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POTENTIAL OF BRYOPHYTES AS THERAPEUTICS

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ABSTRACT: Bryophytes, a small group of lower plant phylogenetically placed between algae and the vascular plants comprise of hornworts, liverworts, and mosses. They are the second largest group of land plants and extremely rich in a variety of biologically active compounds *viz.* terpenoids, phenols, glycosides, and fatty acids. This small slow-growing group of plants is stockroom of naturally occurring materials and have been investigated for the antimicrobial, antioxidant, anti-inflammatory, anti-venomous, and anti-leukemic activity. In recent years, bryophytes have emerged as a potential biopharming tool for the production of complex biopharmaceuticals. Even though bryophytes could be used in medicine, the use of bryophytes for applied research with implications for human health is still not fully explored. Investigations are hindered commonly because of minute size and difficulties in identifying diverse species of bryophytes. In the present review, we focused on therapeutic uses of bryophytes in detail that will widely open the door for the use of different bryophytes in plant biotechnology and to meet the demand of novel drug discovery.

INTRODUCTION: Bryophytes are the second largest group of higher plants (comprising hornworts, liverworts, and mosses) after lower plants, with estimated about 20,000 to 25,000 species worldwide [1, 2, 3]. They are the most exotic and captivating species on earth with a unique combination of distinguishing characteristics. They belong to the group of oldest known land plant devoid of true leaves, stem or true vascular system but like all land plants (embryophytes), they show 'alternation of generations.' They are confined to damp shaded areas with high humidity and frequent rainfall.

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Most of the bryophytes are either liverworts or mosses. Liverworts grow horizontally and are flattened or 'leafy,' whereas mosses have an upright stalk with spirally arranged leaf-like structures. The pleurocarpous (carpet-forming) moss constitutes the major groups of mosses. They are characterized by extensive branching and lateral sporophyte placement compared to the terminal sporophytes in acrocarpous (erect) mosses.

Bryophytes are considered as a 'remarkable reservoir' of novel natural products or secondary metabolites, which have shown interesting biological activity and could be used in medicine. Bryophytes especially moss and liverworts are the sources of many biologically active novel compounds about pharmaceutical uses [4-7]. The occurrence of antibiotic substances in bryophytes has been well documented by botanists and microbiologists [8]. They possess compounds such as alkaloids (clavatoxine, clavatine, nicotine, lycopo-

dine) polyphenolic acids (dihydrocaffeic) and flavonoids (apigenin, triterpenes, *etc*.) But only a few of the species have yet been thoroughly studied. Recently, public demand for plant-based medicine and the rise of antibiotic-resistant bacteria have motivated biologists to look for new plant-based natural products. Therefore, bryophytes can be a promising source of many new biologically active compounds in nature. Apart from the medicinal properties, bryophytes are important component of ecosystem diversity and add up to the species richness [9, 10, 11] and also increases the plant biomass in forests in some cases [12, 13]. Further, bryophytes are important environmental indicators and have been used as predictors of past climate change to validate climate models and potential indicators of global warming [14]. They play a chief role in ecosystem functions, such as soil development [15], nutrient biogeochemical cycling, [16, 17] water retention, [17] plant colonization seed germination, seedling growth, and forest renovation [12, 15, 17].

Although bryophytes are important source of various plant derivatives, only a few studies have been conducted to get an in-depth knowledge regarding the role of various metabolites present across various species of bryophytes. The antibiosis of bryophytes has been studied in few cases. Some of the species of bryophytes like *Marcantia polymorphya*, *Polytrichum* sp. are used against pulmonary tuberculosis and to treat gingivitis. Literature is available showing the presence of antidotal, antipyretic antihypersensitive, and antihypoxic [18] activities of bryophytes. Nevertheless, the reason for the less investigation on bryophytes includes difficulties in identification, fewer specialists, literature on bryophyte, and the high-costs for searching and identifying bryophytes. The present study likewise focused on the therapeutic uses of bryophytes and the various photochemical obtained from the bryophytes.

Range of Active Metabolites of Bryophytes as Pharmaceuticals: Bryophytes are known to produce diverse secondary metabolites to combat several biotic and abiotic stress such as predation, UV-radiation, extreme temperature and microbial decomposition [19]. They are the source of a large variety of secondary metabolites [20, 21]and thus provide a great potential for biotechnological and biopharmaceutical applications. In the past few years, more than 400 novel chemical compounds were isolated from bryophyte, and they were structurally elucidated [18]. Some of the biologically active compounds isolated from mosses include bioflavonoids, terpenes and terpenoids (like di- and triterpenoids) and flavonoids whereas liverworts reported containing a large variety of lipophilic mono-, di- and sesquiterpenoids as well as aromatic compounds like bibenzyls, benzoates, cinnamates, and naphthalenes [18]. Even though many plant secondary metabolites are the potential therapeutic introduction of novel drugs in the market has decreased in the past few years. Higher plants and bryophytes have a similar evolutionary history, but search for novel therapeutic compounds within biodiversity of bryophyte remained neglected due to the small size and lack of awareness among people. These small plants remained unexploited so far in the drug discovery process in spite of few reports from the past depicts some of their ethnomedicinal uses. Studies on secondary metabolites of bryophytes have revealed the presence of a few original compounds, some of which are not synthesized by higher plants.

Antimicrobial Aspects of Bryophytes: Bryophytes have been reported as antibiotics [22, 23, 24, 25]. Various organic solvent extracts of bryophytes have been investigated in the past. The literature emphasizes that the alcoholic and the aqueous extracts or the various compound isolated from around 150 different species of bryophytes (hepatic and mosses) have shown antimicrobial effects against various group of fungi, as well as Gram-negative and Gram-positive bacteria. Recently extracts of few of the selected species of bryophytes (seven mosses and three liverworts) viz the *Radula flacida, Cyatodium africanum, Frullania spongiosa, Thuidium gratum, Ectropothecium aeruginosum, Sematophyllum caespitosum, Stereophyllum radiculosum, Babulalam berenensis, Campilopusa spericuspis*, and *Calympereserosumlam berenensis, Campilopusa spericuspis* and *Calympereserosum* have shown interesting antimicrobial activity [26]. Therefore, the potential antimicrobial properties of bryophyte can be harnessed for the therapeutic purpose against the respective pathogen. The antibacterial and antifungal activities of bryophytes have been discussed below.

Antibacterial Aspects of Bryophytes: In recent year, extensive studies have been conducted for the search of antibacterial properties in different species of plant. Organic extracts of various medicinal plants containing flavonoids have been reported to show antimicrobial activity [27- 33]. The antibacterial activities of isoflavonoids and flavonoids, and glycosides of luteolin and apigenin have also been reported [34]. But most of the investigations were centered on angiosperms. Few data are presently available about these smaller groups of plants, bryophytes [35-38]. However, few of the recent study on bryophytes has shown some of the antibacterial activity against gram-positive and gram-negative bacteria [39, 40, 41].

Also, various phenolic compounds isolated from *Atrichum*, *Dicranum*, *Mnium*, *Polytrichum*, and *Sphagnum* spp. are known to show antimicrobial properties. Apart from this the antimicrobial activity for three moss species *Eurhynchium angustirete*, *Rhytidia delphussquarrosus*, and *Rhodo bryumroseum*, and two liverwort species *Frullaniadilatata* and *Lophocolea heterophylla* has been reported for the first time [42]. Frahm has also shown that aqueous extract of few bryophytes has some inhibitory effect on the growth of *Escherichia coli* as tested on plates [43]. However, this antibacterial activity seems to be specific for certain bryophyte species, as the extracts of *Marchantia polymorpha*, *Porella platyphylla*, and the moss *Dicranum scoparium* showed antimicrobial effects on the gram-positive bacteria namely *Bacillus subtilis*, *Staphylococcus aureus*, and *Sarcinalutea*, but no activity against gram-negative *E. coli* [44, 45].

Antifungal Property of Bryophytes: Many of the bryophyte species are also known to show antifungal property [45, 46]. Different crops growing in greenhouses, like tomatoes, wheat, and green pepper were infected with the pathogens *Phytophorainfestans*, *Erysiphegraminis*, and *Botrytis cinerea* and later treated with alcoholic extracts from different bryophytes. All bryophyte extracts showed a species-specific antifungal activity against the plant pathogenic fungi depending on the concentration[5]. Furthermore, extracts from *Neckeracrispa* and *Porellaobtusata* showed antifeeding effects against the Portuguese slug *Aarionlusitanicus* [47]. Given the above features that bryophyte extracts showed fungicidal and antifeedant effects, a commercial product was developed and is sold as natural pesticide [5]. Apart from these studies conducted in the past have revealed few of the compounds isolated from bryophytes extracts have shown the reversal of conventional antibiotic resistance development in pathogenic fungi [48]. Therefore, the problem of drug resistance development in pathogenic fungi can be solved easily. A list of some bryophytes showing antifungal activity against human pathogenic fungi is given below in **Table 1.**

Also, in addition to this studies conducted on one of the model species of moss *Physcomitrellapatens* revealed that this moss under axenic condition produces a tetracyclic diterpene, namely 16α–hydroxykaurane (16α-hydroxy-ent-kaurane, Kaurenol, $C_{20}H_{34}O$) [61]. Although, the utility of 16α–hydroxykaurane is not yet revealed, it is presumed to be bioactive. This, the compound is known to be produced by lichen species and fungi [62]and it is commonly known from *Gibberella fujikuroi*, a plant pathogenic fungus that infects rice plants and causes foolish rice seedling disease. As recently shown, 16α–hydroxykaurane is involved in spore germination in *Physcomitrella patens* and leads to complete inhibition of spore germination when applied in high concentrations (2-3 µM) [63]. Also, few bryophyte extracts are effective on human pathogenic fungi although the bioactive compounds may cause allergenic effects and dermatitis in few cases [64]. Nevertheless, due to the risk of allergic reactions, bryophyte extracts were not recommended for scientific medicinal use so far.

Bryophytes as a Source of Active Metabolites having Pharmacological Activity: Since bryophytes are the reservoir of complex secondary metabolites, their vast application in traditional medicine is not astonishing. A large number of bryophytes are used as medicines in homeopathy. About 3.2% of mosses and 8.8% of liverworts taxa have been chemically investigated. Species like *Sphagnum*, *Marchantia*, *Riccia*, *Barbula*, *Bryum*, *Octeblepharum* and *Fontinalis* are used to treat different diseases, including cardiovascular diseases, inflammation, fever, lung diseases, infections, wounds, and skin diseases [65]. In China, more than 30 species can be bought at the local

pharmacist [66], and around 40 different kinds of bryophytes have been used to treat diseases of the cardiovascular system, tonsillitis, tympanitis cystitis, and bronchitis and to cure skin disease and burns. Many of the species, for example, *Polytrichum commune* which is used as antipyretic and anti-inflammatory agent [67] or boiled as a tea for treating the cold [68]. *Rhodobryum giganteum* is another species traditionally used to treat, other diseases like cardiovascular diseases or angina [64]. According to some of the recent report, bryophytes are the source of numerous chemical compounds of biotechnological and biopharmaceutical interest. Several secondary metabolites have been isolated so far from different species, but the mechanisms behind their activity are still widely unexplored. Given table shows the list of some medicinal bryophytes along with their active components.

TABLE 1: BRYOPHYTES SHOWING ANTIFUNGAL ACTIVITY AGAINST SOME HUMAN PATHOGENIC FUNGI

S. no.	Bryophyte	Family	Isolated compound/ extracts	Investigated against	Ref.
1	*Asterellaagusta*	Aytoniaceae	Asterelin A, asterelin B, 11-O- demethylmarcantin I and dihydroptychantolAdibenzo furan [bis(bibenzyl)]	*Candida albicans*	49
2	*Atrichumundulatum*	Polytrichaceae	Dimethyl sulfoxide (DMSO) extract	*Asperigulus versicolor, A. fumigates*	50
3	*Bryum argentums*	Bryaceae	Ethanolic extract	*Penicillin ochrochloron, Aspergillus niger, C. albicans, Trichophytonmenta gryophytes*	51
4	*Dumortiera hirsute*	Marchantiacea	Riccardin D [Macrocyclicbis(bibenzyl)]	*C. albicans*	52
5	*Fontinalisantipyretica*	Fontinalaceae	Various organic solvents extract	*Aspergillus parasiticus, A. fumigates*	24
6	*Frullaniamuscicola*	Jubulaceae	3- Hydroxy – 4'-methoxylbibenzyl 7,4 – dimethyl- apigenin	*C. albicans, T. rubyum, Microsporum lonasum, M. gypseum,*	53
7	*Marchantiapolymorphya*	Marchantiacea	Plagiochin E, Riccardin H, Marchantin E, Neomarchantin, A. Marchantin A and B	*C. albicans*	54
8	*M. polymorphya*	Marchantiacea	Plagiochin E	*C. albicans*	55
9	*M. polymorphya*	Marchantiacea	Plagiochin E	*C. albicans*	56, 57, 58
10	*M. polymorphya* spp. *Ruderalis*	Marchantiacea	DMSO extract	*A. versicolor , A. fumigatus*	50
11	*Pallavicinia lyellii*	Pallaviciniaceae	Water, alcohol and hexane extracts, steroids	*Fusarium oxysporum, C. albicans*	59
12	*P. leyelli*	Pallaviciniaceae	n-hexane fraction of alcohol extract	*A. fuigatus*	60

TABLE 2: MEDICINAL BRYOPHYTES ALONG WITH THEIR ACTIVE COMPONENTS/ EXTRACTS

S. no.	Medicinal bryophyte species	Medicinal Uses	Active components	Reference
	MOSSES			
1	Bartramiaceae *Philonotis*sp.	Heal burns for adenopharyngitis, antipyretic and antidotal	Triterpenoid saponins	18
2	Bryaceae *Rhodobryum giganteum* (Schwaegr.) Par.	Treating cardiovascular problem and nervous prostration, anti-hypoxia, antipyretic, diuretic and antihypertensive	p-Hydroxycinnamic Acid, 7-8-Dihydroxycoumarin Extract	18
		Extract to cure angina	Extract	69
	*Bryum*sp.	Can increase aorta blood transit		70

		by 30% in animals	Triterpenoidal saponins	
		Healing wounds, burns and cure fungal infections		43
3	Fissidentaceae *Fissidens nobilis* Griff.	Diuretics and hair growth stimulation tonic		71
4	Mniaceae *Plagiomnium* sp. *Mnium*sp.	Against infections and swellings. Poultice as padding under splints to set broken bones	Triterpenoid saponins	72
5	Polytrichaceae *Polytrichum juniperinum*	Anticancerous activity against sarcoma 37 in mice	Extracts	73
		Reduce inflammation and fever		
		Used as diuretic, laxative and hemostatic agent		67
		Boiled to make tea for treating cold and use to dissolve stones of the kidney and gall bladder		74
				68
6	Potiaceae *Barbula*sp.	Boiled as a tea for treating fever and body ache		75
7	Sphagnaceae *Sphagneum sericeum* C. Mull.	Brewed like a tea as heart tonic. Dressing wounds, with anti-microbial properties. For skin ailments)		72
	S. teres	To treat eye disease		67
	LIVERWORTS			
8	Aneuraceae *Riccardia* sp.	Exhibits anti-leukemic activity	Riccardins A and B, Sacullatal	72
9	*Scapaniaceae* *Diplophyllum albicans* *D. taxifolium*	Significant activity against human epidermoid carcinoma	Diplophylline	70
11	Marchantiae *Marcantia polymorpha*	Used as diuretics, for liver ailments, insect bites, boils and abscesses, treat pulmonary tuberculosis; Used to cure cuts, poisonous snake bites, burns, for cardiovascular disease	Marchantin A, MB-G	43
			Marchantin D and E	43
	M. palmate	To treat boils and abscess		
	Dumortiera hirsute	As a source of antibiotics		76
12	Plagiochilaceae *Pallavicinia* sp.	Exhibits antileukemic/anti-microbial activity	Bicyclohumulenone , Plagiochiline A, Plagiochilide, Plagiochilal B,	72
	Plagiochila sp.	Extracts show antimicrobial activity	Menthanemonoterpenoids Sacullatal	72

The Antioxidant Property of Bryophytes: Few of the bryophyte species have been studied in context to antioxidant activity. A recent study suggests that some of the liverworts and moss possess strong antioxidative machinery which helps them to survive in the extreme climate and stress condition. Heavy metal, desiccation, and ultraviolet radiation have been found to trigger an array of different enzymes in bryophytes [77]. Few of the bryophyte species have been found to hyper accumulate metals, and few others were able to sequester the toxic metals. The study conducted on antioxidant activity of the Antarctic mosses *Sanioniauncinata* (Hedw.) Loeske and *Polytrichastrum alpinum* (Hedw.) G.L. Sm. var. alpinum has indicated their potential to be used as antioxidants for medicinal and cosmetic purpose [78, 79].

Also, also the antioxidant activity of some of the species of bryophyte like *Atrichumundulatum* (Hedw.) P. Beauv., *Polytrichum formosum* (Hedw.), *Pleurozium schreberi* (Brid.) Mitt. and *Thudiumtam ariscinium* (Hedw.) Schimp. has been screened, and all tested species have shown antioxidant effects lower than the positive control, caffeic acid [80].

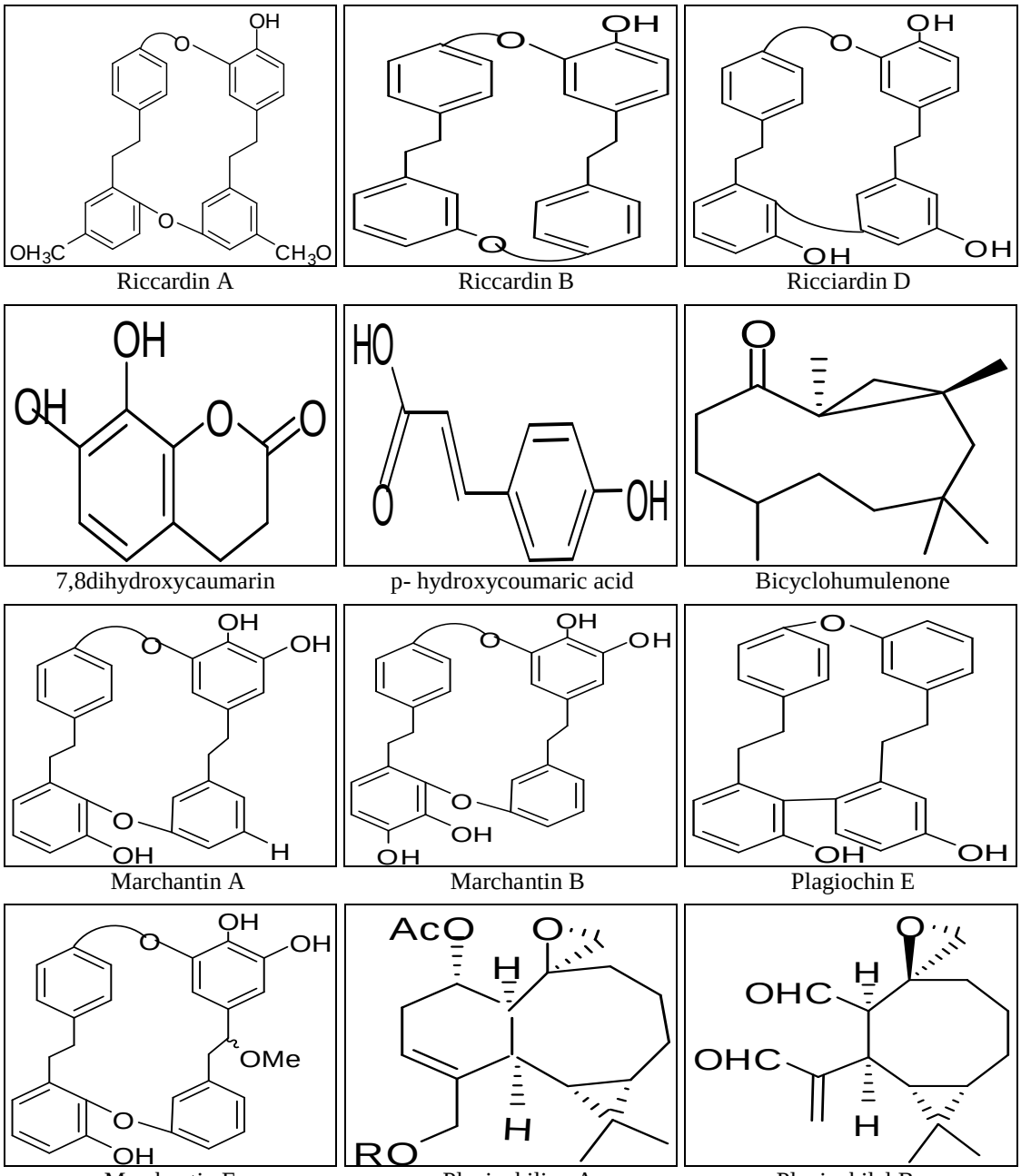

FIG 1: STRUCTURES OF FEW ACTIVE COMPONENTS PRESENT IN BRYOPHYTES

Moreover, the screening for the antioxidant property of the aqueous extract of the three moss namely *Brachythecium rutabulum, Calliergonella cuspidate* and *Hypnum mammillatum* in context of their ABTS (2, 2- azino- bis (3-ethlybenzthiozoline- 6 sulphonic acids) cation scavenging activities and phenolic content have known to show some positive response. Out of the three extracts, *Brachythecium rutabulum* have shown the highest of the phenolic content, which further suggested the potential of this extract in search of many other novel antioxidant compounds in this moss. Apart from this methanolic and ethyl acetate extract of *Marchantia polymorpha* L.[81] have also shown the antioxidant property. Summing up, bryophyte could be the source of many novel antioxidants if screened which could be used for novel drug discovery.

Bryophytes as a Potential Biopharming for Production of Complex Biopharmaceuticals: Bryophytes have indeed penetrated the forefront of modern medicines. Although an avast variety of biopharmaceuticals has been produced in microbial or mammalian cells, plants based production system possesses several advantages over the mammalian and microbial system, thus, making them interesting alternatives.

Microbial systems are favored because of easy cultivation and high productivity, whereas mammalian cell lines (preferentially Chinese Hamster Ovary cells) are favored for complex multimeric proteins or those requiring posttranslational modifications [82, 83]. In contrast to these currently used systems, plants based production system possesses several advantages over this system, thus making them interesting alternatives. As higher eukaryotes, they perform posttranslational modifications closely resembling those of humans, thus minimizing the risk of product contamination by infectious agents derive from the used cells or media [84, 85]. Also, bryophytes offer the researchers and the company a high production system which can be grown without antibiotics, hence avoiding the danger of contamination of the final product. Apart from these advantages, mosses are the only plants known to show a high frequency of homologous recombination. They allow the stable integration of inserted genes into the host cell.

Furthermore, the highly complex moss system, compared to bacteria and fungi, permits a much wider array of expression than is possible in other systems. Given the above advantages of mosses over another production system, today, many complex biopharmaceuticals are being produced by moss bioreactors. The Chair of plant Biotechnology from the University of Freiburg, Germany, and the biopharmaceutical company Greenovation Biotech Gmbh in Heilbronn, Germany; have started a cooperation to enhance the yield of recombinant proteins from moss. The moss (*Physcomitrella patens*) has been successfully grown in a bioreactor which requires only water and minerals to nourish the moss, in the presence of light and CO_2 (Greenovation). Consequently, many complex proteins can be produced in moss bioreactor. Other products are human growth factor that is required by the researcher for tissue culture. This plant has successfully been able to produce human proteins [86, 87,] and is the only plant being used to produce the blood-clotting factor IX for pharmaceutical use.

CONCLUSION: Use of medicinal plants has been appreciated due to low cost and lesser side effects. Herbal drugs have been used successfully in the treatment of various ailments over the last few decades. 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. Several herbal compounds have been discovered with immense therapeutic potential. Therefore, to meet the potential future demand for various bioactive compounds used as drugs, a new production system is required significantly. Bryophyte, a small and insignificant group of plants, may serve as a source of some unique biologically active molecules. Many of the bryophytes are important source of medicine, antibacterial, and antifungal agents. Antifungal efficacy of certain liverworts and mosses can substitute the conventional synthetic fungicides used in crop protection, especially in the countries where fungal invasion in the crop fields is a common phenomenon.

The problem of the development of drug resistance in common human pathogenic fungi can be solved by using antifungal compounds harvested from uncommon sources like bryophytes. Several bryophytes are able to produce antifungal compounds. Furthermore, the use of moos bioreactor has opened new possibilities for the production of many plant and animal metabolites.

Future scope: In the past few years, rapid progress has been made to isolate various plant-based therapeutic compounds. Bryophytes being a rich source of a variety of secondary metabolites could be a promising source of the bioactive compounds with immense therapeutic potential. Being present in the varied niche and occupying the most diverse group of the plant kingdom, they could be the source of various evolved metabolic pathways that could be wisely manipulated for the development of various novel therapeutic compounds.

Therefore, bioprospecting of bryophytes is required to discover the natural wealth of bryophytes. Creation and development of a production system by using bryophyte cells could solve the future demand of a novel plant-based production system. Hence, engineering of a metabolic pathway for the production of novel metabolites, and strategies for the development of the bioprocess for bryophyte cell system is the need of time to dig out some more information to satisfy the thirst of novel drug discovery.

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