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Therapeutic potential of bryophytes and derived compounds against cancer

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ABSTRACT

Bryophytes, taxonomically placed between the algae and the pteridophytes, are divided into three classes such as Liverworts, Hornworts and Mosses. Indigenous use involves this small group of plants to treat various diseases. Bryophytes have been investigated pharmacologically for active biomolecules. Several constituents with therapeutic potential have been isolated, characterized and investigated for antibacterial, antifungal, antiviral, antioxidative, antiinflammatory and anticancerous efficacy. The present review deals with the literature covering the anticancerous potential of bryophytes. Apart from the examples of the compounds and the containing bryophyte genera, the authors have tried to include the examples of cancer cell lines on which the efficacy have been tested and the mode of action of certain cytotoxic agents. Crude extracts and isolated compounds from bryophytes were found to possess potent cytotoxic properties. Different types of terpenoids and bibenzyls have been reported among the most potent cytotoxic compounds. Most of these compounds were found to induce apoptosis by activating a number of genes and enzymes. Biochemical markers such as DNA fragmentation, nuclear condensation, proteolysis of poly (ADP-ribose) polymerase, activation of caspases, inhibition of anti-apoptotic nuclear transcriptional factor-kappaB, activation of p38 mitogen-activated protein kinase etc. have been found to be associated with apoptotic and necrotic response. This review summarizes recent scientific findings and suggests further investigations to evaluate the cytotoxic efficacy of bryophytes.

1. Introduction

Plants and natural products have been used as a source of potential anticancer agents^[1–8]. Antitumor agents such as vincristine, vinblastine the epidophyllotoxin derivatives, maytansine, bruceantin, thalicarpine, camptothecin, and lapachol have been reported from higher plants and their pharmacology have been reported^[9]. Members of Algae^[10,11], Lichen^[12,13], Fungi^[14,15], pteridophytes^[16,17], gymnosperms^[18,19] and angiosperms^[20,21] have been evaluated for cytotoxic properties. Traditional anticancerous and antitumorigenic plant reports have been pharmacologically investigated and in many cases scientists have found positive correlation between folklore use and scientific analyses^[22,23].

Bryophytes are a small group of plants devoid of true vascular tissue. Being small and of insignificant use, bryophytes have been neglected in scientific investigations. Chemical analysis of active constituents and phytopharmacology of bryophytes came into the field only in the last few decades. With the advent of modern techniques and methods such as gas chromatography, gas chromatography-mass spectrometry, nuclear magnetic resonance, high performance liquid chromatography, high performance thin layer chromatography and X-ray crystallography, it has been possible to isolate and structurally elucidate bioactive molecules present in bryophytes^[24]. Bryophytes serve as a source of biologically active, naturally occurring material^[25–27]. Antifungal^[28,29], antibacterial and antiviral^[30–32], anti inflammatory^[33], and antioxidative^[34,35] potential in liverworts and mosses has been recorded.

The present review deals with the literature covering the cytotoxicity and related therapeutic potential of bryophytes. Several bryophytes have been screened for cytotoxic activity^[36,37]. Crude extracts or various bioactive compounds have been isolated from liverworts and mosses for anticancerous

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efficacy on cancer cell lines such as pharyngeal squamous carcinoma (KB), P-388 murine leukemia tumor, liver hepatoblastoma (HEP-G2), lung carcinoma (A549), breast ductal carcinoma (MDA-MB-435), and colon adenocarcinoma (LOVO) cell lines, glioma A172 cells, T98G, U87 glioma, osteosarcoma U2OS, leukemia HL-60, K562 and MDR K562/A02, MCF-7 breast cancer *etc.* For reversal activity analyses of multidrug resistance cancer cell lines, adriamycin-resistant K562/A02 cells, vincristine-resistant KB/VCR lines *etc.* have been utilized. Cytotoxic efficacy of the bryophytes was reflected in terms of several biochemical markers of apoptosis and necrosis induction such as DNA fragmentation, nuclear condensation, proteolysis of poly (ADP-ribose) polymerase (PARP), activation of caspases (a family of cysteine aspartic proteases), inhibition of antiapoptotic nuclear transcriptional factor-kappaB, activation of p38 (mitogen-activated protein kinase) *etc.* Most/some of these genetic and biochemical machinery play a crucial role in apoptosis induction. Table 1 depicts the cytotoxic compounds isolated from bryophytes with their chemical structures,

systematic names and molecular formula. Structures were taken from the chemical structure database <http://www.chemspider.com>.

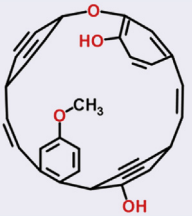
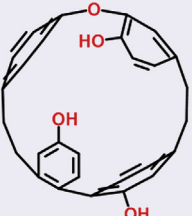
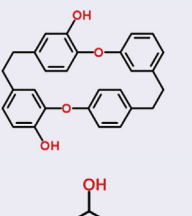
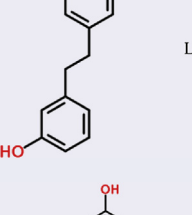
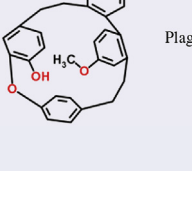
2. Cytotoxic compounds from bryophytes

2.1. Liverworts

Liverworts contain a number of bioactive molecules which have been utilized to classify them chemosystemically^[38,39]. Terpenes are naturally occurring hydrocarbons made up of several combined isoprene units. Bryophytes possess a number of terpenoid compounds such as mono, sesqui, di and triterpenoids, flavonoids, sterols and characteristic phenolic bibenzyls. Bibenzyls or dihydrostilbene are characteristic phenolic compounds found in liverworts. Apart from its occasional existence in some higher plants, these are absent in hornworts and mosses. Bis (bibenzyls) are derived from two bibenzyl units linked by some ether linkage^[24]. The chemicals

Table 1

Structures of cytotoxic phytochemicals from bryophytes.

Cytotoxic phytochemicals from hepatics	Scientific names and molecular formulae
 <p>Riccardin A</p>	<p>Systematic name (8Z,20Z)-5-Methoxy-14-oxapentacyclo[20.2.2.2^{10,13}.1^{15,19}.0^{2,7}]nonacos-2,4,6,8,11,15(27),16,18,20,23,25,28-dodecaene-16,24-diol Molecular formula: C₂₉H₂₆O₄</p>
 <p>Riccardin C</p>	<p>Systematic name 14-Oxapentacyclo[20.2.2.2^{10,13}.1^{15,19}.0^{2,7}]nonacos-1(24),2,4,6,10,12,15(27),16,18,22,25,28-dodecaene-5,16,24-triol Molecular formula: C₂₈H₂₄O₄</p>
 <p>Riccardin B</p>	<p>Systematic name 2,14-Dioxapentacyclo[20.2.2.2^{10,13}.1^{3,7}.1^{15,19}]triaconta-1(24),3(30),4,6,10,12,15(27),16,18,22,25,28-dodecaene-4,12-diol Molecular formula: C₂₈H₂₄O₄</p>
 <p>Lunularin</p>	<p>Systematic name 3-[2-(4-Hydroxyphenyl)ethyl]phenol Molecular formula: C₁₄H₁₄O₂</p>
 <p>Plagiochin D</p>	<p>Systematic name 19-Methoxy-2-oxapentacyclo[22.2.2.1^{3,7}.0^{10,15}.0^{16,21}]nonacos-1(26),3(29),4,6,10,12,14,16,18,20,24,27-dodecaene-4,12-diol Molecular formula: C₂₉H₂₆O₄</p>

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Table 1 (continued)

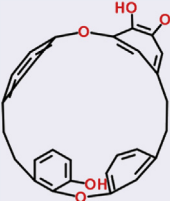
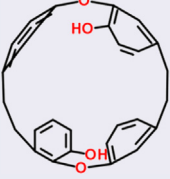
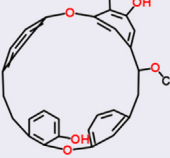
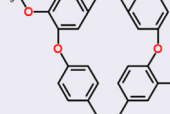
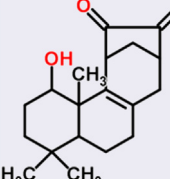
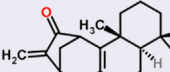
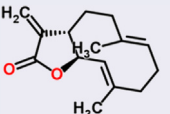
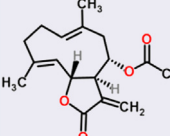
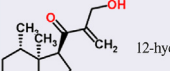
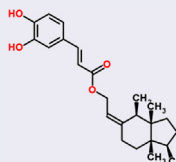
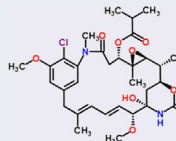
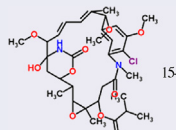
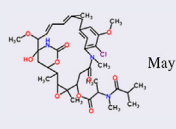
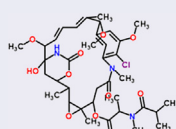
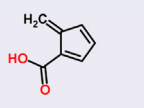
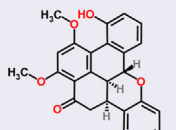
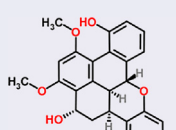
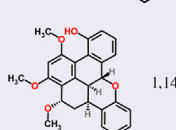
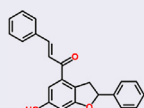
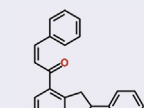
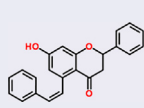
Cytotoxic phytochemicals from hepatics	Scientific names and molecular formulae
 <p>Marchantin A</p>	<p>Systematic name 2,15-Dioxapentacyclo[22.2.2.1^{3,7}.1^{10,14}.0^{16,21}]triaconta-1(26),3(30),4,6,10(29),11,13,16,18,20,24,27-dodecaene-4,5,17-triol Molecular formula: C₂₈H₂₄O₅</p>
 <p>Marchantin C</p>	<p>Systematic name 2,15-Dioxapentacyclo[22.2.2.1^{3,7}.1^{10,14}.0^{16,21}]triaconta-1(26),3(30),4,6,10(29),11,13,16,18,20,24,27-dodecaene-4,17-diol Molecular formula: C₂₈H₂₄O₄</p>
 <p>Marchantin E</p>	<p>Systematic name 8-Methoxy-2,15-dioxapentacyclo[22.2.2.1^{3,7}.1^{10,14}.0^{16,21}]triaconta-1(26),3(30),4,6,10(29),11,13,16,18,20,24,27-dodecaene-4,5,17-triol Molecular formula: C₂₉H₂₆O₆</p>
 <p>Pakyonol</p>	<p>Systematic name 4-Methoxy-2,15-dioxapentacyclo[20.2.2.2^{16,19}.1^{3,7}.1^{10,14}]triaconta-1(24),3(30),4,6,10(29),11,13,16,18,22,25,27-dodecaen-17-ol Molecular formula: C₂₉H₂₆O₄</p>
 <p>Jungermannone A</p>	<p>Systematic name 1-Hydroxy-11,16-cycloabieta-8,15(17)-dien-16-one Molecular formula: C₂₀H₂₈O₂</p>
 <p>Jungermannone B</p>	<p>Systematic name (5β,10α,13ξ)-11,16-Cycloabieta-8,15(17)-dien-16-one Molecular formula: C₂₀H₂₈O</p>
 <p>Costunolide</p>	<p>Systematic name (3aS,6E,10E,11aR)-6,10-Dimethyl-3-methylene-3a,4,5,8,9,11a-hexahydrocycloclodeca[b]furan-2(3H)-one Molecular formula: C₁₅H₂₀O₂</p>
 <p>Tulipinolide</p>	<p>Systematic name (3aR,4S,6E,10E,11aR)-6,10-Dimethyl-3-methylene-2-oxo-2,3,3a,4,5,8,9,11a-octahydrocycloclodeca[b]furan-4-yl acetate Molecular formula: C₁₇H₂₂O₄</p>
 <p>12-hydroxychiloscyphone</p>	<p>Systematic name 1-[(1S,7S,7aS)-7,7a-Dimethyl-2,3,5,6,7,7a-hexahydro-1H-inden-1-yl]-2-(hydroxymethyl)-2-propen-1-one Molecular formula: C₁₅H₂₂O₂</p>

Table 1 (continued)

Cytotoxic phytochemicals from hepatics	Scientific names and molecular formulae
 <p>Naviculyl caffeate</p>	<p>Systematic name (2Z)-2-[(1R,3aS,4R,7aS)-1,3a,4,7a-Tetramethyloctahydro-5H-inden-5-ylidene]ethyl (2E)-3-(3,4-dihydroxyphenyl)acrylate Molecular formula: C₂₄H₃₂O₄</p>
Cytotoxic phytochemicals from mosses	Scientific names and molecular formulae
 <p>Ansamitocin P-3</p>	<p>Systematic name (1S,2R,3S,5S,6S,16E,18E,20R,21S)-11-Chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]hexacos-10(26),11,13,16,18-pentaen-6-yl 2-methylpropanoate Molecular formula: C₃₂H₄₃ClN₂O₉</p>
 <p>15-methoxyansamitocin P-3</p>	<p>Systematic name 11-Chloro-21-hydroxy-12,15,20-trimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]hexacos-10(26),11,13,16,18-pentaen-6-yl 2-methylpropanoate Molecular formula: C₃₃H₄₅ClN₂O₁₀</p>
 <p>Maytanbutine</p>	<p>Systematic name 11-Chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]hexacos-10(26),11,13,16,18-pentaen-6-yl 2-[isobutyryl(methyl)amino]propanoate (non-preferred name) Molecular formula: C₃₆H₅₀ClN₃O₁₀</p>
 <p>Trewiasine</p>	<p>Systematic name 11-Chloro-21-hydroxy-12,15,20-trimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.1^{10,14}.0^{3,5}]hexacos-10(26),11,13,16,18-pentaen-6-yl 2-[isobutyryl(methyl)amino]propanoate (non-preferred name) Molecular formula: C₃₇H₅₂ClN₃O₁₁</p>
 <p>Fulvic acid</p>	<p>Systematic name 5-Methylene-1,3-cyclopentadiene-1-carboxylic acid Molecular formula: C₇H₆O₂</p>
 <p>1-O-methylhoiiosin B</p>	<p>Systematic name (7bR,12bS,14cS)-4-Hydroxy-1,3-dimethoxy-7b,12b,13,14c-tetrahydro-14H-benzo[c]naphtho[2,1,8-mna]xanthen-14-one Molecular formula: C₂₅H₂₀O₅</p>
 <p>1-O-methyldihydrohoiiosin B</p>	<p>Systematic name (7bR,12bS,14S,14cS)-1,3-Dimethoxy-12b,13,14,14c-tetrahydro-7bH-benzo[c]naphtho[2,1,8-mna]xanthene-4,14-diol Molecular formula: C₂₅H₂₂O₅</p>
 <p>1,14-di-O-methyldihydrohoiiosin B</p>	<p>Systematic name (7bR,12bS,14S,14cS)-1,3,14-Trimethoxy-12b,13,14,14c-tetrahydro-7bH-benzo[c]naphtho[2,1,8-mna]xanthen-4-ol Molecular formula: C₂₆H₂₄O₅</p>
 <p>Pallidisetin A</p>	<p>Systematic name (2E)-1-(6-Hydroxy-2-phenyl-2,3-dihydro-1-benzofuran-4-yl)-3-phenyl-2-propen-1-one Molecular formula: C₂₃H₁₈O₃</p>
 <p>Pallidisetin B</p>	<p>Systematic name (2Z)-1-(6-Hydroxy-2-phenyl-2,3-dihydro-1-benzofuran-4-yl)-3-phenyl-2-propen-1-one Molecular formula: C₂₃H₁₈O₃</p>
 <p>Communin A</p>	<p>Systematic name 7-Hydroxy-2-phenyl-5-[(Z)-2-phenylvinyl]-2,3-dihydro-4H-chromen-4-one Molecular formula: C₂₃H₁₈O₃</p>

are responsible for characteristic fragrance, odour, pungency, and bitterness associated with the bryophytes. It was noted that, 80% of the sesqui- and diterpenoids found in liverworts are the enantiomers of those found in higher groups of plants^[26].

2.1.1. Monoterpenes

Many of the Isoprenyl phenyl ethers from *Trichocolea* had shown cytotoxic activity. New Zealand liverwort *Trichocolea mollissima* was found to contain methyl 4-[(5-oxogeranyl)oxy]-3-methoxybenzoate as the major cytotoxic agent. Geranyl ethers were also found in the Japanese *Trichocolea tomentella*^[40]. Three geranyl phenyl ethers based on the cytotoxic monoterpenoids were synthesized from the *Trichocolea* from New Zealand^[41]. Hemi- and monoterpene moieties of isoprenyl phenyl ethers from *Trichocolea tomentella* have been biosynthesized^[42]. Presence of monoterpenes has been recorded from the liverwort *Conocephalum conicum*^[43,44]. A monoterpene ester, 2 alpha, 5 beta-dihydroxybornane-2-cinnamate from Chinese *Conocephalum conicum* has been found to be moderately cytotoxic against human HepG2 cells^[45]. Another liverwort, *Jungermannia vulcanicola* was also recorded for possessing monoterpenes^[46].

2.1.2. Sesquiterpenes

Isolation, determination of structure, synthesis, chemical and microbiological transformations of natural sesquiterpenoids^[47] and disesquiterpenoids^[48] has been reviewed. Bryophytes contain a number of sesquiterpenoid compounds, some of which have shown cytotoxicity. An ent-eudesmanolide known as diplophyllin was isolated from *Diplophyllum albicans* and *Diplophyllum taxifolium*. Diplophyllin showed significant activity against human epidermoid carcinoma^[49]. Sesquiterpenoids costunolide and tulipinolide, the tumor growth-inhibitors, also known from higher plants were isolated from the liverworts *Conocephalum supra-decompositum*, *Frullania monocera*, *Frullania tamarisci*, *Marchantia polymorpha* (*M. polymorpha*), *Porella japonica* and *Wiesnerella denudata*^[25,50]. Later on *Lepidozia vitrea*, *Plagiochila semidecurrans* and *Plagiochila ovalifolia* were added to the list^[51–55]. In another study, some compounds isolated from bryophytes were assayed for anticancer potential^[56]. Potential anticancer activity of sesquiterpenes of *Porella cordeana*, *Frullania nisquellensis* and *Chiloscyphus rivularis* were found and these were categorized among the DNA-damaging natural products^[57]. Methyl ethyl ketone extract of the aquatic liverwort *Chiloscyphus rivularis* produced a sesquiterpene, 12-hydroxychiloscyphone, which was selectively bioactive in yeast-based DNA-damaging assay and cytotoxic to human lung carcinoma cells^[58]. 2,3-Secoaromadendrane-type sesquiterpenoids were reported from the Japanese liverwort *Plagiochila ovalifolia*. The compounds present in the ether extract were plagiociline-A-15-yl octanoate, 14-hydroxyplagiociline-A-15-yl 2E,4E-dodecadienoate and 14-hydroxyplagiociline-A-15-yl 2E,4E,8Z-tetradecatrienoate of which the first two were significantly cytotoxic against P-388 murine leukemia tumor cells^[59]. A cytotoxin selectively active against human tumor cell lines was isolated from the liverwort *Bazzania novae-zelandiae*. The active compound was naviculyl caffeate, a sesquiterpene^[60]. Another cytotoxic sesquiterpenoid compound was reported from the liverwort from New Zealand *Schistochila glaucescens* (*S. glaucescens*). A sesquiterpene lactone glaucescenolide was found as a cytotoxic agent against P388 leukemia cells^[61].

Cytotoxic activity of herbertane type sesquiterpenoids (–)-alpha-herbertenol, (–)-herbertenediol, (–)-mastigophorene C, (–)-mastigophorene D and (–)-Diplophyllolide A from the Tahitian liverwort *Mastigophora diclados* against HL-60 and KB cell lines was reported^[62]. A zierane sesquiterpene gamma-lactone, chandolide from Tahitian liverwort *Chandonanthus hirtellus* had shown weak cytotoxic activity against HL-60^[63]. Germacrane- and pinguisane-type sesquiterpenoids from Indonesian and Tahitian *Frullania* sp. and Japanese *Porella perrottetiana* (*P. perrottetiana*) were found to be active against human promyelocytic leukemia (HL-60) and human pharyngeal squamous carcinoma (KB) cell lines which were determined by the water soluble tetrazolium-8 colorimetric assay^[64].

Some other examples of sesquiterpenoid containing liverworts are *Jungermannia infusca*^[65,66], *Mylia taylorii*^[67], *Mylia nuda*^[68], *Bryopteris filicina*^[69], *Frullania densiloba*^[70], *Frullania tamarisci* subsp. *obscura*^[71], *Ptilidium ciliare*^[72], *Jubula japonica*^[73], *Dumortiera hirsuta*^[74,75], *Lejeunea aquatica*, *Lejeunea flava* and *Lejeunea japonica*^[76], *Plagiomnium acutum*^[77], *Chiloscyphus polyanthus*^[78], *Chiloscyphus subporosus*^[79], *Porella swartziana*^[80], *Porella recurva*^[81], *Porella subobtusata*^[82], *Porella acutifolia* subsp. *tosana*^[83,84], *Scapania undulata*^[85], *Lepicolea ochroleuca*^[86], *Gackstroemia* sp., *Dendromastigophora* sp.,^[87] *Lepidozia fauriana*^[88], etc. These liverwort genera possessing sesquiterpenoid compound could be exploited as a natural source of cytotoxic compounds.

2.1.3. Diterpenoids

Cytotoxic 8,9-secokaurane diterpenes active against human tumor cell lines from a New Zealand liverwort, *Lepidolaena taylorii* were reported^[89]. 8,9-Secokauranes from the same species were reported as cytotoxic against human tumor cell lines. In addition, two 8,9-secokauranes from the New Zealand liverwort *Lepidolaena palpebrifolia* showed cytotoxicity^[90]. Some human tumor cells were found to be inhibited by cytotoxic effects of a novel ent-labdane type diterpenoid, muscicolone isolated from the liverwort *Frullania muscicola*^[91]. New ent-kaurene-type diterpenoids found in the liverwort *Jungermannia* sp. showed cytotoxicity against a human leukemia cell line^[92]. Ent-11alpha-hydroxy-16-kauren-15-one from the liverwort *Jungermannia truncata* was found to have apoptosis-inducing properties. Cytotoxicity of the compound against HL-60 cells may be dependent on caspases activation^[93]. It was noted that, ent-kaurene-type diterpenoids acted in a caspase-dependent manner in HL-60 cells^[94]. Ent-11alpha-hydroxy-16-kauren-15-one promoted apoptosis by tumor necrosis factor in human leukemia cells^[95]. Novel cytotoxic kaurene- and ent-kaurene-type diterpenoids from the same plant was recorded^[96]. Ent-11alpha-hydroxy-16-kauren-15-one induced apoptosis could be mediated by p38 mitogen-activated protein kinase p38 (MAPK)^[97]. In another study, new ent-kaurene diterpenoids jungermannenones A,B,C and D isolated from the same were reported to be tumor inhibiting through a caspase-dependent pathway^[98]. Cis-Clerodane diterpenoids have been reported from the wild liverwort *Gottschelia schizopleura* and their cytotoxic activity have been tested against liver hepatoblastoma (HEP-G2), lung carcinoma (A549), breast ductal carcinoma (MDA-MB-435), and colon adenocarcinoma (LOVO) cell lines^[99]. Cembrane-type diterpenoids and a known diterpenoid anadensin isolated from Tahitian liverwort *Chandonanthus hirtellus* had shown weak cytotoxicity against HL-60.

Fusicoccane-type diterpenoids, fusicocauritone 6 α -methyl ether had indicated weak cytotoxicity against KB cell lines^[63].

Examples of diterpenoids from other liverworts include *Jungermannia atrobrunnea*^[100], *Jungermannia exsertifolia* ssp. *cordifolia*^[101], *Jungermannia rotundata*^[102], *Jungermannia hattoria* na^[103], *Jungermannia infusca*^[104–106], *Jungermannia subulata* (cell suspension culture)^[107], *Jackiella javanica*^[108,109], *Pellia endiviifolia*^[110], *P. perrottetiana*^[111], *Porella densifolia*^[112], *Porella chilensis*^[113], *Odontoschisma denudatum*^[114], *Barbilophozia hatcheri*^[115], *Frullania inouei*^[116], *Frullania hamachiloba*^[117], *Pallavicinia subciliata*^[118], *Scapania undulata*^[119], *Jamesoniella colorata*^[120], *Jamesoniella kirkii*^[121], *Trichocolea mollissima*^[122], etc. Anticarcinogenic potential of widely distributed diterpenoids from bryophyte genera could lead to its possible use as a therapy against several human cancers.

2.1.4. Triterpenoids

Antitumor effect with apoptosis-inducing activity of pentacyclic triterpenoids and their saponins has been reported and their structure-activity relationships (SARs) were discussed^[123]. Plant-derived triterpenoids had shown promising activity on various cancer cell lines^[124]. Cytotoxicity of different secondary metabolites isolated from the liverwort *Ptilidium pulcherrimum* have been reported against the PC3, MDA-MB-231, and HeLa cells lines of which ursane triterpenoids had shown moderate cytotoxicity against PC3 cells^[125]. Other liverwort genera reported for triterpenes are *Fossombronina alaskana* and *Fossombronina pusilla*^[126], *Conocephalum japonicum*^[127], *Nardia scalaris*^[128], *Blepharidophyllum densifolium*^[129], etc.

2.1.5. Bibenzyls and bisbenzyls

2.1.5.1. Riccardin

Cytotoxicity against the KB cells was shown by bis(bibenzylyl) riccardin from *Riccardia multifida* (*R. multifida*)^[50]. Riccardin A and riccardin B reported from *R. multifida* were found to possess cytotoxic activity^[130]. Total syntheses of riccardin B from liverworts have been reported^[131]. Riccardin D, isolated from a Chinese liverwort was found to possess pronounced antiproliferative effect on human leukemia cell lines HL-60, K562 and MDR K562/A02 cells. No induction of apoptosis in topoisomerase-II-deficient HL-60/MX2 cells indicates the mode of action of riccardin D is DNA topoisomerase-II dependent^[132].

2.1.5.2. Marchantin

Total syntheses of cytotoxic bis(bibenzylyl) marchantin A from liverworts were reported^[131]. Cyto-chromes P-450 have been found to catalyze the formation reaction of marchantins A and C in *M. polymorpha*^[133,134]. Marchantin A from *M. polymorpha* and *M. tosana* had shown cytotoxicity against the KB cells^[50]. Marchantin C from the New Zealand liverwort *Schistochila glaucescens* was reported to be cytotoxic against P388 leukemia cells^[61]. Marchantin C was found to promote apoptosis in human glioma A172 cells. Bax-Bcl-2 regulation could have been the factor of its pro-apoptotic nature^[135]. Marchantin C from liverwort exhibited anti-tumor activity *in vivo* and *in vitro* by arresting cell cycle at G(2)/M phase in A172 and HeLa cells and decreased microtubule quantity. Marchantin C-treated human cervical carcinoma xenografts showed increased cyclin B1, Bax, caspase-3 activity^[136]. Antimicrotubule activities of marchantin A and C from the liverwort *Reboulia hemisphaerica* were examined on human

tumor cell line HeLa (cervical carcinoma) and the compounds were found to possess strong microtubule depolymerization activities. Liquid chromatography with diode array detection/mass spectroscopy (LC-DAD/MS/MS) techniques have been utilized to detect the macrocyclic bisbenzyls^[137]. Marchantin C was found to inhibit the migration in T98G and U87 glioma cells. Matrix metalloproteinase 2, the key factor behind cancer cell migration was found to be reduced in the treated cells. Thus the compound could be used to prevent recurrent tumors^[138]. Marchantin C was found to act as a potent reversal agent against vincristine-resistant KB/VCR cells by retarding P-gp activity^[139]. Marchantin A found in the liverwort *Marchantia emarginata* subsp. *tosana* induced cell growth inhibition leading to apoptosis in human MCF-7 breast cancer cells. The compound increased the expression of p21 and p27 genes while genes like cyclin B1 and D1 were expressed in a reduced manner^[140].

2.1.5.3. Neomarchantins

The bisbenzyls, neomarchantins A and B isolated from the New Zealand liverwort *Schistochila glaucescens* were reported to be cytotoxic against P388 leukemia cells^[61].

2.1.5.4. Plagiochin

Another macrocyclic bisbenzylyl plagiochin E, isolated from *M. polymorpha* had shown reversal effect on multidrug resistance in adriamycin-resistant K562/A02 cells^[141]. In addition, plagiochin E was reported to induce apoptosis in *Candida albicans*^[142].

2.1.5.5. Isoplagiochin

Antimitotic macrocyclic bis(bibenzylyl), isoplagiochins A and B from the liverwort *Plagiochila fruticosa* had shown inhibitory effect on tubulin polymerization^[143].

2.1.5.6. Perrottetin

Cytotoxicity against the KB cells was shown by perrottetin E from *Radula perrottetii*^[50].

2.1.5.7. Dihydroptychantol A (DHA)

Reversal effect of DHA, another macrocyclic bisbenzylyl from the liverwort *Asterella angusta* on multidrug resistance was demonstrated^[144]. Chemoresistant cancer cells like adriamycin-resistant K562/A02 and vincristine-resistant KB/VCR lines had exhibited reverting activity when exposed to DHA. This could be a significant aspect of multidrug resistance cancer cells chemotherapy^[145]. Chemically synthesized DHA was found to induce autophagy, apoptotic cell death and cell cycle arrest at G₂/M-phase in human osteosarcoma U2OS cells. Expression of nuclear p53 was found to increase while the cytoplasmic p53 expression was decreased in the treated cells^[146].

2.1.5.8. Lunularin

Lunularin from *Dumortiera hirsuta* showed moderate cytotoxicity against human HepG2 cells^[45].

2.1.5.9. Other bis(bibenzylyl)

Cyclic bisbenzyls, riccardin C, pakyonol, marchantin M and plagiochin E isolated from *Asterella angusta*, *Plagiochasma intermedium* and *M. polymorpha* respectively were found to be effective against chemoresistant prostate cancer PC3 cells. The

compounds were found to decrease the antiapoptotic protein Bcl-2, increase in expression of proapoptotic Bax and showed PARP cleavage and caspase-3 activity. The changes were detected by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay and Western blotting^[147]. Cytotoxicity tests of methoxylated bibenzyls from the liverwort *Frullania inouei* showed cytotoxic activity against human tumor KB, KB/VCR, K562 or K562/A02 cells reversal effect in vincristine-resistant KB/VCR and adriamycin-resistant K562/A02 cells^[116]. Cytotoxic bibenzyls from Indonesian and Tahitian *Frullania* sp. and Japanese *P. perrottetiana* were found effective against human promyelocytic leukemia (HL-60) and human pharyngeal squamous carcinoma (KB) cell lines determined by the water soluble tetrazolium-8 colorimetric assay^[64]. *Blasia pusilla* was found to possess bis(bibenzyl) dimers, pusilatins showing moderate cytotoxicity against KB cell line^[148]. Cyclic bis(bibenzyls) isomarchantin C and isoriccardin C from the Indian liverworts *M. polymorpha* and *Marchantia palmata* have been reported^[149].

Bis(bibenzyls) in bryophytes were studied using electron ionization time-of-flight and electrospray ionization triple-quadrupole mass spectrometry^[150]. Bryophyte crude extracts were rapidly screened for bisbibenzyls using liquid chromatography/tandem mass spectrometry^[151]. Bibenzyls and/or their derivatives were also recorded from liverworts such as *Plagiochila* sp.^[152,153], *Plagiochila fruticosa*^[154,155], *Marchantia paleacea*^[156], *Ptychantus striatus*^[157], *Ricciocarpos natans*^[158], *Bazzania trilobata*^[159], *Jubula japonica*^[73], *R. multifida* subsp. *decrescens*^[160], *Marsupidium epiphytum*^[161], *Radula marginata*^[162], *Lepidozia incurvata*^[163], etc.

2.2. Hornworts

This is by far the most neglected class of bryophyte in terms of phytochemical and pharmacological investigations. Being phylogenetically important, the group is expected to possess some unique metabolites with possible therapeutic value. Presence of structurally different xyloglucans is noted in the cell wall of hornworts which is similar to vascular plants and differs from liverworts and mosses^[164]. A sesquiterpene ether, veticadin oxide from *Anthoceros caucasicus* was reported^[165]. Phytochemical analyses were performed in some other hornwort members such as *Anthoceros agrestis*^[166–169], *Anthoceros caucasicus*^[170], *Megaceros flagellaris*^[171], etc. Authors did not find any report in relation to cytotoxic compounds from the members of this group.

2.3. Mosses

Mono- and sesquiterpenoids are very rare in mosses, but di- and triterpenoids have been reported from certain moss genera^[26]. Extracts of *Polytrichum juniperinum* had shown activity against sarcoma 37 in mice^[172]. Variation in cytotoxicity and antitumor activity among samples of a moss, *Claopodium crispifolium* was noted. Enhancement of antitumor activity of the moss could have been resulted due to interaction with the cyanobacterium *Nostoc* cf. *microscopicum* or due to the cyanobacterium itself^[173]. Antitumor maytansinoids and the members of the ansamycin group isolated from mosses are ansamitocin P-3, 15-methoxyansamitocin P-3, maytanbutine and trewasine from different mosses such as *Claopodium crispifolium*, *Anomodon attenuates*, *Isothecium subdiversiforme*

and *Thamnobrium sandei*^[173–175]. Ansamitocin P-3, with a very low yield from *Claopodium crispifolium* and *Anomodon attenuatus* exhibited significant cytotoxicity against human solid tumor cell lines A-549, HT-29^[175]. However, there are debates of actual occurrence of maytansinoids in mosses^[176]. Oncostatic as well as therapeutic nature of the peat preparation in some types of human cancer were reported^[177]. Cytotoxic effect of fulvic acid (FA) extracted and purified from Canadian Sphagnum peat on RBL-2H3 cells was analyzed by MTT assay^[178]. In another investigation, novel cytotoxic agents from *Polytrichum pallidisetum*, ohioensins and pallidisetins have been recorded. In this study, 1-O-methyl Ohioensin B, 1-O-methyl dihydro Ohioensin B and 1,14-di-O-methyl dihydro Ohioensin B, and two novel cinnamoyl bibenzyls, pallidisetin A and pallidisetin B had shown cytotoxicity against the human tumor cell lines RPMI-7951 melanoma and U-251 glioblastoma multiforme^[179]. Ohioensins, a kind of benzonaphthoxanthones from *Polytrichum ohioense* was reported earlier^[180]. Communins A and B and a new benzonaphthoxanthone, ohioensin H isolated from the moss *Polytrichum commune* were tested against cancer cell lines^[181], sanionins A and B from the Antarctic moss *Sanionia georgico-uncinata* collected from Livingston Island had shown weak cytotoxicity^[133]. Photoprotective effects of extracts of Antarctic moss *Polytrichum juniperinum* against UV induced DNA damage was noted in hamster lung fibroblasts (V79 cells)^[182]. Triterpenes have been reported from other moss genera such as *Thuidium tamariscifolium*^[183], *Floribundaria aurea* subsp. *nipponica*^[184], etc. However their cytotoxic efficacy is not yet being tested.

2.4. Others

In a study, several species of bryophytes have been screened for antitumor agents of which 43 species were found to be active and 75 species were toxic to mice. The most activity was noted in the families such as Brachytheciaceae, Grimmiaceae, Dicranaceae, Mniaceae, Neckeraceae, Hypnaceae, Polytrichaceae and Thuidiaceae^[36]. Methyl ethyl ketone extract of *Porella cordeana* produced drimenin and aristolone which were found to exhibit moderate toxicity towards DNA-repair-deficient mutants of *Saccharomyces cerevisiae*^[185]. Petroleum ether, ethyl acetate and *n*-butanol leaf extracts of the folk medicinal hepatic *Marchantia convoluta* showed cytotoxic effects to non-small cell lung carcinoma (H1299) and liver carcinoma (HepG2) determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay^[186]. *In vitro* cytotoxic activity of *M. convoluta* ethyl acetate extract on human liver and lung cancer cell lines (H1299 and HepG2) were reported, where petroleum ether and *n*-butanol extracts showed no activity^[187]. Bryophytes extracts which inhibit growth and induce abnormal phenotypes in human HeLa cancer cells with significant effects on interphasic and mitotic cells, have been screened pharmacologically^[188]. Luteolin, another biologically active compound, reported from various bryophytes and higher groups of plants is reported to induce apoptosis, prevent carcinogenesis and reduce tumor growth *in vivo*. This suggests that the flavonoid has cancer chemopreventive and chemotherapeutic potential^[189]. Crude extracts of the Tahitian *Mastigophora diclados* and *Frullania* sp. and the Indonesian *Frullania* sp. exhibited cytotoxic activity against HL-60 and KB cell lines^[190]. A few aromatic

compounds from the liverwort *Conocephalum japonicum* have been evaluated for cytotoxicity against the human KB cell line^[19].

3. Discussion

Cancer is one of the most common diseases taking millions of life per year. Apart from conventional treatments such as surgery, radiation and chemotherapy against different types of tumors and cancers, search for alternative and complementary medicine to combat the disease is going on. Discovery of anti-cancer agents from natural sources has been a major field of investigation in the last few decades. Various types of chemically diverged compounds have been isolated from natural sources and screened for cytotoxicity against cancer cell lines. Drug resistant cancer cell lines had shown reversal effect when exposed to certain natural and novel compounds. However the exact molecular mechanism remains unknown in many of the inhibitory reactions.

Bryophytes are phylogenetically placed between algae and pteridophytes and considered among the first land plants. A number of bryophytes have been used in traditional system of medicine to treat various ailments. Several bioactive and medicinally important compounds have been isolated and pharmacologically tested for their efficacy. Some of the active biomolecules such as terpenoids and phenolic bibenzyls have been studied for cytotoxicity against different human cancer cell lines. Many of the experiments have produced positive results indicating anticancerous efficacy of the compounds. Several genetic and biochemical pathways were found to be activated in order to induce apoptosis and necrosis by the biomolecules. It was also noted that, a very small fraction of bryophytes has been tested for their pharmacological efficacy. Although the exact mode of action of some of these bioactive compounds remains unknown, bryophytes could serve as an attractive candidate for therapeutic properties. Isolation, characterization, structural elucidation, pharmacological evaluation, determination of mode of action and clinical trial of these active principles could open an exciting aspect of future drug development programs. In addition, Structure-activity relationship of some of the cytotoxic compounds has been worked out. But, a number of such compounds are yet to be investigated. With the advent of modern tools such as high performance liquid chromatography, high performance thin layer chromatography, liquid chromatography, mass spectroscopy, liquid chromatography with diode array detection, X-ray crystallography etc. it has become easier to elucidate the relationship between the structure and activity of several biomolecules. However, active constituents of plants may vary depending on the season, altitude, type of tissue harvested and extraction condition. Therefore, it is important to consider all these factors while analyzing pharmacological efficacy of crude extracts. Most of these antiproliferative compounds belong to the liverwort genera while the mosses possess a few of them. The authors have found no report on cytotoxic potential of the hornworts. Keeping in mind its evolutionary significance, phytochemical and pharmacological studies of this group may lead to the discovery of certain novel metabolites having unique therapeutic potential.

Bryophytes, considered as the earliest land plants, synthesize a number of secondary metabolites to combat against different kinds of stress. Due to the presence of these phytochemicals they are able to cope up with infection, predation, radiation and temperature and salinity fluctuation. The diverse and novel

nature of secondary constituents could be exploited by pharmacological investigation, phytochemical evaluation and clinical trials. Development of drug resistance in proliferative cells as well as in microbes can be controlled by using such novel natural products. The possible use of bryophytes as medicine may lead to cure of different ailments which have been difficult to treat by conventional medicine.

Conflict of interest statement

We declare that we have no conflict of interest.

References

- [1] Barclay AS, Perdue RE Jr. Distribution of anticancer activity in higher plants. *Cancer Treat Rep* 1976; **60**(8): 1081-113.
- [2] Wall ME, Wani MC. Antineoplastic agents from plants. *Annu Rev Pharmacol Toxicol* 1977; **17**: 117-32.
- [3] Cragg G, Suffness M. Metabolism of plant-derived anticancer agents. *Pharmacol Ther* 1988; **37**(3): 425-61.
- [4] Cassady JM, Baird WM, Chang CJ. Natural products as a source of potential cancer chemotherapeutic and chemopreventive agents. *J Nat Prod* 1990; **53**(1): 23-41.
- [5] Sinha S, Jain S. Natural products as anticancer agents. *Prog Drug Res* 1994; **42**: 53-132.
- [6] Lee KH. Anticancer drug design based on plant-derived natural products. *J Biomed Sci* 1999; **6**(4): 236-50.
- [7] Kim J, Park EJ. Cytotoxic anticancer candidates from natural resources. *Curr Med Chem Anticancer Agents* 2002; **2**(4): 485-537.
- [8] Dholwani KK, Saluja AK, Gupta AR, Shah DR. A review on plant-derived natural products and their analogs with anti-tumor activity. *Indian J Pharmacol* 2008; **40**(2): 49-58.
- [9] Sieber SM, Mead JA, Adamson RH. Pharmacology of antitumor agents from higher plants. *Cancer Treat Rep* 1976; **60**(8): 1127-39.
- [10] Khanavi M, Nabavi M, Sadati N, Shams Ardekani M, Sohrabipour J, Nabavi SM, et al. Cytotoxic activity of some marine brown algae against cancer cell lines. *Biol Res* 2010; **43**(1): 31-7.
- [11] Broniatowska B, Allmendinger A, Kaiser M, Montamat-Sicotte D, Hingley-Wilson S, Lalvani A, et al. Antiprotozoal, antitubercular and cytotoxic potential of cyanobacterial (blue-green algal) extracts from Ireland. *Nat Prod Commun* 2011; **6**(5): 689-94.
- [12] Ivanova V, Backor M, Dahse HM, Graefe U. Molecular structural studies of lichen substances with antimicrobial, antiproliferative, and cytotoxic effects from *Parmelia subrudecta*. *Prep Biochem Biotechnol* 2010; **40**(4): 377-88.
- [13] Backorová M, Backor M, Mikeš J, Jendzelovsky R, Fedorocko P. Variable responses of different human cancer cells to the lichen compounds parietin, atranorin, usnic acid and gyrophoric acid. *Toxicol In Vitro* 2011; **25**(1): 37-44.
- [14] Tarman K, Lindequist U, Wende K, Porzel A, Arnold N, Wessjohann LA. Isolation of a new natural product and cytotoxic and antimicrobial activities of extracts from fungi of Indonesian marine habitats. *Mar Drugs* 2011; **9**(3): 294-306.
- [15] Bury M, Punzo B, Berestetskiy A, Lallemand B, Dubois J, Lefranc F, et al. Evaluation of the anticancer activities of two fungal polycyclic ethanones, altermethanoxins A and B, and two of their derivatives. *Int J Oncol* 2011; **38**(1): 227-32.
- [16] Chang SH, Bae JH, Hong DP, Choi KD, Kim SC, Her E, et al. *Dryopteris crassirhizoma* has anti-cancer effects through both extrinsic and intrinsic apoptotic pathways and G0/G1 phase arrest in human prostate cancer cells. *J Ethnopharmacol* 2010; **130**(2): 248-54.
- [17] Radhika NK, Sreejith PS, Asha VV. Cytotoxic and apoptotic activity of *Cheilanthes farinosa* (Forsk.) Kaulf. against human hepatoma, Hep3B cells. *J Ethnopharmacol* 2010; **128**(1): 166-71.

- [18] Rowinsky EK, Cazenave LA, Donehower RC. Taxol: a novel investigational antimicrotubule agent. *J Natl Canc Inst* 1990; **82**(15): 1247-59.
- [19] Chen CC, Wu JH, Yang NS, Chang JY, Kuo CC, Wang SY, et al. Cytotoxic C(35) terpenoid cryptotriene from the bark of *Cryptomeria japonica*. *Org Lett* 2010; **12**(12): 2786-9.
- [20] Munawir A, Sohn ET, Kang C, Lee SH, Yoon TJ, Kim JS, et al. Proteinaceous cytotoxic component of *Allium sativum* induces apoptosis of INT-407 intestinal cells. *J Med Food* 2009; **12**(4): 776-81.
- [21] Dey A, De JN. *Rauvolfia serpentina* (L). Benth. ex Kurz.-a review. *Asian J Plant Sci* 2010; **9**(6): 285-98.
- [22] de Mesquita ML, de Paula JE, Pessoa C, de Moraes MO, Costa-Lotufo LV, Grougnet R, et al. Cytotoxic activity of Brazilian Cerrado plants used in traditional medicine against cancer cell lines. *J Ethnopharmacol* 2009; **123**(3): 439-45.
- [23] Atjanasuppat K, Wongkham W, Meepowpan P, Kittakoop P, Sobhon P, Bartlett A, et al. *In vitro* screening for anthelmintic and antitumor activity of ethnomedicinal plants from Thailand. *J Ethnopharmacol* 2009; **123**(3): 475-82.
- [24] Banerjee RD. Recent advances in the chemistry of liverworts. In: Nath V, Asthana AK, editors. *Perspectives in Indian bryology (Proceedings National Conference on Bryology)*. Dehra Dun, India: Bishen Singh Mahendra Pal Singh; 2001, p. 171-207.
- [25] Asakawa Y. Biologically active substances obtained from bryophytes. *J Hattori Bot Lab* 1981; **50**: 123-42.
- [26] Asakawa Y. Biologically active compounds from bryophytes. *Pure Appl Chem* 2007; **79**(4): 557-80.
- [27] Zinsmeister HD, Becker H, Eicher T. Bryophytes, a source of biologically active, naturally occurring material? *Angew Chem Int Ed Engl* 1991; **30**(2): 130-47.
- [28] Cheng A, Sun L, Wu X, Lou H. The inhibitory effect of a macrocyclic bisbibenzyl riccardin D on the biofilms of *Candida albicans*. *Biol Pharm Bull* 2009; **32**(8): 1417-21.
- [29] Wu XZ, Cheng AX, Sun LM, Lou HX. Effect of plagiochin E, an antifungal macrocyclic bis(bibenzyl), on cell wall chitin synthesis in *Candida albicans*. *Acta Pharmacol Sin* 2008; **29**(12): 1478-85.
- [30] van Hoof LD, Vanden Berghe DA, Petit E, Vlietnick AJ. Antimicrobial and antiviral screening of bryophyta. *Fitoterapia* 1981; **52**(5): 223-9.
- [31] Scher JM, Schinkovitz A, Zapp J, Wang Y, Franzblau SG, Becker H, et al. Structure and anti-TB activity of trachylobanes from the liverwort *Jungermannia exsertifolia* ssp. cordifolia. *J Nat Prod* 2010; **73**(4): 656-63.
- [32] Singh M, Govindarajan R, Nath V, Rawat AK, Mehrotra S. Antimicrobial, wound healing and antioxidant activity of *Plagiochasma appendiculatum* Lehm. et Lind. *J Ethnopharmacol* 2006; **107**(1): 67-72.
- [33] Ivanova V, Kolarova M, Aleksieva K, Dornberger KJ, Haertl A, Moellmann U, et al. Sanionins: anti-inflammatory and antibacterial agents with weak cytotoxicity from the Antarctic moss *Sanionia georgico-uncinata*. *Prep Biochem Biotechnol* 2007; **37**(4): 343-52.
- [34] Dey A, De JN. Antioxidative potential of bryophytes: stress tolerance and commercial perspectives: a review. *Pharmacol* 2012; **3**(6): 151-9.
- [35] Cioffi G, Montoro P, De Ugaz OL, Vassallo A, Severino L, Pizza C, et al. Antioxidant bibenzyl derivatives from *Notholaena nivea* Desv. *Molecules* 2011; **16**(3): 2527-41.
- [36] Spjut RW, Suffness M, Cragg GM, Norris DH. Mosses, liverworts, and hornworts screened for antitumor agents. *Econ Bot* 1986; **40**(3): 310-38.
- [37] Spjut RW, Kingston DGI, Cassidy JM. Systematic screening of bryophytes for antitumor agents. *Trop Bryol* 1992; **6**: 193-202.
- [38] Asakawa Y. Chemosystematics of the hepaticae. *Phytochemistry* 2004; **65**(6): 623-69.
- [39] Asakawa Y. Liverworts-potential source of medicinal compounds. *Curr Pharm Des* 2008; **14**(29): 3067-88.
- [40] Pery NB, Foster LM, Lorimer SD, May BC, Weavers RT. Isoprenyl phenyl ethers from liverworts of the genus *Trichocolea* cytotoxic activity, structural corrections, and synthesis. *J Nat Prod* 1996; **59**(8): 729-33.
- [41] Baek SH, Perry NB, Weavers RT. Synthesis of geranyl phenyl ethers based on the cytotoxic monoterpenoids from the liverwort genus *Trichocolea*. *J Nat Prod* 1998; **61**(9): 1143-5.
- [42] Barlow AJ, Becker H, Adam KP. Biosynthesis of the hemi- and monoterpene moieties of isoprenyl phenyl ethers from the liverwort *Trichocolea tomentella*. *Phytochemistry* 2001; **57**(1): 7-14.
- [43] Valterová I, Unelius CR, Vrkoč J, Norin T. Enantiomeric composition of monoterpene hydrocarbons from the liverwort *Conocephalum conicum*. *Phytochemistry* 1992; **31**(9): 3121-3.
- [44] Adam KP, Croteau R. Monoterpene biosynthesis in the liverwort *Conocephalum conicum*: demonstration of sabinene synthase and bornyl diphosphate synthase. *Phytochemistry* 1998; **49**(2): 475-80.
- [45] Lu ZQ, Fan PH, Ji M, Lou HX. Terpenoids and bisbibenzyls from Chinese liverworts *Conocephalum conicum* and *Dumortiera hirsuta*. *J Asian Nat Prod Res* 2006; **8**(1-2): 187-92.
- [46] Yokouchi Y, Satake K, Ambe Y. Monoterpene composition of the essential oil of the aquatic liverwort *Jungermannia vulcanicola* Steph. *Bryologist* 1984; **87**(4): 323-6.
- [47] Fraga BM. Natural sesquiterpenoids. *Nat Prod Rep* 2012; **29**(11): 1334-66.
- [48] Zhan ZJ, Ying YM, Ma LF, Shan WG. Natural disesquiterpenoids. *Nat Prod Rep* 2011; **28**(3): 594-629.
- [49] Ohta Y, Andersen NH, Liu CB. Sesquiterpene constituents of two liverworts of genus *Diplophyllum*: novel eudesmanolides and cytotoxicity studies for enantiomeric methylene lactones. *Tetrahedron* 1977; **33**(6): 617-28.
- [50] Asakawa Y, Toyota M, Taira Z, Takemoto T. Biologically active cyclic bisbenzyls and terpenoids isolated from liverworts. In: *Proceeding of the 25th Symposium on Chemistry of Natural Products*. Tokyo; 1982, p. 337-44.
- [51] Matsuo A, Atsumi K, Nadaya K, Nakayama M, Hayashi S. ¹³C NMR chemical shifts of ovalifoliene and related compounds with 2,3-seco-alloaromadendrane skeleton: structure of (+)-9 α -acetoxyovalifoliene, a plant growth inhibitor. *Phytochemistry* 1981; **20**(5): 1065-8.
- [52] Matsuo A, Atsumi K, Nakayama M, Hayashi S. Structure of ent-2,3-secoalloaromadendrane sesquiterpenoids having plant growth inhibitory activity from *Plagiochila semidecurrans* (liverwort). *J Chem Soc Perkin Trans* 1981; **1**: 2816-24.
- [53] Matsuo A, Nadaya K, Nakayama M, Hayashi S. Plant growth inhibitors isolated from the liverwort, *Plagiochila ovalifolia*. *Nippon Kagaku Kaishi* 1981; **1981**(5): 665-70.
- [54] Matsuo A, Kubota N, Nakayama M, Hayashi S. (-)-Lepidozenal, a sesquiterpenoid with a novel trans-fused bicycle [8.1.0] undecane system from the liverwort *Lepidozia vitrea*. *Chem Lett* 1981; **10**(8): 1097-100.
- [55] Matsuo A, Nozaki A, Kubota N, Uto S, Nakayama M. Structures and conformation of (-)-isobicyclogermacrenal and 9(-)-lepidozenal, two key sesquiterpenoids of the *cis*- and *trans*-10,3-bicyclic ring system, from the liverwort *Lepidozia vitrea*. *J Chem Soc Perkin Trans* 1984; **1**: 203-14.
- [56] Gunatilakaa AAL, Kingston DGI, Johnson RK. Mechanism-based isolation and structures of some anticancer active natural products. *Pure Appl Chem* 1994; **66**(10-11): 2219-22.
- [57] Gunatilakaa AAL, Kingston DGI. DNA-damaging natural products with potential anticancer activity. *Stud Nat Prod Chem* 1997; **20**(Part F): 457-505.
- [58] Wu C, Gunatilaka AA, McCabe FL, Johnson RK, Spjut RW, Kingston DG. Bioactive and other sesquiterpenes from *Chiloscyphus rivularis*. *J Nat Prod* 1997; **60**(12): 1281-6.
- [59] Toyota M, Tanimura K, Asakawa Y. Cytotoxic 2,3-secoaromadendrane-type sesquiterpenoids from the liverwort *Plagiochila ovalifolia*. *Planta Med* 1998; **64**(5): 462-4.
- [60] Burgess EJ, Larsen L, Pery NB. A cytotoxic sesquiterpene caffeine from the liverwort *Bazzanianovae-zelandiae*. *J Nat Prod* 2000; **63**(4): 537-9.
- [61] Scher JM, Burgess EJ, Lorimer SD, Pery NB. A cytotoxic sesquiterpene and unprecedented sesquiterpene-bisbibenzyl

- compounds from the liverwort *Schistochila glaucescens*. *Tetrahedron* 2002; **58**(39): 7875-82.
- [62] Komala I, Ito T, Nagashima F, Yagi Y, Asakawa Y. Cytotoxic, radical scavenging and antimicrobial activities of sesquiterpenoids from the Tahitian liverwort *Mastigophora diclados* (Brid.) Nees (Mastigophoraceae). *J Nat Med* 2010; **64**(4): 417-22.
- [63] Komala I, Ito T, Nagashima F, Yagi Y, Kawahata M, Yamaguchi K, et al. Zierane sesquiterpene lactone, cembrane and fusicoccane diterpenoids, from the Tahitian liverwort *Chandonanthus hirtellus*. *Phytochemistry* 2010; **71**(11-12): 1387-94.
- [64] Komala I, Ito T, Nagashima F, Yagi Y, Asakawa Y. Cytotoxic bibenzyls, and germacrane- and pinguisane-type sesquiterpenoids from Indonesian, Tahitian and Japanese liverworts. *Nat Prod Commun* 2011; **6**(3): 303-9.
- [65] Nagashima F, Suzuki M, Takaoka S, Asakawa Y. Clerodane-type diterpenoids from the Japanese liverwort *Jungermannia infusca* (Mitt.) Steph. *Chem Pharm Bull (Tokyo)* 2000; **48**(11): 1818-21.
- [66] Nagashima F, Suzuki M, Takaoka S, Asakawa Y. Sesqui- and diterpenoids from the Japanese liverwort *Jungermannia infusca*. *J Nat Prod* 2001; **64**(10): 1309-17.
- [67] von Reuß SH, Wu CL, Muhle H, König WA. Sesquiterpene constituents from the essential oils of the liverworts *Mylia taylorii* and *Mylia nuda*. *Phytochemistry* 2004; **65**(15): 2277-91.
- [68] Liu HJ, Wu CL, Hashimoto T, Asakawa Y. Nudenoic acid: a novel tricyclic sesquiterpenoids from the Taiwanese liverwort *Mylia nuda*. *Tetrahedron Lett* 1996; **37**(52): 9307-8.
- [69] Nagashima F, Izumo H, Takaoka S, Tori M, Asakawa Y. Sesqui- and diterpenoids from the Panamanian liverwort *Bryopteris filicina*. *Phytochemistry* 1994; **37**(2): 433-9.
- [70] Nagashima F, Tanaka H, Takaoka S, Asakawa Y. Eudesmane-type sesquiterpene lactones from the Japanese liverwort *Frullania densiloba*. *Phytochemistry* 1997; **45**(3): 555-8.
- [71] Toyota M, Nishimoto C, Asakawa Y. Eudesmane-type sesquiterpenoids from Japanese liverwort *Frullania tamarisci* subsp. *obscura*. *Chem Pharm Bull* 1998; **46**(3): 542-4.
- [72] Nagashima F, Takaoka S, Huneck S, Asakawa Y. Sesqui- and diterpenoids from *Ptilidium ciliare* and *Barbilophozia* species (Liverworts). *Phytochemistry* 1999; **51**(4): 563-6.
- [73] Toyota M, Asakawa Y. Bibenzyl and sesquiterpenoids from the liverwort *Jubula japonica*. *Phytochemistry* 1993; **34**(4): 1135-7.
- [74] Toyota M, Bardon A, Kamiya N, Takaoka S, Asakawa Y. Dumorteniols, novel sesquiterpenoids from the Argentinean liverwort *Dumortiera hirsuta*. *Chem Pharm Bull* 1997; **45**(12): 2119-21.
- [75] Toyota M, Yoshida T, Matsunami J, Asakawa Y. Sesquiterpenes and other constituents of the liverwort *Dumortiera hirsuta*. *Phytochemistry* 1997; **44**(2): 293-8.
- [76] Toyota M, Koyama H, Asakawa Y. Sesquiterpenoids from the three Japanese liverworts *Lejeunea aquatica*, *L. flava* and *L. japonica*. *Phytochemistry* 1997; **46**(1): 145-50.
- [77] Toyota M, Kimura K, Asakawa Y. Occurrence of ent-sesquiterpene in the Japanese moss-*Plagiomnium acutum*: first isolation and identification of the ent-sesqui- and dolabellane-type diterpenoids from the Musci. *Chem Pharm Bull* 1998; **46**(9): 1488-9.
- [78] Toyota M, Saito T, Asakawa Y. The absolute configuration of eudesmane-type sesquiterpenoids found in the Japanese liverwort *Chiloscyphus polyanthos*. *Phytochemistry* 1999; **51**(7): 915-20.
- [79] Nagashima F, Murakami M, Takaoka S, Asakawa Y. New sesquiterpenoids from the New Zealand liverwort *Chiloscyphus subporosus*. *Chem Pharm Bull (Tokyo)* 2004; **52**(8): 949-52.
- [80] Bovi Mitre G, Kamiya N, Bardón A, Asakawa Y. Africane-type sesquiterpenoids from the Argentine liverwort *Porella swartziana* and their antibacterial activity. *J Nat Prod* 2004; **67**(1): 31-6.
- [81] van Klink JW, Zapp J, Becker H. Pinguisane-type sesquiterpenes from the South American liverwort *Porella recurva* (Taylor) Kuhnemann. *Z Naturforsch C* 2002; **57**(5-6): 413-7.
- [82] Nagashima F, Asakawa Y. Sesqui- and diterpenoids from two Japanese and three European liverworts. *Phytochemistry* 2001; **56**(4): 347-52.
- [83] Hashimoto T, Irita H, Tanaka M, Takaoka S, Asakawa Y. Two novel Diels-Alder reaction type dimeric pinguisane sesquiterpenoids and related compounds from the liverwort *Porella acutifolia* subsp. *tosana*. *Tetrahedron Lett* 1998; **39**(19): 2977-80.
- [84] Hashimoto T, Irita H, Tanaka M, Takaoka S, Asakawa Y. Pinguisane and dimeric pinguisane-type sesquiterpenoids from the Japanese liverwort *Porella acutifolia* subsp. *tosana*. *Phytochemistry* 2000; **53**(5): 593-604.
- [85] Adio AM, Paul C, Kloth P, König WA. Sesquiterpenes of the liverwort *Scapania undulata*. *Phytochemistry* 2004; **65**(2): 199-206.
- [86] Liu HJ, Wu CL, Becker H, Zapp J. Sesquiterpenoids and diterpenoids from the Chilean liverwort *Lepicolea ochroleuca*. *Phytochemistry* 2000; **53**(8): 845-9.
- [87] Nagashima F, Kuba Y, Ogata A, Asakawa Y. Sesqui- and diterpenoids from three New Zealand liverworts, *Bazzania novaezelandiae*, *Gackstroemia* sp. and *Dendromastigophora* sp. *Nat Prod Res* 2010; **24**(1): 68-75.
- [88] Paul C, König WA, Wu CL. Sesquiterpenoid constituents of the liverworts *Lepidozia fauriana* and *Lepidozia vitrea*. *Phytochemistry* 2001; **58**(5): 789-98.
- [89] Perry NB, Burgess EJ, Tangney RS. Cytotoxic 8,9-secokaurane diterpenes from a New Zealand liverworts, *Lepidolaena taylorii*. *Tetrahedron Lett* 1996; **37**(52): 9387-90.
- [90] Perry NB, Burgess EJ, Baek SH, Weavers RT, Geis W, Mauger AB. 11-oxygenated cytotoxic 8,9-secokauranes from a New Zealand liverwort, *Lepidolaena taylorii*. *Phytochemistry* 1999; **50**(3): 423-33.
- [91] Lou HX, Li GY, Wang FQ. A cytotoxic diterpenoid and antifungal phenolic compounds from *Frullania muscicola* Steph. *J Asian Nat Prod Res* 2002; **4**(2): 87-94.
- [92] Nagashima F, Kasai W, Kondoh M, Fujii M, Watanabe Y, Braggins JE. New ent-kaurene-type diterpenoids possessing cytotoxicity from the New Zealand liverwort *Jungermannia* species. *Chem Pharm Bull* 2003; **51**(10): 1189-92.
- [93] Nagashima F, Kondoh M, Kawase M, Simizu S, Osada H, Fujii M, et al. Apoptosis-inducing properties of ent-kaurene-type diterpenoids from the liverwort *Jungermannia truncata*. *Planta Med* 2003; **69**: 377-9.
- [94] Suzuki I, Kondoh M, Nagashima F, Fujii M, Asakawa Y, Watanabe Y. A comparison of apoptosis and necrosis induced by ent-kaurene-type diterpenoids in HL-60 cells. *Planta Med* 2004; **70**(5): 401-6.
- [95] Suzuki I, Kondoh M, Harada M, Koizumi N, Fujii M, Nagashima F, et al. An ent-kaurene diterpene enhances apoptosis induced by tumor necrosis factor in human leukemia cells. *Planta Med* 2004; **70**(8): 723-7.
- [96] Nagashima F, Kondoh M, Fujii M, Takaoka S, Watanabe Y, Asakawa Y. Novel cytotoxic kaurane-type diterpenoids from the New Zealand Liverwort *Jungermannia* species. *Tetrahedron* 2005; **61**(19): 4531-44.
- [97] Kondoh M, Suzuki I, Harada M, Nagashima F, Fujii M, Asakawa Y, et al. Activation of p38 mitogen-activated protein kinase during ent-11 α -hydroxy-16-kauren-15-one-induced apoptosis in human leukemia HL-60 cells. *Planta Med* 2005; **71**(3): 275-7.
- [98] Kondoh M, Nagashima F, Suzuki I, Harada M, Fujii M, Asakawa Y, et al. Induction of apoptosis by new ent-kaurene diterpenoids isolated from type-the New Zealand liverworts *Jungermannia* species. *Planta Med* 2005; **71**(11): 1005-9.
- [99] Liu CM, Zhu RL, Liu RH, Li HL, Shan L, Xu XK, et al. cis-Clerodane diterpenoids from the liverwort *Gottschelia schizopleura* and their cytotoxic activity. *Planta Med* 2009; **75**(15): 1597-601.
- [100] Qu JB, Zhu RL, Zhang YL, Guo HF, Wang XN, Xie CF, et al. ent-kaurane diterpenoids from the liverwort *Jungermannia atrobrunnea*. *J Nat Prod* 2008; **71**(8): 1418-22.
- [101] Nagashima F, Tanaka H, Takaoka S, Asakawa Y. Ent-kaurane-type diterpenoids from the liverwort *Jungermannia exsertifolia* ssp. *cordifolia*. *Phytochemistry* 1996; **41**: 1129-41.

- [102] Nagashima F, Tanaka H, Asakawa Y. Ent-kaurane-type diterpenoids from the liverwort *Jungermannia rotundata*. *Phytochemistry* 1997; **44**: 653-7.
- [103] Nagashima F, Tanaka H, Takaoka S, Asakawa Y. Sesqui- and diterpenoids from the Japanese liverwort *Jungermannia hattori-ana*. *Phytochemistry* 1997; **45**: 353-63.
- [104] Nagashima F, Suzuki M, Takaoka S, Asakawa Y. New sesqui- and diterpenoids from the Japanese liverwort *Jungermannia infusca* (Mitt.) Steph. *Chem Pharm Bull* 1998; **46**: 1184-5.
- [105] Nagashima F, Takaoka S, Asakawa Y. Diterpenoids from the Japanese liverwort *Jungermannia infusca*. *Phytochemistry* 1998; **49**: 601-8.
- [106] Nagashima F, Suzuki M, Takaoka S, Asakawa Y. New acorane- and cuparane-type sesqui- and new labdane- and *seco*-labdane-type diterpenoids from the Japanese liverwort *Jungermannia infusca* (Mitt.) Steph. *Tetrahedron* 1999; **55**: 9117-32.
- [107] Nozaki H, Hayashi K, Okuda K, Kuyama F, Ono K, Matsuo A. ent-Kaurane-type diterpenoids from a cell suspension culture of the liverwort *Jungermannia subulata*. *Planta Med* 2007; **73**: 689-95.
- [108] Nagashima F, Kishi K, Hamada Y, Takaoka S, Asakawa Y. ent-Verticillane-type diterpenoids from the Japanese liverwort *Jackiella javanica*. *Phytochemistry* 2005; **66**: 1662-70.
- [109] Nagashima F, Wakayama K, Ioka Y, Asakawa Y. New ent-verticillane diterpenoids from the Japanese liverwort *Jackiella javanica*. *Chem Pharm Bull* 2008; **56**: 1184-8.
- [110] Hashimoto T, Okumura Y, Asakawa Y. The absolute structures of new 1b-hydroxysacculatane-type diterpenoids with piscicidal activity from the liverwort *Pellia endiviifolia*. *Chem Pharm Bull (Tokyo)* 1995; **43**: 2030-2.
- [111] Hashimoto T, Shiki K, Tanaka M, Takaoka S, Asakawa Y. Chemical conversion of labdane-type diterpenoid isolated from the liverwort *Porella perrottetiana* into (̄)-ambrox. *Heterocycles* 1998; **49**: 315-25.
- [112] Quang DN, Asakawa Y. Chemical constituents of the Vietnamese liverwort *Porella densifolia*. *Fitoterapia* 2010; **81**: 659-61.
- [113] Gilabert M, Ramos AN, Schiavone MM, Arena ME, Bardón A. Bioactive sesqui- and diterpenoids from the Argentine liverwort *Porella chilensis*. *J Nat Prod* 2011; **74**: 574-9.
- [114] Hashimoto T, Kikkawa A, Yoshida M, Tanaka M, Asakawa Y. Two novel skeletal diterpenoids, neodenudatenones A and B, from the liverwort *Odontoschisma denudatum*. *Tetrahedron Lett* 1998; **39**: 3791-4.
- [115] Nagashima F, Murakami Y, Asakawa Y. A novel skeletal diterpenoid from the German liverwort, *Barbilophozia hatcheri* (Evans) Loeske. *Chem Pharmaceut Bull* 1999; **47**: 138-9.
- [116] Guo DX, Xiang F, Wang XN, Yuan HQ, Xi GM, Wang YY, et al. Labdane diterpenoids and highly methoxylated bibenzyls from the liverwort *Frullania inouei*. *Phytochemistry* 2010; **71**: 1573-8.
- [117] Toyota M, Nagashima F, Asakawa Y. Labdane-type diterpenoids from the liverwort *Frullania hamachiloba*. *Phytochemistry* 1988; **27**: 1789-93.
- [118] Toyota M, Saito T, Asakawa Y. Novel skeletal diterpenoids from the Japanese liverwort *Pallavicinia subciliata*. *Chem Pharmaceut Bull* 1998; **46**: 178-80.
- [119] Yoshida T, Toyota M, Asakawa Y. Scapaundulins A and B, two novel dimeric labdane diterpenoids, and related compounds from the Japanese liverwort *Scapania undulata* (L) Dum. *Tetrahedron Lett* 1997; **38**: 1975-8.
- [120] Hertewich UM, Zapp J, Becker H. Secondary metabolites from the liverwort *Jamesoniella colorata*. *Phytochemistry* 2003; **63**: 227-33.
- [121] Nagashima F, Kuba Y, Asakawa Y. Diterpenoids and aromatic compounds from the three New Zealand liverworts *Jamesoniella kirkii*, *Balantiopsis rosea*, and *Radula* species. *Chem Pharm Bull* 2006; **54**: 902-6.
- [122] Nagashima F, Murakami M, Takaoka S, Asakawa Y. ent-Iso-pimarane-type diterpenoids from the New Zealand liverwort *Trichocolea mollissima*. *Phytochemistry* 2003; **64**: 1319-25.
- [123] Wang SR, Fang WS. Pentacyclic triterpenoids and their saponins with apoptosis-inducing activity. *Curr Top Med Chem* 2009; **9**: 1581-96.
- [124] Setzer WN, Setzer MC. Plant-derived triterpenoids as potential antineoplastic agents. *Mini Rev Med Chem* 2003; **3**: 540-56.
- [125] Guo DX, Du Y, Wang YY, Sun LM, Qu JB, Wang XN, et al. Secondary metabolites from the liverwort *Ptilidium pulcherrimum*. *Nat Prod Commun* 2009; **4**: 1319-22.
- [126] Grammes C, Burkhardt G, Becker H. Triterpenes from *Fossombronia* liverworts. *Phytochemistry* 1994; **35**: 1293-6.
- [127] Toyota M, Asakawa Y. Sesqui- and triterpenoids of the liverwort *Conocephalum japonicum*. *Phytochemistry* 1993; **32**: 1235-7.
- [128] Benes I, Vaněk T, Buděšínský M, Herout V. A triterpenoid of the serratane type from the liverwort *Nardia scalaris*. *Phytochemistry* 1981; **20**: 2591-2.
- [129] Flegel M, Becker H. Di- and triterpenoids from the liverwort *Blepharidophyllum densifolium*. *Z Naturforsch C* 1999; **54**: 481-7.
- [130] Asakawa Y, Toyota M, Taira Z, Takemoto T, Kido M, Riccardin A and riccardin B, two novel cyclic bibenzyls possessing cytotoxicity from the liverwort *Riccardia multifida* (L.) S. Gray. *J Org Chem* 1983; **48**: 2164-7.
- [131] Kodama M, Shiobara Y, Sumitomo H, Matsumura K, Tsukamoto M, Harada C, et al. Total syntheses of marchantin A and riccardin B, cytotoxic bis(bibenzyls) from liverworts. *J Org Chem* 1988; **53**: 2-77.
- [132] Xue X, Qu XJ, Gao ZH, Sun CC, Liu HP, Zhao CR, et al. Riccardin D, a novel macrocyclic bisbibenzyl, induces apoptosis of human leukemia cells by targeting DNA topoisomerase II. *Invest New Drugs* 2012; **30**(1): 212-22.
- [133] Friederich S, Maier UH, Deus-Neumann B, Asakawa Y, Zenk MH. Biosynthesis of cyclic bis(bibenzyls) in *Marchantia polymorpha*. *Phytochemistry* 1999; **50**: 589-98.
- [134] Friederich S, Rueffer M, Asakawa Y, Zenk MH. Cyto-chromes P-450 catalyze the formation of marchantins A and C in *Marchantia polymorpha*. *Phytochemistry* 1999; **52**: 1195-202.
- [135] Shi YQ, Liao YX, Qu XJ, Yuan HQ, Li S, Qu JB, et al. Marchantin C, a macrocyclic bisbibenzyl, induces apoptosis of human glioma A172 cells. *Cancer Lett* 2008; **262**: 173-82.
- [136] Shi YQ, Zhu CJ, Yuan HQ, Li BQ, Gao J, Qu XJ, et al. Marchantin C, a novel microtubule inhibitor from liverwort with anti-tumor activity both *in vivo* and *in vitro*. *Cancer Lett* 2009; **276**: 160-70.
- [137] Gao J, Li X, Lv BB, Sun B, Zhu CJ, Lou HX, et al. LC-DAD/MS/MS detection of Macrocyclic Bisbibenzyls from the liverwort *Reboulia hemisphaerica* and the cell-based screening of their microtubule inhibitory effects. *Chin J Nat Med* 2009; **7**: 123-8.
- [138] Shen J, Li G, Liu Q, He Q, Gu J, Shi Y, et al. Marchantin C: a potential anti-invasion agent in glioma cells. *Cancer Biol Ther* 2010; **9**: 33-9.
- [139] Xi GM, Sun B, Jiang HH, Kong F, Yuan HQ, Lou HX. Bisbibenzyl derivatives sensitize vincristine-resistant KB/VCR cells to chemotherapeutic agents by retarding P-gp activity. *Bioorg Med Chem* 2010; **18**(18): 6725-33.
- [140] Huang WJ, Wu CL, Lin CW, Chi LL, Chen PY, Chiu CJ, et al. Marchantin A, a cyclic bis(bibenzyl ether), isolated from the liverwort *Marchantia emarginata* subsp. *tosana* induces apoptosis in human MCF-7 breast cancer cells. *Cancer Lett* 2010; **291**(1): 108-19.
- [141] Shi YQ, Qu XJ, Liao YX, Xie CF, Cheng YN, Li S, et al. Reversal effect of a macrocyclic bisbibenzyl plagiochin E on multidrug resistance in adriamycin-resistant K562/A02 cells. *Eur J Pharmacol* 2008; **584**(1): 66-71.
- [142] Wu XZ, Chang WQ, Cheng AX, Sun LM, Lou HX. Plagiochin E, an antifungal active macrocyclic bis(bibenzyl), induced apoptosis in *Candida albicans* through a metacaspase-dependent apoptotic pathway. *Biochim Biophys Acta* 2010; **1800**(4): 439-47.
- [143] Morita H, Tomizawa Y, Tsuchiya T, Hirasawa Y, Hashimoto T, Asakawa Y. Antimitotic activity of two macrocyclic bis(bibenzyls), isoplagiochins A and B from the liverwort *Plagiochila fruticosa*. *Bioorg Med Chem Lett* 2009; **19**(2): 493-6.
- [144] Li X, Sun B, Zhu CJ, Yuan HQ, Shi YQ, Gao J, et al. Reversal of p-glycoprotein-mediated multidrug resistance by macrocyclic bisbibenzyl derivatives in adriamycin-resistant human

- myelogenous leukemia (K562/A02) cells. *Toxicol In Vitro* 2009; **23**(1): 29-36.
- [145] Sun B, Yuan HQ, Xi GM, Ma YD, Lou HX. Synthesis and multidrug resistance reversal activity of dihydrotychantonol A and its novel derivatives. *Bioorg Med Chem* 2009; **17**: 4981-9.
- [146] Li X, Wu WK, Sun B, Cui M, Liu S, Gao J, et al. Dihydrotychantonol A, a macrocyclic bisbibenzyl derivative, induces autophagy and following apoptosis associated with p53 pathway in human osteosarcoma U2OS cells. *Toxicol Appl Pharmacol* 2011; **251**(2): 146-54.
- [147] Xu A, Hu ZM, Qu JB, Liu SM, Syed AK, Yuan HQ, et al. Cyclic bisbibenzyls induce growth arrest and apoptosis of human prostate PC3 cells. *Acta Pharmacol Sin* 2010; **31**(5): 609-15.
- [148] Yoshida T, Hashimoto T, Takaoka S, Kan Y, Tori M, Asakawa Y. Phenolic constituents of the liverwort: four novel cyclic bisbibenzyl dimers from *Blasia pusilla* L. *Tetrahedron* 1996; **52**(46): 14487-500.
- [149] Asakawa Y, Tori M, Takikawa K, Krishnamurty HG, Kar SK. Cyclic bis(bibenzyls) and related compounds from the liverworts *Marchantia polymorpha* and *Marchantia palmata*. *Phytochemistry* 1987; **26**(6): 1811-6.
- [150] Guo H, Xing J, Xie C, Qu J, Gao Y, Lou H. Study of bis(bibenzyls) in bryophytes using electron ionization time-of-flight and electrospray ionization triple-quadrupole mass spectrometry. *Rapid Commun Mass Spectrom* 2007; **21**(8): 1367-74.
- [151] Xing J, Xie C, Qu J, Guo H, Lv B, Lou H. Rapid screening for bisbibenzyls in bryophyte crude extracts using liquid chromatography/tandem mass spectrometry. *Rapid Commun Mass Spectrom* 2007; **21**(15): 2467-76.
- [152] Anton H, Kraut L, Mues R, Maria IZM. Phenanthrenes and bibenzyls from a *Plagiochila* species. *Phytochemistry* 1997; **46**(6): 1069-75.
- [153] Anton H, Schoeneborn R, Mues R. Bibenzyls and bisbibenzyls from a neotropical *Plagiochila* species. *Phytochemistry* 1999; **52**(8): 1639-45.
- [154] Hashimoto T, Kanayama S, Fukuyama Y, Takaoka S, Tori M, Asakawa Y. Two novel macrocyclic bis(bibenzyls), isoplagiochins A and B from the liverwort *Plagiochila fruticosa*. *Tetrahedron Lett* 1994; **35**(6): 911-2.
- [155] Hashimoto T, Kanayama S, Kan Y, Tori M, Asakawa Y. Isoplagiochins C and D, new type of macrocyclic bis(bibenzyls), having two biphenyl linkages from the liverwort *Plagiochila fruticosa*. *Chem Lett* 1996; **25**(9): 741-2.
- [156] So ML, Chan WH, Xia PF, Cui Y. Two new cyclic bis(bibenzyl)s, isoriccardinquinone A and B from the liverwort *Marchantia paleacea*. *Nat Prod Lett* 2002; **16**(3): 167-71.
- [157] Hashimoto T, Ikeda H, Takaoka S, Tanaka M, Asakawa Y. Ptychantols A-C, macrocyclic bis(bibenzyls), possessing a trans-stilbene structure from the liverwort *Ptychantus striatus*. *Phytochemistry* 1999; **52**(3): 501-9.
- [158] Kunz S, Becker H. Bibenzyl derivatives from the liverwort *Ricciocarpos natans*. *Phytochemistry* 1994; **36**(3): 675-7.
- [159] Martini U, Zapp J, Becker H. Chlorinated macrocyclic bisbibenzyls from the liverwort *Bazzania trilobata*. *Phytochemistry* 1998; **47**(1): 89-96.
- [160] Yoshida T, Toyota M, Asakawa Y. Isolation, structure elucidation, and chemical derivatization of a new cyclic bisbibenzyl dimer, pusilatin E, from the liverwort *Riccardia multifida* subsp. *decrescens*. *J Nat Prod* 1997; **60**: 145-7.
- [161] Toyota M, Omatsu I, Braggins J, Asakawa Y. Novel prenyl bibenzyls from the New Zealand liverwort *Marsipidium epiphytum*. *Chem Pharm Bull* 2011; **59**: 480-3.
- [162] Toyota M, Shimamura T, Ishii H, Renner M, Braggins J, Asakawa Y. New bibenzyl cannabinoid from the New Zealand liverwort *Radula marginata*. *Chem Pharm Bull (Tokyo)* 2002; **50**: 1390-2.
- [163] Scher JM, Zapp J, Schmidt A, Becker H, Bazzanins L-R. chlorinated macrocyclic bisbibenzyls from the liverwort *Lepidozia incurvata*. *Phytochemistry* 2003; **64**: 791-6.
- [164] Peña MJ, Darvill AG, Eberhard S, York WS, O'Neill MA. Moss and liverwort xyloglucans contain galacturonic acid and are structurally distinct from the xyloglucans synthesized by hornworts and vascular plants. *Glycobiology* 2008; **18**: 891-904.
- [165] Sonwa MM, König WA. Chemical constituents of the essential oil of the hornwort *Anthoceros caucasicus*. *Flavour Frag J* 2003; **18**: 286-9.
- [166] Trennheuser F, Burkharda G, Becker H. Anthocero-diazonin an alkaloid from *Anthoceros agrestis*. *Phytochemistry* 1994; **37**: 899-903.
- [167] Sewón P, Hellevuo T, Schmidt A, Becker H. Fatty acid composition of monogalactosyldiacylglycerols in *Anthoceros agrestis* and *Conocephalum conicum*. *J Hattori Bot Lab* 2000; **89**: 283-7.
- [168] Petersen M. Cinnamic acid 4-hydroxylase from cell cultures of the hornwort *Anthoceros agrestis*. *Planta* 2003; **217**: 96-101.
- [169] Vogelsang K, Schneider B, Petersen M. Production of rosmarinic acid and a new rosmarinic acid 3'-O-beta-D-glucoside in suspension cultures of the hornwort *Anthoceros agrestis* Paton. *Planta* 2006; **223**: 369-73.
- [170] Popper ZA, Sadler IH, Fry SC. α -D-Glucuronosyl-(1 \rightarrow 3)-l-galactose, an unusual disaccharide from polysaccharides of the hornwort *Anthoceros caucasicus*. *Phytochemistry* 2003; **64**: 325-35.
- [171] Buchanan MS, Hashimoto T, Asakawa Y. Phytyl esters and phaeophytins from the hornwort *Megaceros flagellaris*. *Phytochemistry* 1996; **41**: 1373-6.
- [172] Belkin M, Fitzgerald DB, Felix MD. Tumor-damaging capacity of plant materials. II. Plants used as diuretics. *J Natl Canc Inst* 1952; **13**: 741-4.
- [173] Spjut RW, Cassady JM, McCloud T, Norris DH, Suffness M, Cragg GM, et al. Variation in cytotoxicity and antitumor activity among samples of a moss, *Claopodium crispifolium* (Hook.) Ren. & Card. (Thuidiaceae). *Econ Bot* 1988; **42**: 62-72.
- [174] Sakai K, Ichikawa T, Yamada K, Yamashita M, Tanimoto M, Hikita A, et al. A nitumor principles in mosses: the first isolation and identification of maytansinoids, including a novel 15-methoxyansamitocin P-3. *J Nat Prod* 1988; **51**: 845-50.
- [175] Suwanborirux K, Chang CJ, Spjut RW, Cassady JM. Ansamitocin P-3, a maytansinoid, from *Claopodium crispifolium* and *Anomodon attenuatus* or associated actinomycetes. *Experimentia* 1990; **46**: 117-20.
- [176] Cassady JM, Chan KK, Floss HG, Leistner E. Recent developments in the maytansinoid antitumor agents. *Chem Pharm Bull (Tokyo)* 2004; **52**: 1-26.
- [177] Adamek W. Introductory report on oncostatic and therapeutic nature of the peat preparation in human neoplastic disease. In: *International Peat Congress*. Warsaw: Proceedings of the 5th International Peat Congress; 1976, p. 417-29.
- [178] Yamada P, Isoda H, Han JK, Talorete TP, Abe Y. Inhibitory effect of fulvic acid extracted from Canadian sphagnum peat on chemical mediator release by RBL-2H3 and KU812 cells. *Biosci Biotechnol Biochem* 2007; **71**: 1294-305.
- [179] Zheng GQ, Ho DK, Elder PJ, Stephens RE, Cottrell CE, Cassady JM. Ohioensins and pallidisetins: novel cytotoxic agents from the moss *Polytrichum pallidisetum*. *J Nat Prod* 1994; **57**: 32-41.
- [180] Zheng GQ, Chang CJ, Stout TJ, Clardy J, Cassady JM. Ohioensin-A: a novel benzonaphthoxanthone from *Polytrichum ohioense*. *J Am Chem Soc* 1989; **111**: 5500-1.
- [181] Fu P, Lin S, Shan L, Lu M, Shen YH, Tang J, et al. Constituents of the moss *Polytrichum commune*. *J Nat Prod* 2009; **72**: 1335-7.
- [182] Pereira BK, Rosa RM, da Silva J, Guecheva TN, Oliveira IM, Ianistcki M, et al. Protective effects of three extracts from Antarctic plants against ultraviolet radiation in several biological models. *J Photochem Photobiol B* 2009; **96**: 117-29.
- [183] Marsilia A, Morelli I. Triterpenes from *Thuidium tamariscifolium*. *Phytochemistry* 1970; **9**: 651-3.
- [184] Toyota M, Masuda K, Asakawa Y. Triterpenoid constituents of the moss *Floribundaria aurea* subsp. *nipponica*. *Phytochemistry* 1998; **48**: 297-9.
- [185] Harrigan GG, Ahmad A, Baj N, Glass TE, Gunatilaka AA, Kingston DG. Bioactive and other sesquiterpenoids from *Porella cordeana*. *J Nat Prod* 1993; **56**: 921-5.

- [186] Xiao JB, Chen XQ, Zhang YW, Jiang XY, Xu M. Cytotoxicity of *Marchantia convoluta* leaf extracts to human liver and lung cancer cells. *Braz J Med Biol Res* 2006; **39**: 731-8.
- [187] Chen X, Xiao J. *In vitro* cytotoxic activity of extracts of *Marchantia convoluta* on human liver and lung cancer cell lines. *Afr J Tradit Complement Altern Med* 2006; **3**: 32-6.
- [188] Krzaczkowski L, Wright M, Rebérioux D, Massiot G, Etiévant C, Gairin JE. Pharmacological screening of bryophyte extracts that inhibit growth and induce abnormal phenotypes in human HeLa cancer cells. *Fund Clin Pharmacol* 2009; **23**: 473-82.
- [189] López-Lázaro M. Distribution and biological activities of the flavonoid luteolin. *Mini Rev Med Chem* 2009; **9**(1): 31-59.
- [190] Komala I, Ito T, Yagi Y, Nagashima F, Asakawa Y. Volatile components of selected liverworts, and cytotoxic, radical scavenging and antimicrobial activities of their crude extracts. *Nat Prod Commun* 2010; **5**: 1375-80.
- [191] Liu N, Guo DX, Wang YY, Wang LN, Ji M, Lou HX. Aromatic compounds from the liverwort *Conocephalum japonicum*. *Nat Prod Commun* 2011; **6**: 49-52.