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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, antiinflamatory 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 epiodophyllotoxin 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 antitumourogenic plant reports have been pharmacologically investigated and in many cases scientists have found positive correlation between folklore use and scientific analyses[22,23].

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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 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.

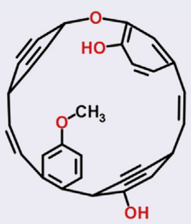
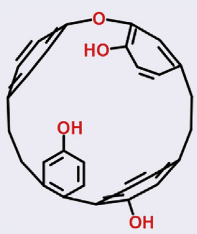
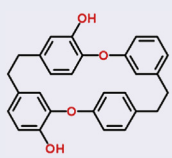
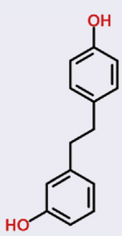
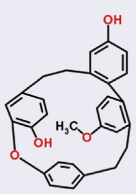
2. Cytotoxic compounds from bryophytes

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 dihydrostelbene 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
 Riccardin A	Systematic name (8Z,20Z)-5-Methoxy-14-oxapentacyclo[20.2.2.2^{10,13}.1^{15,19}.0^{2,7}]nonacosa-2,4,6,8,11,15(27),16,18,20,23,25,28-dodecaene-16,24-diol Molecular formula: $C_{29}H_{26}O_4$
 Riccardin C	Systematic name 14-Oxapentacyclo[20.2.2.2^{10,13}.1^{15,19}.0^{2,7}]nonacosa-1(24),2,4,6,10,12,15(27),16,18,22,25,28-dodecaene-5,16,24-triol Molecular formula: $C_{28}H_{24}O_4$
 Riccardin B	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: $C_{28}H_{24}O_4$
 Lunularin	Systematic name 3-[2-(4-Hydroxyphenyl)ethyl]phenol Molecular formula: $C_{14}H_{14}O_2$
 Plagiochin D	Systematic name 19-Methoxy-2-oxapentacyclo[22.2.2.1^{3,7}.0^{10,15}.0^{16,21}]nonacosa-1(26),3(29),4,6,10,12,14,16,18,20,24,27-dodecaene-4,12-diol Molecular formula: $C_{29}H_{26}O_4$

(*continued on next page*)

Table 1 (*continued*)

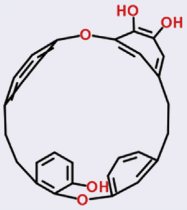
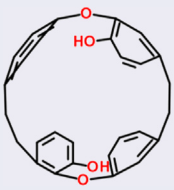
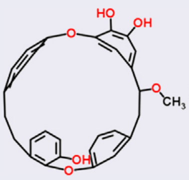
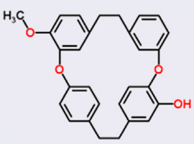
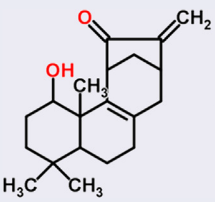
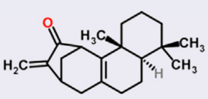
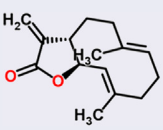
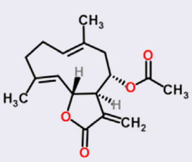
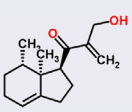
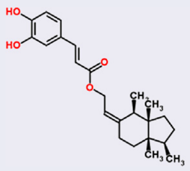
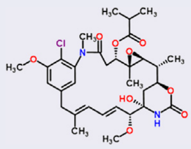
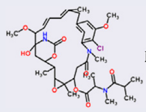
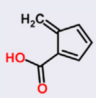
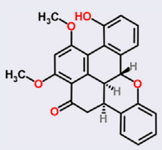
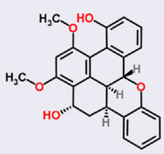
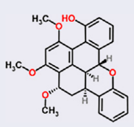
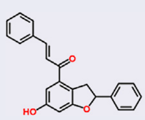
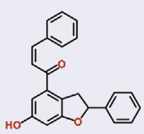
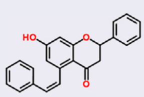
Cytotoxic phytochemicals from hepatics	Scientific names and molecular formulae
 Marchantin A	Systematic name 2,15-Dioxapentacyclo[22.2.2.$1^{3,7}$.$1^{10,14}$.$0^{16,21}$]triaconta-1(26),3(30),4,6,10(29),11,13,16,18,20,24,27-dodecaene-4,5,17-triol Molecular formula: $C_{28}H_{24}O_5$
 Marchantin C	Systematic 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: $C_{28}H_{24}O_4$
 Marchantin E	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: $C_{29}H_{26}O_6$
 Pakyonol	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: $C_{29}H_{26}O_4$
 Jungermannenone A	Systematic name 1-Hydroxy-11,16-cycloabieta-8,15(17)-dien-16-one Molecular formula: $C_{20}H_{28}O_2$
 Jungermannenone B	Systematic name (5β,10α,13ξ)-11,16-Cycloabieta-8,15(17)-dien-16-one Molecular formula: $C_{20}H_{28}O$
 Costunolide	Systematic name (3aS,6E,10E,11aR)-6,10-Dimethyl-3-methylene-3a,4,5,8,9,11a-hexahydrocyclodeca[b]furan-2(3H)-one Molecular formula: $C_{15}H_{20}O_2$
 Tulipinolide	Systematic name (3aR,4S,6E,10E,11aR)-6,10-Dimethyl-3-methylene-2-oxo-2,3,3a,4,5,8,9,11a-octahydrocyclodeca[b]furan-4-yl acetate Molecular formula: $C_{17}H_{22}O_4$
 12-hydroxychiloscyphone	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: $C_{15}H_{22}O_2$

Table 1 (*continued*)

Cytotoxic phytochemicals from hepatics	Scientific names and molecular formulae
 Naviculyl caffeate	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: $C_{24}H_{32}O_4$
Cytotoxic phytochemicals from mosses	**Scientific names and molecular formulae**
 Ansamitocin P-3	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}]hexacosa-10(26),11,13,16,18-pentaen-6-yl 2-methylpropanoate Molecular formula: $C_{32}H_{43}ClN_2O_9$
 15-methoxyansamitocin P-3	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}]hexacosa-10(26),11,13,16,18-pentaen-6-yl 2-methylpropanoate Molecular formula: $C_{33}H_{45}ClN_2O_{10}$
 Maytanbutine	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}]hexacosa-10(26),11,13,16,18-pentaen-6-yl 2-[isobutyryl(methyl)amino]propanoa te (non-preferred name) Molecular formula: $C_{36}H_{50}ClN_3O_{10}$
 Trewiasine	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}]hexacosa-10(26),11,13,16,18-pentaen-6-yl 2-[isobutyryl(methyl)amino]prop anoate (non-preferred name) Molecular formula: $C_{37}H_{52}ClN_3O_{11}$
 Fulvic acid	Systematic name 5-Methylene-1,3-cyclopentadiene-1-carboxylic acid Molecular formula: $C_7H_6O_2$
 1-O-methylohioensin B	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: $C_{25}H_{20}O_5$
 1-O-methyldihydroohioensin B	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: $C_{25}H_{22}O_5$
 1,14-di-O-methyldihydroohioensin B	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: $C_{26}H_{24}O_5$
 Pallidisetin A	Systematic name (2E)-1-(6-Hydroxy-2-phenyl-2,3-dihydro-1-benzofuran-4-yl)-3-phenyl-2-propen-1-one Molecular formula: $C_{23}H_{18}O_3$
 Pallidisetin B	Systematic name (2Z)-1-(6-Hydroxy-2-phenyl-2,3-dihydro-1-benzofuran-4-yl)-3-phenyl-2-propen-1-one Molecular formula: $C_{23}H_{18}O_3$
 Communin A	Systematic name 7-Hydroxy-2-phenyl-5-[(Z)-2-phenylvinyl]-2,3-dihydro-4H-chromen-4-one Molecular formula: $C_{23}H_{18}O_3$

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 diplophylline was isolated from *Diplophyllum albicans* and *Diplophyllum taxifolium*. Diplophyllin showed significant activity against human epidermoid carcinoma[49]. Sesquiterpenoids costunolide and tulipinolide, the tumor growth-inhibiters, also known from higher plants were isolated from the liverworts *Conocephalum supradecompositum*, *Frullania monocera*, *Frullania tamarisci*, *Marchantia polymorpha* (*M. polymorpha*), *Porella japonica* and *Wiesnerella denudata*[25,50]. Later on *Lepidozia vitrea*, *Plagiochila semidecurrens* 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 plagiochiline-A-15-yl octanoate, 14-hydroxyplagiochiline-A-15-yl 2E,4E-dodecadienoate and 14-hydroxyplagiochiline-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 activitiy 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 subobtusa*[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 linex[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, fusicoauritone 6alpha-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 hattoriana*[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 *Fossombronia alaskana* and *Fossombronia 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(bibenzyl) 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(bibenzyl) 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 bisbibenzyls[137]. Marchantin C was found to inhibit the migration in T98G and U87 glioma cells. Matrix metallopeptidase 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 bisbibenzyls, 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 bisbibenzyl 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(bibenzyls), 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 bisbibenzyl 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 G_2/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(bibenzyls)

Cyclic bisbibenzyls, 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-dimethythiazol-2-yl)-2,5-diphenyl-tetrazolium 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, veticadinoxide 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 trewiasine 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-methylohioensin B, 1-O-methyldihydroohioensin B and 1,14-di-O-methyldihydroohioensin 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 benzonaphthoxanthenones from *Polytrichum ohioense* was reported earlier[180]. Communins A and B and a new benzonaphthoxanthenone, 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[33]. 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[191].

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 anticancer 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.

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