



An Insight in to Potential Anticancer Activity of Bryophytes

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Abstract: Bryophytes, "amphibians of plant kingdom", are primitive group of non vascular land plants which inhabit damp, shaded and humid localities. Exceptionally, a few are floating in water even though they are with gametophytic and sporophytic phases. The plant group is intermediate between algae and pteridophytes that broadly classified into 3 lineages viz. Marchantiophyta (Liverworts), Bryophyta (Mosses) and Anthoceroophyta (Hornworts). About 18500 species are identified till date which distributed all over the world. These are poorly studied plant groups in turn using in many of the traditional medicines due to the presence of secondary metabolites having pharmaceutical activities. To date, by conducting an extensive screening for anticancer activity in approximately 35,000 plants species, the National Cancer Institute (NCI) has built a database of 3,000 plant species with reproducible anticancer activity. Most commonly, the liverwort and moss metabolites including phenolic compounds, terpenoids, bibenzyls and (bis) bibenzyls show cytotoxic activity against many of the cancer cell lines. Various secondary metabolites extracted from bryophytes such as marchantin A, marchantin C, bisbibenzyls, riccardin, 2 alpha 5 beta- dihydroxyboranane-2-cinnamate, costunolide, tulipinolide, jungermannone, Radulapin, (-)-ent-Arbusculin B, (-)-entcostunolide, eudesmanolides, germacranolides and guaianolides shows tumour suppressing activity towards various cancer cell lines.

Keywords: Anticancer, bryophytes, phenols, terpenoids, bibenzyls

Cancer is a broad collection of illnesses that can begin in practically any organ or tissue of the body. These illnesses are brought on when abnormal cells grow out of control, cross their normal boundaries to infect nearby body parts and spread to other organs. Plants are a source of anticancer chemicals, and it has been demonstrated that their derivatives can be used to cure or prevent cancer in people. The prevention of cancer depends heavily on plant secondary metabol-

ites such as flavonoids, polyphenols, anthraquinones, triterpenoids, alkaloids, terpenoids and quinones. Even if some natural chemicals have specific anticancer effects according to their physicochemical characteristics, a number of new secondary metabolites are derived from plants every year, offering a supply of possibilities to study against malignant disorders. When aberrant cells proliferate uncontrollably, cross their normal borders to infiltrate other body parts and move to other

organs in turn result in cancer, a broad category of disorders which can begin in nearly any organ or tissue of the body.

Generally, the bryophytes are nonvascular, small, green, simple, spore bearing plants and having relatively large perennial, photosynthetic, free living, haploid gametophytes and unbranched diploid sporophytes that remain attached to the maternal gametophyte throughout their lifespan. Thus it is heteromorphic in their lifespan (Shaw & Beer, 1999). The primitive group of land plants inhabits damp and shaded and humid localities, while a few of them are floating in water. The term 'Bryophyta' derived from Greek words Bryon (moss) and Phytion (plants). These non vascular plants commonly called "Amphibians of plant kingdom" which occurs intermediate position between algae and pteridophytes. Bryophytes are broadly classified into 3 lineages viz. Marchantiophyta (Liverworts), Bryophyta (Mosses) and Anthoceroophyta (Hornworts) and that include about 18500 species, distributed all over the world. Among them, some of the species show anticancerous properties.

1. Anticancer plants in Marchantiales

1.1. *Marchantia* L.

Marchantia is the most common highly differentiated genus grows in large mats. Thallus is dichotomously branched, green to dark green coloured with broad and distinct midrib bearing saucer shaped gemma cups. The rhizoids are two kinds, smooth walled and tuberculate. Sexually matured thallus bears gamatangiophores, antheridiophores and archegoniophores (Vasishta, 1963).

Anticancer activities: Marchantin A, a cyclic bis

(bibenzyl ether), isolated from the liverwort, *M. emarginata* subsp. *tosana*, induces apoptosis in human MCF-7 breast cancer cells (Huang et al., 2010). Marchantin A, (cyclic bis (bibenzyl ether) and plagiochin E (macrocyclic bis (bibenzyl) isolated from *M. polymorpha* which are responsible for its anticancer and antifungal activity respectively (Jantwal, 2019). The ethyl acetate extract of *M. convoluta* is most cytotoxic against human non small cell lung carcinoma cell lines, H1299 and human liver carcinoma, HepG2 (Chen, 2006). Marchantin A obtained from *M. paleacea*, *M. polymorpha* and *M. tosana*, has shown cytotoxicity against the leukemic KB cells (Jantwal, 2019). Marchantin A from *M. emarginata* sub sp. *tosana* which effectively actuates cell development restraint in human breast cancer cells (MCF-7) (Jantwal, 2019).

1.2. *Plagiochasma* Lehm. & Lindenb.

Plagiochasma species grow on exposed conditions and prefer calcium as rich substrate. The gametophytic plant body is thalloid with ill defined midrib. Ventral surface bears 2 rows of ventral scales. Both smooth walled and tuberculate rhizoids are present (Vasishta, 1963).

Anticancer activities: *P. appendiculatum* shows the presence of alkaloids, flavonoids, carbohydrates, phenols, terpenes, steroids, glycosides and lipids. The liverwort is a rich source of bisbibenzyls including marchantin A-C, riccardin C, riccardin D and neomarchantin A. The bisbibenzyls isolated from *P. appendiculatum* show excellent antitumour and antifungal activities (Zhao, 2022).

1.3. *Dumortiera* Nees

Monoicous or dioicous, dark greenish

thallus of the species is formed in dense overlapping patches as mats in comparatively less illuminated areas along streamside or on wet rocks. The dorsal surface is smooth without air pores. The ventral scales are in two rows, sex organs formed on stalked receptacles, involucre tubular, pseudoperianth absent, seta short, capsule wall single layered, dehiscence of capsule by the splitting of wall into irregular longitudinal valves, elaters long and 2-3 spiral (Mufeed, 2021).

Anticancer activities: Riccardin D is a novel macrocyclic bisbibenzyl compound extracted from Chinese liverwort plant, *D. hirsuta*. The compound is a DNA topo II inhibitor and has therapeutic potential for treatment of cancers. It displays the anticancer effect on growth of human lung carcinoma cells by the inhibitory activity of riccardin D and related angiogenesis (Xue, 2012).

1.4. *Conocephalum Hill*

The thalli are flat, smooth and have a pungent odour. They have dark green, leathery surfaces and purplish edges. The surface of the thalli is covered with a series of lines and air pores that may be seen in the spaces in between the lines. Thallus is dichotomously branched, dorsal surface with elongated polygonal areas with elevated air pores in the middle and margin hyaline. Airpores are simple and surrounded by 4-6 concentric rings of 6-8 cells. Ventral scales are large, hyaline or slightly purplish and one row on either side of midrib. Air chambers are in single row and photosynthetic filaments vestigial. The male receptacle is terminal, sessile, discoid and unlobed. The female receptacle is stalked, carpocephalum conical, not deeply lobed, pseudoperianth absent, peduncle

with single rhizoid furrow, involucre tubular, 7-8 per receptacle and each bear single sporogonium. The capsule wall is unistratose, cells with annular thickening, dehiscence by splitting in to 4-8 valves and spores with lamellate ornamentation (Mufeed, 2021).

Anticancer activities: Presence of monoterpenes has been recorded from the liverwort *C. conicum*. A monoterpene ester, 2 alpha, 5 beta-dihydroxyboranane-2-cinnamate, from Chinese *C. conicum* is cytotoxic against human HepG2 cells (Adam, 1998).

1.5. *Asterella P. Beauv*

Thallus is prostrate, aromatic and dichotomously branched. Fleshy thallus is leathery, dorsal surface smooth with air pores, ventral surface and scales usually purplish, rhizoids smooth or pegged. Thallus differentiated into photosynthetic region and storage region. Photosynthetic region is aerenchymatous, usually with empty air chambers in many rows, storage region broad. Midrib is absent (Mufeed, 2021).

Anticancer activities: Marchantin C, isolated from *Asterella angusta*, strongly inhibits the growth of human cervical tumour. It is a novel microtubule inhibitor that induces mitotic arrest of tumour cells and suppresses tumour cell growth (Nandy, 2020).

2. Anticancer plants in Metzgeriales

2.1. *Riccardia L.*

The monoecious or dioicous thallus is narrow, delicate, irregularly or pinnately branched. Rhizoids are scarce in nature. The oil bodies present in the epidermal cells; antheridial branches once or twice arched, archegonial branches short, antheridial branches branched; calyptra cylindrical or

clavate, seta elongated; capsule blackish-brown, ovoid or slightly cylindrical, dehiscing by 4 valves; spores spherical or globose, pale yellow or brown, elaters unispiraled, broad in the middle, sometimes branched (Mufeed, 2021).

Anticancer properties: The majority of Hepaticae have been shown to primarily consist of lipophilic mono-, sesqui- and diterpenoids, aromatic compounds (bibenzyls, bis-bibenzyls, benzoates, cinnamates, long-chain alkyl phenols, naphthalenes and phthalides) and lipids. Riccardins A and B from *R. multifida* inhibit KB cells. *R. perrottetii* contained plagiochiline and perrottetin E shows cytotoxicity against KB cell (Alam, 2012).

3. Anticancer plants in Jungermanniales

3.1. *Frullania* Raddi

The gametothallus is dorsiventral and differentiated into a branched, prostrate, central stem like axis and leaves. The stem is pinnately or bipinnately branched. The leaves on the stem are inserted in three rows. There are two rows of dorsal leaves arranged laterally on the stem. A third row of smaller leaves arranged on the lower or ventral side of the stem, known as the underleaves or amphigastria. The closely set lateral (dorsal) leaves are almost transversely inserted on the stem with the anterior edge of each leaf covering the posterior edge of the leaf in front. Such an overlapping arrangement of the leaves is described as incubous. Each lateral leaf is bilobed (Vasishta, 1867).

Anticancer activities: The sesquiterpenoids, costunolide and tulipinolide, isolated from *F. monocera* show the anticancer activity against human carcinoma of the nasopharynx (Chand-

ra, 2017). An extract from *F. nisquallensis* exhibits anticancer activity against lung cancer cells.

3.2. *Porella* L.

Porella (Madotheca) is generally found in the moist, shady places growing flat on logs, tree trunks and rocks over which water trickles. It grows in dense layers forming large mats closely covering substratum. The plant body is greenish, leafy and fairly large up to 15 cm or even more in length. It consists of a branched central axis or stem that bears leaf like expansions. The stem is thin and cylindrical and bears branches in a bipinnate or tripinnate manner. The branching is monopodial. The branch primordium lies close to the apical cell. The stem and branches bear two kinds of leaves, large dorsal and small ventral. They are arranged in three rows. The dorsal leaves are closely set in two lateral rows (Vasishta, 1963).

Anticancer activities: *P. cordeuna* consisted of sesquiterpenes, pinguisanin, norpinguisone methyl ester, porella pinguisanolide, porella pinguisenone, spiropinguisan and striatenone. Pinguisanin and porella pinguisenone show selective activity against the RAD52 strain RS322YK of *Saccharomyces cerevisiae* and inactive against the wild type strain RS188N (RAD). The compound, drimenin 111, is inactive in P388 (Murine leukemia) and CHO (Chinese hamster ovary) cytotoxicity assays. The extract shows cytotoxicity against breast, colon and lung cancer cells (Harrigan, 1993).

3.3. *Jungermannia* L.

The majority of the species can be found in temperate climates with succubus leaves. The leaves are unlobed with a smooth edge. The perianth is terminal on the leading

shoot. When the plants branched, the branches do not emerge from the base of stem. Rhizoids are found all over the underside of stem, not just in a few concentrated areas close to the under leaves (Vasishta, 1963).

Anticancer activities: Ent-kaurane diterpenoids, jungermannenone A and B, exhibit the highest cytotoxic activity against several cancer cell lines. Jungermannenone A and B are able to arrest the cell cycle, induce apoptosis and cause mitochondrial damage. Jungermannenone A (1.5 $\mu\text{mol/L}$) causes a significant increase in PC-3 apoptotic cells (Cianciullo, 2022).

3.4. *Radula Dumort.*

It is a leafy liverwort. In a protected wet outdoor setting, the plants appear as a scaly, green surface on the trunk of a tree, log or rock. The leaves have two uneven lobes and are rounded with overlap. Folded beneath the bigger lobe is the smaller one (Mufeed, 2021)

Anticancer activities: The prenylated bibenzyls, radulapin A-H, from *R. apicata*, 2-carbomethoxy-3,5-dihydroxystilbene and 3, 5-dimethoxybibenzyl from *R. amoena* exhibit cytotoxic activity against several cancer cell lines (Zhang, 2019). The extract of *R. marginata* is cytotoxic against breast, lung and colon cancer cells.

3.5. *Diplophyllum (Dumort.) Dumort.*

In hilly areas with base poor acid soils, *D. albicans* is one of the commonest leafy liverworts. Oddly for such a distinctive looking liverwort, it is quite variable in size, colour and growth form. Plants are usually in thin flat patches or mats. Stems are with few intercalary and axillary branches, usually with subfloral innovations; cortex in 3-5 layers, cells some-

what to strongly flattened, smaller, more strongly thick walled than medullary cells; branches few; rhizoids scattered, colorless. Leaves are complicate 2 lobed with smaller dorsal and larger ventral lobes, not decurrent, the most proximal leaves usually smaller, rounded to apiculate, sheathing, nearly or almost parallel to the stem (Redfearn, 2008).

Anticancer activities: Diplophyllin from *D. albicans* and *D. taxifolium* has methylene- lactone unit that shows significant activity against human epidermoid carcinoma (Marko, 2001).

3.6. *Hepatostolonophora J. J. Engel & R. M. Schust.*

It is a taxonomic genus having a group of leafy liverworts forming mats. Branches are mostly of lateral-intercalary type; *Frullania* type branches less common; *Andrewsianthus* type present in *Evansianthus*; ventral-intercalary branches much less frequent, present in some taxa. Rhizoids are typically from stem in a sharply defined region at under leaf base, in *Leptophyllopsis* from cells of underleaf. Leaves are alternate to subopposite (Engel & Briscoe, 2021).

Anticancer activities: (-)-ent-Arbusculin B and (-)-entcostunolide from *H. paucistipula* show cytotoxic activity against P388 murine leukemia cells, with IC_{50} values of 1.1 and 0.7 $\mu\text{g/mL}$, respectively (Baek et al., 2003).

3.7. *Lophocolea (Dumort.) Dumort.*

Plants are yellowish green to light green, sparingly branched, prostrate, delicate, branches lateral or intercalary; stem usually undifferentiated, rarely outer layers thick walled; leaves closely imbricate or distant, alternate, ovate to oblong, quadrate or rectangular,

usually entire at margins, rarely toothed; apex acute, retuse or obtuse; cells thin walled, with or without trigones; under leaves remote, free or narrowly united at base with leaves, usually deeply bilobed; dioecious or monoecious, male and female inflorescence terminal or intercalary on main branches or lateral branches, perianth oblong or campanulate, usually triplicate; capsule ovoid or dark brown, spores granulate, elaters bispiral (Mufeed, 2021).

Anticancer activities: Several sesquiterpene lactones such as eudesmanolides, germacranolides and guaianolides isolated from liverworts exhibit cytotoxic activity against KB nasopharyngeal and P-388 lymphocytic leukemia cells. However, *L. heterophylla* shows cytotoxicity against P-388 cells (Cianciullo, 2022).

4. Anticancer plants in Porellales

4.1. *Lepidolaena* Dumort.

The leaves of leafy forms lack a midrib and often have lobes, flaps or pockets. Thalloid liverworts form a flat growth (thallus) on the substrate. Some have pores. Liverworts are attached to the substrate with single celled filaments, rhizoids. The sporophyte, consisting of a stalk or seta and capsule, is very delicate, short lived and often greatly reduced in size. The capsule opens by splitting into segments.

Anticancer activities: 8, 9-Secokauranes, rabdoubrosanin and 8,14-epoxyabdoubrosanin, isolated from a New Zealand *L. taylorii* show in vitro and in vivo model system for antitumour activity (Bandyopadhyay, 2022).

5. Anticancer plants in Ptilidiales

5.1. *Ptilidium* Nees

The plants grow in dense mats, with

stems growing either prostrate or ascending. Individual stems are once or twice pinnate, rarely with branches and only a few short rhizoids. The leaves are incubous and divided deeply into three to five portions, and edges of the leaf divisions are fringed with cilia. The under leaves are similar to the lateral leaves, but are slightly smaller. All species are dioecious, producing antheridia and archegonia on separate plants. The archegonia are terminal on a main stem. Mature sporophytes develop from a large perianth with three distal folds.

Anticancer properties: Cytotoxicity of different secondary metabolites isolated from the liverwort *P. pulcherrimum* have been reported against the PC3, MDA-MB-231 and Hela cell lines of which ursane triterpenoids had shown moderate cytotoxicity against PC3 Cells (Guo, 2009).

6. Anticancer plants in Polytrichales

6.1. *Polytrichum* Hedw.

Polytrichum is one of the largest mosses. It is commonly called the hairy cap moss because of the luzzy calyptra enclosing the mature capsule. The genus comprises over 100 species found all over the world. *P. commune* is a cosmopolitan perennial woodland moss which occurs in clonal groupings. Many aerial leafy stems are interconnected by underground rhizomes. The erect aerial shoots may attain a length up to 45 cm and the rhizomes may reach a depth of about 30 cm. The conspicuous part of the plant body is an erect leafy shoot, but it is not the entire gametophyte. In fact the leafy shoots arise from the haploid branched, alga like, green filamentous structure called the protonema

(Vasishta, 1963).

Anticancer activities: *P. commune* plays very significant role especially for the therapy of lymphocytic leukemia. It has been found that *P. ohioense* and *P. pallidisetum* show cytotoxicity against the 9PS murine leukemia and several other tumour cell lines (Chandra, 2017).

7. Anticancer plants in Bryales

7.1. *Bryum Hedw.*

Plants usually short, up to 2 cm high; pure white, silver green, yellow, yellowish green and green with red tints; stem julaceous or gemmiform; leaves usually shorter, 1.5 mm long, ovate-lanceolate, base not decurrent; apex broadly rounded to acute; costa percurrent or excurrent; alar cells usually absent or somewhat differentiated in juxta costal region; sporophytes seen on tip of the plant, seta long twisted when dry, capsule inclined to pendent, ovate or clavate to pyriform, spores finely papillose, pale brown or yellow brown in colour (Mufeed, 2021).

Anticancer activities: Plants have the ability to synthesize aromatic substances such as phenolic and nitrogen containing compounds, vitamins, terpenoids and some other endogenous metabolites, which are active against herbivores, insects, bacteria and fungi. The extract inhibits the genotoxic activity of H₂O₂. Methanol

extract of *B. argenteum* inhibits the growth of breast, liver and lung cancer cells (Onbasli, 2021).

8. Outlook

Bryophytes are nonvascular plants, small, green, simple, spore bearing and unique among land plants. These are poorly studied plant groups in turn using in many of the traditional medicines due to the presence of secondary metabolites having pharmaceutical activities. Anticancer agents discovered from primitive plant group such as bryophytes have played a major role in cancer treatment. Studies reveal many bryophytes have antitumour and cytotoxic activities, which inhibit the growth of tumour. Among the plants, *Marchantia*, *Plagiochasma*, *Dumortiera*, *Conocephalum*, *Asterella*, *Riccardia*, *Frullania*, *Porella*, *Jungermannia*, *Radula*, *Diplophyllum*, *Hepatostolonophora*, *Lophocolea*, *Lepidolaena*, *Ptilidium*, *Polytrichum* and *Bryum* show anticancerous activities. Various secondary metabolites extracted from bryophytes such as marchantin A, marchantin C, bisbibenzyls, riccardin A, D, 2 alpha, 5 beta-dihydroxyboranane-2-cinnamate, costunolide, tulipinolide, jungermannenone A and B, radulapin A-H, (-)-ent-arbusculin B and (-)-entcostunolide, eudesmanolides, germacranolides and guaianolides show tumour suppressing activity towards various cancer cell lines.

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