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REVIEW ARTICLE **OPEN ACCESS**

Bryophytes as source of antiviral compounds

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ABSTRACT
The world is facing crisis in the form of viral diseases, with sporadic incidences turning in to pandemics. Effective management of viral disease is the need of the hour with search for new chemicals that can prevent entry and multiplication of viruses. Plants are a source of diverse chemicals and many of these are potential candidates against viral infection. Bryophytes are the least explored group among plants and no viral diseases has been assigned to bryophytes. This can be due to the strong biochemical defense mechanism seen in bryophytes. Bryophytes have a long history of evolution from their aquatic ancestor towards the terrestrial environment. In the course of evolution, several new metabolic pathways were developed and as such bryophytes are a hoard of biochemicals. Studies indicate bryophytes to possess molecules with antiviral activities and if properly screened, many bryophytes can become potential sources of novel antiviral compounds.
KEYWORDS: Bryophyte, antiviral, bioprospecting

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INTRODUCTION

Bryophytes, known as the 'Amphibians of Plant Kingdom', form the second largest class of higher plants. Bryophytes display wide geological distribution, growing under varied ecological niches, and often are pioneers in inhabiting extreme habitats [1]. As reported by the European commission on Nature and Biodiversity (2020), bryophytes constitute about 18000 to 23000 described species all over the world, with molecular studies supporting the addition of more taxa to the list. Due to small size and low quantity of biomass, bryophytes remain as an ignored group in bioprospecting studies [2]. Also, taxonomic classification and identification is difficult in view of the similarities in vegetative and reproductive structures among various taxa.

Bryophytes have been used in traditional medicine for a long period of time, mostly for treating various skin diseases and injuries, as they are believed to safeguard skin and open wounds from microbial attack [3]. Thalloid forms are rich source of pharmacologically active compounds which provide characteristic odors, pungent, sweet or bitter taste and protect them from microbial and pest attack. Several biologically active terpenoids and aromatic compounds were isolated from thalloid bryophytes that were cytotoxic, allergenic, antimicrobial, antioxidant, plant growth retardant, antifeedant, piscicidal, insecticidal, nematicidal, antithrombin and with antagonist or inhibitory effect against DNA polymerase, 5-lipoxygenase b, calmodulin, hyaluronidase, cyclooxygenase, vasopressin, cathepsin B and L, nitric oxide production and tubulin polymerization [4].

Drug discovery is one of the leading areas of bioscience research as often new and pathogenic microbes evolve out. Many microbial diseases that were easily managed by antibiotics have become tough to treat due to the multiple drug resistance attained by microbes. Viral infections are at spike with mortalities reaching millions, each year new strains develop making it difficult for vaccine preparation. Though bryophytes seems to be less significant, studies reveal them as a hoard of natural remedies with a wide range of biochemical not found in other plant groups [5]. Though several virus infecting angiosperm plants have been reported and characterized, there are no reports on virus capable of infecting bryophytes. This may be due to the structural nature or more probably the biochemical defense these plants show against virus. Recent Covid-19 claiming millions of life has surged the search for antiviral compounds. The present review deals with literature relating to target molecules in virus and antiviral compounds isolated from bryophytes.

TARGET MOLECULES IN VIRUS

1. Viral nucleic acid

Virus consists of a nucleic acid and protein coat and the complete virus particle is called a virion. In addition, some viruses have an envelope made of lipo protein. The nucleic acid occupies the core position in the virion and is either a DNA or a RNA but never both. The nucleic acid may be single stranded or double stranded DNA or single stranded or double stranded RNA. For the multiplication of virus this viral nucleic acid is essential. RNA virus can replicate through one of the pathways- either by RNA dependent RNA synthesis or RNA dependent DNA synthesis (reverse transcription) followed by DNA replication and then transcription to RNA. DNA viruses use DNA molecule as a template for DNA replication. Thus targeting the genome of virus either by preventing its replication using antisense technology or allowing replication but resulting in defective nucleic acid is considered as a method for antiviral therapy.

2. Viral coat protein and other proteins

Viral coat proteins have great role in adsorption of viral particles on the cell surface. Specific receptors on cell surface can recognize these proteins and thus help in docking of the viral particles. Antiviral therapy thus should focus on preventing the viral docking which can be either targeted to blocking the specific viral particles from attaching the cell receptor or blocking the cell receptors thus preventing the docking of viral particles. Development of antibodies are an easy task but they show little penetration to host tissue. Smaller peptides can often be used for the purpose.

3. Viral envelope

Many viruses have a lipoprotein envelope around the capsid. This envelope is partly of the virus and partly of the host cell. The lipid layer is obtained from the host cell during the viral escape or budding out, while the spike proteins are of viral origin. Such enveloped virus attaches the host cell through the spike protein-cell receptor interactions. Thus antiviral therapy again is directed towards preventing the docking of enveloped viruses on to the membrane either by inactivating the spike protein or by inactivating the cell receptors for viral envelope proteins. Also altering endosomal pH can prevent the entry of virus in to cytoplasm.

4. Inhibitors of infection, replication, assembly and release

Once a virus enters the cell, it requires several proteins of the host cell for viral particle synthesis and assembly. Virus hacks the cell machinery to multiply and liberate the newly formed virions. Host proteins and enzymes that help in these processes if inactivated can prevent viral multiplication and release.

ANTIVIRAL COMPOUNDS FROM BRYOPHYTES

Several antiviral compounds have been identified from higher plants. This include lycoricinidol, emetine, okrobamine, cryptopleurine, elenoic acid, parasorbic acid, motin, fisetin, naringenin, hesperidin, poriolide, angelicin, chelerythrine [6]. Phytochemicals like oxyresveratrol, samarangenin B, lignin-carbohydrate complex PPS-2b, pterocarnin A, scopadulcic acid B, spiroketalenol ether derivative are active against HSV virus and Saikosaponin b2, chalepin, pseudane IX are antiviral against HCV [7].

Bryophytes have a number of bioactive compounds, many of which are not found in other groups of plants. These include volatile oils, terpenoids, phenolics, alkaloids, saponins, coumarins, pigments etc. Bioprospecting studies by various researchers have identified several compounds that have promising results as antiviral agents. Phytochemicals derived from liverworts including marchantins A, B and E, plagiochin A were found to inhibit influenza PA endonuclease at a concentration of 10 μM [8]. *Marchantia* species are considered as a source of antiviral compounds. Studies conducted by Jimenez-Aleman *et al* [9], indicate chlorophyll derivative pheophorbide a (Pheo A) has potential antiviral activity. The compound showed broad spectrum antiviral activity against enveloped RNA viruses. When crude extract of *Marchantia polymorpha* were tested on Vero E6 cells, cell protection against SARS-CoV-2 infection was noted without signs of cytotoxicity. Studies in mutant plants defective in secondary metabolites indicated the compound to be a primary metabolite and that further studies using *Physcomitrium patens* and non-bryophyte taxa like *Hypericum androsaemum*, *Blechnum spicant*, *Urtica dioica*, *Arabidopsis thaliana* and *Nicotiana benthamiana* indicate the compound to be universal occurrence in plants. The compound was purified and identified as pheophorbide a, indicating a constitutive cell protection strategy in plants against viruses.

The liverwort *Blasia pusilla* was found to produce bis-biphenyl dimers pusilatins A-D, pusilatin B, pusilatin C and these compounds possess inhibitory activity against DNA polymerase B. They also showed weak HIV reverse transcriptase inhibition [10]. Marchantins A, B, D, perrottetin F and Paleatin B was active against HIV-1 with IC_{50} value of 5.3 μg/ml to 23.7 μg/ml [5]. *Marchantia polymorpha* have 1-ethyl adamantine which is commonly used in treatment of viral fever. The derivatives like amantadine, adapalene, dopamantin, karmantadin, rimantadine etc are commonly used against HIV infections [11].

Bryophytes often have phthalates and they occur in diverse forms. Studies conducted by Rameshthangam and Ramasamy [12], in *Pongamia pinnata* indicate bis(2-methylheptyl) phthalate to have antiviral activity against white spot syndrome virus. Cellulose acetate phthalate was found to show antiviral activity against herpes simplex virus [13]. Though many phthalates are found to show cytotoxic and teratogenic effects, some phthalates show no such toxicity. One such pthalic acid ester 2''-(methoxycarbonyl)-5''- methylpentyl 2'-methylhexyl phthalate from *Acrostichum aureum* displayed antiviral activity against dengue virus, human parainfluenza virus and chikungunya [14]. Bryophytes being a hoard of diverse phthalates can be a potential source of antiviral phthalates that lack cytotoxicity.

Klocking *et al*. [15], found that at least some peat humic acids have antiviral action against herpes simplex virus types 1 and 2, interfering chiefly with the adsorption of viruses to cells. *Sphagnum* synthesizes numerous antiviral humic acids, and *Camptothecium* extracts were found to inhibit multiplication of poliovirus [16-17]. Ethanol, methanol, benzene, acetone and petroleum ether extracts of *Imbibryum* sp., *Trichostomum* sp., *Barbula convoluta*, *Fissidens* sp., *Splachnobryum obtusum*, *Funaria hygrometrica*, *Didymodon* sp., *Barbula* sp. showed antiviral activity against Zucchini Yellow Mosaic Virus infecting cucumber. An inhibition activity of 90% or above was noted with methanolic extract of *Imbibrym* sp., *Barbula convoluta* and *Trichostomum* sp. Studies also revealed that foliar application of bryophyte extracts could enhance growth of plants and also inhibit viral [18]. In a study conducted by Hillhouse [19] on antiviral activity, 41 bryophytes were screened against Potato Virus X (PVX). Twenty nine bryophytes showed an inhibition greater than 75%. Among the bryophyte families, Hylocomiaceae, Polytrichaceae and Sphagnaceae showed high levels of antiviral activities while bryaceae, Mniaceae and brachytheciaceae showed very low antiviral activity. Bryophytes like *Atrichum undulatum*, *Buckiella undulatum*, *Hypnum circinale*, *Polytrichum piliferum*, *Rhytidiadelphus loreus*, *Sphagnum capillifolium* and *Tetraphis pellucida* showed 100 % inhibitory activity against PVX. Pardee [20] did a similar study using 31 algal species of which only 7 species showed 75 % or more inhibition to PVX. This indicates the potential of bryophytes as novel source of antiviral agents. Flavonoid content in mosses vary with climatic factors and stress conditions [21]. Thus absence of antiviral activity in some bryophytes may be due to the seasonal variation or due to the nature of stress experienced by the taxa.

Common antiviral chemicals used in therapy

The antiviral drugs currently used in treating viral infections are listed in Table 1.

Table 1. Antiviral drugs and mode of action

Functional class	Compound	Mode of action	Reference
Nucleoside analog	Acyclovir, Valacyclovir, Ganciclovir, Penciclovir, Famciclovir	Compete with dGTP during viral DNA replication. The drug lacks 3' OH group and thus incorporation can result in chain termination.	[22]
	Idoxuridine, trifluridine, brivudine	Substitutes for thymidine and prevent viral replication	[23]
	Vidarabine, Didanosine	Compete with dATP to inhibit the activity of viral DNA polymerase	[24]
	Foscarnet	Pyrophosphate analog, inhibit viral DNA polymerase by interfering with exchange of pyrophosphate from deoxynucleoside triphosphate	[25]
	Lamivudine, Zalcitabine, Emtricitabine	Compete with dCTP to inhibit viral DNA synthesis	[23]
	Zidovudine, Stavudine	Compete with dTTP to inhibit viral DNA synthesis	[23]
Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTI)	Nevirapine, delaviridine, efavirenz, etravirine, rilpivirine	Noncompetitive binding to reverse transcriptase and inhibit DNA synthesis	[26]
Protease Inhibitor	Ritonavir, Indinavir, nelfinavir, amprenavir, tipranavir, darunavir, Amprenavir, Lopinavir, Saquinavir, Atazanavir	Inhibitor of viral Protease and prevent cleavage of viral precursor protein	[26]
Integrase inhibitor	Raltegravir, Elvitegravir, Bictegravir, Dolutegravir	Prevent strand transfer activity and integration of viral DNA into human chromosomes	[26]

Entry Inhibitors	Docosanol	Interfere with binding of viral envelope proteins to cell membrane	[27]
	Enfuvirtide	Prevent fusion of viral envelope with the cell membrane and thus prevent entry of virus	[26]
	Maraviroc	Block chemokine co receptor in host which is necessary for viral uptake	[26]
Inhibitors of uncoating	Pleconaril, Amantadine, Rimantadine	Prevent viral penetration and uncoating	[22]
Antimitotic drug	Podofilox	Interrupts cell division	[28]

CONCLUSION

Viral diseases are difficult to control and recent hike in viral diseases are often posing threat to human existence. Viruses get mutated easily and thus evade defense mechanisms developed in host. Antiviral drugs target specific viruses and again resistance developed by virus can become a problem in maintaining health. Plants can be source of novel biochemical that can be effectively used against viruses. Though higher plants and algae have been extensively exploited for antiviral compounds, bryophytes remain a neglected group. This is due to the small size, less availability of biomass and difficulty in identification of taxa. Studies indicate bryophytes to be a potential source of antimicrobials including antiviral compounds. Absence of any visible viral infections in the plant group indicate the presence of strong biochemical defense mechanism in these plants. Studies on the metabolites can thus pave way for novel phytochemicals that can be used as antiviral compounds

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CONFLICT OF INTEREST

None

AUTHOR'S CONTRIBUTION

Meenu Mathew- Manuscript preparation; Tess Babu- resources finding; Meenu Elizabath- analysis of data; Abraham Mathew- checking accuracy and integrity of work

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