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Antifungal Bryophytes: A Possible Role Against Human Pathogens and in Plant Protection

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ABSTRACT

Fungi are associated with a number of plant and human diseases. Plant extracts have been used as efficient fungicides inhibiting the growth of many fungal pathogens. Bryophytes, a small group of lower plants, evolutionarily placed between the algae and the pteridophytes, have been reported to store a number of compounds having antifungal efficacy. This review includes a list of bryophytes investigated against a number of plant and human pathogenic fungi with special reference to the compounds, nature of the compounds, name of the fungi and mode of action on the basis of available information. Bisbibenzyl was found to be the predominant antifungal active principle present in the bryophytes showing efficacy by inhibiting different types of biological activities of the pathogens.

Key words: Antifungal, human pathogen, plant protection, bisbibenzyl, hepatic

INTRODUCTION

Different plant groups have been reported to possess antifungal efficacy against a number of plant and human pathogens (Zafar *et al*., 2002; Sibtain *et al*., 2002; Saadabi, 2006). Members of lichen (Halama and Van Haluwin, 2004), pteridophyta (Sahayaraj *et al*., 2009), gymnosperms (Krauze-Baranowska *et al*., 2002), monocots (Wannissorn *et al*., 1996) and dicots (Dey, 2011a,b; Dey and De, 2011) have been investigated against various fungi, either pathogenic or non pathogenic.

Bryophyta are the most primitive and simplest member of the Embryophyta. This small and inconspicuous group of plants is placed between the algae and the pteridophyta in the line of evolution. The group is divided into three classes such as Hepaticopsida (Hepatics), Anthocerotopsida (Hornworts) and Bryopsida (Mosses). Bryophyta houses a number of secondary metabolites with diverse pharmacological significance.

Pharmacological importance of bryophytes: Bryophytes are able to produce diverse secondary metabolites to cope up with a number of biotic and abiotic stresses such as predation, ultraviolet radiation, extreme temperature and microbial decomposition (Xie and Lou, 2009). This

comparatively unexplored group of medicinal plants contains a number of unique and valuable secondary metabolites having therapeutic potential (Krzaczkowski *et al.*, 2008). Bryophytes are known to produce a number of medicinally important compounds (Asakawa, 2008). A number of hepatics and mosses have been investigated for antibacterial (Kang *et al.*, 2007), antioxidative (Dey and De, 2012), cytotoxic (Perry *et al.*, 1996), anti snake venom (Pereanez *et al.*, 2010), anti-inflammatory and anti-ulcer (Nakagawara *et al.*, 1992) activities. Use of bryophytes in traditional system of medicine has also been recorded (Harris, 2008).

Potential as alternative fungicide: Bryophytes have been reported as antibiotic (Banerjee and Sen, 1979; Banerjee, 2000; Singh *et al.*, 2007; Shirzadian *et al.*, 2009; Savaroglu *et al.*, 2011a). They have shown antibiosis against a number of plant pathogenic fungi (Mekuria *et al.*, 2005). Compounds isolated from bryophytes have shown reversal of conventional antibiotic resistance developed in human pathogenic fungi (Xie and Lou, 2008). The problem of drug resistance development in pathogenic fungi (Vanden Bossche *et al.*, 1998) can be solved by using novel biomolecules derived from unique natural sources like bryophytes. Development of antifungal drug resistance in human pathogenic *Candida* sp. is a major concern and many of the experiments in the present review have been performed with the bryophyte derived crude extracts or isolated compounds against *C. albicans*.

In the present study, the role of certain bryophytes extracted in different solvents or the purified isolated compounds having antifungal efficacy on plant, animal pathogenic and mild/non pathogenic fungi have been recorded. In different experiments, antifungal (fungicidal and/or fungistatic) activity has been measured in terms of disc diffusion assay and/or microdilution method. Different plant parts such as gametophytes and sporophytes have shown variation in their antifungal efficacy (Wolters, 1964). Fungicidal effect of the group was found to be mediated by inhibiting a number of pathways present in the fungi at cellular, genetic or metabolic level. Development of drug resistance in pathogenic fungi due to the use of conventional antibiotics could be dealt with the natural and novel antibiotics with diverse mechanisms of action from some unique sources like bryophytes.

Enumeration of Bryophytes active against fungi/fungal pathogens: The names of the bryophytes are listed alphabetically along with their family, antifungal extract/fraction/compound, mode of action and reference(s). Authors have included a few mild pathogenic fungi in the pathogenic categories although very few reports are available on their pathogenecity. Species such as *Asperigillus flavus* is included as both human and plant pathogen while *A. fumigatus* is a common human pathogen. *A. parasiticus* is being included as human pathogenic fungi as a producer of aflatoxin. Different strains of species like *Fusarium oxysporum* have a very broad host range from animals to plants. The antifungal bryophytes, in this review, are enumerated in two sections. Table 1 includes the reports of antifungal bryophytes reported or investigated against human pathogens mentioning the active extract and/or the isolated compounds while Table 2 represents the reports on mode of antifungal action. Table 3 denotes bryophyte extracts and/or isolated compounds against plant pathogenic fungi.

Table 1: Reports on bryophytes showing activity and/or investigated against human pathogenic fungi

Bryophyte	Family	Extract/ fraction/ isolated compound	Active/investigated against	Reference
Asterella angusta	Aytoniaceae	Asterelin A, asterelin B, 11-O-demethyl marchantin I and dihydroptychantol Adibenzofuran [bis(bibenzyl)s]	*Candida albicans*	Qu *et al.* (2007)
Atrichum undulatum	Polytrichaceae	Dimethyl sulfoxide (DMSO) extract	*Aspergillus versicolor, A. fumigatus*	Sabovljevic *et al.* (2011)
Bryum argenteum	Bryaceae	Ethanolic extract	*Aspergillus niger, Penicillium ochrochloron, C. albicans, Trichophyton mentagrophytes*	Sabovljevic *et al.* (2006)
Dumortiera hirsuta	Marchantiaceae	Riccardin D [macrocyclic bisbibenzyl]	*C. albicans*	Cheng *et al.* (2009)
Fontinalis antipyretica	Fontinalaceae	various organic solvent extracts	*Aspergillus parasciticus, A. flavus, A. fumigatus*	Savaroglu *et al.* (2011b)
Frullania muscicola	Jubulaceae	3-Hydroxy-4′-methoxylbibenzyl, 7,4′-Dimethoxyl-apigenin	*C.albicans, Trichophyton gypseum, T. rubyum, Microsporum lanosum, M. gypseum, Epidermophyton floccoum*	Lou *et al.* (2002)
F. muscicola	Jubulaceae	Pakyonol (bisbibenzyl)	*T. gypseum, M. gypseum, E. floccoum*	Lou *et al.* (2002)
Homalia trichomanoides	Neckeraceae	3 beta-methoxyserrat-14-en-21beta-ol atranorin, methyl 2,4-dihydroxy-3, 6-dimethylbenzoate	*C. albicans,*	Wang *et al.* (2005)
Marchantia polymorpha	Marchantiaceae	Plagiochin E, 13,13'-O-isoproylidenericcardin D, riccardin H, marchantin E, neomarchantin A, marchantin A and marchantin B (macrocyclic bisbibenzyls)	*C. albicans*	Niu *et al.* (2006)
M. polymorpha	Marchantiaceae	Plagiochin E [macrocyclic bis(bibenzyl)]	*C. albicans*	Sun *et al.* (2009)
M. polymorpha	Marchantiaceae	Plagiochin E	*C. albicans*	Wu *et al.* (2008)
M polymorpha	Marchantiaceae	Plagiochin E	*C. albicans*	Wu *et al.* (2009)
M. polymorpha	Marchantiaceae	Plagiochin E	*C. albicans*	Wu *et al.* (2010)
M. polymorpha ssp. *ruderalis*	Marchantiaceae	DMSO extract	*A. versicolor, A. fumigatus,*	Sabovljevic *et al.* (2011)
Orthotrichum rupestre	Orthotrichaceae	various organic and inorganic solvents	*C. albicans*	McCleary *et al.* (1960)
Pallavicinia lyellii	Pallaviciniaceae	water, alcohol and hexane extracts; steroid	*A. fumigatus, Fusarium oxysporum, C. albicans*	Subhisha and Subramoniam (2005)
P. lyellii	Pallaviciniaceae	n-hexane fraction of alcohol extract	*A. fumigatus*	Subhisha and Subramoniam (2006)

Table 1: Continued

Bryophyte	Family	Extract/ fraction/ isolated compound	Active/investigated against	Reference
Physcomitrella patens	Funariaceae	DMSO extract	*A. versicolor, A. fumigatus*	Sabovljevic *et al.* (2011)
Plagiochasma intermedium	Aytoniaceae	Pakyonol, neomarchantin A, isoriccardin C, marchantin H, riccardin F and riccardin C [macrocyclic bis(bibenzyl)]	*C. albicans*	Xie *et al.* (2010)
Plagiochila banksiana	Plagiochilaceae	bibenzyl	*C. albicans, T. mentagrophytes*	Lorimer *et al.* (1993)
P. deltoidea	Plagiochilaceae	4-hydroxy-3'-methoxybibenzyl	*C. albicans*	Lorimer *et al.* (1993)
P. fasciculata	Plagiochilaceae	bibenzyl	*T. mentagrophytes*	Lorimer *et al.* (1993)
P. fasciculata	Plagiochilaceae	2-hydroxy-4,6-dimethoxyacetophenone, 2-hydroxy-3,4,6-trimethoxyacetopheno	*T. mentagrophytes, Cladosporium resinae*	Lorimer and Perry (1994)
P. stephensoniana	Plagiochilaceae	4-hydroxy-3'-methoxybibenzyl	*C. albicans, T. mentagrophytes*	Lorimer *et al.* (1993)
P. suborbiculata	Plagiochilaceae	bibenzyl	*C. albicans*	Lorimer *et al.* (1993)
Ptilidium pulcherrimum	Ptilidiaceae	methanolic extract	*A. versicolor, A. ochraceus*	Veljic *et al.* (2010)
Riccardia marginata	Aneuraceae	chlorinated bibenzyls	*C. albicans, T. mentagrophytes*	Baek *et al.* (2004)
Scapania verrucosa	Scapaniaceae	ether extract; essential oil	*C. albicans, Cryptococcus neoformans, Trichophyton rubrum, A. fumigates*	Guo *et al.* (2008)
Tortella tortuosa	Pottiaceae	acetone extract	*C. albicans*	Elibol *et al.* (2011)

Table 2: Mode of action of some antifungal bryophytes

Bryophyte	Active/investigated against	Mode of action	Reference
Dumortiera hirsuta	*C. albicans*	Biofilm formation	Cheng *et al.* (2009)
M. polymorpha	*C. albicans*	Ergosterol biosynthesis	Sun *et al.* (2009)
M. polymorpha	*C. albicans*	Cell wall chitin synthesis	Wu *et al.* (2008)
M polymorpha	*C. albicans*	Mitochondrial dysfunction-induced Reactive oxygen species accumulation	Wu *et al.* (2009)
M. polymorpha	*C. albicans*	Induction of apoptotic pathway	Wu *et al.* (2010)
Plagiochasma intermedium	*C. albicans*	Reduction of minimum inhibitory coucentration (MIC) of antibiotic fluconazole when combined with riccardin C	Xie *et al.* (2010)
Dumortiera hirsuta	*Alternaria alternata, A. niger, B. cinerea, Botryodiploidia theobromae, Fusarium oxysporum* f. sp. *gladioli, Penicillium expansum, P. chrysogenum*	Spore germination inhibition, anomalies in the hyphae, flaccid cell wall, granulated cytoplasm	Alain *et al.* (2011)

Antifungal extracts/compounds: Most of these reports were found to involve the crude extracts in different solvents, some were able to purify and isolate the actual active compound with specific mode of inhibition. Siddiqui *et al.* (2005) was able to synthesize fungicidal bibenzyls by acetylation of bibenzyl compound derived from Bryophyta. However, bibenzyls from *Scorzonera humilis*, an angiosperm, were unable to show fungicidal activity (Zidorn *et al.*, 2002). Apart from the macrocyclic bisbibenzyls, some other constituents from bryophytes such as steroids, sesquiterpenoids, acetophenones, stilbenes and essential oil have exhibited antagonism to fungal pathogens. (E)-4-hydroxylated stilbenes and related bibenzyls were analyzed against the brown rot fungi *GloeophylIum trabeum* and *Poria placenta* for antifungal activity. Other bibenzyls were also found to be effective against the white rot fungus *Coriolus versicolor* (Schultz *et al.*, 1991). Although the experiments were performed mostly *in vitro*, some of the antifungal fractions have been evaluated *in vivo* (Subhisha and Subramoniam, 2006). However, *Palustriella commutata* extracts did not exhibit any activity against yeast and mould strains. Lack of activity was ascribed to low concentration of active substances in the extracts. In addition, the acetone extract of *Lunularia cruciata* did not show activity against *C. albicans* and *A. niger*. Absence of antifungal activity could be due to inability of the molecule(s) present in the extract to cross the fungal cell wall (Basile *et al.*, 1998). Interestingly, *Sphagnum* associated bacteria have been reported to produce some antifungal compounds (Opelt and Berg, 2004). Antagonistic effect of bacteria isolated from *Sphagnum* has shown antifungal potential against *Rhizoctonia solani* and *Verticillium dahlia*. The plant and the associated bacteria could be used as a natural fungicide (Opelt *et al.*, 2007). In addition to that generation specific variation of antifungal activity has also been noted in certain bryophytes (Wolters, 1964). The degree of antifungal activity of a particular bryophyte species is said to be dependent on the age of the gametophyte (Banerjee and Sen, 1979). It could be an exciting aspect of study if the seasonal, altitudinal, age, generation and tissue specific variation of secondary metabolites of bryophytes are analyzed and their pharmacological potential is determined.

Mode of antifungal action: Bryophytes extracts or the isolated active compounds have exhibited activity by inhibiting biofilm formation, ergosterol biosynthesis, cell wall chitin synthesis, reactive

Table 3: Reports on bryophytes showing activity and/or investigated agaiust plant pathogenic fungi

Bryophyte	Family	Extract/ fraction/ isolated compound	Active or investigated agaimst	Reference
Atrichum undulatum	Polytrichaceae	solvent extracts	*Botrytis allii, Coniophora cerebella, Polyporus versicolor, Fusarium bulbigenum, Pyricularia oryzae*	Wolters (1964)
A. undulatum	Polytrichaceae	DMSO extract	*Penicillium funiculosum, Trichoderma viride*	Sabovljevic *et al.* (2011)
Balantiopsiscancellata	Balantiopsaceae	*Trans*-β-methylthioacrylate	*Cladosporium herbarum*	Labbe *et al.* (2005)
Bazzania trilobata	Lepidoziaceae	Dichloromethane and a methanol extract; 5- and 7-hydroxycalamenene, drimenol, drimenal, viridiflorol, gymnomitrol and three bisbibenzyls: 6',8'-dichloroisoplagiochin C, isoplagiochin D and 6'-chloroisoplagiochin D (sesquiterpenes)	*Botrytis cinerea, Cladosporium cucumerinum, Phythophthora infestans, Pyricularia oryzae, Septoria tritici*	Scher *et al.* (2004)
Bryum argentium	Bryaceae	Acetone, ethanolic, chloroform and aqueous extracts	*Aspergillus niger, Rhizoctonia bataticola, Fusarium moniliformae*	Bodade *et al.* (2008)
B. cellulare	Bryaceae	Acetone, ethanolic, chloroform and aqueous extracts	*A. niger, Rhizoctonia bataticola, F. moniliformae*	Bodade *et al.* (2008)
B. pallens	Bryaceae	Solvent extracts	*C. cerebella, P. versicolor, F. bulbigenum, P. oryzae*	Wolters (1964)
Ctenidium molluscum	Hypnaceae	Methanolic extract	*Trichoderma viride, A. niger, A. flavus, P. funiculosum*	Veljic *et al.* (2009)
Dicranella heteromalla	Dicranaceae	Solvent extracts	*P. oryzae*	Wolters (1964)
Diobelon squarrosum	Dicranaceae	Solvent extracts	*C. cerebella, P. versicolor, B. alli, P. oryzae*	Wolters (1964)
Diplophyllum albicans	Scapaniaceae	Solvent extracts	*C. cerebella, P. versicolor, B. alli, F. bulbigenum, P. oryzae*	Wolters (1964)
Dumortiera hirsuta	Marchantiaceae	Aqueous extract	*Alternaria alternata, A. niger, B. cinerea, Botryodiploidia theobromae, Fusarium oxysporum* f. sp. *gladioli, Penicillium expansum, P. chrysogenum*	Alam *et al.* (2011)
Fontinalis antipyretica	Fontinalaceae	Methanolic extract	*T.viride, A. niger, A. flavus, P. funiculosum*	Veljic *et al.* (2009)
F. antipyretica	Fontinalaceae	Different organic solvent extracts	*A. flavus, Fusarium solani, F. graminearum, Geotrichum candidum*	Savaroglu *et al.* (2011b)
Herberta adunca	Herbertaceae	α-Herbertenol, β-Herbertenol, α-Formylherbertenol, β-Bromoherbertenol (herbertane sesqniterpenoids)	*Botrytis cinerea, Rhizoctonia solani*	Matsuo *et al.* (1986)
Hypnum cupressiforme	Hypnaceae	Methanolic extract	*T. viride, A. niger, A. flavus, P. funiculosum*	Veljic *et al.* (2009)
Marchantia polymorpha	Marchantiaceae	Methanol and chloroform extracts	*Tilletia indica,Fusarium oxysporum,Sclerotium rolfsii, Rhizoctonia solani*	Gahtori and Chaturvedi (2011)
M. polymorpha ssp. *ruderalis*	Marchantiaceae	DMSO extract	*P. funiculosum, T. viride*	Sabovljevic *et al.* (2011)
Mniobryum carneum	Bryaceae	Solvent extracts	*F. bulbigenum, P. oryzae*	Wolters (1964)

Table 3: Continued

Bryophyte	Family	Extract/ fraction/ isolated compound	Active or investigated against	Reference
Mnium hornum	Mniaceae	Solvent extracts	*C. cerebella, P. versicolor, B. allii, R. solani, P. oryzae*	Wolters (1964)
Oligotrichumhercynicum	Polytrichaceae	Solvent extracts	*F. bulbigenum, P. oryzae*	Wolters (1964)
Pallavicinia lyellii	Pallaviciniaceae	Water, alcohol and hexane extracts; steroid	*A. niger, F. oxysporum*	Subhisha and Subramoniam (2005)
Physcomitrella patens	Funariaceae	DMSO extract	*P. funiculosum, T. viride*	Sabovljevic *et al.* (2011)
Plagiochasma appendiculatum	Aytoniaceae	Aqueous extract	*Alternaria solani*	Deora and Jain, 2008
P.appendiculatum	Aytoniaceae	Acetone, ethanolic, chloroform and aqueous extracts	*A. niger*	Bodade *et al.* (2008)
Plagiothecium	Plagiotheciaceae	Solvent extracts *P. oryzae, C. cerebella*	*B. allii, R. solani, P. versiclor, F. bulbigenum,*	Wolters, *denticulatum* (1964)
Pogonatum aloides	Polytrichaceae	Solvent extracts	*P. versicolor, B. allii,* F. *bulbigenum, P. oryzae*	Wolters (1964)
P. urnigerum	Polytrichaceae	Solvent extracts	*P. versicolor, B. allii*	Wolters (1964)
Polytrichum communae	Polytrichaceae	Solvent extracts	*P. versicolor, B. allii, F. bulbigenum, P. oryzae*	Wolters (1964)
P. formosum	Polytrichaceae	Solvent extracts	*R. solani*	Wolters (1964)
Ptilidium pulcherrimum	Ptilidiaceae	Methanolic extract	*A. flavus, A. niger, T. viride, P. funiculosum*	Veljic *et al.* (2010)
Riccardia marginata	Aneuraceae	Polychlorinated bibenzyls	*C. herbarum*	Labbe *et al.* (2007)
Riccia gangetica	Ricciaceae	Cold and boiling water extract	*F. moniliforme*	Deora and Suhalka (2010)
Scapania verrucosa	Scapaniaceae	Ether extract; essential oil	*P. oryzae*	Guo *et al.* (2008)
Scleropodium purum	Brachythecaceae	Solvent extracts	*C. cerebella, B. allii, P. oryzae*	Wolters (1964)
Sphagnum fimbriatum	Sphagnaceae	Solvent extracts	*C. cerebella, P. versicolor, F. bulbigenum, P. oryzae*	Wolters (1964)
S. nemoreum	Sphagnaceae	Solvent extracts	*C. cerebella, P. versicolor, F. bulbigenum, P. oryzae*	Wolters (1964)
S. subseeundum	Sphagnaceae	Solvent extracts	*C. cerebella, P. versicolor, F. bulbigenum, P. oryzae*	Wolters (1964)
Thuidium cymbifolium	Thnidiaceae	Acetone, ethanolic, chloroform and distilled water extracts	*A. niger, Rhizoctonia bataticola, F. moniliformae*	Bodade *et al.* (2008)
T. delicatulum	Thnidiaceae	Acetone, ethanolic, chloroform and distilled water extracts	*A.* niger, *R. bataticola, F. moniliformae*	Bodade *et al.* (2008)

oxygen species accumulation, apoptotic pathway induction etc. Aqueous extract of the liverwort *Dumortiera hirsuta* was found to inhibit a number of phytopathogenic fungi mediated by different modes of action such as spore germination inhibition, development of anomalies in the hyphae, formation of flaccid cell wall and granulated cytoplasm etc. (Alam *et al*., 2011). A number of biologically active macrocyclic bis (bibenzyl) have shown antagonistic effect against the conventional antibiotic resistant human pathogen *Candida albicans*. Expression of m-RNA specific genes responsible for hyphae and later biofilm formation in *C. albicans* was found to be inhibited by riccardin D (Cheng *et al*., 2009). When fluconazole sensitive and fluconazole resistant strains of *C. albicans* were treated with another macrocyclic bisbibenzyl plagiochin E alone and in combination with fluconazole, ergosterol pathway gene was found to be transcribed at a lower rate (Sun *et al*., 2009). In another experiment, the same compound has exhibited *in vitro* and *in situ* inhibition of cell wall chitin synthetase genes in *C. albicans* at the post transcriptional or at the enzymatic level (Wu *et al*., 2008). In addition to that, Wu *et al*. (2009) have reported the same compound affecting the same pathogen by inducing the accumulation of Reactive Oxygen Species (ROS) associated with mitochondrial dysfunction. Moreover, plagiochin E, in another case, was found to activate the apoptotic pathway in *C. albicans* while showing antifungal efficacy. G (2)/M cell cycle arrest and activation of metacaspase were found to be related with the apoptototic induction (Wu *et al*., 2010). Therefore, different bryophytes were found to follow various modes of action to inhibit fungi *in vitro*. The mechanism of activity was not only dependent on the compound but was also pathogen specific. Same compound was reported to follow different mode of action while inhibiting the same or different fungi.

Bryotechnology as a tool: Lack of enough plant material and problems regarding the chemistry and isolation of compounds are the major constrains in the phytochemistry and pharmacology of bryophyte research. However, some *in vitro* techniques have been utilized in this group for large scale production of active constituents (Sabovljevic *et al*., 2009). In addition, Sabovljevic *et al*. (2011) have shown that some of the bryophytes grown axenically *in vitro* with greater antifungal potential than that of their natural counterparts. *In vitro* techniques not only save space but also generate microbe free plants. Tissue culture of bryophyte may generate higher amount of plant body and active compounds which can be utilized in a bioreactor for large scale production of secondary metabolites.

CONCLUSION

Use of medicinal plants has been popularized due to low cost and lesser side effects. Herbal drugs have been used successfully in the treatment of various ailments. Development of drug resistance in pathogens is one of the major problems in medicine. Natural products derived from the botanicals can be used as a substitute to solve the problem. A number of herbal compounds have been discovered with immense therapeutic potential. Bryophyte, a small and apparently insignificant group of plants may serve as a source of some unique biologically active molecules. Antifungal efficacy of certain liverworts and mosses can substitute the conventional synthetic fungicides used in crop protection especially in the countries where fugal invasion in the crop fields is a common phenomenon. Similarly, development of drug resistance in common human pathogenic fungi can be regulated by using antifungal compounds harvested from uncommon sources like bryophytes. Cost effectiveness and less or no side effects of the natural compounds may be used as an alternative to the conventional biocidal chemicals especially in the poor and underprivileged

third world countries. Although researches involving pharmacological properties of bryophytes are mostly done *in vitro* but *in vivo* analyses and clinical trials may lead to the novel drug discovery programs in future. Lack of reports on antifungal activity from the group of hornworts is another lacuna in this field. Authors did not find any report on biological activity of the group antagonist to fungi. The group is thought to be evolutionary placed between hepatics and mosses and supposed to possess some compounds with novel therapeutic value.

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