RJPHYTO Research Journal of **Phytochemistry**

OPEN ACCESS

# Utilization of the First Land Plants (Bryophytes) as a Source of Beneficial Bioactive Chemicals

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**ABSTRACT**
Bryophytes are considered the first land plants or amphibians of the plant kingdom, with unique thallus structures with no roots and a cuticle over the thallus surface and peculiar water relations as they are considered Poikilohydric plants. These plants have proven ecological significance as water reservoirs, but economically, their worth has to be proven. Usually, sphagnum is considered an economically important plant because of its utility in various fields such as horticulture, fuel, medicine, etc. However, apart from this moss genus, only a few species have been designated with economic implications and, there are lots of species in bryophytes that have shown the presence of economically important phytoconstituents. But, generally, they are somewhat neglected for their phytochemistry and curative properties, aside from their huge diversity, second only to angiosperms. As a result of this knowledge gap about bryophytes, this study will concentrate on the valuable bioactive phytoconstituents that have been documented to date from bryophytes and have useful bioactive components. Currently, bryophytes are expected to supply a vast reservoir of new phytoconstituents for therapeutic use. The phytochemistry of various commonly occurring and easy-to-collect bryophytes has been discussed in almost complete detail in this review, along with their confirmed phytotoxic, antimicrobial, antifungal and cytotoxic properties. This effort has demonstrated that bryophytes hold tremendous promise as a source of various significant and novel bioactive compounds with medicinal and preventive functions. Researchers in bryology, phytochemistry and drug discovery will find the compilation particularly useful.

**KEYWORDS**
Bryophytes, bioactive compounds, cytotoxicity, antioxidants, liverworts, mosses



## INTRODUCTION

Bryophytes constitute the second largest diversity among land plants, but they are lesser known for their bioactive compounds and potential for therapeutic uses. The major work on bryophytes available to date is on diversity, morpho-taxonomy, ecological uses, etc[1]. and the economic aspects especially in herbal formulations are very limited. Hence, this review has been done to provide insight into the bioactive potential of bryophytes. It encompasses all the attainable information related to the bioactivity of bryophytes[2,3]. The term Bryophyta was coined by Robert Brown in 1864, derived from the Greek words Bryon meaning moss and phyton meaning plant and they are considered the first land plants[4]. In 1879 the first person who gave the well-defined group of plants under the division of Bryophytes was Schimper. In comparison to vascular plants, this group of terrestrial plants has received much lesser attention on the

ISSN: 2151-6081 (Online)
ISSN: 1819-3471 (Print)
https://doi.org/10.3923/rjphyto.2023.26.36

Received: 15 Mar. 2023
Accepted: 30 Jul. 2023
Published: 28 Aug. 2023

status of their phytochemical potential and conservation. One of the reasons for the exhaustion of these plant species is the destruction of their habitats directly or indirectly. Hence an effective step aiming to save them from getting extinct must be taken[5]. In India, bryophytes comprise 2504 species out of which 642 species are endemic which forms 17.27% of species comprising the world's bryophytes[3]. The 3 diverse groups of bryophytes are (1) Liverworts (2) Mosses and (3) Hornworts.

Therefore, in India and adjacent countries, there is a need to evaluate this huge and valuable diversity of bryophytes for their phytochemical profiles and bioactive potential on which appreciable work has been done in Japan, China and some European countries[6,7]. Since they are older than angiosperms in evolution there are bright chances to get a few novel phytoconstituents in future. During the last decades, hundreds of novel phytochemicals were isolated from bryophytes and elucidated chemically. Among three classes of bryophytes, hornworts are not well known for the bioactive phytoconstituents, whereas mosses have been reported to have usually flavonoids, bioflavonoids, terpenes, terpenoids, etc. While, liverworts possess a great variety of lipophilic mono-, di- and sesquiterpenoids along with several aromatic compounds, viz., benzoates, bibenzyls, cinnamates, etc. These bioactive compounds are well known for their anti-inflammatory, anticancer, antioxidant, antimicrobial activities, etc.[3].

Hence, in the present review, an attempt has been made to highlight the worth of these small-sized and somewhat neglected amphibious plants as the potential hoard of useful bioactive phytoconstituents by compiling the relevant information on the bioactivity of bryophytes-derived phytoconstituents.

## METHODOLOGY

The present appraisal has been compiled with the help of various relevant works of literature that are liberally available on the internet via NCBI, PubMed, Web of Science, Google Scholar, Scopus, etc.

## LIVERWORTS

In India, at present, there are about 2000 species of mosses 34 species of hornworts and 816 species of liverworts[8]. The distributions of bryophytes are very immense with diverse ecological conditions ranging from polar and alpine regions to the tropics. They are mostly found in the Eastern and Western Himalayas and Western Ghats in India (1). Due to heavy rain, humidity and higher altitudes in the Rajasthan Region, Ranthambore forest and Mount Abu is the richest spot for bryodiversity[9]. Bryophytes come under non-vascular plants and their growth potential is not highly polarized like vascular plants. They have rhizoids instead of roots and they absorb the needful from the soil through rhizoids and can grow where vascularized plants cannot. Bryophytes survive in moist places like soil, rocks, bark, trunks and branches of trees and fallen logs. The substances dissolved in ambient moisture are the source of nutrients for bryophytes which help them to grow and survive[10,11].

There is a regular alternation of sporophytic and gametophytic generation in bryophytes. A haploid gametophyte has a certain number of unpaired chromosomes that alternate with a diploid sporophyte, having two sets of paired chromosomes. A diploid zygote is formed through the fusion of haploid sperm and egg, which eventually develops into the sporophyte. Through meiosis, a sporophyte produces a haploid spore that grows into a gametophyte. They have enclosed reproductive structures (sporangia and gametangia)[12].

Bryophytes are a boon for the forest system as they act as a "buffer for plants". They control the rate of water loss and equilibrate the water potential to available external water. Bryophytes are used in various fields such as for household purposes, clothing, packing and pharmaceutical products (antibiotics, anti-tumor and surgical dressings). They are also used as bioindicators of heavy metals and radioactive substances, acid rain indicators, etc.[13].

Bryophytes can grow on most parts of the earth where enough moisture is present to sustain a plant life[14]. Due to their minute size and difficulty to collect these plants are neglected as a source of phytochemical and bioactive compounds. However, bryophytes have shown high biological activities in several phytochemicals that have been isolated from many species[15-17].

**Phytochemical properties:** Phytochemicals are naturally occurring in plants. These phytochemicals have a vital role in the protection of plants from diseases as well as in defence mechanisms[18]. Bryophytes especially liverworts are very much rich in phenols, terpenoids some aromatic compounds and fatty acids. Bryophytes are considered a remarkable reservoir of secondary metabolites, out of which many show an interesting biological activity and provide a huge potential for pharmaceutical and biotechnological applications[19]. Phytochemicals come under primary compounds that include secondary compounds which have terpenoids, alkaloids and phenolic compounds. Bryophytes are a rich storehouse of biologically active compounds as about 400 novel chemical compounds were isolated and elucidated such as tannin, glycoside and terpenoids[20,21].

**Antioxidant properties:** In the context of antioxidant activity, very few bryophytes have been studied. Liverworts possess the strong antioxidative machinery suggested by recent studies. They have the stamina to survive in extreme climates and stressful conditions[18]. Conducted studies have indicated the potential of a few bryophytes to be used as antioxidants for cosmetic and medicinal purposes[19,20]. If screened, then bryophytes could be the source of many novel antioxidants and could be used for novel drug discovery and can be a boon for the pharmaceutical industries[21].

**Medicinal and cytotoxic properties:** Bryophytes are considered a hoard of remedies. Ancient knowledge of therapies referred to as ethno-therapeutics has been a boon in the medicinal fields for providing information regarding clinically active drugs from lower plants, useful for humans[22]. Bryophytes are being used in a wide spectrum as antibacterial, antifungal, antitumor and insecticidal and in medicinal areas[13,17,23,24]. Liverworts have been used for medicinal practices from ancient times for curing hepatic disorders, skin diseases, hepatitis, cardiovascular diseases, bronchitis and cystitis. Liverworts possess anti-leukemic activity also. Bryophytes are the reservoir of biologically active compounds and these compounds have a high potential to act as chemotherapeutic agents against cancerous cells and might contribute to the prevention of cancer and other life-threatening diseases[25,26].

Bryophytes can grow on most parts of the earth where enough moisture is present to sustain their life. For reproduction and growth, they prefer moist environments but can survive in drier habitats too[14]. Their sizes vary from millimetres to meters. Despite their great ecological significance, surprisingly their investigation is still in a nascent stage due to some reasons like (1) Specificity of its habitat (2) Seasonal dependency and (3) Limited amount of availability in nature[27]. From polar and alpine regions to the tropics, bryophytes can survive in diverse ecological conditions. Eastern and Western Himalayas, South and Central India are the main hubs of these bryophytes[28]. They consist of 21 orders belonging to 66 families which include 328 genera and 1578 species[29].

Due to the presence of large amounts of bioactive novel compounds, bryophytes especially liverworts are considered as a "remarkable reservoir of secondary metabolites"[30-33]. Liverwort consists of terpenoids, phenols (flavonoids and bibenzyl derivatives), glycosides and fatty acids. Botanists and microbiologists have well-documented the presence of antibiotic substances in these species (3). A huge variety of lipophilic mono, di and sesquiterpenoids bibenzyls benzoates are reported in liverwort

*Marchantia polymorpha*[31]. Antibacterial activity against gram-positive and gram-negative bacteria has been shown by a few bryophytes species in recent studies[34-36]. Many species of the family Marchantiaceae have been reported with antifungal properties. It has been reported that the leafy liverwort species show significant activity against human epidermoid carcinoma which has Diplopylline as its active compound[24,37]. *Marchantia polymorpha* exhibited many antioxidant properties reported after studying the methanolic and ethyl acetate extract of it[37].

Phytochemicals play a very decisive role in plant protection against pathogens. To identify the different phytochemical constituents from *Plagiochasma* species extracts (ethanol, ether, petroleum, methanol and acetone) preliminary phytochemical screening was carried out along with total phenolic and flavonoid content[14].

Recent studies have been done on the bryophyte (*Asterella* spp.) to investigate the various phytochemicals which play a vital role in the protection of plants from different pathogens, using different types of tests in the aqueous, methanolic and ethanolic extracts of *Asterella* sp.[38]. These results suggest that the undertaken bryophytes can be the potential source of useful drugs in treatments of ailments.

Bryophytes, particularly liverwort consist of large amounts of biologically active compounds like some aromatic compounds (bibenzyls, bisbibenzyls, cinnamates, phthalides) benzoates, glycosides, fatty acids, Phenolics, terpenoids and their saponins, etc. These compounds have a high potential to act as chemotherapeutic agents against cancerous cells and might contribute to the prevention of cancer and other life-threatening diseases[39]. It has been reported that certain species possess cytotoxicity against EYF-P-tubulin HeLa cells due to the presence of marchantin A and C, riccardin B and Marchantin A isolated from *Marchantia* sp. induces apoptosis in MCF-7 cells[40]. The extraction of compounds for antiproliferative activity from *Lepidozia borneensis* is done using a rotary evaporator and further freeze-dried using freeze-dryer[41]. Malaysian liverwort exhibits some compounds that have anticancer properties and have the potential to be used as anticancer agents. A study conducted revealed that flavonoids of *Marchantia linearis* have apoptotic activity on SW480 cancer cell lines showed by MTT assay[42]. Against cancerous cells bryophytes have been found as a great candidate due to their great anticarcinogenic potential, although their number is few in the case of liverworts, there is a crucial need to explore more species of liverworts that have high bioactive compounds against life-threatening cancerous cells.

**Mosses:** Mosses are more frequently distributed than liverworts and hornworts, hence, from several species of mosses distinct bioactive substances have been isolated in recent times. Moss contains benzoic, phthalic, cinnamic and terpenoids and a few nitrogen-containing aromatic compounds, sometimes these are found structurally similar in vascular plants[43,44]. Adebiyi *et al.*[45] reported the presence and varying quantities of alkaloids, flavonoids, saponins, phenols and steroids of two tropical moss plants, whereas it was found that the absence of phenol in one of these mosses. Mitra *et al.*[46] reported that epiphytic mosses in Darjeeling hills from the Dicranaceae family have significant ethnomedicinal uses. Their phytochemical investigation reveals the abundance of terpenoids in the chloroform extract and the presence of phenolics and flavonoids in ethanolic and methanolic extracts of both plants. Whereas, ferric ion reducing property and free radical scavenging activity indicate the significant antioxidant potential of chloroform, ethanol and methanol extracts of these two mosses. Therefore, these mosses pretend to have significant pharmaceutical and a source of drugs and bioactive chemicals. A common moss, *Hyophila* showed a high intensity of colors in the presence of flavonoids, terpenoids, saponins, cardiac glycosides and methanolic extracts which was further followed by ethanolic and aqueous crude extracts[47].

Makinde *et al.*[48] studied the presence and absence of secondary metabolite and their antibiotic potential in *Hyophila* using different extracts of acetone and ethanol of selected organisms. Only acetone extract tested positive for the presence of flavonoids, whereas alkaloids and cardiac glycosides were identified as present in both acetone and ethanolic extracts. The extracts showed significant activity on both bacterial and fungal strains. The present study indicates that *Hyophila* has medicinal important compounds that and have therapeutic potential from which antimicrobial medicine can be obtained.

Savaroğlu *et al.*[7] studied to investigate the antimicrobial and anticancer properties of aquatic moss. They obtained 8 different extracts (chloroform, methanol, acetone, ethyl acetate A, B, C and D) by using two different extraction processes. The diffusion method was used against bacterial and fungal strains to assess the antimicrobial activity of these extracts of acetone, chloroform and ethyl acetate A and C were active against all the tested species. In which the most effective extract was C. whereas *in vitro* toxicity of the active component of extract C was tested at different concentrations. It was resulted by the present study that aquatic moss possesses antimicrobial and anticancer agents. Dey and Mukherjee[49] studied that extracts of *Polytrichum juniperium* had shown activity against sarcoma in mice. *Claopodium crispifolium* also exhibited significant cytotoxicity against human tumor cell lines A-549 and HT-29. The moss *Polytrichum commune* Hedw. A new benzonaphtho×anthenone and communins A and B have been isolated and were tested against cancer cell lines[50]. Two foreign moss species were studied and examined for their antibacterial and antifungal effects and antimicrobial activity[51]. The antiproliferative, phytochemical and cytotoxic effects of the extracts obtained from these mosses were determined. It resulted that the ethyl acetate and hexane extracts of these two mosses have immense antiproliferative activities against human cervical carcinoma (HeLa) cells and C6 glioma cells at higher concentrations which was detected by Lactate Dehydrogenase Leakage Assay. These mosses have shown therapeutic properties against different cell lines.

Bryologically, India is one of the most highly diversified countries. Apart from some work done on phytochemical, antioxidant and bioactive compounds, mostly Indian bryologists concentrated their research focus on morpho taxonomy and biodiversity-related activities along with some initial molecular studies[52].

Nevertheless, various researchers in the recent past have done substantial work on the above-mentioned aspects and not all but many of the bryophytes are now well-established as reservoirs of bioactive compounds. Some of them have distribution in India, they are listed here (Table 1).

Bryophytes, phylogenetically positioned amid the avascular algae and vascular pteridophytes, consist of three classes: Liverworts, mosses and hornworts. Conventional system of prevention and cure, all over the globe has been exploiting this group of plants to treat numerous diseases. The most remarkable feature of these first land plants is their phytochemistry, especially in the case of liverworts. To date, many liverwort taxa have evaluated and yielded an amazing array of phytoconstituents in the form of terpenoids, particularly sesqui- and diterpenoids[61-65]. Various researchers have characterized plenty of bioactive compounds using miniatured photosynthetic plants. Most of the promising taxa in this regard are the liverworts followed by mosses in which the chemical constituents and their biological action have been studied comprehensively. Though many taxa have been worked out yet there is great scope for the future to find out novel phytochemicals from these amphibious plants.

Table 1: Phytochemicals of bryophytes with anti-proliferative/cytotoxic potential[3,8,53-62]

| Liverworts | | |
|---|---|---|
| **Terpenes** | | |
| Monoterpenes | *Trichocolea mollissima* Hatcher | Methyl 4-[(5-oxogeranyl) oxy]- 3-methoxybenzoate |
| | *Trichocolea tomentella* (Ehrh.) Dumort. | Geranyl ethers, Hemi- and monoterpene moieties of isoprenyl phenyl ethers Monoterpene ester, 2 alpha, 5 beta-dihydroxybornane-2-cinnamate (moderately cytotoxic against human HepG2 cells) |
| | *Jungermannia vulcanicola* (Schiffner) Steph. | Monoterpene ester |
| Sesquiterpenes | *Diplophyllum albicans* (L.) Dumort., *Diplophyllum taxifolium* (Wahlenb.) Dumort. | Diplophylline (An ent-eudesmanolide) |
| | *Conocephalum supradecompositum* Steph., *Frullania monocera* (Taylor) Gottsche, Lindenb. and Nees, *Frullania tamarisci* (L.) Dumort., *Marchantia polymorpha* L., *Porella japonica* (Sande Lac.) Mitt., *Wiesnerella denudata* (Mitt.) Steph., *Lepidozia vitrea* Steph., *Plagiochila semidecurrens* (Lehm. and Lindenb.) Lehm. and Lindenb., *Plagiochila ovalifolia* Mitt. | Sesquiterpenoids costunolide and tulipinolide |
| | *Porella cordaeana* (Huebener) Moore, *Chiloscyphus rivularis* (Schrad.) Hazsl. | Sesquiterpenes with DNA damaging potential |
| | *Chiloscyphus rivularis* (Schrad.) Hazsl. | Sesquiterpene, 12- hydroxychiloscyphone |
| | *Plagiochila ovalifolia* Mitt. | 2,3-Secoaromadendrane-type sesquiterpenoids (plagiochiline-A-15-yl octanoate, 14-hydroxyplagiochiline-A-15-yl 2E, 4E-dodecadienoate and 14-hydroxyplagiochiline-A-15-yl 2E, 4E, 8Z-tetradecatrienoate) |
| | *Bazzania mittenii* (Steph.) Steph. | Naviculyl caffeate, a sesquiterpene |
| | *Schistochila glaucescens* (Hook.) A. Evans | A sesquiterpene lactone glaucescenolide |
| | *Mastigophora diclados* (Brid. ex. F. Weber) Nees | Herbertane type sesquiterpenoids (−)-alpha-herbertenol, (−)-herbertenediol, (−)-mastigophorene C, (−)-mastigophorene D and (−)-Diplophyllolide A |
| | *Chandonanthus hirtellus* (F. Weber) Mitt. | Zierane sesquiterpene gamma-lactone, chandolide |
| | *Porella perrottetiana* (Mont.) Trevis. | Germacrane- and pinguisane-type sesquiterpenoids |
| | *Lepidolaena taylorii* (Gottsche) Trevis., *Lepidolaena palpebrifolia* (Hook.) Dumort. ex. Trevis. | 8, 9-secokaurane diterpenes |
| | *Frullania muscicola* Steph. | A novel ent-labdane type diterpenoid, muscicolone |
| | *Jungermannia* sp. | Entkaurene-type diterpenoids |
| | *Jungermannia truncata* Nees | Ent-11alpha-hydroxy-16-kauren-15-one, kaurene- and entkaurene-type diterpenoids |
| | *Gottschelia schizopleura* (Spruce) Grolle | Cis-Clerodane diterpenoids |
| | *Chandonanthus hirtellus* (F. Weber) Mitt. | Cembrane-type diterpenoids and diterpenoid anadensin |
| | *Ptilidium pulcherrimum* (Weber) Hampe i *Fossombronia alaskana* Steere and Inoue, *Fossombronia pusilla* (L.) Dumort., *Conocephalum japonicum* (Thunb.) Grolle, *Nardia scalaris* (Schrad.) Gray, *Blepharidophyllum densifolium* (Hook.) Ångström ex. C. Massal. | Pentacyclic triterpenoids and their saponins Tri-terpenes |
| | *Riccardia multifida* (L.) Gray | Riccardin A and riccardin B, Riccardin D |
| Marchantin | *Marchantia polymorpha* L., *Marchantia emarginata* subsp. *tosana* (Stephani) Bischl. | Cytotoxic bis(bibenzyl) marchantin A |

Table 1: Continue

| | Liverworts | |
|---|---|---|
| **Terpenes** | | |
| | *Schistochila glaucescens* (Hook.) A. Evans | Marchantin C neomarchantins A and B |
| | *Marchantia polymorpha* L. | Macrocyclic bisbibenzyl plagiochin E |
| | *Plagiochila fruticosa* Mitt. | Antimitotic macrocyclic bis(bibenzyls), isoplagiochins A and B |
| | *Radula perrottetii* Gottsche ex. Stephani | Perrottetin E |
| | *Asterella angusta* (Steph.) Pandé, K.P. Srivast. and Sultan Khan | Macrocyclic bisbibenzyl |
| | *Dumortiera hirsuta* (Sw.) Nees | Lunularin |
| | *Asterella angusta* (Steph.) Pandé, K.P. Srivast. and Sultan Khan, *Plagiochasma intermedium* Lindenb. and Gottsche, *Marchantia polymorpha* L. | Cyclic bisbibenzyls, riccardin C, pakyonol, marchantin M and plagiochin E |
| | *Frullania inouei* S. Hatt. | Methoxylated bibenzyls |
| | *Blasia pusilla* L. | bis(bibenzyl) dimers, pusilatins |
| | *Marchantia polymorpha* L. *Marchantia palmata* Reinw., Nees and Blume | Cyclic bis(bibenzyls) isomarchantin C and isoriccardin |
| Sesquiterpenes | *Anthoceros caucasicus* Steph. | A sesquiterpene ether, veticadinoxide |
| di and triterpenoids | *Claopodium crispifolium* (Hook.) Renauld and Cardot, *Anomodon attenuatus* (Hedw.) Huebener, *Isothecium subdiversiforme* Broth., *Thamnobryum subseriatum* (Mitt. ex. Sande Lac.) B.C. Tan | Antitumor maytansinoids and the members of the ansamycin group (are ansamitocin P-3, 15-methoxyansamitocin P-3, maytanbutine and trewiasine) |
| | *Claopodium crispifolium* (Hook.) Renauld and Cardot, *Anomodon attenuatus* (Hedw.) Huebener | Ansamitocin P-3 |
| | *Sphagnum* spp. | Fulvic acid |
| | *Polytrichum pallidisetum* Funck, *Polytrichastrum ohioense* (Renauld and Cardot) G.L. Sm., Polytrichastrum pallidisetum (Funck) G.L. Sm. | -O-methylohioensin B, 1-Omethyldihydroohioensin B and 1,14-di-O-methyldihydroohioensin B and two novel cinnamoyl bibenzyls, pallidisetin A and pallidisetin B |
| | *Polytrichastrum ohioense* (Renauld and Cardot) G.L. Sm. | Ohioensins, a kind of benzonaphthoxanthenones |
| | *Polytrichum commune* Hedw. | Communins A and B and a new benzonaphthoxanthenone, ohioensin H |
| | *Sanionia georgicouncinata* (Müll. Hal.) Ochyra and Hedenäs i | Sanionins A and B |
| | *Thuidium tamariscinum* (Hedw.) Schimp. | Triterpenes |

## CONCLUSION

Based on several past and contemporary attempts regarding the bioactive potential of bryophytes it has been revealed that usually, these minute plants contain several lipophilic terpenoids (mono-, sesqui- and diterpenoids) and aromatic compounds that were isolated and characterized in different species. A few of these compounds have also been found to have nitrogen or sulfur components. It is notable that mostly the phytoconstituents of bryophytic origin (especially liverworts) are the enantiomers of those characterized in tracheae plants. Hence, there is a great opportunity to work with these first land plants to make amazing discoveries in terms of their phytochemistry. To date, roughly 5-6% of the total bryophytes have been evaluated for their chemical constituents and the data available is insufficient.

## SIGNIFICANCE STATEMENT

This study discovered the bioactive potential of bryophytes due to their unique phytochemistry that can be beneficial for humankind in the development of various remedies in the future to fight against various pathogens including a few viruses. This study will help the researchers uncover the critical areas of phytochemistry and drug discovery that many researchers were not able to explore in these amphibians of the plant kingdom which were usually ignored in the past.

**ACKNOWLEDGMENT**

The authors extend their gratitude to Professor Ina Aditya Shastri, Vice Chancellor, Banasthali Vidyapith (Rajasthan), India.

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