Review article

Bryophytes in Medicines

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Abstract: Bryophytes are small, thalloid, non-vascular plants that pioneered terrestrial habitation. Except ocean, they can be found in all types of habitats. They comprise about 28,000 species worldwide and are the second largest plant group after the flowering plants. They are grouped into three divisions, Marchantiophyta, Anthocerotophyta and Bryophyta. Bryophytes serve as a phytochemical treasure chest owing to its stunning variety of bioactive compounds comprising of more than 3000 different metabolites. Terpenoids, with 2200 different molecules, constitute the largest fraction, followed by hundreds of phenolics and other molecules such as saccharides, lipids, acetogenins, proteins, and compounds that contain nitrogen and sulphur. This assortment of compounds suggests their potential to be used as remedies to many diseases. Approximately, 1000 species of bryophytes have been analysed for their potential medicinal properties. The review explores the potential of bryophytes in treating various diseases, such as, microbial, cancerous, diabetic, osteoarthritic, cardiovascular, insect bites, as well as their role in immunomodulation and antioxidant activities. It also discusses the bioactive compounds isolated from bryophytes and their mechanism of action in treating these diseases. The article throws light on the feasibility of mass production of bioactive compounds and vaccines via *in vitro* culture of bryophytes. However, there are gaps in the knowledge in the understanding of the mechanism of action of these compounds and their side effects on humans as well. The article also suggests perspectives on which future research should be directed for complete understanding of the topic and to facilitate the use of bryophytes for safe drug.

Key words: Bryophytes, bioactive compounds, medicinal plants, secondary metabolites

Introduction

Bryophytes are small, thalloid, non-vascular land plants showing a distinct haplo-diplontic life cycle in which the gametophytic phase is the dominant generation. They are considered to be the oldest terrestrial plants. With 28,000 species worldwide, they are second to angiosperms in terms of species diversity. These species are grouped into three phyla, namely Marchantiophyta (the liverworts) which comprises 8,500 species, Anthocerotophyta (the hornworts) comprising 300 species and Bryophyta (the mosses) with approximately 11,500 species worldwide (Shaw *et al.*, 2011; Patino and Vanderpoorten, 2018). They are found in all types of habitats, except oceans (Stark and Whittemore, 2000; Dey and Mukherjee, 2015, Commisso *et al.*, 2021). They are called 'Amphibians of Plant Kingdom', owing to their requirement of water for sexual reproduction (Dey and Mukherjee, 2015).

Bryophytes have been used as medicines for treatment of various kinds of diseases in China, India and some parts of native America (Chandra *et al.*, 2017; Glime,

2017). Worldwide, approximately 1000 bryophyte species are used for treatment of various diseases (Asakawa 2004). They are bestowed with a great range of compounds such as carbohydrates, proteins, lipids, terpenes, polyphenols, steroids, organic acids, fatty acids, sugar alcohols, aromatic and aliphatic compounds, phenylquinones, acetogenins and phenolic substances which show significant bioactivities (Halder and Mitra, 2020). These plant products have the potential to function as antibacterial, antifungal, anticancer, insecticidal and antioxidant sources (Figure 1) (Sabovljevic *et al*., 2001; Asakawa 2007; Pejin *et al*., 2012). In addition, a bryophyte genus, *Sphagnum,* has been used as surgical dressing due to its better and faster absorbent qualities than cotton. The antibiotic qualities of the plant are an added feature (Ayres, 2015).

Plants based medicines offer a safe and alternative medicine over synthetic drugs. Hence, in recent years, researches on medicinal uses of bryophytes have drawn major attention of scientists. Many studies have identified several new bioactive compounds and reported their effects on different disease models and conditions. Most recently, bioactive compounds from 14 species of bryophytes were screened and found to have antimicrobial properties as well as impart antiproliferative effects on cancer cells (Vollár *et al*., 2018). Though limited, these studies are opening a treasure of bioactive compounds in bryophytes that can be used in treating many diseases. The bioactive potential of bryophytes as antimicrobial, anticancerous, insecticidal and antioxidants have been extensively reviewed (Sabovljevic *et al*., 2016; Chandra *et al*., 2017; Ludwiczuk and Asakawa, 2019; Commisso *et al*., 2021). However, there is limited information regarding the mechanism of action of many compounds isolated from the bryophytes. In this regard, this article attempts to discuss the role and mechanism of bryophytes as antibacterial, antifungal, anticancerous, insecticidal and antioxidative plants. In addition, it explores the potential of bryophytes in treating diabetes, osteoarthritis and cardiovascular diseases. The article can serve as a reference for future research based on medicinal properties of bryophytes.

Medicinal properties of bryophytes

Antimicrobial activities

Bryophytes are traditionally used in different cultures among the people of Asia and native Americans for treating burns, wounds, cuts and skin diseases, suggesting that they protect the skin and open wounds from pathogenic microbes (Alam *et al*., 2015; Chandra *et al*., 2017; Ludwiczuk and Asakawa, 2019). It is interesting to note that bryophytes are not infected by bacteria and fungi, suggesting that they are equipped with defences against such infections (Ludwiczuk and Asakawa, 2019). This antibiotic property of bryophytes may also be attributed, in part to the bacterial and fungal biomass associated with phyllosphere of bryophytes (Davey *et al.,* 2009) as moss-associated bacteria have shown two-folds higher production of active substances than in plant-associated bacteria (Opelt and Berg, 2004). Many studies have demonstrated antimicrobial activities of different species of bryophytes against gram positive and gram negative bacteria, and fungi. Studies involving bacteria and fungi are discussed hereunder:

Antibacterial activities

Bacterial diseases are the most common type of diseases that humans, plants and animals suffer from in everyday life. This is mainly because bacteria are ubiquitous organisms inhabiting the air, water, soil and other organisms and can easily come in contact or enter into one's system (Barbaren *et. al*., 2014). While many of them are non-pathogenic (harmless or even beneficial), some can cause serious infections and diseases by secreting toxic substances (Ryan *et al*., 2014). Common bacterial diseases include typhoid, tuberculosis, gastroenteritis, pneumonia, urinary tract infections (UTIs) and skin infections (eczema, rashes and dermatitis) which are caused by *Salmonella* species, *Mycobacterium tuberculosis, Bacillus* species, *Klebsiella pneumoniae, Enterobacter aerogenes* and *Pseudomonas aeruginosa*, respectively (Santosham *et al*., 2013). If these bacterial actions are not controlled at the early stage, they can lead to serious conditions which can even damage body organs like lungs, kidneys and bladder. More importantly, most of these infectious diseases are communicable and often become epidemic or pandemic.

The antibacterial properties of bryophytes were discovered as early as 1979 (Banerjee and Sen, 1979). Recently, crude drug extracts of bryophytes viz. *Marchantia* species, *Calymperes motleyi* Mitt., *Fissidens* species, *Hypnum cupressiforme* Hedw., *Plagiochila* species and *Sematophyllum demissum* (Wilson) Mitt. have shown potent antibacterial activity against disease-causing *Bacillus subtilis, Pseudomonas aeruginosa* and *Staphylococcus aureus* (Kirisanth *et al*., 2020). Previously, Ruiz-Molina *et al*. (2019) also demonstrated antibacterial activity of protonema suspension and naturally growing *Polytrichum juniperinum* Hedw. against *Bacillus cereus, Escherichia coli, Salmonella typhimurium* and *Staphylococcus aureus.* The protonemal suspension extract inhibited the growth of all test bacteria, however, the extract of field collected species was more effective in inhibiting the growth of gram positive bacteria (*B. cereus* and *S. aureus*) as against gram-negative bacteria (*Escherichia coli* and *S. typhimurium*) (Ruiz-Molina *et al*., 2019). Likewise, *Archidium ohioense* Schimp. ex Müll. Hal., *Hyophila involuta* (Hook.) A. Jaeger and *Pelekium gratum* (P. Beauv.) Touw extracts showed significant inhibitory activity against *Bacillus subtilis*, *S. aureus*, *E. coli* and *Pseudomonas aeruginosa* (Olasoji *et al*., 2019).

The efficacy of bryophytes to exhibit antibacterial activity depends on many factors, especially the extraction medium and the bacterial species. For example, Kumar and Chaudhary (2010) reported that methanolic extract of *Entodon myurus* (Hook.) Hampe showed maximum inhibition of growth of *Enterobacter aerogenes* while acetone extract showed maximum activity against *Klebsiella pneumoniae* amongst all tested solvents (petroleum ether, benzene, acetone, and methanol). Similarly, Vats and Alam (2013) also reported that ethanolic extracts of *Atrichum undulatum* (Hedw.) P. Beauv. were more efficient in inhibiting the growth of bacterial strains (*B. subtilis, E. coli* and *S. typhimurium*) than their methanolic extracts. The study also revealed that *E. coli* is more sensitive to the test followed by *S. typhimurium* and *B. subtilis.* Ilhan *et al*. (2006) reported that extracts of a moss, *Palustriella commutata* (Hedw.) Ochyra can potentially inhibit the growth of gram-negative bacteria viz. *K. pneumoniae, Yersinia enterocolitica, P. aeruginosa, E. coli* and *E. aerogenes*. This is interesting, since conventional antibiotics are generally more active against gram-positive than gram-negative bacteria. Thus, this study can serve as an alternative path that can be employed to inhibit the growth of gram negative bacteria.

Antibacterial activity of bryophytes can be credited to the presence of a variety of compounds, such as marchantin and neomarchantin (phenylpropanoids), lunularin (stilbenes), riccardiphenol (sesquiterpene derivatives), monoterpenoids, tetraterpenoids caratenoids, trachylobane diterpenoids (Table 1) (Asakawa and Ludwiczuk, 2018). However, the type of compounds in bryophytes may vary from species to species. These compounds can (i) disrupt mitochondrial integrity; (ii) prevent biomolecules production (like DNA, RNA etc.); (iii) depolarise bacterial cell walls leading to abnormal metabolic activity;(iv) disrupt cell wall integrity leading to leakage of protein and nucleic acids and; (v) prevent the formation of biofilms (Greeshma and Murugan 2018, Onbasli and Yuvali 2020). Despite these information, much remains to be deciphered to assign specific functions to the bryophyte specific bioactive compounds. Thus, directing future research to characterize these compounds can increase the understanding of the bioactivities of these compounds.

Antifungal activities

Fungi are ubiquitous organisms with their abundance next to bacteria. More than hundreds of fungi are known to be pathogenic to humans, causing various kinds of infections and diseases (Kohler *et al*., 2015). Over a billion people suffer from fungal diseases every year (Bongomin *et al*., 2017). While some fungi cause superficial fungal infections (skin, hair and nails infection), a few of them can invade host cells and develop a chronic disease condition called invasive fungal disease (IFD). The IFDs rarely develop in those with strong innate immunity, while an individual suffering from immunocompromised conditions such as asthma, cancer; AIDS etc. are more susceptible to IFDs (Chang et. al., 2017).

One of the earliest studies associated with antifungal properties of bryophytes was reported in 1982 by Asakawa.

Since then, many studies have reported antifungal activities of bryophytes (Table 1). Recently, Negi *et al.* (2020) reported that the acetone extract of the liverwort *Conocephalum conicum* (L.) Dumort. showed potent antifungal activity against *Aspergillus flavus*, an opportunist pathogenic fungal species that causes a wide range of diseases in plants and humans. Similarly, methanolic extract of liverwort, *Porella platyphylla* (L.) Pfeiff. and two mosses, *Cinclidotus fontinaloides* (Hedw.) P. Beauv. and *Anomodon viticulosus* (Hedw.) Hook. & Tayl. showed growth inhibition of fungal species *Botrytis cinerea* Pers., which causes grey mould disease of dicotyledonous plants (Latinoviæ *et al.*, 2019).

Various compounds which exhibit antifungal activity have been isolated from bryophytes (Table 1). Compounds such as marchantin A, bis-bibenzyls neomarchantin A, riccardin D, isopropylidene riccardin D, prenyl phenyl ethers, glaucescenolide, tetracyclic diterpene, have been classified as antifungal. Bryophytes exhibit antifungal activities by: (i) inhibiting spore germination and hyphal growth (Deora and Suhalka, 2017), (ii) inducing reactive oxygen species (ROS) generation and subsequent apoptosis through activating metacaspase (Wu *et al.*, 2010), (iii) preventing biofilm formation (Cheng *et al.*, 2009) and (iv) inhibiting cell wall chitin synthesis (Wu *et al.*, 2008).

Anticancer activities

Cancer is one of the deadliest diseases and remains the second most leading cause of death worldwide. It causes over 9.6 million deaths annually (Henamayee *et al.*, 2020). It develops because of uncontrollable division of cells due to dysfunction or mutation in their DNA. The mutations may be caused by exposure to radiation, chemicals, hormones and other factors in the surrounding environment (Jain *et al.*, 2016). The common methods for treatment of cancer include chemotherapy, immunotherapy and radiotherapy. However, these techniques massively affect the healthy cells leading to various types of infections. Therefore, it is essential to develop a new, safe and an efficient treatment method which will have less toxicity or minimal side effects (Roy *et al.*, 2018).

Herbal medicines for treatment of cancer have gained much attention in recent years because the use of natural products derived from medicinal plants and herbs halt the chance of possible adverse side effects while yielding promising outcomes/ results (Tripathy and Singh, 2017). Bryophytes, among other plant groups, have the potential to treat a wide range of diseases including cancer. In fact, the effects of extracts and metabolites of bryophytes on various types of cancer lines were reported as early as 1986 (Spjut *et al.*, 1986). Moreover, their abundance in all habitats is another reason for the number of therapeutic studies being made on them in the last decade (Yayintas *et al.*, 2019). Most recently, Naidu *et al.* (2020) reported that daucosterol (glucoside of â-sterol) and friedelin (triterpenoid), isolated from the moss *Octoblepharum albidum* Hedw. inhibited the growth of three types of cancer cells viz. ovary (PA1), Cervical (C-33A) and Lung (NCI-H358).

Anticancer properties of bryophytes are attributed to the presence of various phytochemical compounds in them, such as sesquiterpenoids, monoterpenoids, diterpenoids, triterpenoids, flavonoids, bibenzyls and bisbibenzyls etc. (Dey and Mukherjee, 2015). For example, marchantin C (a macrocyclic bisbibenzyl) can induce apoptosis of human glioma tumor cells (A172) by up-regulation of proapoptotic *Bax* gene and down-regulation of anti-apoptotic *Bcl-2* gene expression (Shi *et al.*, 2009). It can also depolymerise microtubules and arrest cell cycles at G_2/M phase and cause apoptosis of A172 and HeLa cells in concentration and time-dependent manners, respectively (Shi *et al.*, 2009). Similar activity was reported for marchantin A, which showed antiproliferative activity against human MCF-7 breast cancer cells (IC_{50} of 4.0 lg/mL) (Huang *et al.*, 2010). Cleavage of apoptotic proteins caspase 3, caspase 8, caspase 9 and poly (ADP ribose) polymerase (PARP) were increased on treatment with marchantin A to breast cancer cells inducing cell-death (Huang *et al.*, 2010). Another report on breast cancer cell lines, MCF7, A256 and T47D, showed that marchantin A, in synergism with kinase inhibitor, decrease tubulin polymerization in microtubules and inhibit growth and proliferation of the cells (Jensen *et al.*, 2012). Marchantin A was also reported to have significant cytotoxic effects on

Table 1. Some studies in which antimicrobial activities of bryophytes were elucidated.

Bryophyte species	Phylum	Chemical(s) reported	Against microbes	References
Anthoceros erectus Steph.	Anthocerotophyta	Alkaloids, Coumarins, Flavonoids, Phenols, Steroids, Sugars	*Bacillus subtilis, Staphylococcus aureus Escherichia coli,Klebsiella pneumoniae, Vibriocholera, Pseudomonas aeruginosa* and *Shigella flexneri*	Sangeetha (2019)
Anthoceros longii Steph.	Anthocerotophyta	NR	*Agrobacterium tumefaciens*	Deora and Bhati (2007)
Asterella angusta (Steph.) Pandé, K.P. Srivast. & Sultan Khan	Marchantiophyta	Ten bis (bibenzyls), riccardin D, riccardin B, perrottetin E, asterellin A, asterellin B, 11-demethylmarchantin I, dihydroptychantol, marchantin H, marchantin M and marchantin P	*Candida albicans*	Qu *et al.* (2007)
Atrichum undulatum (Hedw.) P. Beauv.	Bryopsida	NR	*Bacillus subtilis, Escherichia coli* and *Salmonella typhimurium*	McCleary andWalkington (1966); Vats and Alam (2013)
Bazzania sp.	Marchantiophyta	Cyclomyltaylyl-3-caffeate, viridiflorol, gymnomitrol, 5-hydroxycalamenene, 7-hydroxycalamenene, drimenol, drimenal, naviculylcaffeate, lipophilic, sesquiterpenoids viz. gymnomitrol, 5-hydoxycalamenene, 7-hydroxycalamenene, drimenol, and drimenal	*M. graminicola, Botrytis cinerea, Cladosporium cucumerinum, Pyricularia oryzae, Phytophthora infestans* and *Septoria tritici*	Scher *et al.* (2004); Asakawa and Ludwiczuk (2018); Ludwiczuk and Asakawa (2019)
Barbula convoluta Hedw.	Bryophyta	NR	*Pseudomonas aeruginosa*	Abdel-Shafi *et al.* (2017)
Bryum capillare Hedw.	Bryophyta	Triterpenoids, saponins	*Bacillus subtilis, Salmonella sp., Staphylococcus aureus, Pseudomonas aeruginosa* and *Saccharomyces cerevisiae.*	Sturtevant (1954); Elibol *et al.* (2011)
Bryum cellulare Hook.	Bryophyta	NR	*Curvularia lunata*	Deora and Guhil (2016)
Cinclidotus fontinaloides (Hedw.) P.Beauv.	Bryophyta	Flavonoids	*Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans*	Yayintas *et al.* (2017)
Conocephalum conicum (L.) Dumort.	Marchantiophyta	Eudesmanolides, germacranolides, bicyclogermacrenal, 2a, 5b-dihydroxybornane-2-cinnamate, lipophilic	*Staphylococcus aureus*	Singh *et al.* (2011);Ding (1982); Ando(1983); Alam (2012); Toyota (2000); Asakawa (1984); Asakawa and Ludwiczuk (2018)
Entodon myurus (Hook.) Hampe	Bryophyta	NR	*Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Enterobacter aerogenes* and *Klebsiella pneumonia*	Kumar and Chaudhary (2010); Singh *et al.* (2011)
Frullania dilatata (L.) Dum	Marchantiophyta	NR	*Staphylococcus aureus*	Nikolajeva *et al.* (2012)
Fissidens bryoides Hedw.	Bryophyta	NR	*Agrobacterium tumefaciens*	Deora and Bhati (2007)

Herbertus aduncus (Dicks.) Gray	Marchantiophyta	NR	*Botrytis cinerea*, *Rhizoctonia solani* and *Pythium debaryanum*	Matsuo *et al.* (1982a, 1982b)
Hypnum cupressiforme Hedw.	Bryophyta	NR	*Bacillus subtilis, Escherichisa coli, Staphylococcus aureus, Micrococcus flavus* and *Salmonella enteritidis*	Veljic *et al.* (2009)
Imbribryum sp.	Bryophyta	Phenols	*Pseudomonas aeruginosa*	Lashin *et al.* (2015); Abdel-Shafi *et al.* (2017)
Isothecium alopecuroides (Lam. ex Dubois) Isov.	Bryophyta	NR	*Bacillus subtilis, Candida albicans, Escherichia coli, Listeria monocytogenes, Salmonella enteritidis, Shigella flexneri, Staphylococcus aureus* and *Yersinia enterocolitica*	Altuner and Cetin (2018)
Isotheceum myurum Brid.	Bryophyta	NR	*Bacillus subtilis*	Yayintas *et al.* (2019)
Jungermannia exsertifolia ssp. cordifolia (Dumort.) Váòa	Marchantiophyta	14 trachylobane diterpenoids (*ent*-trachylobane-17-al)	*Mycobacterium tuberculosis*	Scher *et al.* (2010)
Lophocoleoa heterophylla (Schrad.) Dum.	Marchantiophyta	NR	*Bacillus cereus*	Nikolajeva *et al.* (2012)
Marchantia palmata Reinw., Nees & Blume	Marchantiophyta	NR	*Staphylococcus aureus*	Pant and Tiwari (1989)
Marchantia papillata Raddi subsp. grossibarba (Steph.) Bischl.	Marchantiophyta	Sesquiterpenes or diterpenes, steroids, fatty acids and alcohol derivatives.	*Staphylococcus aureus*	Negi *et al.* (2018)
Marchantia polymorpha L.	Marchantiophyta	Marchantin, bis-bibenzyls neomarchantin A, riccardin D and 13,130-O-isopropylidene riccardin D	*Acinetobacter calcoaceticus*, *Alcaligenes faecalis, Bacillus cereus, B. megaterium, B. subtilis*, *Cryptococcus neoformans*, *Enterobacter cloacae*, *E. coli*, *Proteus mirabilis, Pseudomonas aeruginosa, Salmonella typhimurium, Staphylococcus aureus* and *Candida albicans*	Niu *et al.* (2006); Guo *et al.* (2008)
Marchesinia mackaii (Hook.) S.F. Gray	Marchantiophyta	Essential oils	*Bacillus subtilis, Escherichia coli, Salmonella pullorum, Staphylococcus aureus* and *Yersinia enterocolitica*	Figueiredo *et al.* (2002).
Mnium stellar Hedw.	Bryophyta	NR	*Bacillus subtilis, Staphylococcus aureus, S. carnosus, S. typhimirium* and *S. epidermidis.*	Singh *et al.* (2011); Canli *et al.* (2015)
Orthostichella rigida (Müll. Hal.) B.H. Allen & Magill	Bryophyta	NR	*Staphylococcus aureus, Escherichia coli, Salmonellaenteritidis, Candida albicans, Listeria monocytogenes* and *Cryptococcus neoformans*	Rodrigues *et al.* (2020)
Palustriella commutata (Hedw.) Ochyra	Bryophyta	Flavonoid compounds (Gallic acid), Phenols.	*Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Candida albicans*	Yayintas *et al.* (2017)

Paraschistochila pinnatifolia (Hook.) R.M. Schust.	Marchantiophyta	Ent-1b-Hydroxykauran-12-one	*Candida albicans*	Lorimer *et al.* (1997)
Pellia endiviifolia (Dicks.) Dumort.	Marchantiophyta	Succulatal, Phenols and flavanoids.	*Streptococcus mutans*	Asakawa (2008); Waterman *et al.* (2017)
Plagiochasma appendiculatum Lehm. & Lindenb	Marchantiophyta	Phenols	*Alternaria alternata, Aspergillus flavus* and *Aspergillus niger*	Sharma *et al.* (2015)
Plagiochila beddomei Steph.	Marchantiophyta	Phenolic acids like coumaric, ferulic, gallic, caffeic, protocatechol, cinnamic, sinapate, chlorogenate and hydroxyl benzoate.	*Salmonella species, Escherichia coli, Staphylococcus aureus, Candida albicans* etc.	Manoj and Murugan (2012); Alam(2012)
Plagiochila fasciculata Lindenb.	Marchantiophyta	2-hydroxy-3,4,6-trimethoxyacetopnenone and 2-hydroxy-4,6-dimethoxyacetophenone	*Trichophyton mentagrophytes* and *Cladosporium resinae*	Lorimer and Perry (1994)
Plagiomnium sp.	Bryophyta	NR	*Staphylococcus aureus*	Chandra *et al.* (2017); Vollar *et al.* (2018)
Pogonatum microstomum(R. Br. ex Schwägr.) Brid.	Bryophyta	flavonoids, glycosides, triterpenoids, phenols and sterols.	*Agrobacterium tumefasciens, Streptomyces pneumonia, Escherichia coli, Klebsiella pneumoniaeand Pseudomonas aeruginosa* and fungi *Candia albicans* and *Trichophyton rubrum.*	Aruna and Krishnappa (2018)
Polytrichum commune Hedw.	Bryophyta	Acids and amino acids, sterols and terpenoids, polyphenols,	*Pseudomonas aeruginosa* and *Staphylococcus aureus.Bacillus cereus* and *Escherichia coli.*	Klavina *et al.* (2015); Beike *et al.* (2010); Hu(1987); Belkin *et al.* (1952)
Porella sp.	Marchantiophyta	Sesquiterpene hydrocarbons and Monoterpene hydrocarbons.	*Saccharomyces cerevisiae, Zygosaccharomyces bailii, Aerobasidium pullulans, Pichia membranaefasciens, Pichia anomala, Yarrowia lipolytica, Salmonella enteritidis, Escherichia coli* and *Listeria monocytogenes*	Bukvicki *et al.* (2012); Dey and Mukherjee (2015)
Riccardia crassa (Schwägr.) C. Massal.	Marchantiophyta	Riccardiphenol C	*Bacillus subtilis*	Perry and Foster (1995)
Schistochila glaucescens (Hook.) A. Evans	Marchantiophyta	Marchantin C, neomarchantins A and B, Glaucescenolide	*Bacillus subtilis* and *Trichophyton mentagrophytes*	Scher *et al.* (2002)

*NR= Not reported

Table 2. Some studies in which anticancerous activities of bryophytes were elucidated.

Bryophyte species	Phylum	Chemical reported	Against cell line	References
Bryum capillare Hedw.	Bryophyta	NR	MCF-12A (human breast epithelial cells), SKBR 3 (human breast cancer cells) and HeLa (human cervix cancer cells),	Onbasli and Yuvali (2020)
Conocephalum conicum (L.) Dumort.	Marchantiophyta	Eudesmanolides, germacranolides, bicyclogermacrenal, 2a, 5b-dihydroxybornane-2-cinnamate	HepG2 cells	Singh *et al.* (2011);Ding (1982); Ando(1983); Alam (2012)

Diplophyllum sp.	Marchantiophyta	Diplophyllin, eudesmanolides	HeLa cells	Hong (1980)
Marchantia convoluta C. Gao & K.C. Chang	Marchantiophyta	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.	HepG2 and H1299 cell lines	Chen and Xiao (2006)
Marchantia polymorpha L.	Marchantiophyta	Marchantin A, marchantin B, marchantin C, marchantin E	Leukemic KB cells; human carcinoma	Asakawa (1982); Miller and Miller (1979); Hu (1987); Bland (1971); Pant and Tewari (1989)
Octoblepharum albidum Hedw.	Bryophyta	Daucosterol and Friedelin	Ovary (PA1), Cervical (C-33A), and Lung (NCI-H358) cancer cell lines.	Naidu *et al.* (2020)
Plagiochila sp.	Marchantiophyta	Plagiochiline A, plagiochiline C, 13-octa-noate, 12-hydroxy13-2E, 4E-dodecadienoate, sacculatal, polygodial,2,3-secoaromadendranes, plagiochilide, plagiochilalB, Plagiochin A, Isoplagiochilide	P-388 murine leukemia tumor cells	Ramirez *et al.* (2010); Dey and Mukherjee (2015)
Polytrichum commune Hedw.	Bryophyta	Ohioensin-A	L1210 cells	Harris (2008); Sabovljevic *et al.* (2001); Hart (1981); Beike *et al.* (2010); Hu (1987); Cheng *et al.* (2013)
Polytrichastrum ohioense Renauld & Cardot	Bryophyta	Ohioensin-A	PS and MCF-7	Zheng *et al.* (1989)
Polytrichastrum pallidisetum (Funck) G.L. Sm.	Bryophyta	1-*O*-methylohioensin B, 1-*O*-methyldihydroohioensin B and 1,14-di- *O*-methyldihydroohioensin B	Human colon adenocarcinoma (HT-29), human melanoma (RPMI-7951), and human glioblastoma multiforme (U-251 MG) cells.	Hart (1981); Belkin *et al.*(1952); Zheng *et al.* (1994); Asakawa *et al.* (2013)
Ptilidium pulcherrimum (Weber) Vain.	Marchantiophyta	Ursane triterpenoids	Against PC3, MDA-MB-231 and Hela cells	Guo *et al.* (2009)
Porella sp.	Marchantiophyta	Norpinguisone, perrottetianal A, porelladiolide, 11,13-dehydroporella-diolide	Human promyelocytic leukemia (HL-60) and human pharyngeal squamous carcinoma (KB) cells.	Dey and Mukherjee (2015)
Riccardia multifida (L.) Gray	Marchantiophyta	Riccardin	KB cells	Asakawa (1982)
Wiesnerella denudate (Mitt.) Steph.	Marchantiophyta	Guaianolides	P-388 lymphocytic leukemia	Asakawa (1982)

*NR= Not reported

Table 3. Some studies in which antioxidant activities of bryophytes were elucidated.

Bryophyte species	Phylum	Chemical(s) reported	References
Atrichum undulatum (Hedw.) Pal. de B.	Bryophyta	Phenols	Chobot *et al.* (2008)
Brachythecium rutabulum (Hedw.) Schimp.	Bryophyta	Phenols	Pejin and Bogdanovic-Pristov (2012c)
Calliergonella cuspidata (Hedw.) Loeske	Bryophyta	Phenols	Pejin and Bogdanovic-Pristov (2012c)
Ceratodon purpureus (Hedw.) Brid.	Bryophyta	Biflavonoids and phenols	Waterman *et al.* (2017)
Cinclidotus fontinaloides (Hedw.) P.Beauv.	Bryophyta	Flavonoid compounds such as gallic acid	Yayintas *et al.* (2017)
Ctenidium molluscum (Hedw.) Mitt.	Bryophyta	Polyphenols and flavonoids	Erturk *et al.* (2015)
Eurhynchium striatulum (Spruce) Schimp.	Bryophyta	Polyphenols and flavonoids	Erturk *et al.* (2015)
Hypnum plumiforme Wilson	Bryophyta	NR	Sun *et al.* (2009)
Hypnum cupressiforme Hedw.	Bryophyta	NR	Yayintas *et al.* (2019)
Jungermannia sp.	Marchantiophyta	Subulatin	Tazaki *et al.* (2002)

Marchantia polymorpha L.	Marchantiophyta	Peroxidase phenols, flavonoids, saponins, tannins, and glycosides	Hirata *et al.* (2002); Krishan and Murugan (2013)
Mastigophora diclados (Brid.) Nees	Marchantiophyta	(-)-diplophyllolide, (-)-a-herbertenol (100), (-)-herbertene-1,2-diol (101a), (-)-mastigophorene C (102), (-)-mastigophorene D (103), (-)-diplophyllin (104) and mastigophorene A (207).	Komala *et al.* (2010)
Neckera complanata (Hedw.) Huebener	Bryophyta	NR	Yanyintas *et al.* (2019)
Plagiochasma appendiculatum Lehm. et Lindenb.	Marchantiophyta	NR	Singh *et al.* (2006)
Plagiochila beddomei Steph.	Marchantiophyta	Flavonoids and phenols	Manoj and Murugan (2012)
Palustriella commutata (Hedw.) Ochyra	Bryophyta	Flavonoid compounds as gallic acid.	Yayintas *et al.* (2017)
Polytrichastrum alpinum (Hedw.) G.L. Sm.	Bryophyta	NR	Bhattarai *et al.* (2009)
Sphagnum magellanicum Brid.	Bryophyta	Phenolic compounds such as caffeic, gallic, vanillic, chlorogenic, p-coumaric, 3-4 hydrozybenzoic, and salicylic acid.	Montenegro (2009)
Sanionia uncinata (Hedw.) Loeske	Bryophyta	NR	Bhattarai *et al.* (2008)

*NR= Not reported

Table 4. Some studies in which insecticidal activities of bryophytes were elucidated.

Bryophyte species	Phylum	Chemical(s) reported	Effective against Insect(s)	References
Aneura pinguis (L.) Dum	Marchantiophyta	Pinguison	*Spotoptera littoralis*	Wada and Munakata (1971); Benešova *et al.* (1969)
Conocephalum conicum (L.) Dumort.	Marchantiophyta	Myristic acid, Palmitic and lauric acids	*Sitophilus granaries*	Abay *et al.* (2013)
Dicranum scoparium Hedw.	Bryophyta	Myristic acid, Palmitic and lauric acids	*Sitophilus granaries*	Abay *et al.* (2013)
Lepidolaena hodgsoniae Grolle	Marchantiophyta	Hodgosonox	larvae of the blowfly *Lucilia cuprina*	Ainge *et al.* (2001)
Lepidolaena clavigera Dumort.	Marchantiophyta	Clavigerins B and C	*Anthrenocerus australis* and *Tineola bisselliella*	Perry *et al.* (2003)
Plagiochila bursata Lindenb.	Marchantiophyta	b-barbatene , ergosterol, globulol, phytol, sitosterol, squalene, spathulenol and stigmasterol.2,3-secoaromadendrane 1 and plagiochilines A and M.	*Spodoptera frugiperda*	Sporle (1990); Ramirez *et al.* (2010)
Polytrichastrum formosum (Hedw.) G.L. Sm.	Bryophyta	Myristic acid, palmitic acid and lauric acids	*Sitophilus granaries*	Abay *et al.* (2013)
Riccardia polyclada (Mitt.) Hässel	Marchantiophyta	Two chlorinated bibenzyls, 2,6,30-trichloro-3- hydroxy-40-methoxybibenzyl and 2,4,6,30-tetrachloro-3,40-dihydroxybibenzyl.	*Spodoptera littoralis*	Labbé *et al.* (2007)

*NR= Not reported

human malignant melanoma cells A375 with lower toxicity towards normal skin cells *i.e.,* immortalized human keratinocytes HaCa T-cells with IC_{50} values ranging from 7.45 to 11.97ìg/mL (Gawe³-Bêben *et al.*, 2019). The study suggested marchantin A as a chemotherapeutic agent against the human skin cancer melanomas without adverse effects on skin

pigmentation (Gawe³-Bêben *et al*., 2019). The other cyclic bisbibenzyls compounds of bryophytes, viz., marchantin M, plagiochin E, pakyonol and riccardin C have been shown to inhibit cell proliferation and induce apoptosis in prostate cancer cells (PC3)with IC_{50} values 5.45 ìmol/L, 5.99 ìmol/L, 7.98 ìmol/L and 3.22 ìmol/L respectively (Xu *et al*., 2010). The cytotoxic effects of these compounds on the PC3 cells were associated with induction of apoptosis with activation of caspase 3 and cleavage of poly(ADP-ribose) polymerase (PARP) proteins leading to increase in pro-apoptotic BAX protein expression and inhibition of anti-apoptotic BCL2 protein (Xu *et al*., 2010). Another type of marchantin M was shown to induce apoptosis in prostate cancer cells PC3 and DU145 by increasing the levels of CHOP and GRP78 (HSPA5) suggesting its role in inducing unfolded proteins endoplasmic reticulum stress response pathway (Zhang *et al*., 2015). In addition, the administration of riccardin D (a macrocyclic bisbibenzyl) inhibited the topoisomerase II activity in leukemia cell lines like $K_{5}6_{2}$ and $K_{5}6_{2}/A_{02}$ cells, leaving the DNA in supercoiled state and thus inhibiting their proliferation (Xue *et al*., 2012). The Chinese liverwort *Heteroscyphus tener* Schiûn have been known to contain different bioactive compounds, and newly identified ent-labdane diterpenoids commonly called as heteroscyphins have been reported to have antiproliferative effects on cancer cells (Lin *et al*., 2014). These heteroscyphins inhibit cell proliferations in prostate cancer cells PC3 and DU145 and arrest the cell cycle at the G0/G1 phase, inducing apoptosis of the cancer cells which were associated with increase in the levels of cleaved apoptotic proteins caspase-3 and PARP (Lin *et al*., 2014).

Although numerous studies have successfully isolated various active chemical constituents from these plants, the mechanisms of anticancer activity of all these compounds are yet to be revealed. All possibly known phytomolecules responsible for anticancerous properties of bryophytes are listed in Table 2.

Antioxidant activities

Antioxidants are compounds that inhibit or retard the oxidation of chemicals caused by free radicals (Gulcin, 2020). Free radicals are unstable molecules produced by an organism as a result of environmental and other pressures (Gahtori and Chaturvedi, 2019). These free radicals are also called reactive oxygen species (ROS) which induces oxidative stress. ROS-generated oxidative stress deregulates a series of cellular functions leading to serious diseases like asthma, arthritis, AIDS, autoimmune diseases, Alzheimer's, cardiovascular dysfunction, cancer, diabetes, neurodegenerative diseases etc. (Uttara *et al*., 2009; Liu *et al*., 2018). Thus, a balance between ROS and antioxidants is essential to neutralize these harmful free radicals (Gahtori and Chaturvedi, 2019).

The antioxidants are broadly classified into three following groups:

1. Antioxidant enzymes such as, catalase, glutathione reductase, peroxidase and superoxide dismutase (Sindhi *et al*., 2013).
2. Antioxidant molecules such as glutathione, vitamin C, vitamin E (tocopherols), albumin, lipoic acid, carotenoids (vitamin A), flavonoids and phenolics (Sindhi *et al*., 2013).
3. Complex group of enzymes like lipases, transferases, methionine sulfoxide reductase, proteases and DNA repair enzymes etc., which are used for repair of damaged proteins and DNA, oxidized peroxides and lipids (Irshad and Chaudhuri, 2002; Sindhi *et al*., 2013; Gahtori and Chaturvedi, 2019).

Since bryophytes are reservoirs of many compounds including phenolics, flavonoids, alkaloids and terpenoids which can scavenge ROS, they serve as a source of antioxidant molecules (Mohandas and Kumaraswamy, 2018). Antioxidant activities have been reported in many bryophyte species, such as *Hypnum cupressiforme* Hedw., *Homalothecium sericeum* (Hedw.) Schimp., *Thuidium delicatulum* (Hedw.) Schimp., *Homalothecium lutescens* (Hedw.) H. Rob., *Leucodon sciuroides* (Hedw.) Schwagr., *Ctenidium molluscum* (Hedw.) Mitt., *Eurhynchium striatulum* (Spruce) Schimp. and *Ceratodon purpureus* (Hedw.) Brid. (Table 3) (Erturk *et al*., 2015; Waterman *et al*., 2017). However, the efficacy of scavenging ROS is dependent on bryophyte species as well as the extraction medium. For example, the ethyl acetate fraction of *Marchantia polymorpha* L. showed higher antioxidant activity than *n*-hexane and chloroform in DPPH (1,1-diphenyl-2-picrylhydrazyl) free radical scavenging with lowest IC_{50} value

of 439.31 ìg ml^{-1} (Tran *et al*., 2020). Some recent reports on antioxidant activity were also reported for species like *Leucobryum aduncum* Dozy & Molk. and *Campylopus schmidii* (Müll. Hal.) A. Jarger (Makajanma *et al.,* 2020).

Bryophytes act as antioxidants by slowing down the degenerative process mainly by (a) inhibiting lipid peroxidation (b) increasing superoxide anion scavenging activity (Sokurenko *et al*., 2018), (c) detoxification of oxygen generated by photo-oxidation (Tazaki *et al*., 2002) and (d) converting DPPH into DPPH-H by losing a H-atom which inhibited chromogen cation production of 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) (Chandra *et al*., 2019).

Insecticidal activities

Insects are known as carriers and transmitters of a number of bacterial and viral diseases (Sarwar, 2015). The disease symptoms like fever, headache, skin rashes, stomach pain, chills, nausea, swelling of body parts, dizziness, vomiting etc. can be developed upon an insect's bite (Morsy, 2012; Mansour *and* Abu-Naser, 2019). Some of the insect-borne diseases include malaria, Lyme disease, yellow fever, West Nile and encephalitis (Gao *et al*., 2020). Apart from having pathological effects on human health, insects are also known to cause serious destruction to numerous plants and animals. Insects adversely affect plants by boring and parasitizing (eating) them and thus, causing severe damage and loss to vegetable and crop plants (Nicoletti, 2020). To control this problem, various insecticides or pesticides are used, which in turn, exerts harmful effects on other organisms and the environment. Hence, insects and pest management require an alternative and safe approach.

Plant-derived curatives are efficient when employed as insecticides with less or no harmful effects to humans and the environment (Isman, 2020). One such activity of bryophytes involves showing toxicity towards insects (Atwood and Buck, 2020). Table 4 lists the compounds derived from plants that have insecticidal activity. In fact, one of the earliest reports on insecticidal properties of bryophytes was reported by Benesova and his team in 1969. Thenceforth, the use of bryophytes as natural remedies to insects has gained much importance over the years. Ande *et al*. (2010) reported that application of four mosses, namely *Calymperes afzelii* Sw., *Thuidium gratum* (P. Beauv.) Jaeg., *Bryum coronatum* Schwaegr., and *Barbula lambarenensis* (Hook) Spreng., increased the mortality rate of maize stem borer (an insect that damages young maize by lodging, tunnelling and girdling inside the stem internodes, thereby resulting in stem breakage). Also, the use of chemical constituents ((13S) 13 hydroxylabda 8, 14 diene, fusicogigantone B, 3 α, 14-diacetoxy-2-hydroxybicycl-ogermacrene) isolated from *Plagiochila diversifolia* Lindenb. reduced larval growth of *Spodoptera frugiperda*, thereby increasing its mortality rate. The study also revealed that the incorporation of these compounds resulted in abdomen and wing malfunction which eventually led to mating impossibilities in adults of *Spodoptera frugiperda* (Ramirez *et al*., 2017). However, there is no concrete report on insecticidal activity of bryophytes against insects that act as vectors and transmit various diseases to humans, thereby calling for the attention of the researchers in this topic.

Treatment of Cardiovascular diseases

Cardiovascular diseases are one of the most life threatening diseases (Curry *et al*., 2018). Bryophyte species such as *Rhodobryum giganteum* (Schwägr.) Paris, *Rhodobryum roseum* (Hedw.) Limpr., *Rhodobryum ontariense* (Kindb.) Paris, *Marchantia polymorpha* L. and *Cratoneuron filicinum* (Hedw.) Spruce have shown potential in treating cardiovascular diseases (Harris and Yang, 2009; Pejin *et al*., 2012; Chandra *et al*., 2017; Ozturk *et al*., 2018). *Rhodobryum* species are the most commonly reported bryophytes for cardiovascular treatment and have been used in treating cardiovascular diseases as early as 1977 (Wu, 1977). In fact, ether extract of *Rhodobryum giganteum* has been reported to increase the rate of oxygen flow in the aorta of white mice by more than 30% (Wu in 1982). This can be attributed to the presence of amino acids, lactones and volatile oils. In fact, in *Rhodobryum ontariense,* linolenic acid has been found to increase oxygen flow in the blood (Pejin *et al*., 2012a). Linolenic

acid is an essential fatty acid belonging to the omega-fatty acid group, which has been shown to decrease the risk of cardiovascular disease (Pejin *et al*., 2012a). Pejin *et al*. (2012b) recommended *Rhodobryum ontariense* tea for persons suffering from cardiovascular diseases as it reduces hypertension by maintaining membrane fluidity of erythrocytes and nitric oxide (NO) balance. Decreasing erythrocyte membrane fluidity and impairment of NO are triggers for hypertension. However, there is no concrete report on its mechanisms of action yet. Therefore, further studies will be required for the better understanding of the subject.

Antidiabetic activities

Diabetes mellitus is one of the biggest health problems of the 21st century (Fan, 2017). It is caused due to the increased activity of alpha-amylase and alpha-glucosidase enzymes (Mukhia *et al*., 2015). These enzymes hydrolyse starch to produce simple sugars (glucose and maltose), which in turn, increase the blood glucose level. Therefore, the inhibition of these enzyme activities can reduce glucose absorption and post-prandial (excessive sugar production by liver after meal) sugar levels in the blood, thus, controlling diabetes.

Bryophytes, among other plants, have been known to have anti-diabetic activities (Mukhia *et al*., 2015, 2019). Mukhia *et al*. (2015) reported that the liverworts viz. *Ptychanthus striatus* (Lehm. & Lindenb.) Nees (Lejeuneaceae), *Pellia epiphylla* (L.) Corda (Pelliaceae) and *Bazzania oshimensis* (Steph.) Horik. (Lepidoziaceae) showed anti-diabetic properties by inhibiting the action of carbohydrate hydrolyzing enzymes, alpha-amylase and alpha-glucosidase (in goat liver). Amongst these, *B. oshimensis* showed the highest anti-diabetic activity due to the presence of high levels of flavonoids. Flavonoid compounds can increase phosphorylation of IRS (Insulin Receptor Substrate) and decrease autoxidation of glucose and gluconeogenesis which improve glucose homeostasis and lower insulin resistance, thus, controlling diabetes (Vinayagam and Xu, 2015). Other species that have shown anti-diabetic activity include *Plagiochasma cordatum* Lehm. & Lindenb., *Marchantia subintegra* Mitt. and *M. emarginata* Reinw., Blume & Nees (Mukhia *et al*., 2017). In addition to flavonoids, bryophyte extracts contain alkaloids and terpenes (Mukhia *et al*., 2019). It is speculated that these compounds inhibit the activity of alpha-amylase and alpha-glucosidase enzymes, thereby, reducing post-prandial hyperglycemia and subsequently treating diabetes (Kirisanth *et al*., 2020). Since bryophytes are rich in flavonoids, terpenes and alkaloids, which have anti-diabetic properties, it is necessary that future research be directed towards identification of more of such compounds as well as exploration of the anti-diabetic potential in many more species, including hornworts.

Immunomodulatory activities

Immunomodulation is modulation or regulation of the immune system to gain desirable impacts on disease prevention (Martinez *et al*., 2014). It can be either natural (homeostasis) or in human-induced defence mechanism form (immunotherapy).

In recent times, plant-derived immunomodulators (substances that affect functioning of the immune system) have been employed to improve the body's immune system to fight against various infections and diseases. Bryophytes have shown potential to act as immunomodulators. Bryophytes like *Fissidens, Barbula, Mnium, Thuiduim, Marchantia, Plagiochasma, Asterella, Pellia,* and *Dumortiera* species have been reported as major constituents of shilajit, which is a blackish brown exudate, found in mountain ranges and is popularly used for treating various ailments including immunodeficiency (Agarwal *et al*., 2007). Crude extracts of the liverwort *Porella cordaeana* (Hub.) Moore (Porellaceae) and moss *Hypnum cupressiforme* Hedw. showed immunomodulation responses such as antioxidants, anti-diabetic, anti-neuroinflammatory and antitumor activities (Radulovic *et al*., 2016 and Lunic *et al*., 2020). The extracts of *H. cupressiforme* were found to be rich in phenolic, flavonoid and terpenoid compounds. These compounds showed antineurodegenerative properties by inhibiting the activity of enzymes acetylcholinesterase and tyrosinase. They also showed radical scavenging activity (antioxidative properties). In

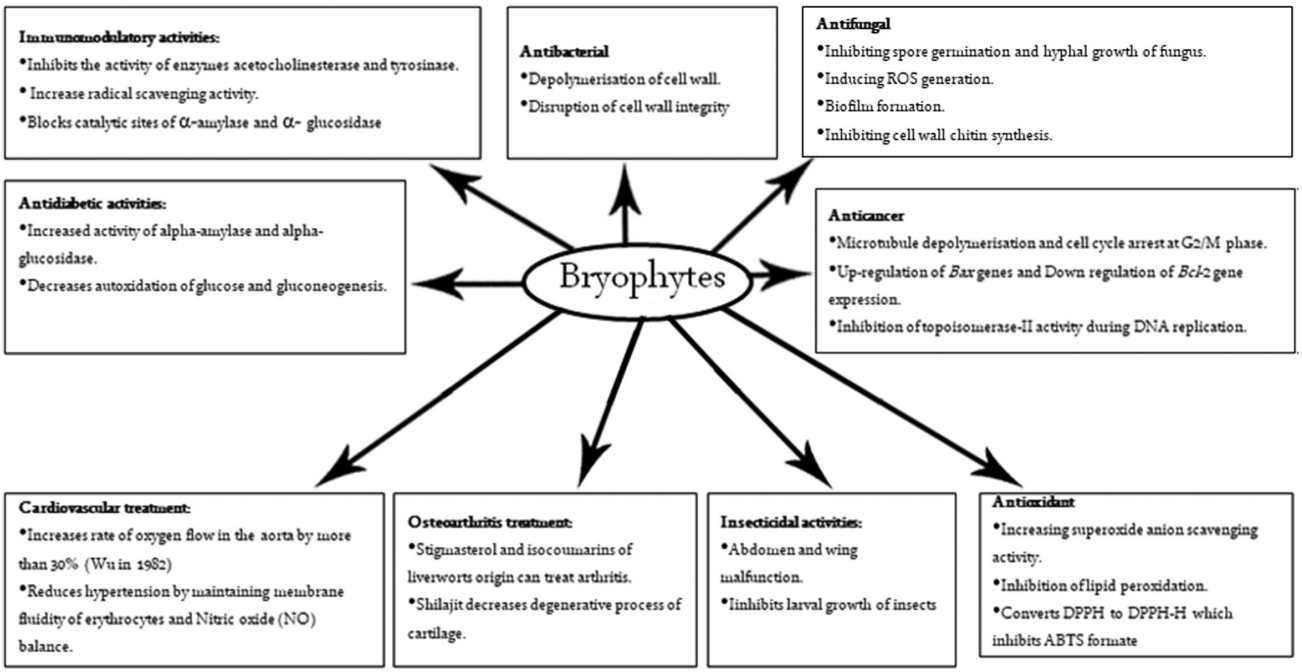

Fig. 1. Proposed mechanism of action of various bioactive compounds present in bryophytes against bacteria, fungi, cancer, insects, oxidative stress, diabetes, cardiovascular diseases, osteoarthritis and immunomodulatory activity.

addition, these compounds also showed an inhibitory effect on the activity of enzymes, á-amylase and á-glucosidase, thus showing antidiabetic properties (Lunic *et al*., 2020). The monomeric polyphenols have been reported to block the catalytic sites of these enzymes, while polymeric polyphenols form a non-digestible complex with the enzymes (Kan *et al*., 2020). Since phenols and flavonoids can successfully induce immunomodulation, the immunomodulatory response of bryophytes may be attributed to the presence of such bioactive compounds. However, only a few bryophytes have been studied for immunomodulatory response. Therefore, the compounds responsible and the mechanism of action must be unravelled to understand the role of bryophytes as immunomodulators.

Osteoarthritis treatment

Osteoarthritis is a form of arthritis in which the cartilaginous tissues protecting the ends of two bones (joint) wear off over the time causing pain, irritation and stiffness (Glyn-Jones *et al*., 2015). Osteoarthritis mainly affects hips, spine, hands and knee joints (Kloppenburg and Berenbaum, 2020). About more than 303 million people suffer from this condition all around the world (Kloppenburg and Berenbaum, 2020).

Osteoarthritis is a chronic joint problem which requires conventional treatments that have potential side effects. In this regard, bryophytes can be an alternative (Maksimovic and Samardzic, 2018). They possess anti-osteoarthritis compounds, such as stigmasterol and isocoumarins (Gabay *et al*. 2010). Among three phyla of bryophytes, liverworts specifically possess isocoumarins, compounds which have been used for treating arthritis (Hussain and Green, 2017). Bryophytes also form a major component of shilajit, which is known to decrease the degenerative process of cartilage, resulting in prevention of knee osteoarthritis (Azizi *et al*., 2018). *Marchantia, Barbula, Fissidens, Asterella, Pellia, Mnium* and *Plagiochasma* are major genera that constitute shilajit (Agarwal *et al*., 2007). However, the study on efficacy of bryophytes for osteoarthritis treatment is still meagre. Therefore, the future study is necessary for discovery of new compounds which can be used for osteoarthritis treatment.

Future perspectives

Bryophytes contain a vast array of secondary metabolites responsible for a wide range of biological activities and are regarded as a significant group of medicinal plants. However, there are gaps in knowledge in this field, such as

(i) Bryophytes as antimicrobial plants are well studied by numerous researchers. A number of phytomolecules have been isolated which are responsible for imparting antimicrobial activity. However, there are a very few studies that have adequately explained the significant mode of actions of these compounds. Thus, studies should be directed towards unravelling of the mechanism of actions of these compounds.

(ii) Approximately 28,000 species of bryophytes have been reported. However, only about 1000 species are reported for their medicinal properties, of which majority are liverworts and mosses, only a few hornwort species have been reported for the same. Therefore, more hornwort species should be included and considered for the therapeutic studies in future.

(iii) The insecticidal activities of bryophytes have been focused mainly on those insects which parasitize plants. Therefore, future studies must include those insects/pests that act as vectors, which cause serious bacterial and viral diseases to human.

(iv) Only a few bryophyte species are being studied for cardiovascular, immunomodulatory, anti-diabetic and osteoarthritic activities. As these are some of the serious health issues that result in loss of so many lives, it is very important that in-depth studies and clinical trials need to be conducted to determine mechanism of action, dosage, mode of delivery as well as side effects on humans so as to exploit the bryophytes to their full potential. In addition, including more species for such analysis can immensely contribute to this treasure house.

(v) Chemically synthesized 14-hydroxylunularin is reported to show antiprotozoal activity against *Leishmania* species (Roldos *et al*., 2008). This suggests that 14-hydroxylunularin can be chosen for leishmanicidal therapy. Liverworts are a rich source of 14-hydroxylunularin and lunularin. Thus, research may be directed to optimise mass propagation techniques of liverworts for optimum extraction of these compounds.

(vi) Moss offers a great potential in molecular farming for production of vaccines. Equipped with a high rate of homologous recombination in mitotic cells, the gametophytes are suited for custom-designed and targeted modifications. In addition, they can be grown under full containment and moss biomass has no toxic effects. For example, *Physcomitrella patens* was successfully used to produce a multi-epitope HIV chimeric protein. Thus, future research should incorporate genetic engineering approaches to optimize molecular farming using mosses for a safe drug.

Conclusion

Bryophytes are known to possess an assortment of bioactive compounds which aid in curing numerous diseases. They have many therapeutical activities starting from as basic as antimicrobial to as advanced as anti-cancerous activity. Owing to these medicinal properties, bryophytes have extensively been used as medicinal plants in India, China and some parts Northern America for many decades. In recent times, pharmaceutical knowledge of bryophytes is being explored for a large spectrum of treatments such as burn treatment, wound healing, common cold, anti-inflammatory, nervous prostration, cardiovascular diseases, anti-leukemia, anti-insectifeedant and for treatment of various cancer cell lines. They are also known to have antioxidant activities against the degenerative process of the human body caused by free radicals.

In this review, we have discussed the role of bryophytes as antimicrobial (antibacterial and antifungal activities), anti-cancerous, antioxidants, insecticidal, cardiovascular, antidiabetic, immunomodulatory and osteoarthritic activities of many species of bryophytes. Despite having a great therapeutic potential, the clinical research on bryophytes is comparatively meagre as compared to that of other plant groups. Therefore, it is very important that more pharmacological studies be conducted on this subject in the future, to determine new bio-molecules and elucidate their chemical nature, which will help in developing potential drugs against various diseases.

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