane-type sesquiterpenoids. It is very noteworthy that different species of the same genera, such as *Frullania tamarisci* and *F. dilatata* (Frullaniaceae), each produces different sesquiterpene lactone enantiomers. Some liverworts, such as *Lepidozia* species (Lepidoziaceae), biosynthesize both enantiomers. Flavonoids, fatty acids and phytosterols are ubiquitous components in bryophytes. However, the presence of nitrogen- or sulfur-containing compounds in bryophytes was very rare. Recently, several compounds with sulfur and nitrogen in the structure **1**–**4** have been isolated from the Mediterranean liverwort *Corsinia coriandrina* (Corsiniaceae, Marchantiales),[27] and also two prenyl indole derivatives (**5**, **6a**) from the *Riccardia* species (Riccardiaceae), Fig. 1.[2] Skatole (**6b**) have been isolated from or detected in *Asterella* or *Mannia* (Aytoniaceae)[28] and the Tahitian *Cyathodium foetidissimum* (Cyathodiaceae)[29]

and benzyl- (**7a** and **b**) and *β*-phenethyl *β*-methylthioacrylates (**7c**) from the Isotachidaceae (Fig. 1).[2]

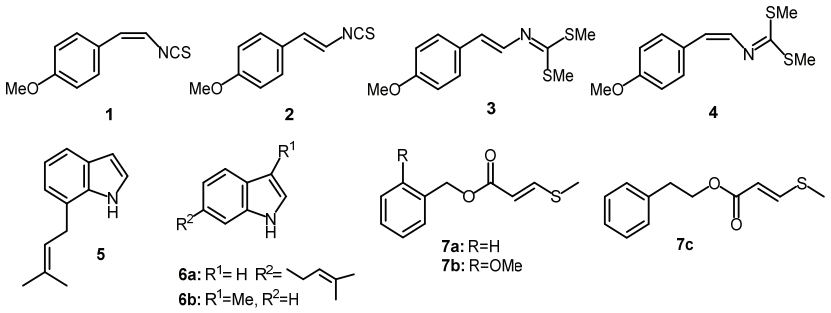


Fig. 1. Compounds isolated from the Corsiniaceae, Riccardiaceae, Aytoniaceae, Cyathodiaceae and Isotachidaceae families.

Highly evolved liverworts belonging to the Marchantiaceae produce phytosterols, such as campe-, stigma- and sitosterol. Almost all liverworts elaborate *α*-tocopherol and the sterol precursor squalene. The characteristic components of the Bryophyta 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 and triterpenoids. Neolignans are one of the most important chemical markers of the Anthoceratophyta.[2] The presence of hydrophobic terpenoids is very rare in the Marchantiophyta. A few bitter kaurene glycosides have been found in *Jungermannia* species. Moreover, a number of flavonoid glycosides have been detected both in liverworts and mosses.[1,2,6]

4. BRYOPHYTES AS FUTURE FOODS

The mosses, *Barbella pendula*, *B. enervis*, *Floribundaria nipponica*, *Hypnum plumaeforme* and *Neckeropsis nitidula* contain high amounts of riboflavin, Vitamin B_2. Chickens and puppies fed on a diet including these powered bryophytes gained more weight than did the control animals. The supplement did not cause any sickness or distaste.[30] Since there are more than 14,000 species of mosses, more species possessing high amount of Vitamin B_2 will be discovered.

The liverworts, *M. polymorpha*, *Pellia endiviifolia* and the mosses *Atrichum undulatum* and *Mnium hornum* produce Vitamin E (*α*-tocopherol) (**8**), Vitamin K (**9**), plastoquinone (**10**), plastohydroquinone (**11**) and *α*-tocoquinone (**12**), Fig. 2).[31,32] The last compound was also found in the moss *Racomitrium japonicum* (Fig. 2).[33–35]

Nishiki and coauthors analyzed 700 liverworts chemically and found that almost all of them contained *α*-tocopherol and squalene.[34] Prostaglandin-like highly unsaturated fatty acids have been found in many mosses, such as *Dicranum scoparium*, *D. japonicum* and *Leucobryum* species (**13**–**17**), Fig. 3.[5,6,36,37] These

and other unsaturated fatty acids are viscous liquids and it is thought that they help in protecting herbivorous animals living in very cold places from cold. For example, arachidonic acid has not been found in higher plants.[38] Such unsaturated fatty acids, like those obtained from fish oils, play an important role as antioxidant in the body. Acetylcholine (**18**) and a cytokinin-like compound N_6-(D_2-isopentenyl)adenine (**19**), Fig. 3, have been found in the hybrid of *Funaria hydrometrica*×*Physcomitrium pyriforme*.[39,40]

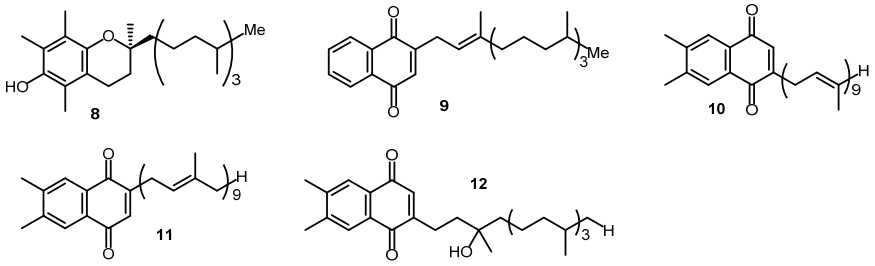


Fig. 2. Lipophilic vitamins and related compounds isolated from *Marchantia polymorpha*, *Pellia endiviifolia*, *Atrichum undulatum* and *Mnium hornum*.

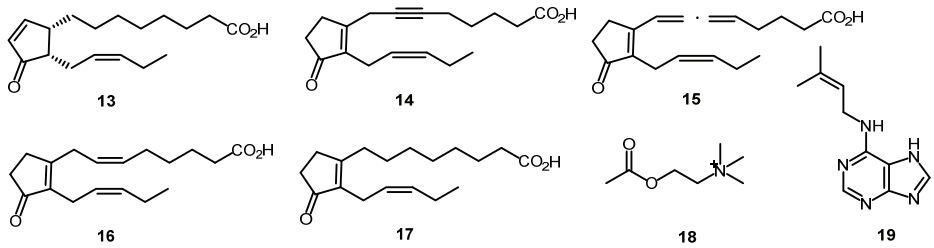


Fig. 3. Prostaglandin-like highly unsaturated fatty acids isolated from *Dicranum* and *Leucobryum* species, and acetylcholine and cytokinin-like compounds from the hybrid of *Funaria hydrometrica* × *Physcomitrium pyriforme*.

Many of the liverworts produce hot-tasting substances that could be used as spices for foods and their food preservation effect because they possess potent antimicrobial and antifungal activity (see later).

5. BIOLOGICALLY ACTIVE COMPOUNDS FROM BRYOPHYTES

The bryophytes could be used as rather medicinal plants as human diet plants at present since they elaborate a number of biologically active secondary metabolites, as shown in this paragraph. The biological characteristics of the secondary metabolites obtained from bryophytes are: 1) characteristic scents, 2) pungency and bitterness, 3) allergenic contact dermatitis, 4) cytotoxic, 5) antimicrobial, antifungal and antiviral, 6) insect antifeedant, mortality, and nematocidal, 7) superoxide anion radical release inhibitory, 8) 5-lipoxygenase, calmodulin, hyaluronidase, cyclooxygenase, DNA polymerase β and α-glucosidase inhibitory, 9) antioxidant, 10) pisci-

cidal, 11) neurotrophic, 12) muscle relaxing and calcium inhibitory, 13) cardiotonic and vasopressin antagonist, 14) liver X-receptor (LXR)α agonist and LXRβ antagonist, 15) cathepsins B and L inhibitory, antithrombin, 16) farnesoid X-receptor (FXR) activation, 17) nitric oxide production inhibitory, 18) plant growth inhibitory, 19) tubulin polymerization inhibitory, 20) sex pheromones. In addition, antiplatelet and brine shrimp lethal activity are included.

5.1. Characteristic scent compounds

All of the liverworts emit a very strong odor when crushed. Lipophilic terpenoids and aromatic compounds found in the oil bodies are responsible for intense sweet-woody, turpentine, sweet-mossy, fungal-like, carrot-like, mushroomy, or seaeed-like scents.[19,31,41–43] Almost all liverworts containing mushroom odor contain 1-octen-3-ol (**20a**) and its acetate (**20b**) which are responsible for the mushroom odor. The unidentified Malaysian liverwort (*Asterella* or *Mannia*) emits 20 % of skatole (**6b**) which is responsible for the unpleasant smell of this liverwort and 80 % of 3,4-dimethoxystyrene (**21**).[28] The stink bug smell of *Cheilolejeunea pallidus* is attributable to (*E*)-dec-2-enal (**22**) and its analogues (**23**-**25**).[44] The characteristic cresol-like smell of *Leptolejeunea elliptica* is due to *p*-ethylanisol (**26**), *p*-ethylphenol (**27**), and *p*-ethylphenylacetate (**28**), Fig. 4.[45]

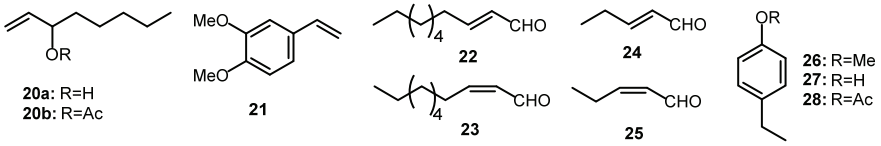


Fig. 4. Some scent compounds from liverworts.

A mixture of (*R*)-dodec-2-en-1,5-olide (**29**) and (*R*)-tetradec-2-en-1,5-olide (**30**) is responsible for the strong milky smell of the liverwort *Cheilolejeunea imbricata* (Fig. 5).[45] *Plagiochila sciophila* elaborates bicyclohumulenone (**31**), which shows an aroma reminiscent of a variety of scents based on a strong woody note, resembling the odor of patchouli, vetiver, cedar wood, iris, moss and carnations.[2] Tamariscol (**32**) from *F. 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 (Fig. 5). Both compounds are commercially important. They are used as perfumes and as perfume components of the powdery floral-, oriental bouquet-, fantastic chypre-, fancy violet- and white rose-types in various cosmetics. It is noteworthy that *Frullania* species producing tamariscol only grow in high mountains.[46,47] Total synthesis of (±)-tamariscol (**32**) has been accomplished using commercially available *p*-methoxyacetophenone in 13 steps.[48] A synthetic minitamariscol, 1-hydroxy-1-(2-methyl-1-propenyl)-cyclohexane (**33**) has a sweet mossy aroma similar to that of tamariscol

itself.[47] There are three chemo-types of liverwort, *Conocephalum conicum*. The types 1, 2 and 3 emit (–)-sabinene (**34a**), (+)-bornyl acetate (**34b**), and methyl cinnamate (**34c**) as the major components, respectively, which are responsible for the characteristic odor of each type.[49] An intense carrot-like odor of *Jungermannia obovata* arises from 4-hydroxy-4-methylcyclohex-2-en-1-one (**35**), Fig. 5.[50,51]

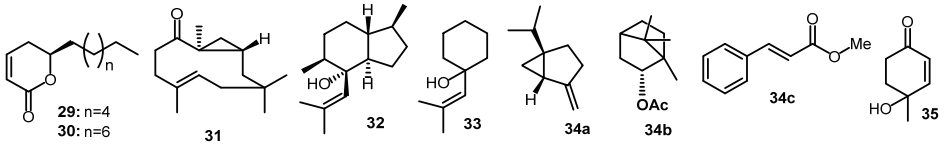


Fig. 5. Scent compounds from *Cheilolejeunea imbricata*, *Plagiochila sciophila*, *Frullania* species, *Conocephalum conicum* and *Jungermannia obovate*.

The strong and distinct mossy odor of *Lophocolea heterophylla* and *L. bidentata* is due to a mixture of (-)-2-methylisoborneol (**36**) and geosmin (**37**) (Fig. 6).[52] The latter compound has also been found in *in vitro* cultured *Symphyogyna brongniartii.*[53] The strong sweet mossy note of *Mannia fragrans* is attributed to grimaldone (**38**).[54] The sweet turpentine-like odor of French *Targionia hypophyll*a is due to a mixture of *cis*- and *trans*-pinocarveyl acetates (**39**, **40**), Fig. 6.[55] The strong sweet-mushroomy scent of the ether extract of *Wiesnerella denudata* is due to (+)-bornyl acetate and a mixture of the monoterpene hydrocarbons, *α*-terpinene, *β*-phellandrene, terpinolene, *α*-pinene, *β*-pinene and camphene.[35] The odor of the steam distillate of *W. denudata* is weaker than that of its ether extract. The steam distillate contains nerol (14%), neryl acetate (27%), and *γ*-terpinene (31 %), but the content of 1-octen-3-ol (7 %, **20a**) and its acetate (**20b**, 2 %), Fig. 4, is lower than that of *C. conicum* belonging to the same genus of *Wiesnerella* (Asakawa, unpublished results). *Gackstroemia decipiens* emits a characteristic scent that is due to the presence of a mixture of (–)-13-hydroxybergamota-2,11-diene (**41**) and the santalene derivatives (**42**–**45**). These compounds were characterized by olfactory effects.[56] Isoafricanol (**46**), Fig. 6, isolated from *Pellia epiphylla* is responsible for the typical odor of its sporophyte.[57]

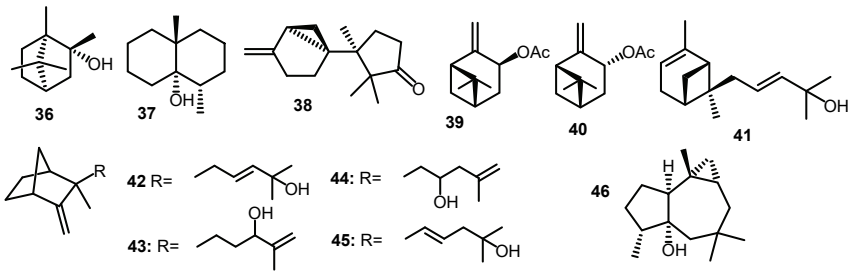


Fig. 6. Scent compounds from *Lophocolea*, *Mania*, *Targionia*, *Wiesnerella*, *Gackstroemia* and *Pellia* species.

5.2. Pungent and bitter tasty compounds

Some genera of liverworts, such as the *Hymenophyton*, *Pellia*, *Porella*, *Trichocoleopsis* and *Wiesnerella* species, elaborate potent pungent constituents,[2,19,58] which exhibit interesting biological activities described in subsequent sections. Most of the North American liverworts contain unpleasant substances, some of which taste like immature green pea seeds or pepper.[59] The *Anastrepta*, *Lophozia*, *Scapania,* and many other stem-leafy liverworts, produce intense bitter principles.

Porella vernicosa complex (*P. arborisvitae*, *P. fauriei*, *P. gracillima*, *P. obtusata* subsp. *macroloba*, *P. roellii* and *P. vernicosa*) contain surprisingly intense pungent substances. *Jamesoniella autumnalis* contains an intense bitter principle the taste of which resembles that of the leaf of lilac and *Swertia japonica* or the root of *Gentiana scabra* var. *orientalis*, but these bitter principles have not yet been isolated. The strong hot taste of the *P. vernicosa* complex is due to (–)--polygodial (**47**),[1,18,41,60] the major component of the Japanese medicinal plant, *Polygonum hydropiper*, Malaysian *P. minus* and Argentinean *P. punctatum* var. *punctatum* (Polygonaceae), Fig. 7.[61] The sacculatane diterpene dialdehyde sacculatal (**48**), two eudesmanolides, diplophyllolide (**50**) and ent-7*α*-hydroxydiplophyllolide (**51**) and germacranolide, tulipinolide (**52**), which possess potent pungency, were isolated from *Pellia endiviifolia*, *Trichocoleopsis sacculata*, *Chiloscyphus polyanthos* and *Wiesnerella denudata*, respectively (Fig. 7). An additional pungent 1-*β*-hydroxysacculatal (**49**) was obtained from *Pellia endiviifolia*, together with several sacculatane-type diterpenoids.[62] The hot taste of *Pallavicinia levieri* and *Riccardia robata* var. *yakushimensis* (belonging to the Metzgeriales) is also due to sacculatal (**48**).[63] Polygodial (**47**) and sacculatal (**48**) have been obtained from cell suspension cultures from *P. vernicosa* Lindb. and polygodial has also been detected in *Pellia neesiana* and *P. endiviifolia*, respectively (Fig. 7).[64,65] When the whole plant of the stem-leafy liverwort, *Plagiochila asplenioides*, *P. fruticosa*, *P. ovalifolia* and *P. yokogurensis* that contain plagiochiline A (**53**) and plagiochiline I (**54**), is chewed a potent pungent taste is slowly felt.

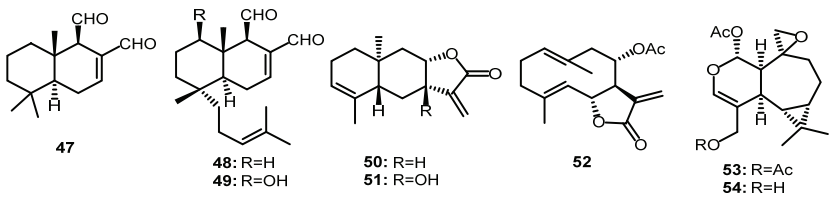


Fig. 7. Pungent and bitter substances from *Porella*, *Pellia*, *Trichocoleopsis*, *Chiloscyphus Wiesnerella* and *Plagiochila* species.

It is suggested that both compounds might be converted into pungent unsaturated dialdehyde by human saliva. In fact, enzymatic treatment of **53** with amyl-

ase in phosphate buffer or with human saliva produces two strong pungent, plagiochilal B (**55**) the partial structure of which is similar to that of the pungent drimane-type sesquiterpene dialdehyde, polygodial (**47**), and furanoplagiochilal (**56**), Fig. 8.[66]

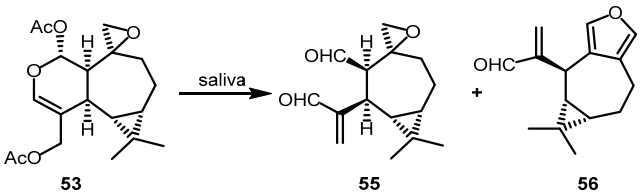


Fig. 8. Formation of pungent di- (**55**) and monoaldehyde (**56**) from plagiochiline A (**53**) by saliva.

The pungent taste of *Porella acutifolia* subsp. *tosana* is due to the presence of hydroperoxysesquiterpene lactones, 1*α*- (**57**), and 1*β*-hydroperoxy-4*α*,5*β*-epoxygermacra-10(14),11(13)-dien-12,18*α*-olides (**58**), Fig. 9.[67] The New Zealand liverwort, *Hymenophyton flabellatum* produces a different pungent tasting substance from the other aforementioned liverworts. 1-(2,4,6-Trimethoxyphenyl)-buta-(2*E*)-en-1-one (**59**) is responsible for the pungency of this liverwort (Fig. 9).[68] Most of the species belonging to the Lophoziaceae produce bitter substances. *Gymnocolea inflata* is persistently bitter and induces vomiting when a few leaves are chewed for several seconds. This surprisingly intense bitterness is due to the clerodane diterpene lactone, gymnocolin A (**60**).[31] *Jungermannia infusca* has an intense bitter taste that is due to the presence of the infuscasides A-E (**61**–**65**), Fig. 9. These were the first reported isolation of glycosides from liverworts.[69]

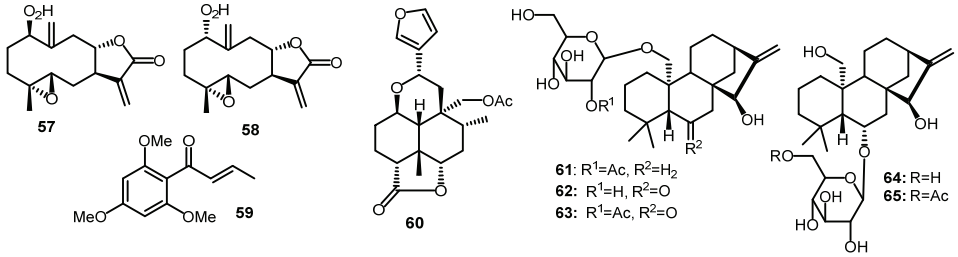


Fig. 9. Pungent and bitter substances from *Porella*, *Hymenophyton*, *Gymnocolea* and *Jungermannia* species.

Anastrepta orcadensis, *Barbilophozia lycopodioides* and *Scapania undulata* are also bitter liverworts from which the highly oxygenated bitter diterpenoids, anastreptin A (**66**), barbilycopodin (**67**)[50,70] and scapanin A (**68**)[71] have been isolated, respectively, Fig. 10.

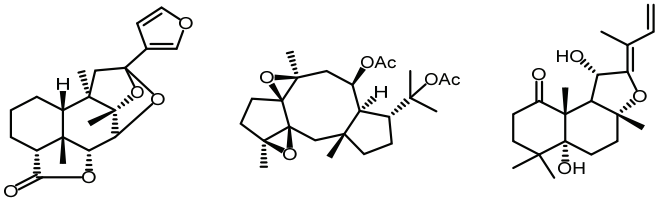


Fig. 10. Bitter substances from *Anastrepta*, *Barbilophozia,* and *Scapania* species.

5.3. Allergenic contact dermatitic compounds

Frullania species are notable as liverworts that cause very intense allergenic contact dermatitis. The allergy-inducing substances are sesquiterpene lactones, (+)-frullanolide (**69**) and (–)-frullanolide (**70**), which have been isolated from *Frullania dilatata* and *F. tamarisci* subsp. *tamarisci*, respectively (Fig. 11).[1] Both dihydrofrullanolides (**71**, **72**) with α-methyl-γ-butyrolactones isolated from the liverworts mentioned above do not cause allergy. *F. asagrayana*, *F. bolanderi*, *F. brasiliensis*, *F. eboracensis*, *F. franciscana*, *F. inflata*, *F. kunzei*, *F. nisquallensis*, *F. riparia* and the other *Frullania* species, which contain sesquiterpenes (**73**–**79**) with α-methylene-γ-butyrolactones, cause strong allergenic contact dermatitis (Fig. 11).[72]

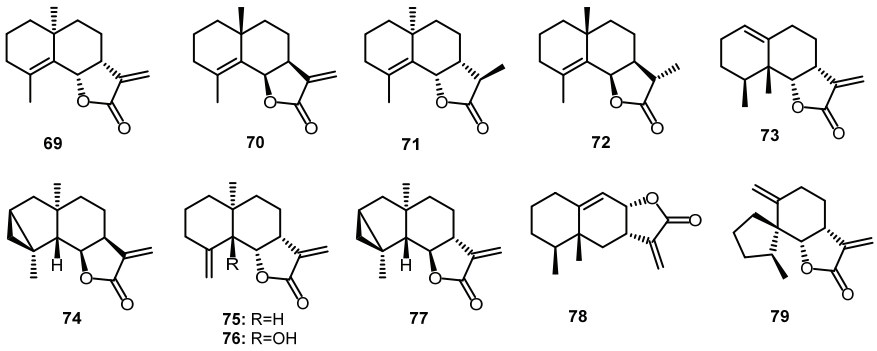
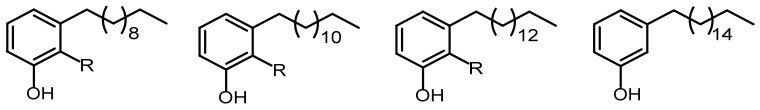


Fig. 11. *Frullania* sesquiterpene lactones.

The allergens of *Schistochila appendiculata* are a mixture of long chain alkylphenols, such as 3-undecyl- (**80**), 3-tridecyl (**81**), 3-pentadecyl (**82**), and 3-heptadecyl phenols (**83**), long chain alkyl salicylic acids, 6-undecyl- (**84**), 6-tridecyl- (**85**), 6-pentadecyl salicylates (**86**) and their potassium salts, potassium 6-undecyl- (**87**), 6-tridecyl- (**88**), and 6-pentadecyl salicylates (**89**) as well as 6-undecyl catechol (**90**), Fig. 12.[72] Such dermatitis is similar to that caused by the long chain alkylphenols of the fruit of *Ginkgo biloba* and Anacardiaceae plants, such as *Toxicodendron vernicifluum* and *Rhus succedranea*.



80: R=H
84: R=CO_2H
87: R=CO_2K
90: R=OH

81: R=H
85: R=CO_2H
88: R=CO_2K

82: R=H
86: R=CO_2H
89: R=CO_2K

83

Fig. 12. *Schistochila appendiculata* allergenic substances.

5.4. Cytotoxic compounds

Germacranolides, and guaianolides isolated from liverworts, exhibit cytotoxic activity against KB nasopharyngeal and P-388 lymphocytic leukemia cells.[2] The crude ether extracts of liverworts *B. 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_{50} value range 4–20 μg mL^{-1}). 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_{50} values > 20 μg mL^{-1} – Asakawa, unpublished results).

Several sesquiterpene lactones, such as eudesmanolides, 2*α*,5*β*-dihydroxybornane-2-cinnamate (**91**) from *C. conicum* and lunularin (**92**), Fig. 13, from *Dumortiera hirsuta*, exhibited cytotoxic activity against human HepG2 cells, with IC_{50} values of 4.5 and 7.4 μg mL^{-1}, respectively.[73] Many *Plagiochila* species contain cytotoxic plagiochiline A (**53**, 0.28 μg mL^{-1}) against KB cell.[31] The ether extract of *Plagiochila ovalifolia* showed inhibitory activity against P 388 murine leukemia cells, and its constituents, plagiochiline A (**53**), plagiochiline A-15-yl octanoate (**94**) and 14-hydroxyplagiochiline A-15-yl (2*E*,4*E*)--dodecadienoate (**95**), Fig. 13, exhibited IC_{50} values of 3.0, 0.05 and 0.05 μg mL^{-1}, respectively.[74] Lunularic acid (**93**) and plagiochiline A-15-yl decanoate (**96**) from *P. ovalifolia*, polygodial (**47**) from *P. vernicosa* complex, as well as sacculatal (**48**), Fig. 7, from *P. endiviifolia* showed cytotoxic activity against a human melanoma cell line (IC_{50} value range 2–4 μg mL^{-1}). Compound **48** was also cytotoxic for Lu1 (IC_{50} 5.7 μg mL^{-1}), KB (3.2), LNCaP (7.6) and ZR-75-1 cells (7.6) (Cordell, Pezzuto, Asakawa, unpublished results). Aponte *et al.*[75] also reported that plagiochilines A (**53**), I (**54**) and M (**96**), Fig. 13, 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 **53** exhibited the strongest activity against all the above-mentioned cell lines at a concentration between GI_{50} 1.4–6.8 μM. Compound **53** possessed antileishmania activity against *Leishmania amazonensis* axenic amastigotes at a concentration of IC_{50}

7.1 μM and trypanocidal activity against *Trypanosoma cruzi* trypmastigotes at *MIC* 14.5 μM. Lepidozenolide (**97**), Fig. 13, showed potent cytotoxicity when evaluated in the P-388 murine leukemia cell line (IC_{50} 2.1 μg mL^{-1}).[76] The liverwort *Chandonanthus hirtellus* produces a new sesquiterpene lactone, chandolide (**98**),[77] 13,18,20-tri-*epi*-chandonanthone (**99**)[78] and anadensin (**100**), Fig. 13, that were evaluated for cytotoxic activity against the HL-60 leukemia cell line, and exhibited IC_{50} values of 5.3, 18.1 and 17.0 μg mL^{-1}, respectively.

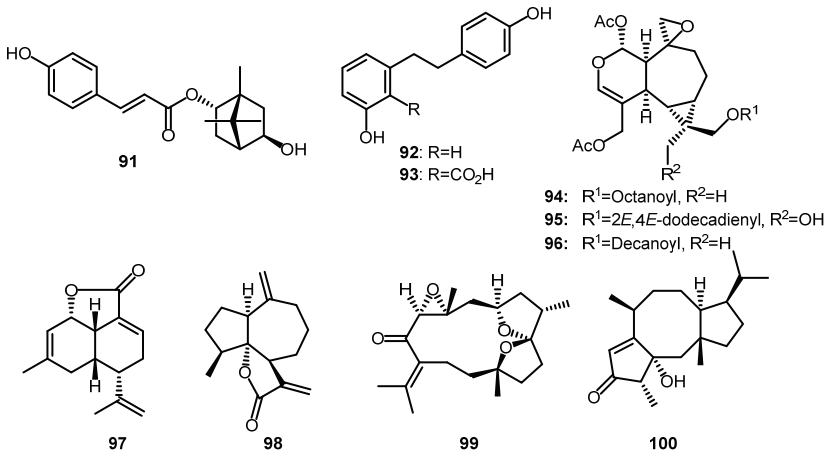


Fig. 13. Cytotoxic compounds from *Conocephalum*, *Dumortiera*, *Plagiochila*, *Pellia*, *Leishmania*, and *Chandonanthus* species.

6*α*-Methoxyfusicoauritone (**101**) isolated from the same liverwort showed some cytotoxicity against KB cells (IC_{50} 11.2 μg mL^{-1}), although compounds **99** and **100** were inactive.[77,79] 13-Hydroxychiloscyphone (**102**) from *Chilosyphus rivularis* was tested against the RS322, RS188N and RS321 yeast strains. It showed IC_{12} values of 75 and 88 μg mL^{-1} for strains RS321 and RS322. These data are characteristic of a selective DNA-damaging agent that does not act as a topoisomerase I or II inhibitor. Compound **102** also showed cytotoxic activity against lung carcinoma A-549 cells (IC_{50} value 2.0 μg mL^{-1}).[80] (–)-*ent*-Arbusculin B (**103**) and (–)-*ent*-costunolide (**104**) from *Hepatostolonophora paucistipula*, showed cytotoxic activity against P388 murine leukemia cells, with IC_{50} values of 1.1 and 0.7 μg mL^{-1} (Fig. 14).[81] Costunolide (**105**) isolated from *Frullania nisquallensis* showed growth inhibitory activity against the A-549 human lung carcinoma cell line with an IC_{50} value of 12 μg mL^{-1} and moderate, but selective, DNA-damaging activity against the RS321N, RS322YK and RS167K mutant yeast strains, with IC_{12} values of 50, 150, and 330 μg mL^{-1}.[82] Naviculyl caffeate (**106**), Fig. 14, from *Bazzania novae-zelandiae*, demonstrated growth inhibitory effects against P-388 murine leukemia cells with a GI_{50} value

of 0.8–1.1 μg mL^{-1}, although naviculol (**107**), Fig. 14, was inactive.[83] Riccardiphenol C (**108**), Fig. 15, from *Riccardia crassa* showed slight cytotoxicity against BSC-1 (African green monkey kidney epithelial) cells at 60 μg disc^{-1}.[84] The ether and methanol extracts of the Tahitian *Mastigophora diclados* showed cytotoxic activity against HL 60 cells at IC_{50} 2.4 and 13.1 μg mL^{-1} and KB cells at 14.6 and 32.5 μg mL^{-1}, respectively.[85]

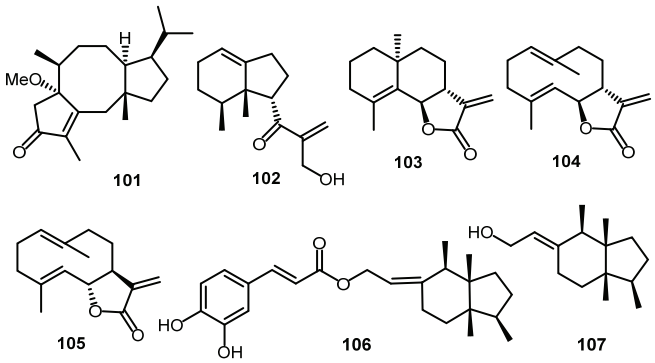


Fig. 14. Compounds from *Chilosyphus*, *Hepatostolonophora*, *Frullania* and *Bazzania* species.

(–)-Diplophyllolide (**43**), *α*-herbertenol (**109**), (–)-herbertene-1,2-diol (**110**), mastigophorene C (**113**) and mastigophorene D (**114**) isolated from both extracts were cytotoxic against HL 60 cells with IC_{50} values of 2.5, 1.4, 12.8, 1.4 and 2.4 μg mL^{-1} (Fig. 15). They also showed cytotoxicity against KB cells (IC_{50} values of 14.2, 3.3, 12.5, 11.8 and 14.8 μg mL^{-1}). 2-Methoxy (**111**) and diacetoxy derivatives (**112**) of (–)-herbertene-1,2-diol (**110**) showed evidence of having less potent cytotoxicity than the parent compound against both HL 60 and KB cells (Fig. 15). However, (–)-diplophyllin (**115**) did not indicate cytotoxicity against either of these cell lines.[85] Glaucescenolide (**116**), Fig. 15, from *Schistochila glaucescens* showed cytotoxic activity against P-388 mouse leukemia cells (IC_{50} 2.3 μg mL^{-1}).[86] *ent*-1*β*-Hydroxykauran-12-one (**117**), isolated from *Paraschistochila pinnatifolia* and 1*α*-hydroxy-*ent*-sandaracopimara-8(14),15-diene (**118**), Fig. 16, from *Trichocolea mollissima* showed IC_{50} values of 15 and >25 μg mL^{-1}, when evaluated against this cell line.[87]

The ethanol-soluble extract of *Lepidolaena taylorii*, which showed cytotoxicity against the P-388 cell line (IC_{50} 1.3 μg mL^{-1}), was purified to give the 8,9--secokaurane diterpenoids, rabdoumbrosanin (**119**), 16,17-dihydrorabdoumbrosanin (**120**), 8,14-epoxyrabdoumbrosanin (**121**) and their related compounds **122**–**125**, and also the *ent*-kaur-16-en-15-ones (**127**–**130**), Fig. 16. In turn, *L. palpebrifolia* also elaborated the 8,9-*seco*kauranes (**119**–**121**). The cytotoxicity of these *ent*-8,9-*seco* and *ent*-kaurenes was tested against mouse P-388 leukemia and several human tumor cell lines, inclusive of six leukemia and a range of

organ-specific cancer cell lines. Compounds **119** and **121** showed the most potent cytotoxic activities (mean IC_{50} values of 0.006 and 0.27 μg mL^{-1}; GI_{50} values of 0.10 and 1.2 μM, respectively). Compound **120** also showed cytotoxicity against P-388 cell at 0.80 μM). Compound **119** (including 10 % of **120**) and **121** showed differential cytotoxicity *in vitro* when tested against five further leukemia cell lines with **119** showing an average IC_{50} value of 0.4 μM; however, cell growth was not inhibited by **121** (IC_{50} > 50 μM). The growth of seven colon cancer cell lines were inhibited also by **119** (mean IC_{50} value, 6 μM).[88,89] Compounds **119** and **121** were tested in an *in vivo* hollow fiber model system, in which neither compound was active at the doses tested (18 and 12 mg kg^{-1} for **108** and 150 and 100 mg kg^{-1} for **110**), Fig. 15. Compound **114** was the most active against several leukemia cell lines (mean GI_{50} 0.3 μM) and least active against various central nervous system cancer cell lines (mean GI_{50} 6 μM).[89] *Ent*-kaurene (**131**) and (**132**) from the New Zealand *Jungermannia* species (Fig. 16) showed weak cytotoxic activity against P-388 at 0.48 and 25 μg mL^{-1}, respectively.[90] Among the isolated compounds, 8,9-secokaurenes (**119**, **121**, **125**), Fig. 16, showed selective toxicity amongst human tumor cell lines at a concentration of 1.2, 2.5 and 1.5 μM, respectively. The mode of action for the cytotoxicity of the *ent*-8,9-*seco*-kaur-16-en-15-one and *ent*-kaur-16-en-15-one series was supported by Michael addition of a thiol to the C-16–C-17 double bond of **119**, but the C-8–C-14 double bond of **120** was relatively unreactive.[88,89] Clavigerins A–D (**133**–**136**) isolated from *Lepidolaena clavigera* (Fig. 16) showed weak cytotoxicity (30 μg disc^{-1}) against BSC cells.[91] A new atisane-2 derivative (**137**) from *Lepidolaena clavigera* exhibited weak inhibitory activity against mouse lymphocytic leukemia cells (P-388) with an IC_{50} value of 16 μg mL^{-1}.[92] *α*-Zeorin (**138**) has been isolated from several liverworts and displayed cytotoxic activity against P-388 cells with an IC_{50} of 1.1 μg mL^{-1}.[93,94] (Fig. 16).

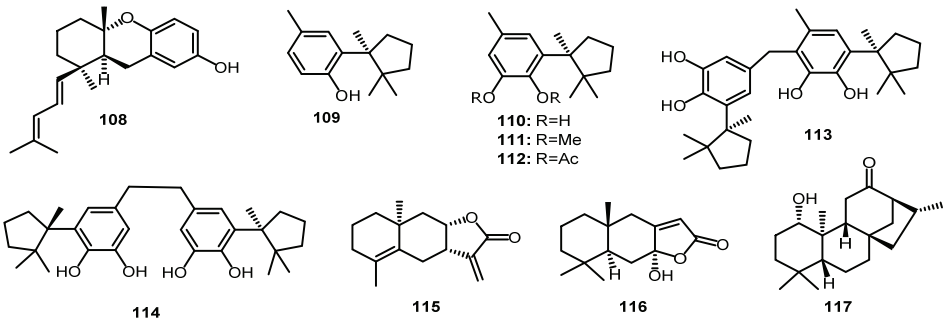


Fig. 15. Cytotoxic compounds from *Riccardia*, *Schistochila* and *Paraschistochila* species.

The crude ether extract of two unidentified Indonesian and Tahitian *Frullania* species exhibited cytotoxic activity against both the HL-60 and KB cell

lines, with at EC_{50} values of 6.7 and 1.6 μg mL^{-1} (HL-60 cells) and 1.6 and 11.2 μg mL^{-1} (KB cells), respectively.[95]

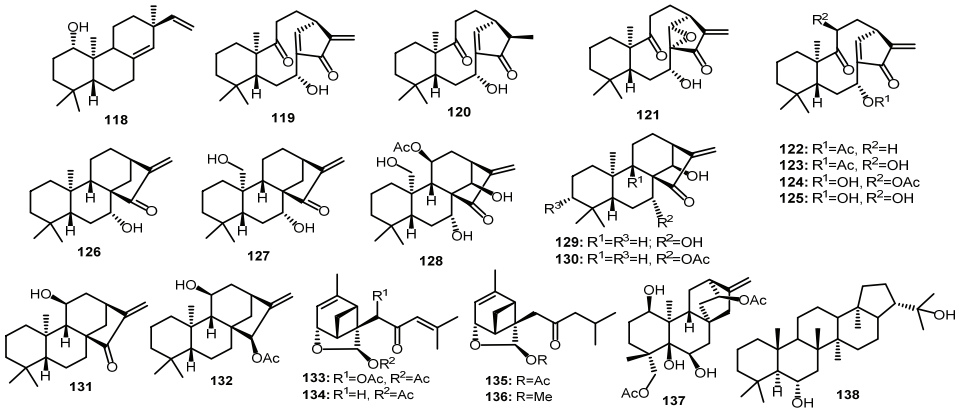


Fig. 16. Cytotoxic compounds from *Lepidolaena* and *Jungermannia* species.

Bioactivity-guided fractionation of the Indonesian sample led to the isolation of (+)-3*α*-(4'-methoxybenzyl)-5,7-dimethoxyphthalide (**139**), (–)-3*α*-(3'-methoxy--4',5'-methylenedioxybenzyl)-5,7-dimethoxyphthalide (**140**), together with 3-methoxy-3',4'-methylenedioxybibenzyl (**141**), 2,3,5-trimethoxy-9,10-dihydrophenanthrene (**142**) and atranorin (**143**), among which **139** possessed the most potent cytotoxic activity against HL-60 and KB cells showing IC_{50} values of 0.92 and 0.96 μM (Fig. 17). The other compounds (**140**–**142**) and the 6'-nitro derivative of **141** indicated much less activity against both cell lines (HL-60 IC_{50} value range, 6.3–96.6 μM; KB IC_{50} value range, 5.5–124.3 μM). From the Tahitian sample, tulipinolide (**52**) and costunolide (**105**) were obtained and the latter germacranolide showed cytotoxic activity against the HL-60 cell line (IC_{50} 4.6 μM).[95] *Porella perrottetiana* produced cytotoxic compounds against both HL-60 and KB cell lines.[95] The same treatment as mentioned above gave 4*α*,5*β*-epoxy-8-*epi*-inunolide (**144**), perrottetianal A (**145**), Fig. 17, and 7-keto-8-carbomethoxy-pinguisenol (**146**), Fig. 18.

The former two compounds exhibited moderate or weak cytotoxicity against HL-60 (IC_{50} 8.5 and 2.7 μM) and KB cells (IC_{50} 52.4 and 46.3 μM).[95] 7*α*-Hydroxy-8-carbomethoxypinguisenol (**147a**) and acutifolone A (**147b**) prepared from **146** by reduction and dehydration (Fig. 18) were evaluated against HL-60 (IC_{50} 83.10 and >177 μM) and KB cells (IC_{50} 2.7 and 46.6 μM). It was suggested that the dienone group plays an important role in the mediation of cytotoxicity on HL-60 cells.[95]

Macrocyclic bis-bibenzyls such as marchantin A (**148a**) and riccardin A (**151b**), Fig. 19, were firstly isolated from liverworts by Asakawa *et al.*[1,3] Up to now, more than 100 macrocyclic and acyclic bis-bibenzyls have been isolated from

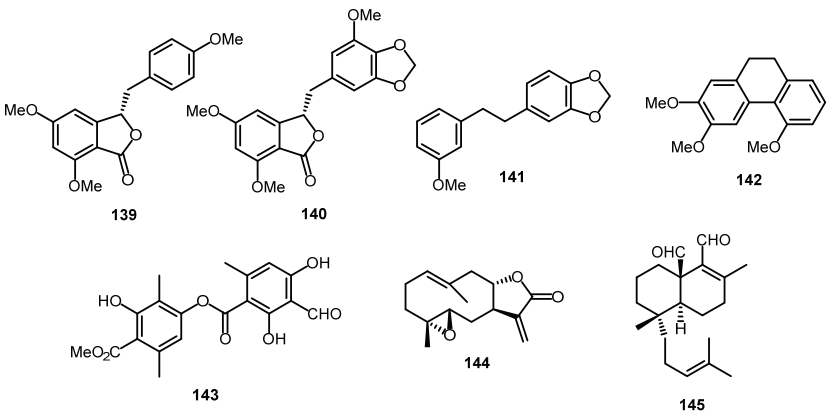


Fig. 17. Cytotoxic compounds from Tahitian and Indonesian *Frullania* species.

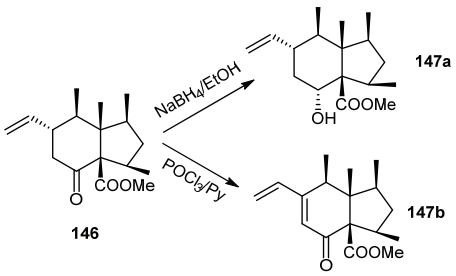
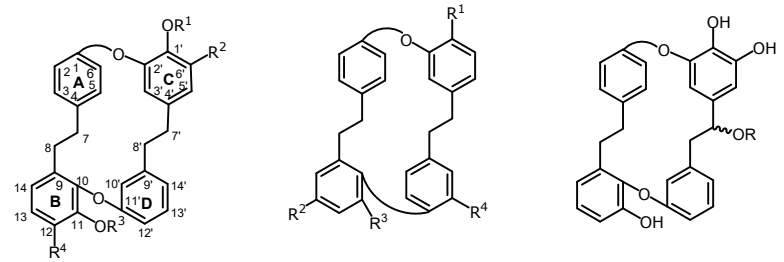


Fig. 18. Preparation of diol (**147a**) and dienone (**147b**) from **146.**



148a: $R^1=R^3=R^4=H$, $R^2=OH$
148b: $R^1=R^3=Me$, $R^2=OMe$, $R^4=H$
148c: $R^1=R^3=Ac$, $R^2=OAc$, $R^4=H$
149a: $R^1=R^3=H$, $R^2=R^4=OH$
149b: $R^1=R^3=Me$, $R^2=R^4=OMe$
150: $R^1=R^2=R^3=R^4=H$

151a: $R^1=R^2=R^4=OH$; $R^3=H$
151b: $R^1=R^4=OH$; $R^3=H$; $R^2=OMe$
151c: $R^1=OMe$; $R^2=R^4=OH$; $R^3=H$
151d: $R^1=OMe$; $R^3=R^4=OH$; $R^2=H$

152: R=H
153a: R=Me
153b: R=Et

Fig. 19. Bis-bibenzyls of the marchantin and riccardin type.

many liverworts and their stereo structures established.[2,15,23,96] The cyclic bis-bibenzyls such as marchantin (*e.g.*, **148**, **149**, **150**) and riccardin series (*e.g.*, **151**), Fig. 19, might be biosynthesized from bibenzyls that correspond chemically to dihydrostilbenes.[97] This assumption was proved by feeding experiments using radioactive and ^{13}C-labelled precursors, such as L-[*U*-^{14}C]-phenylalanine,

[*U*-^{14}C]dihydro-*p*-coumaric acid, [2-^{13}C]acetate and L-[^{13}COOH]phenylalanine.[98,99] Marchantin C (**150**) was biosynthesized by the coupling of two lunularic acid (**93**), followed by cytochrome P-450, named marchantin C hydroxylase to afford marchantin A (**148a**), Fig. 20.

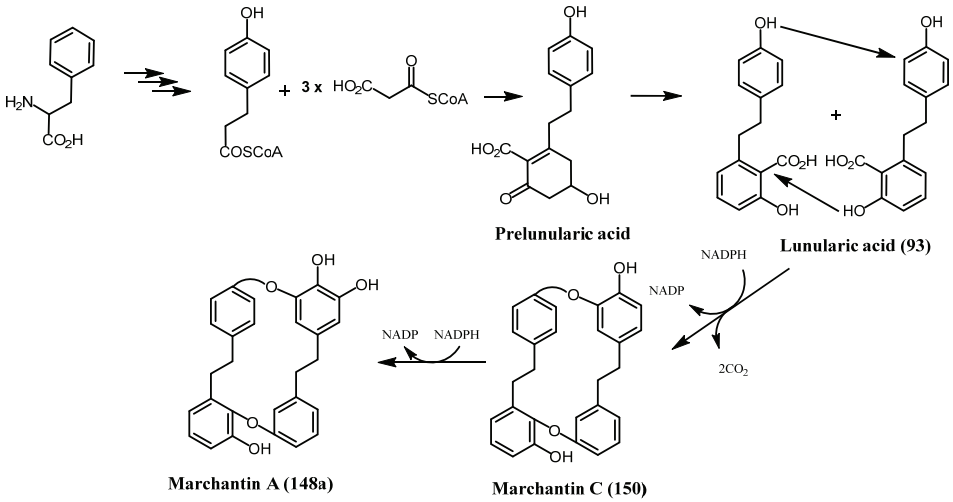


Fig. 20. Biosynthetic pathway of marchantin A.

Macrocyclic bis-bibenzyls produced in liverworts possess various biological activities, such as antimicrobial, antifungal, muscle relaxant, cytotoxicity against KB cells, inhibitory activity against DNA-polymerase *β*, cardiovascular activity, anti-HIV, and antitumor activity.[1,2,32,100] The methanol extract (**105g**) of a Japanese *M. polymorpha* was chromatographed over silica gel and Sephadex LH-20 to give the cyclic bis-bibenzyls, marchantin A (**148a**, 30 g), and its analogues, marchantins B (**148b**), C (**150**), D (**152**), E (**153a**), G (**154**), J (**153b**, Figs. 19 and 21. The yield of marchantin A (**148a**) is dependent upon the particular *Marchantia* species being investigated. Pure **148a** (80–120 g) was isolated from 6.67 kg of dried *M. paleacea* var. *diptera*. This thalloid liverwort elaborates not only the marchantin series, including marchantins A (**148a**), B (**149a**), D (**152**) and E (**153a**, Fig. 19, but also the acyclic bis-bibenzyls, perrottetin F (**155b**) and paleatin B (**156**). Marchantins A (**148a**), B (**149a**), D (**152**), perrottetin F (**155b**) and paleatin B (**156**), Fig. 21, showed cytotoxicity against KB cells (IC_{50} range 3.7––20 μM) and P-388 (*T*/*C* 117).[32]

The Italian liverwort, *Lunularia cruciata* elaborates seven new bis-bibenzyls (**153c**–**i**), along with lunularin (**92**), perrottetins E (**155a**) and F (**155b**), riccardin C (**151a**), F (**151c**), and G (**151d**). Compounds **153e** and **153g** and riccardin G (**151d**) showed cytotoxicity against the A549 lung cancer cell line with IC_{50} values of 5.0, 5.0 and 2.5 μM (Fig. 22).[101]

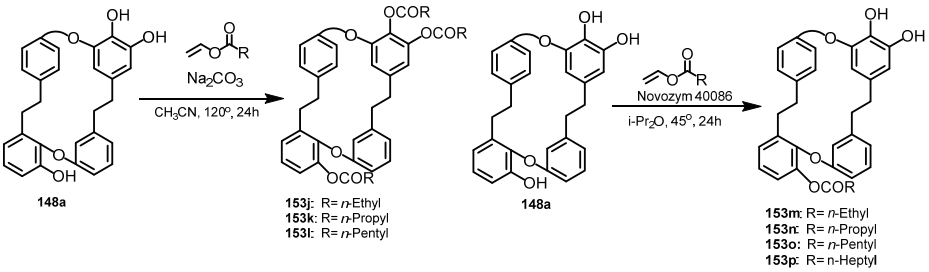


Fig. 21. Marchantin A derivatives obtained by chemical and enzymatic modifications.

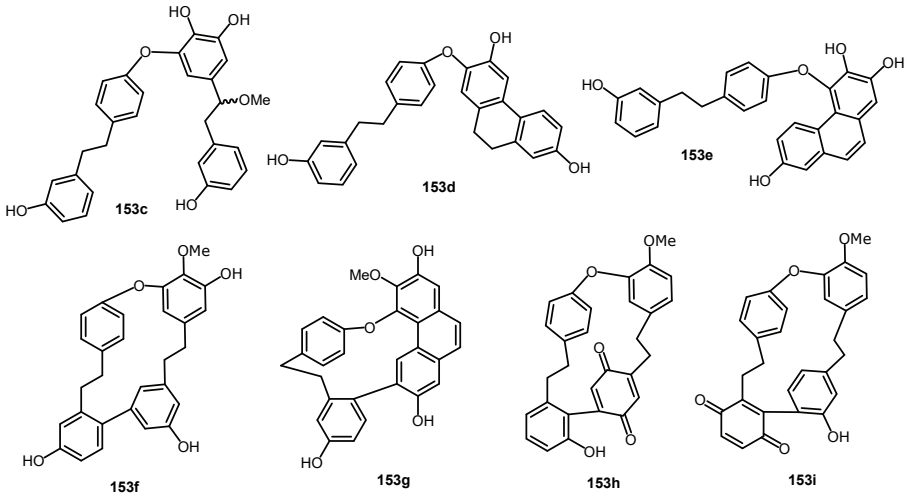


Fig. 22. Seven new bis-bibenzyls from *Lunularia cruciata.*

Marchantin A (**148a**) induced cell growth inhibition in human MCF-7 breast cancer cells at IC_{50} 4.0 μg mL^{-1}. Fluorescence microscopic and a Western blot analysis indicated that compound **148a** induced apoptosis of MCF-7 cells through a caspase-dependent pathway. The phenolic hydroxy groups at C-1′ and C-6′ are responsible for inducing cytotoxic and antioxidant activity.[103] In order to confirm the above hypothesis, seven previously undescribed marchantin A ester derivatives (**153j**–**p**) were synthesized chemically and enzymatically and tested on MRC-5 healthy human lung fibroblast, A549 human lung cancer, and MDA-MB--231 human breast cancer cell lines. All tested compounds were less cytotoxic in comparison to marchantin A (**148a**), but they also exhibited lower cytotoxicity against healthy cells.[102] The above results showed the C-ring plays an important role in cytotoxic activity.

Marchantin C (**150**, Fig. 17, and its dimethyl ether, 7,8-dehydro-marchantin C and its dimethyl ether were synthesized and their possible modulatory effects on P-glycoprotein in VCR-resistant KB/VCR cells were investigated.[104] The

results indicated that **150** was the most potent inhibitor of cell proliferation in both KB and KB/VCR cells among these four synthetic compounds, while the three derivatives of **150** have a little antiproliferative activity. Potent apoptosis in KB/VCR cells was induced by treatment with 16 μM of the dimethyl ether of marchantin C (**150**) and 0.2 μM VCR for 48 h.[104] Marchantin C also showed the induction of apoptosis of human glioma A172 cells at 8–16 μM.[105]

Marchantin C (**150**), neomarchantins A (**157**) and B (**158**), and a mixture of sesquiterpene/bis-bibenzyl dimers, GBB A (**159**) and GBB B (**160**), Fig. 23, from *Schistochila glaucescens* showed growth inhibitory activity against the P-388 cell line, with IC_{50} values of 18, 7.6, 8.5 and 10.3 μg mL^{-1}, respectively.[86] Riccardin D (**161**) from *Monocolea forsteri*[2] and *M. polymorpha*[106,107] indicated antiproliferative activity on human glioma A172 cells and induction of apoptosis at 16 μM. Compound **161** also showed potent effects in reversing P-glycoprotein-mediated multidrug resistance.[106]

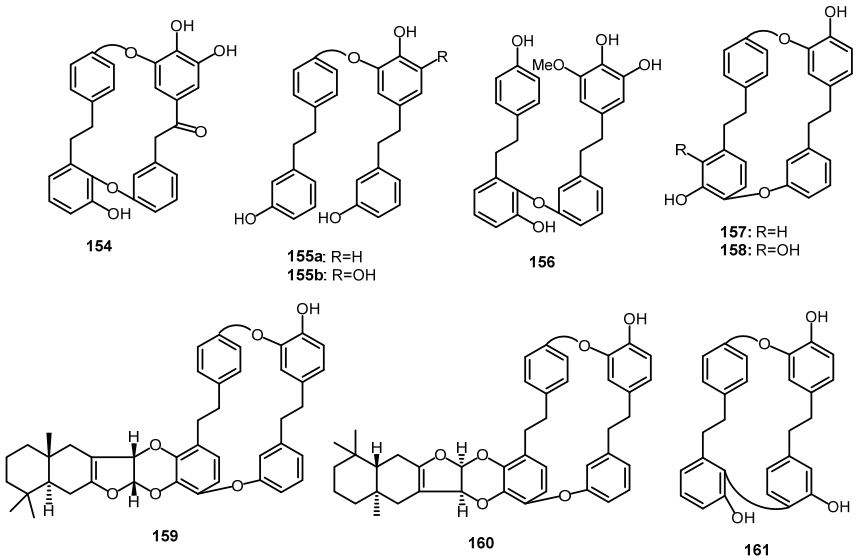


Fig. 23. Bis-bibenzyls from *Schistochila glaucescens* and *Marchantia polymorpha*.

2-Hydroxy-3,4,6-trimethoxyacetophenone (**162**) and 2-hydroxy-4,6-dimethoxyacetophenone (**163**) from *Plagiochila fasciculata* were inactive against the P-388 cell line (IC_{50} values of > 50 μg mL^{-1}).[108] *Trichocolea lanata* and *T. tomentella* produced tomentellin (**164**), Fig. 24, which showed inhibitory activity against African green monkey kidney epithelial (BSC-1) cells at 15 μg mL^{-1}, with no antiviral effects against herpes simplex or polio viruses. Demethoxytomentellin (**165**) from *T. tomentella* showed a similar cell growth inhibitory effect, indicating that both an allylic ether and a conjugated enone substructure are

required for such activity.[109] Methyl-4-[(2*E*)-3,7-dimethyl-2,6-octadienyl]oxy]-3-hydroxybenzoate (**166**), isolated from *T. hatcheri*, showed a lack of cytotoxicity (IC_{50} > 100 μM) against both KB and SK-MEL-3 human melanoma cells, as well as NIT 3T3 fibroblasts (Fig. 24).[110]

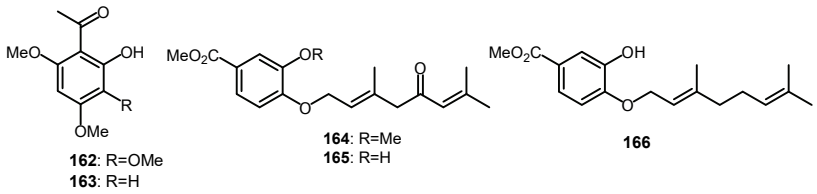


Fig. 24. Some of the isolated compounds from *Plagiochila fasciculata* and *Trichocolea* species.

The *ent*-kauranes and kaurenes **131** and **167**–**169** isolated from *Jungermannia* species inhibited HL-60 cells with IC_{50} values of 0.49, 7.0, 0.59 and 0.28 μM, respectively. Treatment of **131** and **167**–**169** caused proteolysis of ply(ADP--ribose) polymerase, a sign of activation of the apoptotic machinery, whereas the feature of cell death induced by treatment with compounds **167** and **168** was necrosis. Treatment with compound **169** induced apoptosis (see below).[111] The *ent*-kaurene diterpenoids **170**, **171** and **172**–**174** from a *Jungermannia* species showed cytotoxicity for HL-60 cells with IC_{50} values of 1.00, 0.40, 1.21, 1.28, and 0.78 μM, respectively (Fig. 25).[112]

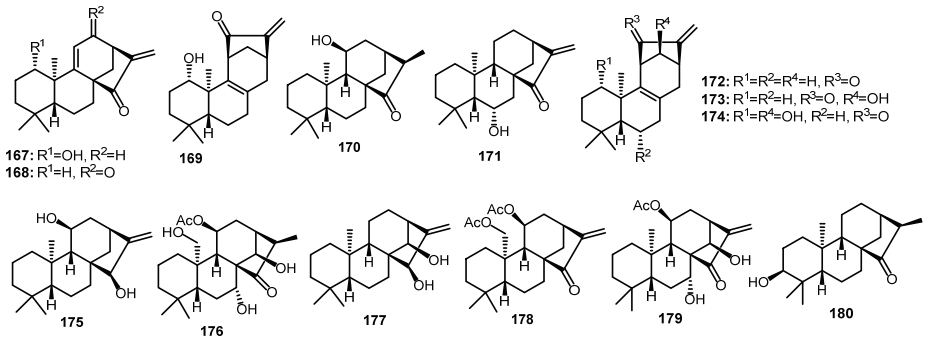


Fig. 25. Cytotoxic kaurenes from *Jungermannia* species.

The *ent*-kaurenes **131**, **175**–**180**, Fig. 25, isolated from the Japanese liverwort *Jungermannia truncata*, were evaluated for cytotoxicity against HL-60 human leukemia cells. Of these, *ent*-11α-hydroxy-16-kauren-15-one (**131**) induced apoptosis (programmed cell death) in this cell line partly through a caspase-8 dependent pathway.[90,113] The presence of an enone group in this class of molecule appears to be essential for the induction of apoptosis and the activation of caspases in human leukemia cell lines.[111,114] *ent*-Kaurenes **131**, **127** and **179** and

ent-9(11),16-kauradien-12,15-dione (**168**) and the rearranged *ent*-kaurene, jungermannenone A (**169**), selectively inhibited the nuclear factor-κB (NF-κB)-dependent gene expression due to treatment with TNF-*α*. Compound **131**, in combination with TNF-*α*, caused a dramatic increase in apoptosis in human leukemia cells accompanied by activation of caspases. Compound **120**, when combined with camptothecin, also caused an increase in apoptosis.[115,116] Jungermannenones A–D (**169**–**174**), Fig. 25, obtained from *Jungermannia* species, induced cytotoxicity against human leukemia HL-60 cells at 50 % inhibitory concentrations of 1.3, 5.5, 7.8 and 2.7 μM, respectively, and DNA fragmentation and nuclear condensation.

Both are biochemical markers of apoptosis induction, and apoptosis was induced through a caspase-independent pathway. Compounds **169** and **174** showed inhibitory activity for NF-κB, which is a transcriptional factor of anti-apoptotic factors. Thus, *ent*-kaurene diterpenoids from liverworts may be promising candidates as antitumor agents.[117,118] Some monoterpenoids, such as bornyl acetate (**181**), Fig. 26, found in liverworts, demonstrated potent apoptosis-inducing activities against the cultured cells of *M. polymorpha.*

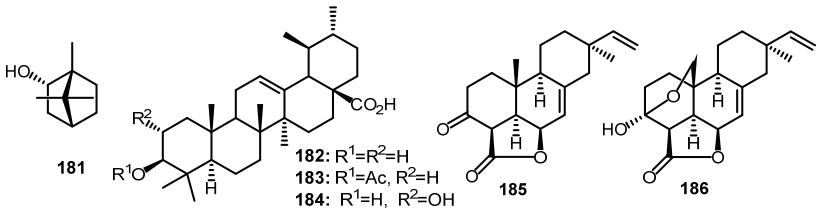


Fig. 26. Cytotoxic compounds from *Ptilidium* and *Hypnum* species.

Apoptosis induced by monoterpenoids occurs *via* the production of active oxygen species such as H_2O_2.[119] The ursane triterpenoids from the liverwort *Ptilidium pulcherrimum*, ursolic acid (**182**), 2*α*,3*β*-dihydroxyurs-12-en-28-oic acid (**183**) and acetoxyursolic acid (**184**), showed inhibition of the growth of PC3 human prostate cancer cells, at concentrations between 10.1±1.00 and 39.7±2.98 μM.[120] Previously, two pimarane diterpenoids momilactones A (**185**) and B (**186**), which were identified as phytoalexins in rice, were isolated from the moss *H. plumaeforme* (Hypnaceae), Fig. 26.[121] Momilactone B (**186**) was shown to have cytotoxicity against human colon cancer HT-29 and SW620 cells at 1 μM.[122]

Pallidisetin A (**187**) and pallidisetin B (**188**), isolated from the moss *Polytrichum pallidiscetum*, showed cytotoxicity against human melanoma (RPMI-7951) and human glioblastoma multiforme (U-251 MG) cells, with ED_{50} values of 1.0 and 1.0 μg mL^{-1} and 2.0 and 2.0 μg mL^{-1}, respectively.[123] Three cytotoxic compounds, 1-*O*-methylohioensin B (**189**), 1-*O*-methyldihydroohioensin B (**190**) and

1,14-di-*O*-methyldihydroohioensin B (**191**), Fig. 27, were also isolated from the moss *P. pallidiscetum.* Compound **189** proved to be cytotoxic for human colon adenocarcinoma (HT-29), human melanoma (RPMI-7951), and human glioblastoma multiforme (U-251 MG) cells, with ED_{50} values of 1.0, 1.0, and 2.0 μg mL^{-1}, respetively. Compound **190** showed inhibitory activity only against U-251 cells (ED_{50} 0.8 μg mL^{-1}) while **191** inhibited the growth of A549 lung carcinoma A549 (ED_{50} 1.0 μg mL^{-1}) and RPMI-7951 melanoma (ED_{50} 1.0 μg mL^{-1}) cell lines.[123] Ohioensin H (**192**) from *P. commune* did not show any cytotoxicity against the five human cancer cell lines in which it was evaluated (IC_{50} in all cases > 5 μg mL^{-1}).[124] Marsupellone (**193**) and acetoxymarsupellone (**194**) from *Marsupella emarginata* showed cytotoxicity (ID_{50} 1.0 μg mL^{-1}) against P388.[16,125] Riccardins A (**151**) and B (**195**) which were the first bis-bibenzyls from the Japanese liverwort, *Riccardia multifida* subsp. *decrescens* inhibited KB cells at a concentration of 10 and 12 μg mL^{-1}, respectively. *Radula perrottetii* contained cytotoxic perrottetin E (**155a**), Fig. 23, against KB cells (12.5 μg mL^{-1}).[31]

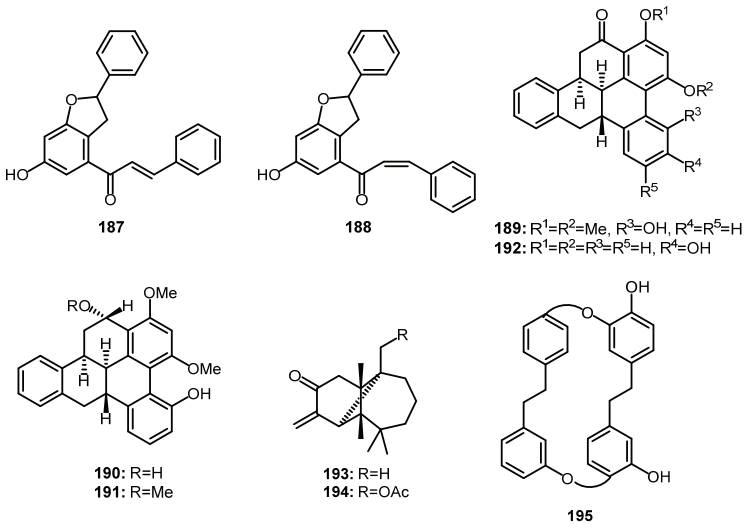


Fig. 27. Cytotoxic compounds from *Polytrichum*, *Marsupella* and *Riccardia* species.

5.5. Antimicrobial, antifungal and antiviral compounds

Several liverworts, *Bazzania* species, *C. conicum*, *Diplophyllum albicans*, *Dumortiera hirsuta*, *M. polymorpha*, *Metzgeria furcata*, *Lunularia cruciata*, *Pellia endiviifolia*, *Plagiochila* species, *P. vernicosa* complex, *P. platyphylla*, and *Radula* species show antimicrobial activity.[31] The essential oil of *Marchesinia mackaii* showed antibacterial activity against *Bacillus subtilis*, *Escherichia coli*, *Salmonella pullorum*, *Staphylococcus aureus* and *Yersinia enterocolitica*.[126] Sacculatal (**48**) from *P. endiviifolia* showed potent antibacterial activity against

Streptococcus mutans (a causative organism for dental caries), exhibiting a LD_{50} value of 8 μg mL^{-1}. Polygodial (**47**), Fig. 7, was inactive (LD_{50} 100 μg mL^{-1}) in the same bioassay.[72] Lunularin (**92**), Fig. 13, from *Dumortiera hirsuta* also showed antimicrobial activity against *Pseudomonas aeruginosa* at a concentration of 64 μg mL^{-1}.[73] Lepidozenolide (**97b**), Fig. 13, from *Lepidozia fauriana* showed a positive response to methicillin-resistant *S. aureus* at 100 μg mL^{-1}. Riccardiphenol C (**108**) from *Riccardia crassa* showed antibacterial activity against *B. subtilis* at 60 μg disc^{-1} but not against fungi *Candida albicans* or *Trichophyton mentagrophytes*.[84] Glaucescenolide (**116**) from *Schistochila glaucescens*, exhibited antifungal activity against *T. mentagrophytes*.[86] *Ent*-1μ-Hydroxykauran-12-one (**117**) from *Paraschistochila pinnatifolia* demonstrated weak antifungal activity against *C. albicans* (Fig. 15).[87]

Marchantin A (**148a**) from many *Marchantia* species shows antibacterial activity against *Acinetobacter calcoaceticus* (*MIC* 6.25 μg mL^{-1}), *Alcaligenes faecalis* (100 μg mL^{-1}), *Bacillus cereus* (12.5 μg mL^{-1}), *B. megaterium* (25 μg mL^{-1}), *B. subtilis* (25 μg mL^{-1}), *Cryptococcus neoformans* (12.5 μg mL^{-1}), *Enterobacter cloacae, E. coli*, *Proteus mirabilis*, *P. aeruginosa*, *Salmonella typhimurium* (100 μg mL^{-1}) and *S. aureus* (3.13–25 μg mL^{-1}).[31] They also exhibit antifungal activity against *Alternaria kikuchiana*, *Aspergillus fumigatus* (*MIC* 100 μg mL^{-1}), *A. niger* (25–100 μg mL^{-1}), *C. albicans*, *Microsprorum gypseum*, *Penicillium chrysogenum* (100 μg mL^{-1}), *Piricularia oryzae* (12.5 μg mL^{-1}), *Rhizoctonia slain* (50 μg mL^{-1}), *Saccharomyces cerevisiae, Sporothrix schenckii* (100 μg mL^{-1}), and dermatophytic *T. mentagrophytes* (3.13 μg mL^{-1}) and *T. rubrum* (100 μg mL^{-1}).[31] Marchantins A (**148a**), B (**148b**), D (**141**), perrottetin F (**155b**) and paleatin B (**156**), Figs. 22 and 23, showed anti-HIV-1 activity (IC_{50} range 5.3–23.7 μg mL^{-1}).[7,72] Marchantin C (**150**), neomarchantins A (**157**) and B (**158**), Fig. 23, from *Schistochila glaucescens* showed antimicrobial activity against the Gram-positive bacterium, *B. subtilis*, with *MIC* values of 2, 1.5 and 2 μg mL^{-1}, and were also active against *T. mentagrophytes*, with *MIC* values of 0.5, 1, and 0.5 μg mL^{-1}, respectively.[86]

Riccardin D (**161**), Fig. 23, from *M. polymorpha* showed antifungal activity against the fluconazole-resistant *C. albicans* strains, QL-14, QL-28, SDEY-24R and SDEY-09R with *MIC* values of 16, 32, 16 and 16 μg mL^{-1}, respectively. When riccardin D (**161**) was mixed with fluconazole, the antifungal activities were substantially more potent (*MIC* values in the range 0.313 to 0.375 μg mL^{-1}).[127] The antifungal activity of **161** in *C. albicans* might be attributed to its inhibitory effect on cell wall chitin synthesis.[126] Riccardin D exerts its antifungal activity through mitochondrial dysfunction-induced accumulation of reactive oxygen species in *C. albicans*. Compound **161** also induced apoptosis in *C. albicans* through the activation of a metacaspase.[129,130]

A disc diffusion assay on 2-hydroxy-3,4,6-trimethoxyacetophenone (**162**) and 2-hydroxy-4,6-dimethoxyacetophenone (**163**) from *Plagiochila fasciculata* at 150 μg disc^{-1} showed both to have antifungal activity against *T. mentagrophytes* and *Cladosporium resinae*, but not against *B. subtilis* or the *Gram*-negative bacteria *E. coli* and *P. aeruginosa.* Compound **162** showed inhibitory activities against *E. coli*, *Proteus mirabilis* and *S. aureus* at a concentration of 100 μg mL^{-1}. Compound **162** also showed antifungal activity against *C. albicans.*[106] Tomentellin (**164**) and demethoxytomentellin (**165**) from *Trichocolea tomentella* and *T. mollissima* showed mild antifungal activity against *C. albicans* and *T. mentagrophytes* (Fig. 24).[107] Methyl-4-[(2*E*)-3,7-dimethyl-2,6-octadienyl)oxy]-3-hydroxybenzoate (**166**), from *T. hatcheri*, showed a lack of antimicrobial activity against *Staphylococcus epidermidis* (*MIC* 1000 μg mL^{-1}).[108] Reinvestigation of the antifungal activity of bis-bibenzyls from *M. polymorpha* using a bioautographic method showed that neomarchantin A (**157**), riccardin D (**161**) and 13,13'-*O*-isopropylidene riccardin D (**196**), Fig. 28, possessed antifungal activity against *C. albicans* with respective *MID* (minimum inhibitory dose) values of 0.25, 0.2 and 0.4 μg, respectively, compared to that of 0.01 μg for the positive control miconazole. Moreover, marchantin A (**148a**), marchantin B (**148b**), marchantin E (**153a**) and riccardin H (**197**) showed moderate growth inhibitory activities against the same fungus, with *MID* values of 2.5, 4.0, 2.5 and 4.0 μg, respectively.[131]

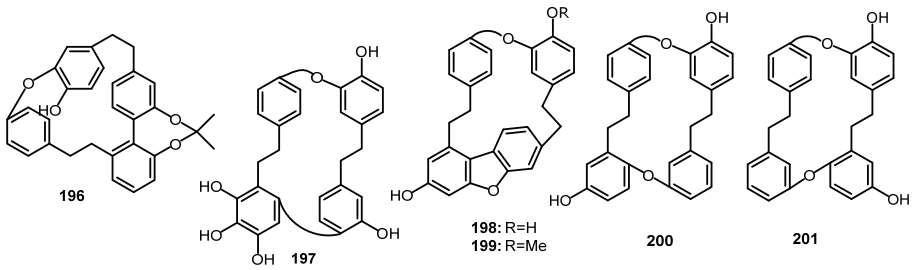


Fig. 28. Bis-bibenzyls from *Asterella angusta* showing activity against *Candida albicans*.

Direct TLC bioautographic detection of the antifungal activity of an ether extract of *Asterella angusta* showed activity against *C. albicans*. Ten bis-bibenzyls, riccardin D (**161**), riccardin B (**195**), perrottetin E (**155a**), asterelin A (**198**), asterelin B (**199**), 11-demethylmarchantin I (**200**), dihydroptychantol (**201**), marchantin H (**202**), marchantin M (**203**) and marchantin P (**204**) (Figs. 23, 27, 28 and 29) were tested against the yeast *C. albicans*. All of the compounds tested showed antifungal activity, exhibiting *MIQ* (minimum inhibitory quantity) values between 0.25–15.0 μg mL^{-1}, and *MIC* values in the range 16–512 μg mL^{-1}.[102,132] The free phenolic hydroxy group seems to play an important role in mediating antifungal activity because bis-bibenzyls possessing a methoxy group displayed decreased

potencies in this regard.[131,133] Six bis-bibenzyls, neomarchantin A (**157**), marchantin H (**202**), riccardin C (**151a**), riccardin F (**151c**), isoriccardin C (**205**) and pakyonol (**206**) isolated from *Plagiochasma intermedium* possessed weak *in vitro* antifungal activity against fluconazole-sensitive and resistant strains of *C. albicans*, with *MIC* valuess ranging from 32 to > 512 μg mL^{-1}. 6',8'-Dichloroisoplagiochin C (**207**), isoplagiochin D (**208**) and 6'-chloroisoplagiochin D (**209**) (Fig. 29) from *Bazzania trilobata*, showed discernible antifungal activity in a microtiter plate test against *P. oryzae* at IC_{50} values of 3.9, 4.0 and 2.6 μg mL^{-1} and *S. tritic* at IC_{50} values of 23.5, 15.9 and 4.5 μg mL^{-1}, respectively. Compounds **207** and **208** also demonstrated inhibitory activity against *B. cinerea* at IC_{50} values of 18.9 and 7.6 μg mL^{-1}. The free hydroxy groups on the benzene rings of bis-bibenzyls play an important role in mediating inhibitory activity against fungi such as *C. cucumerinum* (Fig. 29).[133]

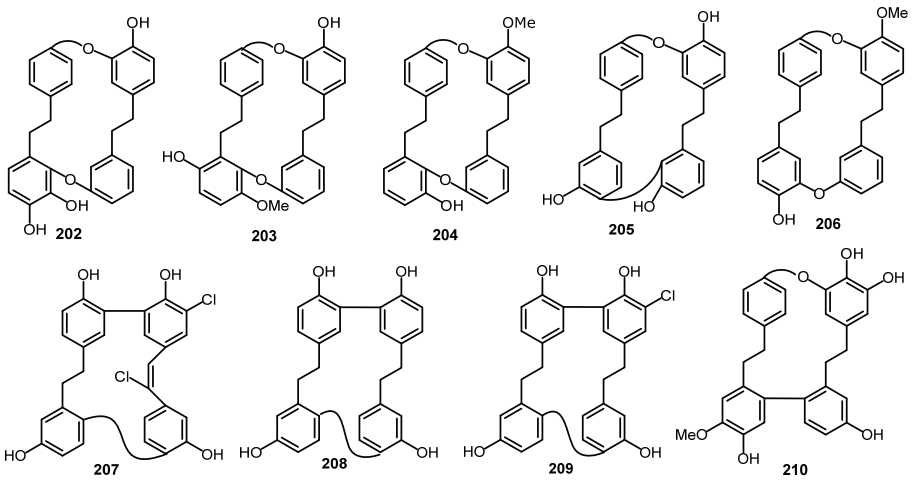


Fig. 29. Antimicrobial compounds from *Asterella*, *Plagiochasma* and *Bazzania* species.

The H1N1 and H5N1 influenza A virus caused pandemics throughout the world in 2009. Influenza A possesses an endonuclease within its RNA polymerase comprised of PA, PB1, and PB2 subunits. In order to obtain potential new anti-influenza compounds, 33 different types of phytochemicals were evaluated using a *in vitro* PA endonuclease inhibition assay.[134] Among them, the bis-bibenzyls, marchantins A (**148a**), B (**148b**) and E (**153a**) and plagiochin A (**210**), Fig. 29, inhibited influenza PA endonuclease activity at a concentration of 10 μM. This was the first evidence that phytochemicals derived from liverworts could inhibit influenza A endonuclease.

The herbertane sesquiterpenoids, *α*-herbertenol (**109**), *β*-herbertenol (**211**), herbertene-1,2-diol (**110**), mastigophorene C (**113**), mastigophoric acid methyl ester (**212**), *α*-formyl herbertenol (**213**) and 1,2-dihydroxyherberten-12-al (**214**),

Fig. 30, isolated from *Mastigophora diclados*, were tested against *S. aureus* strain, using an agar diffusion method. These sesquiterpenoids showed weaker activity than the standard antibiotics chloramphenicol (22 mm) and kanamycin (23 mm). However, of the compounds tested, mastigophorene C (**113**), a dimer of herbertene-1,2-diol (**110**), showed the most potent antibacterial activity (17 mm), while its monomer (**110**) displayed significant activity (13 mm) in this regard.[135]

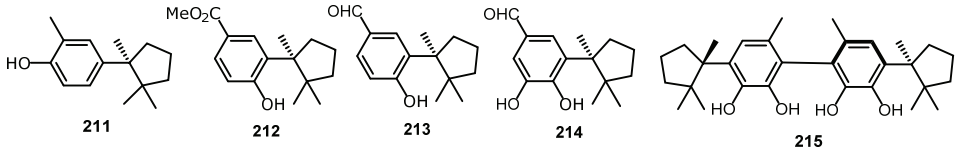


Fig. 30. Antibacterial herbertane sesquiterpenoids from *Mastigophora diclados*.

The crude ether and methanol extracts of the Tahitian *M. diclados* showed antimicrobial activity against *B. subtilis* and *Streptococcus aureus* (*MIC* 16 μg mL^{-1}).[85] Bioactivity-guided fractionation of both extracts gave (–)-*α*-herbertenol (**100**), (–)-herbertene-1,2-diol (**110**), (–)-mastigophorene C (**113**), (–)-mastigophorene D (**114**), diplophyllin (**115**), (–)-diplophyllolide (**43**) and mastigophorene A (**215**) (Fig. 30), among which **110**, **113,** and **114** showed moderate antimicrobial activity against *B. subtilis* at an *MIC* of 2–8 μg mL^{-1}. Only diol (**110**) indicated weak antimicrobial activity against *Klebsiella pneumoniae* at an *MIC* of 100 μg mL^{-1}.[85]

Chlorophyl decomposed compounds, phaeophytin a (**216**), 13^2-hydroxy-(13^2--*S*)-phaeophytin a (**217**), 13^2-hydroxy-(13^2-*R*)-phaeophytin a (**218**), and 13^2--(MeO_2)-(13^2-*R*)-phaeophytin a (=phaeophytin a hydroperoxide) (**219**), Fig. 31, isolated from the methanol-soluble extract of a cell suspension culture of *Plagiochila ovalifolia* showed antimicrobial activity against *E. coli* and *B. subtilis.*[136] *Bazzania trilobata* contained six antifungal active sesquiterpenoids, viridiflorol (**220**), gymnomitrol (**221**), 5-hydoxycalamenene (**222**), 7-hydroxycalamenene (**223**), drimenol (**224**) and drimenal (**225**), Fig. 32.[133] Viridiflorol (**220**) was found to have antifungal activity against *Cladosporium cucumerinum.*[137]

Also showed was the antifungal activity against *Pyricularia oryzae* at an IC_{50} value of 105.2 μg mL^{-1}. Gymnomitrol (**221**) showed strong inhibition against *Phytophthora infestans*, *P. oryzae* and *Septoria tritici* at IC_{50} values of 97.0, 1.7 and 53.0 μg mL^{-1}, respectively.[133] 5-Hydroxycalamenene (**222**) showed inhibitory activity against *Pyricularia oryzae* at an IC_{50} value of 1.7 μg mL^{-1} while 7-hydroxycalamenene (**223**) had potent antifungal activity against *Cladosporium cucumerinum, P. oryzae*, and *Septoria tritici* at IC_{50} values of 97.0, 1.7 and 53.0 μg mL^{-1}, respectively.

Compound **223** was tested for its *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.[133] 7-Hydroxycalamenene (**223**) from *Tilia europaea* is a phytoalexin. Drimenol (**224**) is less active than the calamenenes described above.[138] It inhibited the growth of *C. cucumerinium* and *S. tritici* at concentrations of 6.6 and 80.1 μg mL^{-1}, respectively.[133] Drimenal (**225**) exhibited moderate growth inhibitory activity against *B. cinerea* and *P. oryzae* at IC_{50} values of 81.8 and 61.6 μg mL^{-1}, respectively, and more potent activity against *S. tritici* and *P. infestans* at IC_{50} values of 17.6 μg mL (Fig. 32).[133]

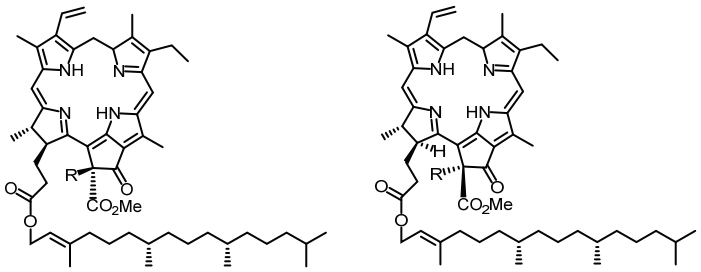


Fig. 31. Antibacterial chlorophyl decomposed compounds from *Plagiochila ovalifolia*.

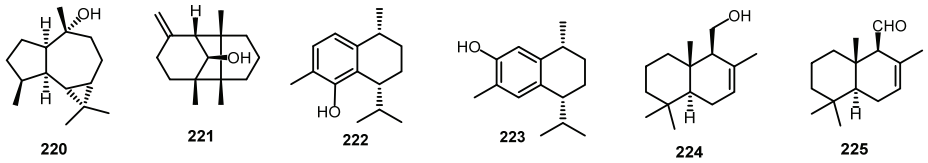


Fig. 32. Antibacterial compounds from *Bazzania trilobata* and *Tilia europaea*.

Dehydrocostus lactone (**226**), acetyltrifloculoside lactone (**227**), and 11α,13-dihydrodehydrocostuslactone (**228**), Fig. 33, from *Targionia lorbeeriana* showed antifungal activity against *Cladosporium cucumerinum* with *MIC* values of 0.5, 10, and 3 μg mL^{-1}, respectively, using a bioautographic TLC method. Dehydrocostus lactone (**226**) exhibited the same activity at 20 μg mL^{-1} against *C. cucumerinum* in an agar dilution assay. Compound **226** also showed larvicidal activity against *Aedes aegypti*, with an LC_{100} value of 12.5 ppm and antifungal activity against *C. albicans* (*MIC* 5 μg mL^{-1}) in a bioautographic TLC method.[139]

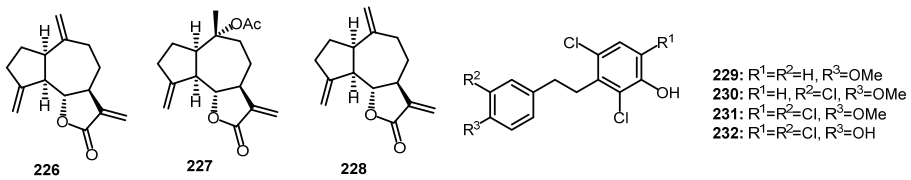


Fig. 33. Antibacterial compounds from *Targionia lorbeeriana*.

Some species of *Riccardia* elaborate high concentrations of the bioactive polychlorinated bibenzyls, 2,6-dichloro-3-hydroxy-4'-methoxybibenzyl (**229**), 2,6,3'-trichloro-3-hydroxy-4'-methoxybibenzyl (**230**), 2,4,6,3'-tetrachloro-3-hydroxybibenzyl (**231**) and 2,4,6,3'-tetrachloro-3,4-dimethoxybibenzyl (**232**), Fig. 33, in order to protect them from pathogens and herbivores. On TLC-bioautography with a *Cladosporium herbarum* culture, compounds **229**, **230** and **232** showed fungicidal activities, as manifested by inhibition zones of 1.2–2.9 cm, which were greater than those obtained with the fungicide, ketoconazole. Compound **231** was inactive against *C. herbarum.*[140]

The dichloromethane extract of *Balantiopsis cancellata* demonstrated strong antifungal activity against *Cladosporium herbarum*, a rot fungus, at 0.01 μg spot^{-1}. Five aromatic esters, isotachin B (**7c**), 2-phenylethyl benzoate (**233**), (*R*)-2-hydroxy-2-phenylethyl benzoate (**234**), 2-phenylethyl (*Z*)-cinnamate (**235**) and its (*E*)-cinnamate (**236**), Figs. 1 and 34, were isolated, among which compound **7c** showed the most potent antifungal activity against *C. herbarum* at 0.006 μg spot^{-1}, on TLC-bioautography.

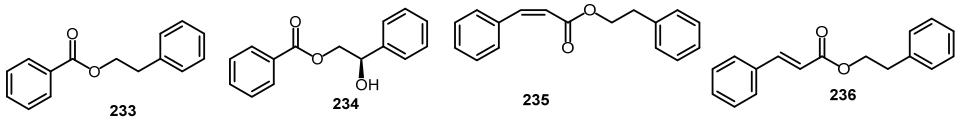
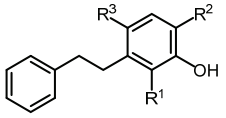


Fig. 34. Antibacterial compounds from *Balantiopsis cancellata*.

This activity is lower than that required with either pure ketoconazole or commercial captan as observed in dilution experiments. The benzoate (**234**) also showed the same activity as mentioned above at 0.05 μg spot^{-1}.[141]

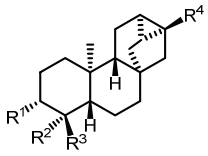
The crude extract of *Riccardia marginata* showed antimicrobial activity against the *Gram*-positive bacterium, *B. subtilis*, and the dermatophytic fungus, *T. mentagrophytes*. The active compounds are the chlorinated bibenzyls, 2,4,6--trichloro-3-hydroxybibenzyl (**237**), 2,4-dichloro-3-hydroxybibenzyl (**238**) and 2-chloro-3-hydroxybibenzyl (**239**), Fig. 35, which showed activity against *B. subtilis*, *T. mentagrophytes*, *C. albicans*, and the plant pathogenic fungus *Cladosporium resinae*, at a concentration of 30 μg disc^{-1}. However, these compounds proved to be inactive against the *Gram*-negative bacteria, *E. coli* and *P. aeruginosa*. Compound **231** showed its most potent activities against *T. mentagrophytes* (12 mm) (zone of inhibition in mm for 5 mm disc) and *C. resinae* (2 mm).[142]



237: $R^1=R^2=R^3=Cl$
238: $R^1=R^2=Cl$, $R^3=H$
239: $R^1=Cl$, $R^2=R^3=H$

Fig. 35. Antibacterial chlorinated bibenzyls from *Riccardia marginata*.

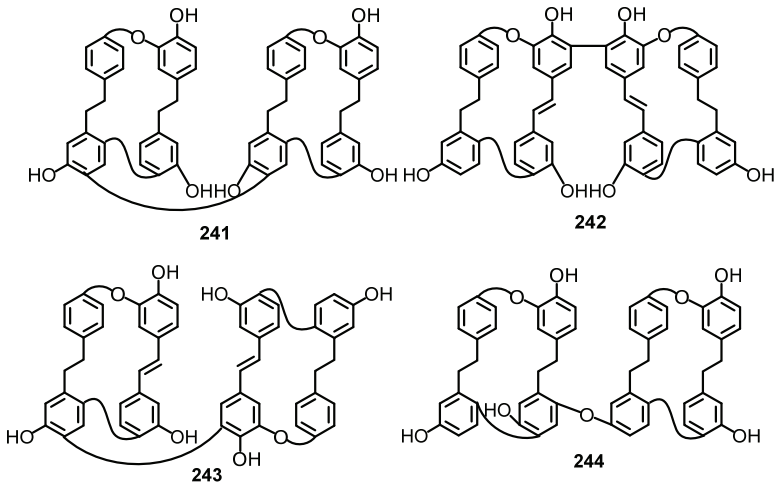
In the critical search for new antituberculosis, compounds from bryophytes lead,[143] 14 trachylobane diterpenoids from the liverwort *Jungermannia exsertifolia* subsp. *cordifolia* were isolated, among which *ent*-trachyloban-17-al (**240a**) showed the most potent activity against the virulent *Mycobacterium tuberculosis* H37Rv strain, with an MIC_{90} value of 24 μg mL^{-1}. *ent*-3*β*-Acetoxy-19-hydroxytrachylobane (**240b**), *ent*-trachylobane-3-one (**240c**), *ent*-3*β*-hydroxytrachylobane (**240d**), and *ent*-3*β*-acetoxytrachylobane (**240e**), Fig. 36, demonstrated moderate inhibitory activities against the same microbe (MIC_{90} values of 59, 50, 61 and 111 μg mL^{-1}, respectively). The remaining trachylobanes (**240f**–**l**) showed *MIC* values of > 128 μg mL^{-1} and were thus considered to be inactive.



240a: R^1=H, R^2= R^3=Me, R^4=CHO
240b: R^1=OAc, R^2=CH_2OH, R^3=R^4=Me
240c: R^1=O, R^2=R^3=R^4=Me
240d: R^1=OH, R^2=R^3=R^4=Me
240e: R^1=OAc, R^2=R^3=R^4=Me
240f: R^1=OAc, R^2=R^4=Me, R^3=CH_2OH
240g: R^1=OH, R^2=R^4=Me, R^3=CH_2OAc
240h: R^1=OAc, R^2=R^4=Me, R^3=CHO
240i: R^1=OH, R^2=CHO, R^3=R^4=Me
240j: R^1=OAc, R^2= R^3=Me, R^4=CH_2OH
240k: R^1=OAc, R^2=CO_2H, R^3=CH_2OAc, R^4=Me
240l: R^1=OH, R^2= R^3=Me, R^4=CO_2H

Fig. 36. Trachylobane diterpenoids from the liverwort *Jungermannia exsertifolia* subsp. *cordifolia*.

Blasia pusilla produces the bis-bibenzyl dimers, pusilatins A-D (**241**–**244**), Fig. 37. Pusilatins B (**242**) and C (**243**) showed weak HIV-RT inhibitory activity.[144]



241 **242** **243** **244**

Fig. 37. Pusilatins from *Blasia pusilla*.

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ИЗВОД

ФИТОХЕМИКАЛИЈЕ ИЗ БРИОФИТА: СТРУКТУРА И БИОЛОШКЕ АКТИВНОСТИ

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На бриофите као изворе за људску исхрану се обраћа мала пажња иако их има преко 23000 врста. Неке маховине садрже витамин Б1, токофероле, простагландинима слична једињења, вишеструко незасићене масне киселине и фенолна једињења. С друге стране, јетрењаче садрже моно-, сескви- и дитерпеноиде енентиомерне онима пронађеним у васкуларним биљкама. Поред њих, оне садрже и бибензиле, бис-бибензиле и поликетиде, од којих многи показују антимикробну, антивирусну, анти-инфламаторну, цитотоксичну на ћелије рака, миорекласантску, антиоксидативну и друге. У овом раду су продискутоване структуре и биолошка активност фитохемикалија из јетрењача.

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REFERENCES

1. Y. Asakawa, in *Progress in the Chemistry of Organic Natural Products*, G. W. Kirby, H.Grisebach, W. Herz, Eds., Springer, Vienna, 1982, p. 1 (https://doi.org/10.1007/978-3-7091-8677-0_1)
2. Y. Asakawa, in *Progress in The Chemistry of Organic Natural Products*, C. Tamm, R. E. Moore, W. Herz, W. B. Kirby, W. Steglich, Eds., Springer, Vienna, 1995, p. 1
3. C. Suire, M. Toyota, N. Tokunaga, T. Takemoto, Y. Asakawa, *J. Hatt. Bot. Lab*. **45** (1979) 395
4. A. Ludwiczuk, Y. Asakawa, *Heterocycles* **86** (2012) 891 (https://dx.doi.org/10.3987/REV-12-SR(N)5)
5. A. Ludwiczuk, F. Nagashima, Y. Asakawa, *Phytochemistry* **55** (2013) 55 (https://doi.org/10.1016/j.phytochem.2012.04.012)
6. A. Ludwiczuk, F. Nagashima, Y. Asakawa, in *Progress in the Chemistry of Organic Natural Products*, D. A. Kinghorn, H. Falk, J. Kobayashi, Eds., Springer, Vienna, 2013, p. 1 (https://doi.10.1007/978-3-7091-1084-3)
7. A. Ludwiczuk, Y. Asakawa, *Rośliny Lecznicze w Polsce i na Świecie (Medical Plants in Poland and in the World)* **2** (2008) 33

8. A. Ludwiczuk, Y. Asakawa, *Rośliny Lecznicze w Polsce i na Świecie (Medical Plants in Poland and in the World)* **3**/**4** (2008) 43
9. A. Ludwiczuk, Y. Asakawa, *J. Nat. Prod*. **81** (2018) 641 (https://doi.org/10.1021/acs.jnatprod.6b01046)
10. Y. Asakawa, A. Ludwiczuk, M. Novakovic, D. Bukvicki, K. Y. Anchang, *J. Nat. Prod.* (2021) in press (https://doi.org/10.1021/acs.jnatprod.1c00302)
11. A. Matsuo, H. Ando, in *Advances in Bryology*, W. J. Schultze-Motel, Ed., Cramer, Vaduz, Liechtenstein, 1984, p. 133
12. G. Bezanger-Beauquensne Debraux, H. Garnier, *Resources Medicinales de la Flore Francaise*, Tome 1, Vigot Freres, Paris, 1961
13. Y. Asakawa, M. Toyota, M. Tori, T. Hashimoto, *Spectroscopy* **14** (2000) 149
14. Y. Asakawa, in *Phytochemicals in Human Health Protection*, *Nutrition, and Plant Defense*, J. Romeo, Ed., Kluwer Academic/Plenum Publishers, New York, 1999, p. 319 (https://doi.org/10.1007/978-1-4615-4689-4_12)
15. Y. Asakawa, in *Bioactive Natural Products: Detection, Isolation, and Structural Determination*, R. J. Molyneux, S. M. Colegate, Eds., Press, Boca Raton, FL, 1993, p. 319
16. Y. Asakawa, *Pure Appl. Chem*. **66** (1994) 2193 (https://doi.org/10.1351/pac199466102193)
17. Y. Asakawa, *Phytochemistry* **56** (2001) 29 (https://doi.org/10.1016/s0031-9422(00)00454-4)
18. Y. Asakawa, *Phytochemistry* **65** (2004) 623 (https://doi.org/10.1016/j.phytochem.2004.01.003)
19. Y. Asakawa, *Aroma Research* **5** (2004) 204 (https://doi.org/10.1016/j.phytochem.2004.01.003)
20. Y. Asakawa, *Chenia* **9** (2007) 73
21. A. Ludwiczuk, Y. Asakawa, *Malaysian J. Sci*. **28** (2009) 229
22. Y. Asakawa, A. Ludwiczuk, F. Nagashima, M. Toyota, T. Hashimoto, M. Tori, Y. Fukuyama, L. Harinantenaina, *Heterocycles* **77** (2009) 99 (https://doi.org/10.1002/chin.200917258)
23. Y. Asakawa, M. Toyota, M. Tori, T. Hashimoto, *Spectroscopy* **14** (2000) 149 (https://doi.org/10.1155/2000/570265)
24. H. Inoue, *Kagaku Asahi* **8** (1988) 116
25. Y. Asakawa, *J. Hattori Bot. Lab*. **5** (1985) 284
26. *Bryology in the New Millenium*, H. Mohamed, B. B. Baki, A. Nasrulhaq-Boyce, P. K. Y. Lee (Eds.), University of Malaya, Kuala Lumpur, 2008. p. 1
27. S. H. von Reuβ, W. A. König, *Phytochemistry* **65** (2004) 3113 (https://doi.10.1016/j.phytochem.2004.10.002)
28. Y. Asakawa, M. Toyota, H. Tanaka, T. Hashimoto, D. Joulain. *J. Hattori Bot. Lab*. **78** (1995) 183 (https://doi.org/10.18968/jhbl.78.0_183)
29. A. Ludwiczuk, I. Komala, A. Pham, J.-P. Bianchini, P. Raharivelomanana, Y. Asakawa, *Nat. Prod. Commun.* **4** (2009) 1387 (https://doi.org/10.1177/1934578X0900401015)
30. S. Sugawa, *Hikobia* **2** (1960) 119
31. Y. Asakawa, in *Bryophyte Development: Physiology and Biochemistry*, R. N. Chopra, S. C. Bhatla, Eds., CRC Press, Boca Raton, FL, 1990, p. 259

32. Y. Asakawa, in *Bryophytes: Their Chemistry and Chemical Taxonomy*, D. H. Zinsmeister, R. Mues, Eds., Oxford University Press, Oxford, 1990, p. 369
33. D. Takaoka, H. Nozaki, H. Udaka, K. Hamazaki, N. Nishimura, N. Takashima, in *Proceedins of 15th International Botanical Congress*, 1993, Yokohama, Japan, p. 370
34. M. Nishiki, M. Toyota, Y. Asakawa, in *Proceedings of 51st Symposium on Chemistry of Terpenes,* 2007, Nagahama, Japan, *Essential Oils and Aromatics*, p. 260
35. Y. Asakawa, F. Nagashima, A. Ludwiczuk, *J. Nat. Prod*. **83** (2020) 756 (https://doi.org/10.1021/acs.jnatprod.9b01132)
36. K. Kondo, K. Sakai, K. Yamada, M. Namikawa, T. Ichikawa, *Tetrahedron Lett*. **24** (1983) 3337 (https://doi.org/10.1016/S0040-4039(00)86263-2)
37. T. Ichikawa, K. Yamada, M. Namikawa, K. Sakai, K. Kondo, *J. Hattori Bot. Lab*. **56** (1984) 209
38. H. H. T. Prins, *Oikos* **38** (1981) 374
39. S. C. Bhatla, S. Dhingra-Babbar, in *Bryophyte development: Physiology and biochemistry*, R. N. Chopra, S. C, Bhatla, Eds., CRC press, Boca Raton, FL, 1990, p. 79
40. T. L. Wang, D. J. Cove, P. Beutelmann, E. Hartmann, *Phytochemistry* **19** (1980) 1103 (https://doi.org/10.1016/0031-9422(80)83064-0)
41. Y. Asakawa, *Bryol. Res.* **9** (2007) 198 (https://doi.org/10.24474/bryologicalresearch.9.6_198)
42. S. Hayashi, T. Kami, A. Matsuo, H. Ando, T. Seki, *Proc. Bryol. Soc. Jap.* **2** (1977) 38
43. M. Mizutani, *Misc. Bryol. Lichenol.* **6** (1972) 64
44. M. Toyota, Y. Asakawa, *Flav. Fragr. J.* **9** (1994) 237 (https://doi.org/10.1002/ffj.2730090507)
45. M. Toyota, H. Koyama, Y. Asakawa, *Phytochemistry* **44** (1997) 1261 (https://doi.org/10.1016/S0031-9422(96)00722-4)
46. Y. Asakawa, M. Sono, M. Wakamatsu, K. Kondo, S. Hattori, M. Mizutani, *Phytochemistry* **30** (1991) 2295 (https://doi.org/10.1016/0031-9422(91)83633-V)
47. M. Sono, *Ph.D. Thesis*, Tokushima Bunri University, Tokushima, 1991, p. 1
48. M. Tori, M. Sono, Y. Nishigaki, K. Nakashima, Y. Asakawa, *J. Chem. Soc. Perkin Trans. 1* (1991) 435 (https://doi.org/10.1039/P19910000435)
49. M. Toyota, T. Saito, J. Matsunami, Y. Asakawa, *Phytochemistry* **44** (1997) 1265 (https://doi.org/10.1016/S0031-9422(96)00723-6)
50. J. D. Connolly, *Rev. Latinoam. Quim.* **12** (1982) 121
51. J. D. Connolly, in *Bryophytes, Their Chemistry and Chemical Taxonomy*, H. D. Zinsmeister, R. Mues, Eds., Oxford University Press, Oxford, 1990, p. 41
52. M. Toyota, Y. Asakawa, J.-T. Frahm, *Phytochemistry* **29** (1990) 2334 (https://doi.org/10.1016/0031-9422(90)83066-A)
53. J. Spörle, *Ph.D. Thesis*, Universität des Saarlandes, Saarbrcken, 1990, p. 1
54. S. Huneck, J. D. Connolly, A. A. Freer, D. S. Rycroft, *Phytochemistry* **27** (1988) 1405 (https://doi.org/10.1016/0031-9422(88)80204-8)
55. Y. Asakawa, M. Toyota, A. Cheminat, *Phytochemistry* **25** (1986) 2555 (https://doi.org/10.1016/s0031-9422(00)84508-2)
56. W. Geis, H. Becker, *Flavour Fragr. J.* **16** (2001) 422 (https://doi.org/10.1002/ffj.1030)
57. F. Cullmann, H. Becker, *J. Hattori Bot. Lab*. **84** (1998) 285 (https://doi.org/10.18968/jhbl.84.0285)

58. Y. Asakawa, *Bryol. Res*. **9** (2007) 227 (https://doi.org/10.24474/bryologicalresearch.9.7_227)
59. H. Inoue, *Koke no Sekai (World of Bryophytes*), Idemitsu Ltd., Tokyo, 1978, p. 1
60. C. Suire, M. Toyota, S. Huneck, T. Takemoto, Y. Asakawa, *J. Hattori Bot. Lab.* **46** (1979) 163
61. Y. Asakawa, A. Ludwiczuk, L. Harinantenaina, M. Toyota, M. Nishiki, A. Bardon, K. Nii, *Nat. Prod. Commun.* **7** (2012) 685 (https://doi.org/10.1177/1934578X1200700601)
62. T. Hashimoto, Y. Okumura, K. Suzuki, S. Takaoka, Y. Kan, M. Tori, Y. Asakawa, *Chem. Pharm. Bull.* **43** (1995) 2030 (https://doi.org/10.1248/cpb.43.2030)
63. L. J. Harrison, M. Toyota, Y. Asakawa, *Phytochemistry* **24** (1985) 261 (https://doi.org/10.1016/S0031-9422(00)83533-5)
64. K. Ono, M. Toyota, Y. Asakawa, *Phytochemistry* **31** (1992) 1249 (https://doi.org/10.1016/0031-9422(92)80270-O)
65. K. Ono, H. Tanaka, T. Sakamoto, Y. Asakawa, *Flav. Fragr. J.* **11** (1996) 53
66. (https://doi.org/10.1002/(SICI)1099-1026(199601)11:1<53::AID-FFJ535>3.0.CO;2-8)
67. T. Hashimoto, H. Tanaka, Y. Asakawa, *Chem. Pharm. Bull.* **42** (1994) 1542 (https://doi.org/10.1248/cpb.42.1542)
68. A. Ueda, M. Toyota, Y, Asakawa, *Phytochemistry* **30** (1991) 567 (https://doi.org/10.1016/0031-9422(91)83728-4)
69. M. Toyota, I. Omatsu, J. Braggins, Y. Asakawa, *Chem. Pharm. Bull*. **57** (2009) 1015 (https://doi.org/10.1248/cpb.57.1015)
70. F. Nagashima, M. Toyota, Y. Asakawa, *Phytochemistry* **29** (1990) 1619 (https://doi.org/10.1016/0031-9422(90)80133-2)
71. D. S. Rycroft, in *Bryophytes: Their Chemistry and Chemical Taxonomy*, Zinsmeister, D. H., Mues, R. Eds., Oxford University Press, Oxford, 1990, p. 109
72. D. S. Rycroft, G. Ferguson, J. D. Connolly, L. J. Harrison, M. Parvez, R. Joseph, S. Huneck, W. Phillip, *J. Chem. Res. (**S**)* (1986) 162
73. Y. Asakawa, T. Masuya, M. Tori, E. O. Campbell, *Phytochemistry* **26** (1987) 735 (https://doi.org/10.1016/S0031-9422(00)84775-5)
74. Z.-Q. Lu, P.-H. Fan, M. Ji, H.-X. Lou, *J. Asian Nat. Prod. Res*. **8** (2006) 187 (https://doi.org/10.1080/10286020420003255 37)
75. M. Toyota, K. Tanimura, Y. Asakawa, *Planta Med*. **64** (1998) 462 (https://doi.org/10.1055/s-2006-957484)
76. J. C. Aponte, H. Yang, A. J. Vaisberg, D. Castillo, E. Malaga, M. Verastegui, L. K. Casson, N. Stivers, P. J. Bates, R. Rojas, I. Fernandez, W. H. Lewis, C. Sarasara, M. Sauvain, R. H. Gilman, G. B. Hammond, *Planta Med*. **76** (2010) 705 (https://doi.10.1055/s-0029-1240681)
77. Y.-F. Shu, H.-C. Wei, C.-L. Wu, *Phytochemistry* **37** (1994) 773 (https://doi.org/10.1016/S0031-9422(00)90356-X)
78. I. Komala, T. Ito, F. Nagashima, Y. Yagi, M. Kawahata, K. Yamaguchi, Y. Asakawa, *Phytochemistry* **71** (2010) 1387 (https://doi.10.1016/j.phytochem.2010.04.023)
79. Y. Wang, L. J. Harrison, B. C. Tan, *Tetrahedron* **65** (2009) 4035 (https://doi.org/10.1016/j.tet.2009.03.026)
80. F. Nagashima, I. Komala, T. Ito,Y. Asakawa, Y. Yagi, in *Proceedings of 53rd Symposium on Chemistry of Terpenes, Essential Oils and Aromatics*, 2009, Nara, Japan, p. 266

81. C. Wu, A. A. L. Gunatilaka, F. L. Mc Cabe, R. K. Johnson, R.W. Spjut, D. G. I. Kingston, *J. Nat. Prod*. **60** (1997) 1281 (https://doi.org/10.1021/np970251u)
82. H. Baek, N. B. Perry, S. D. Lorimer, *J. Chem. Res. (S)* (2003) 14 (https://doi.org/10.3184/030823403103172977)
83. Y. C. Kim, V. da S. Bolzani, N. Baj, A. A. L. Gunatilaka, D. G. I. Kingston, *Planta Med.* **62** (1996) 61 (https://doi.org/10.1055/s-2006-957800)
84. J. Burgess, L. Larsen, N. B. Perry, *J. Nat. Prod*. **63** (2000) 537 (https://doi.org/10.1021/np990492x)
85. N. B. Perry, L. M. Foster, *J. Nat. Prod*. **58** (1995) 1131 (https://doi.org/10.1021/np50121a027)
86. I. Komala, T. Ito, F. Nagashima, Y. Yagi, Y. Asakawa, *J. Nat. Med.* **64** (2010) 417 (https://doi.org/10.1007/s11418-010-0423-8)
87. J. M. Scher, E. J. Burgess, S. D. Lorimer, N. B. Perry, *Tetrahedron* **58** (2002) 7875 (https://doi.org/10.1016/S0040-4020(02)00899-2)
88. S. D. Lorimer, N. B. Perry, E. J. Burgess, L. M. Foster, *J. Nat. Prod*. **60** (1997) 421 (https://doi.org/10.1021/np960733q)
89. N. B. Perry, E. J. Burgess, R. S. Tangney, *Tetrahedron Lett*. **37** (1996) 9387 (https://doi.org/10.1016/S0040-4039(97)82971-1)
90. N. B. Perry, E. J. Burgess, S.-H. Baek, R. T. Weavers, W. Geis, A. B. Mauger, *Phytochemistry* **50** (1999) 423 (https://doi.org/10.1016/s0031-9422(98)00602-5)
91. F. Nagashima, M. Kondoh, T. Uematsu, A. Nishiyama, S. Saito, M. Sato, Y. Asakawa, *Chem. Pharm. Bull*. **50** (2002) 808 (https://doi.org/10.1248/cpb.50.808)
92. N. B. Perry, E. J. Burgess, L. M. Foster, P. J. Gerard, M. Toyota, Y. Asakawa, *J. Nat. Prod.* **71** (2008) 258 (https://doi.org/10.1021/np070644l)
93. N. B. Perry, E. J. Burgess, S.-H. Baek, R. T. Weavers, *Org. Lett*. **3** (2001) 4243 (https://doi.org/10.1021/ol0169224)
94. M. Neves, R. Morais, S. Gafner, K. Hostettmann, *Phytotherapy Res.* **12** (1998) 21 (https://doi.org/10.1002/(SICI)1099-1573(1998)12:1+<S21::AID-PTR238>3.0.CO;2-1)
95. S. M. Wong, Y. Oshima, J. M. Pezzuto, H. H. S. Fong, N. R. Farnsworth, *J. Pharm. Sci*. **75** (1986) 317 (https://doi.org/10.1002/jps.2600750324)
96. I. Komala, T. Ito, F. Nagashima, Y. Yagi, Y. Asakawa, *Nat. Prod. Commun*. **6** (2011) 303 (https://doi.org/10.1177/1934578X1100600301)
97. Y. Asakawa, *Nat. Prod. Commun*. **12** (2017) 1335 (https://doi.org/10.1177/1934578X1701200845)
98. Y. Asakawa, R. Matsuda, *Phytochemistry* **21** (1982) 2143 (https://doi.org/10.1016/0031-9422(82)83073-2)
99. S. Friederich, U. H. Maier, B. Deus-Meumann, Y. Asakawa, M. H. Zenk, *Phytochemistry* **50** (1999) 589 (https://doi.org/10.1016/S0031-9422(98)00557-3)
100. S. Friederich, M. Rueffer, Y. Asakawa, M. H. Zenk, *Phytochemistry* **52** (1999) 1195
101. H. Morita, Y. Tomizawa, T. Tsuchiya, Y. Hirasawa, T. Hashimoto, Y. Asakawa, *Bioorg. Med. Chem. Lett.* **19** (2009) 493 (https://doi.org/10.1016/j.bmcl.2008.11.036)
102. M. Novakovic, D. Bukvicki, B. Andjelkovic, T. Ilic-Tomic, M.Veljic, V. Tesevic, Y. Asakawa, *J. Nat. Prod*. **82** (2019) 694 (https://doi.org/10.1021/acs.jnatprod.8b00390)
103. I. Opsenica, J. Nikodinovic-Runic, L. Koracak, M. Novakovic, M. Zlatovic, S. Simic,T. Ilic Tomic, Y. Asakawa, *Fitoterapia* **142** (2020) 10452 (https://doi.org/10.1016/j.fitote.2020.104520)

104. W.-J. Huang, C.-L. Wu, C.-W. Lin, L.-L. Chi, P.-Y. Chen, C.-J. Chiu, C.-Y. Huang, C.-N. Chen, *Cancer Lett.* **291** (2010) 108 (https://doi.org/10.1016/j.canlet.2009.10.006)
105. C.-F. Xie, J.-B. Qu, X.-Z. Wu, N. Liu, M. Ji, H.-X. Lou, *Nat. Prod. Res.* **24** (2010) 515 (https://doi.org /10.1080/14786410802271587)
106. Y.-Q. Shi, J.-X. Liao, X.-J. Qu, H.-Q. Yuan, S. Li, J.-B. Qu, H.-X. Lou, *Cancer Lett*. **262** (2008) 173 (https://doi.org /10.1016/j.canlet.2007.12.014)
107. Y.-Q. Shi, X.-J. Qu, Y.-X. Liao, C.-F. Xie, Y.-N. Cheng, S. Li, H.-X. Lou, *Eur. J. Pharmacol.* **584** (2008) 66 (https://doi.org /10.1016/j.ejphar.2008.01.039)
108. A. Speicher, M. Groh, J. Zapp, A. Shaumloffel, M. Knauer, G. Bringmann, *Synlett* **11** (2009) 1852 (https://doi.org/10.1055/s-0029-1217510)
109. S. D. Lorimer, N. B. Perry, *Planta Med*. **60** (1994) 386 (https://doi.org/10.1055/s-2006-959511)
110. B. C. H. May, E. Nakaishi, L. M. Foster, M. Toyota, N. B. Perry, R. T. Weavers, S. D. Lorimer, Y. Asakawa, *J. Nat. Prod.* **59** (1996) 729 (https://doi.org/10.1021/np9603378)
111. S. H. Baek, H. J. Oh, J. A. Lim, H. J. Chun, H. O. Lee, J. W. Ahn, N. B. Perry, H. M. Kim, *Bull. Korean Chem. Soc*. **25** (2004) 195 (https://doi.org/10.5012/bkcs.2004.25.2.195)
112. F. Nagashima, W. Kasai, M. Kondoh, M. Fujii, Y. Watanabe, J. E. Braggins, Y. Asakawa, *Chem. Pharm. Bull.* **51** (2003) 1189 (https://doi.org/10.1248/cpb.51.1189)
113. F. Nagashima, M. Kondoh, M. Fujii, S. Takaoka, Y. Watanabe, Y. Asakawa, *Tetrahedron* **61** (2005) 4531 (https://doi.org/10.1016/j.tet.2005.03.010)
114. F. Nagashima, M. Kondoh, M. Kawase, S. Simizu, H. Osada, M. Fujii, Y. Watanabe, M. Sato, Y. Asakawa, *Planta Med*. **69** (2003) 377 (https://doi.org/10.1055/s-2003-38888)
115. M. Kondoh, I. Suzuki, M. Sato, F. Nagashima, S. Simizu, M. Harada, M. Fujii, H. Osada, Y. Asakawa, Y. Watanabe, *J. Pharmacol. Exp. Ther.* **311** (2004) 115 (https://doi.org/10.1124/jpet.104.069690)
116. I. Suzuki, M. Kondoh, M. Harada, N. Koizumi, M. Fujii, F. Nagashima, Y. Asakawa, Y. Watanabe, *Planta Med.* **70** (2004) 723 (https://doi.org/10.1055/s-2004-827202)
117. I. Suzuki, M. Kondoh, F. Nagashima, M. Fujii, Y. Asakawa, Y. Watanabe, *Planta Med.* **70** (2004) 401 (https://doi.org/10.1055/s-2004-818966)
118. M. Kondoh, F. Nagashima, I. Suzuki, M. Harada, M. Fujii, Y. Asakawa, Y. Watanabe, *Planta Med.* **71** (2005) 1005 (https://doi.org/10.1055/s-2005-873133)
119. M. Kondoh, I. Suzuki, M. Harada, F. Nagashima, M. Fujii, Y. Asakawa, Y. Watanabe, *Planta Med.* **71** (2005) 275 (https://doi.org/10.1055/s-2005-837830)
120. I. Shunsuke, N. Yosuke, T. Osamu, H. Toshifumi, *Chem. Let.* **26** (1997) 837 (https://doi.org/10.1246/cl.1997.837)
121. D.-X. Guo, Y. Du, Y.-Y. Wang, L.-M. Sun, J.-B. Qu, X.-N. Wang, H.-X. Lou *Nat. Prod. Commun*. **4** (2009) 1319 (https://doi.org/10.1177/1934578X0900401001)
122. H. Nozaki, K.-I. Hayashi, N. Nishimura, H. Kawaide, A. Matsuo, D. Takaoka, *Biosci. Biotechnol. Biochem.***71** (2007) 3127 (https://doi.org/10.1271/bbb.70625)
123. S.-J. Kim, H.-R. Park, E. Park, S.-C. Lee, *J. Agric. Food Chem*. **55** (2007) 1702 (https://doi.org/10.1021/jf062020b)
124. G.-Q. Zheng, D. K. Ho, P. J. Elder, R. E. Stephens, C. E. Cottrell, J. M. Cassady, *J. Nat. Prod.* **57** (1994) 32 (https://doi.org/10.1021/np50103a005)
125. P. Fu, S. Lin, L. Shan, Y.-H. Shen, J. Tang, R.-H. Liu, X. Zhang, R.-L. Zhu, W.-D. Zhang, *J. Nat. Prod*. **72** (2009) 1335 (https://doi.org/10.1021/np800830v)

126. F. Nagashima, Y. Ohi, T. Nagai, M. Tori, Y. Asakawa, S. Huneck, *Phytochemistry* **33** (1993) 1445 (https://doi.org/10.1016/0031-9422(93)85107-3)
127. A. C. Figueiredo, M. Sim-Sim, J. G. Barroso, L. G. Pedro, P. A. G. Santos, S. S. Fontinha, J. Schripsema, S. G. Deans, J. J. C. Scheffer, *J. Essent. Oil Res*. **14** (2002) 439 (https://doi.org/10.1080/10412905.2002.9699915)
128. X.-L. Guo, P. Leng. Y. Yeng, L.-G. Yu, H.-X. Lou. *J. Appl. Microbiol.* **104** (2008) 831 (https://doi.org/10.1111/j.1365-2672.2007.03617.x)
129. X.-Z. Wu, A.-X., Cheng, L.-M. Sun, H.-X. Lou, *Acta Pharmacol. Sin.* **29** (2008) 1478 (https://doi.org/10.1111/j.1745-7254.2008.00900.x)
130. X.-Z. Wu, A.-X. Cheng, L.-M. Sun, S.-J. Sun, H.-X. Lou, *Biochim. Biophys. Acta* **1790** (2009) 770 (https://doi.org/10.1016/j.bbagen.2009.05.002)
131. X.-Z. Wu, W.-Q. Chang, A.-X. Cheng, L.-M. Sun, H.-X. Lou, *Biochim. Biophys. Acta* **1800** (2010) 439 (https://doi.org/10.1016/j.bbagen.2010.01.001)
132. C. Niu, J.-B. Qu, H.-X. Lou, 2006. *Chem. Biodivers*. **3** (2006) 34 (https://doi.org/10.1002/cbdv.200690004)
133. J. Qu, C. Xie, H. Guo, W. Yu, H. Lou, *Phytochemistry* **68** (2007) 1767 (https://doi.org/10.1016/j.phytochem.2007.04.036)
134. J. M. Scher, J.-B. Speakman, J. Zapp, H. Becker, *Phytochemistry* **65** (2004) 2583 (https://doi.org/10.1016/j.phytochem.2004.05.013)
135. Y. Iwai, K. Murakami, Y. Gomi, T. Hashimoto, Y. Asakawa, Y. Okuno, T. Ishikawa, D. Hatakeyama, N. Echigo, T. Kuzuhara, *PLoS ONE* **6** (2011) 1 (https://doi.org/10.1371/journal.pone.0019825)
136. L. Harinantenaina, Y. Asakawa, *Chem. Pharm. Bull*. **52** (2004) 1382 (https://doi.org/10.1248/cpb.52.1382)
137. A. Matsuo, K. Ono, K. Hamasaki, H. Nozaki, *Phytochemistry* **42** (1996) 427 (https://doi.org/10.1016/0031-9422(96)00017-9)
138. H. J. M. Gijsen, J. B. P. A.Wijnberg, G. A. Stork, A. De Groot, M. A. De Waard, J. G. M. Van Nistelrooy, *Tetrahedron* **48** (1992) 2465 (https://doi.org/10.1016/S0040-4020(01)88765-2)
139. R. S. Burden, M. S. Kemp, *Phytochemistry* **22** (1983) 1039 (https://doi.org/10.1016/doi.org/0031-9422(83)85056-0)
140. M. Neves, R. Morais, S. Gafner, H. Stoeckli-Evans, K. Hostettmann, *Phytochemistry* **50** (1999) 967 (https://doi.org/10.1016/S0031-9422(98)00648-7)
141. C. Labbé, F. Faini, C. Villagran, J. Coll, D. S. Rycroft, *J. Nat. Prod*. **70** (2007) 2019 (https://doi.org/10.1021/np070192c)
142. C. Labbé, F. Faini, C. Villagran, J. Coll, D. S. Rycroft, *J. Agric. Food Chem*. **53** (2005) 247 (https://doi.org/10.1021/jf048935c)
143. S. H. Baek, R. K. Phipps, N. B. Perry, *J. Nat. Prod*. **67** (2004) 718 (https://doi.org/10.1021/np030455c)
144. J. M. Scher, A. Schinkovitz, J. Zapp, Y. Wang, S. G. Franzblau, H. Becker, D. C. Lankin, G. F. Pauli, *J. Nat. Prod*. **73** (2010) 656 (https://doi.org/10.1021/np900806j)
145. T. Yoshida, T. Hashimoto, S. Takaoka, Y. Kan, M. Tori, Y. Asakawa, J. Pezzuto, T. Pengsuparp, G. Cordell *Tetrahedron* **52** (1996) 14487 (https://doi.org/10.1016/0040-4020(96)00889-7).