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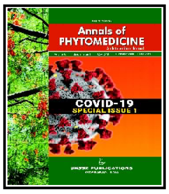

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Potential of bryophytes in prevention and medication of COVID-19

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Abstract

Severe acute respiratory syndrome Corona Virus-2 (SARS-CoV-2) is the latest adherent in the family Coronaviridae. It is an extremely transmissible and transmits through interaction/droplets. Early response in an infected person includes deregulations of cytokine followed by failure of the immune system. World Health Organization (WHO) stated it as worldwide wellbeing emergency regarding this pandemic. The death tally is ever increasing since the first report in Wuhan (China) in December 2019. Consequently, the scientific community of the world started the work on his remedy and suggested the obligatory precautionary actions. Though, few vaccines have been developed, yet the best option is still to take preventive measures at present in future also. Among all preventive measures, the use of herbs in our diet is the easiest and best. Many herbs with great antioxidant profiles and antiviral potential are known to us. But, usually angiosperms are the first choice to be utilized and other plants such as bryophytes have been neglected for their use as remedy to treat many diseases caused by viruses. The purpose of this review to explore and compile those bryophytes which would be the possible candidates as remedy against coronavirus as immunity boosters.

1. Introduction

Due to parasitic nature, viruses are obligate intracellular organisms and utilize the host cells system for its replication and spread (Casadevall, 2008; Helms *et al*., 2015). These infective agents are visible through Electron microscope, but images taken by transmission electron microscope only provide the morphological insight (Goldsmith and Miller, 2009). Though, morphologically these viruses have variable external structures, but they have nucleic acid and capsid called nucleocapsid as common aspect (Tellinghuisen and Kuhn, 2000). They have been classified variously, *viz*., classification proposed by Holmes, Baltimore and LHT system on the basis of certain parameters, such as genome, capsid and host specificity, *etc*. However, the system was developed in the year 1971 by David Baltimore (a Nobel laureate, 1975) for classifying viruses based on the type of genome and its replication strategy is the most recognized and accepted classification.

1.1 Viral epidemics in past

There are no historic hints about the beginning and progression of viruses, but the world has seen many pandemics affecting loads of individuals and mourned millions of deaths. For instance, many pandemics were reported, *viz*., Spanish flu (1918-1920); Ebola viral disease (2014-2016), Zika virus, Chikungunya, Dengue in many countries that resulted into millions of deaths and still active to some extent at present also. A lethal addition in this tally is SARS-CoV-19 or Novel coronavirus 2019 (nCOVID-19) which appeared in December, 2019 and affecting 107,415,710 of people worldwide and caused 2,351,367 deaths. However on a positive note, 79,346,885 people have been recovered (https://www.worldometers .info/coronavirus/ retrieved on 10.2.2021). On the basis of data regarding SARS-CoV-19 one thing is very much evident that level of immunity is the basic difference between life and death when anyone infected with this virus.

1.2 SARS-CoV-19

The name coronavirus is not new to pathology, but the earlier forms of it were only related to mild disease symptoms like common cold and cough. However, in the year 2003, a novel strain was introduced from bats to cats and then to humans. This existence caused severe acute respiratory syndrome (SARS) in humans and designated as SARS-CoV (Lu and Liu, 2012). Afterwards in 2012, another strain was passes from the camels to humans and designated as Middle East Respiratory Syndrome (MERS), and in the year 2019, a novel strain had appeared though, it was closely related to SARS-CoV-1 yet showed certain differences on the basis of its phylogenetic study, hence named as novel coronavirus SARS-CoV-2 (Wu *et al*., 2020). It is probably transmitted from bats (Zhou *et al*., 2020), sea food/animal market in Wuhan, China (WHO, 2020).

So, the evolutionary trends show that the coronavirus is also evolving like other viruses and challenging the human beings to fight for their survival.

1.3 Significance of immunity against viral attacks

A robust resistant mechanism of human being constantly protects the body from the outbreak of countless microorganisms, but when this system weakens, it results into the start of many long-lasting diseases like COVID-19 that cannot be treated perfectly through conventional medicines. Many recent reports indicated a close interaction between Covid-19 and the immune response of an

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infected person. This activated immune response due to SARS-CoV-2 in an infected individual can be alienated into two stages, the initial incubation or non-severe and the following severe stage (Shi *et al*., 2020).If the immune response of the infected person is sturdy, then the progression of initial stage to second stage is retarded which help in the early elimination of the virus. Accordingly, the resistance enhancing approaches are very important to provide protection at this stage. All this depends upon the all-inclusive health of the persons so that an endogenous immune response can prevent the viral activities at the initial stage (Shi *et al*., 2020). If the immunity of the infected individual is weak then the virus will thrive and replicate easily which results in the massive damage to the affected parts of the body, especially the tissues of lungs which become severely exaggerated and result into deadly respiratory disorders at the next stage of infection (Xu *et al*., 2020). It has been seen that SARS-CoV-2 affects respiration, kidney functions, liver metabolism, gastrointestinal tract, cardiac and central nervous system (Huang *et al*., 2020; Liu *et al*., 2020) subsequently many deaths have been happened due to the multiple organ failure.

1.4 Active sites of coronavirus

The structural investigation provided the basis for the vaccine development against COVID-19 and according to those the envelope protein (E-protein) is the minutest amid the main structural proteins having excited cytoplasmic tail and hydrophobic domain. Missing this vivacious protein expressively depresses viral load with undeveloped and ineffectual descendants (Schoeman and Fielding, 2019). Whereas, the membranous protein is responsible for the maintenance of virus capsid's shape and stabilization the overall balance of nucleocapsid by integrating the cellular golgi tool for freshly formed virions (Prajapat *et al*., 2020). The spike (S-glyco protein) is the distinctive ectodomain of COVID-19, which provide the all essential binding of virus particle on the specific receptors (Gordon *et al*, 2020) which is followed by the release of nucleocapsid (N-protein**)** after bulging the membrane into the cell. Like other RNA viruses, the replication and transcription of *m*-RNA genome starts from 5' end, followed by the immune hyperactivity and pulmonary devastation. Hence, the most decisive part in the pathogenicity is performed by the S-glycoprotein (Perlman and Netland, 2009). A study discovered that the binding propensity of S-glycoprotein to ACE2 in SARS-CoV-2 is about 10-to-20 times higher and with easier communication from person to person than the other known strains of this virus (Adhikari *et al*., 2020).

1.5 Potential of plants against the COVID-19

Many countries including China have explored the possibility of the utilization of Traditional Medicine system against the COVID-19. Consequently, the conventional remedies and traditional medications have been found useful in the augmentation the resistance against viral attacks. As evident that the floristic wealth on this planet is a huge reservoir of medicinally important plants and they are the valuable source of numerous bioactive compounds/ secondary metabolites that act as paragon for drug findings. Since the outbreak of COVID-19, many plants have been evaluated for their potential as anti-COVID and many interesting results have been obtained (Mugisha *et al*., 2014; Lamorde *et al*., 2010; Nyamukuru *et al*., 2017; Khan, 2020; Mehrorta, 2020). It seems that angiosperms are the preferred plants for such studies and the second most abundant group of plants, *i.e*., bryophytes have been neglected.

To fill this lacuna, some of the bryophytes have been enlisted in this article that have shown antiviral potential in past.

According to many reports' bryophytes are ubiquitous remedy amid many tribes of the world and these tiny plants being used to cure several diseases, *viz*., to cure skin diseases, hepatic disorders, cardiovascular diseases, inflammations, microbial infection, wound, *etc*., since olden times (Alam, 2012; Alam and Sharma, 2015; Chandra *et al*., 2017). However, recent attempts on the evaluation of bryophytes for their pharmaceuticals and nutraceutical impending show that these amphibious plants have significant antioxidative, anticancerous, antiviral and antimicrobial properties.

1.6 Bioactivity of compounds found in bryophytes

Bryophytes create an assemblage of minor plants which form indispensable part of terrestrial flora. These plants prefer to grow in shade where the water availability is sufficient (Glime and Saxena, 1991). Ecologically, these plants always regarded as vital but for therapeutic potential some what neglect in past. However, in current scenario of herbal formulations, these amphibian plants are more and more explored for their therapeutics utilities. But still less than 10% of bryophytes have been explored for their phytochemistry (Asakawa, 2004). On the basis of attempts made on these plants, it is evident that these plants possess worthy bioactive compounds. These bioactive secondary metabolites have shown varied biological activities, *viz*., antimicrobial, antiviral, antitumor, cytotoxic, cardio-protective, allergy triggering, *etc*. (Asakawa, *et al*. 2014).

Liverworts are the preferred plants as they were used as cure for skin infections and liver ailments since the olden times (Friederich *et al*., 1999; Saroya, 2011; Gokbulut *et al*., 2012). Mosses are comparatively lesser explored for their therapeutic uses than the liverworts though they have more diversity than the liverworts, while hornworts yet to emerge as medicinally important plants. The secondary metabolites identified in bryophytes are usually flavonoids, terpenoids, bibenzyls, *etc*., along with few fatty acids and acetophenols, *etc*. (Asakawa *et al*., 2014).

Being resurrection plants, they produce various secondary metabolites to reinforce their defense to cope up with environmental stress, especially the desiccation (Xie and Lou, 2009; Dey and De, 2012; Alam *et al*., 2019). Since these plants are delicate and have no specific morphological and anatomical adaptation for defense therefore, they have well developed active defense at molecular and chemical level.

The antioxidant defense system delivers fortification to the cellular membranes and organelles to avoid damages due to oxidative burst under stress situations. When stressed, the reactive oxygen species (ROS) react with imperative constituents of the cell, *viz*., proteins and lipids of cellular membranes resulting into the disturbance in cell integrity eventually causing cell destruction. These antioxidants are, therefore, present hugely in the bryophytes, therefore these plants are well able to serve as a valuable reservoir for medicinally important phytochemicals (Aslanbaba *et al*., 2017). Considering this, few bryophytes were evaluated for their bioactive compounds, for instance, in the liverwort, *Marchantia polymorpha*, was characterized for an antioxidant enzyme peroxidase and it was reported that this peroxidase of liverwort is significantly different from any well-known peroxidase of tracheophytes (Hirata *et al*., 2002). Likewise, *Brachythecium velutinum* (moss) and *M. polymorpha* also evaluated for the search of antioxidant enzymes and showed that the enzyme ascorbate peroxidase plays a vital role in the removal of hydrogen peroxide from the plant (Paciolla and Tommasi, 2003). The extract obtained from another liverwort, *Plagiochasma appendiculatum* showed noteworthy antioxidant action in preventing the lipid peroxidation by augmenting the activity of superoxide dismutase and catalase (Singh *et al*., 2006).

The moss, *Sphagnum magellanicum* showed the occurrence of various phenolic compounds like gallic, caffeic, chlorogenic, vanillic, p-coumaric, salicylic acid and 3-4 hydrozybenzoic when reverse-phase high-pressure liquid chromatography was done (Montenegro *et al.*, 2009). The flavonoids extracted from the cell suspension culture of liverwort *Marchantia linearis* showed anticancerous potential against the cell lines of colon cancer (Krishnan and Murugan, 2013 a, b). The antibacterial and antifungal activities of bryophytes have been evidently proved by many studies (Greeshma and Murugan, 2014; Negi *et al*., 2018). However, like other plant groups, the ambient environment has its instrumental effect on the quantity and quality of the secondary metabolites found in bryophytes (Vats and Alam, 2013; Thakur and Kapila, 2017). For instance, the extracts of *Oxytegus tenuirostris*, *Rhynchostegium murale* and *Eurhynchium striatum* were evaluated for their antioxidative properties and it was reported that the climatic factors regulate the antioxidant possessions of these mosses. It was also reported that the differences in antioxidant potential may vary within a species and amid different species (Yayintas et al., 2017). Bryophytes such as *Homalothecium sericeum*, *Sanionia uncinata*, *Eurhynchium striatulum*, *etc*., were evaluated for their free radical scavenging activity and showed appreciable results (Erturk *et al*., 2015).

It was also proved that isolated phytochemicals work better than the extract. Bhattarai *et al.* (2008) reported antioxidant of *Sanionia uncinata* (polar moss). An experiment performed on the extracts of *Polytrichastrum alpinum* revealed that the isolated phyto-constituents have two-to-seven fold augmented antioxidant action than the extract of the plant (Bhattarai *et al*., 2009).

The phytochemical profiling of *Thuidium tamariscellum* showed the occurrence of substantial terpenoids level which was responsible for its high antioxidant possessions (Mohandas and Kumaraswamy, 2018).

Studies also revealed that the total flavonoid contents of liverworts were generally higher than those of mosses, and among mosses the acrocarpous forms showed usually elevated values than the Pleuro-carpous forms. This reveals that the overall content of flavonoidsis related to the light intensity because it has been observed that the species growing in habitats with low light levels contain higher flavonoids than those growing in full sun (Sabovljević, and Sabovljević, 2020).

It is also revealed that the antioxidant potential of some of the liverworts is more or less same as found in vascular plants, *e.g.*, *Plagiochasma appendiculatum* showed remarkable activity of guaiacol peroxidase and catalase and *Pellia endivaefolia* showed excellent activity of superoxide dismutase, proline, ascorbic acid, glutathione, and total phenols when stressed (Sharma *et al*., 2015).

Both, antioxidant and free radical scavenging activities are of great significance for medical practitioners and dieticians. The occurrence of excessive free radicals is thought to have a crucial role in the development of many diseases (Castro and Freeman, 2001). Oxidative progressions may also decline the constancy and value of drugs and foods. These reactive oxygen species (ROS) and reactive nitrogen species (RNS) are generated during the environmental stresses and among all plants, the bryophytes have a special position because the dominant haploid (n) gametophytic phase in their life cycle. Consequently, few species have been evaluated for their tolerances against drought and floods (Robinson *et al*., 2002; Wasley *et al*., 2006) and extraordinary nitrogen concentrations (Koranda *et al*., 2007). It was found that these plants are well able to adapt and answer to these stresses because of their superior and highly effectual antioxidative defense mechanism which comprises of defensive non-enzymatic as well as enzymatic strategies that competently hunt the harmful ROS and avert the damaging possessions of these nasty free radicals (Breusegem *et al*., 2001).

Recently, bryophytes like *Claopodium crispifolium* and *Anomodon attenuates* showed remarkable occurrence of cytotoxic and/or antitumor compounds that have been isolated and identified as an samitocin P-3. While, ohioensins and pallidisetums compounds were isolated from *Polytrichum* spp. (Sabovljevicì, *et al*., 2016).

1.7 Antiviral activities

Viruses are unique type of pathogens. They are nucleo-protein particles with complete dependency on the host cell machinery to survive and replicate (Webster's *et al*., 1998). Antiviral activity has been reported in numerous plants including bryophytes. Interestingly, there wer no evidence available regarding the infectivity of viruses to any bryophytes in past which proves that bryophytes have strict defense response in the form of their chemical constituents against the viruses. Hence, numerous bryophyte species have been identified having antiviral action against many animal and plant viruses, *viz*., Herpes simplex type 1, Polio type 1, Potato virus X(PVX), Zucchini Yellow Mosaic Virus (ZYMV), *etc*. Therefore, now the bryophytes have been recognized as a new reservoir of antiviral secondary metabolites.

Recently, few attempts have been made to find out the antiviral compounds in many bryophytes and bioflavonoids were reported to cause a controlling effect on a broad range of viral strains (Hillhouse, 2003). The secondary metabolites recognized in the bryophytes are basically terpenoids, flavonoids and bibenzyls. Among the investigated taxa, liverworts appeared as the main sources of these terpenoids, flavonoids and alkaloids (Chaudhary and Kumar, 2011).

Mosses such as *Imbibryum* sp., *Trichostomum* sp. and *Barbula convoluta* have been screened for antiviral properties and substantial antiviral activity was reported against Zucchini Yellow Mosaic Virus (ZYMV), the methanolic extracts of these taxa have shown about 90% inhibitory effect on the virus due to their high phenolic contents (Abdel-Shafi *et al*., 2017).

Phytoconstituents obtained from bryophytes, *viz*., Marchantins A, B and D, perrottetin F, and paleatin B exhibited anti-HIV-1 activity (Asakawa and Ludwiczuk, 2017) confirming the antiviral potential of bryophytes.

2. Material and Methods

A simple method was implemented to register those plants either having the property to cure the viral infections closely related to the coronavirus or they have the possessions to offer relief from the peculiar symptoms pragmatic in the COVID-19 patients where they can trigger and reinforce the immune system. The literature search was carried out using keywords like, immune-enhancer bryophytes, medicinal bryophytes, ethnobryology, antiviral bryophytes, *etc*. The list of some of the bryophytes is specified (Table 1) along with their family, traditional uses, bioactive compounds and consuming methodology.

Table 1: List of some bryophytes and their reported compounds showing antioxidant activity and antiviral potential (Asakawa and Ludwiczuk, 2018; Gahtori and Chaturvedi, 2019; Sabovljević, and Sabovljević, 2020)

Sl. No.	Name of bryophyte	Antioxidant compounds
1.	*Anomodon rostratus*	Phenolics
2.	*Asterella angusta*	Asterelin A, asterelin B, 11-O- demethylmarcantin I, and dihydroptychan to ladibenzofuran [bis(bibenzyl)]
3.	*Atichum undulatum*	Phenolics
4.	*Atrichum angustatum*	Phenolics
5.	*Barbula* sp.	Triglycerides
6.	*Bryum cuspidatum*	Phenolics
7.	*Bryum moravicum*	Phenolics
8.	*Camptothecium* sp.	1-o-methylohioensin-B, 1-o-methyldihydroxyohioensin-B
9.	*Chiloscyphus polyanthus* (Plate 1: Figure 1)	Diplophyllin, sesquiterpene, lactones, diplophylloide-14, tulpinolide
10.	*Conocephalum conicum* (Plate 1: Figure 2)	Tulpinolide, Zaluzanin-C
11.	*Dicranium* sp.	Triglycerides
12.	*Diplophyllum albicans* (Plate 1: Figure 3)	Diplophylline
13.	*Diplophyllum taxifolium*	Diplophylline
14.	*Dumortiera hirsuta* (Plate 1: Figure 4)	RiccardinD [macrocyclicbis(bibenzyl)]Cell wall peroxidases and tyrosinases
15.	*Fissidens* sp.	Phenolics
16.	*Frullania muscicola*	3-Hydroxy–42 - methoxylbibenzyl7,4–dimethyl-apigenin
17.	*Frullania tamarisci* (Plate 1: Figure 5)	Antileukemic compounds
18.	*Haplocladium microphyllum*	Phenolics
19.	*Hyophila involuta*	Phenolics
20.	*Jungermannia subulata*	Subulatin
21.	*Lophocolea heterophylla*	Subulatin
22.	*Lunulari acruciata*	Flavonoids and sesquiterpenes
23.	*Marchantia paleacea* var.*diptera*	Superoxide dismutase
24.	*Marchantia palmata*	neomarchantin A, marchantins A and B
25.	*Marchantia polymorpha* (Plate 1: Figure 6)	Plagiochin E, riccardin H, marchantin E,neomarchantin A, marchantins A and BCustunolide, α-himachalene, cuparenemarchantin, δ-elemene
26.	*Mastigophor adiclados*	Sesquiterpenoids
27.	*Mnium* sp. (Plate 2: Figure 7)	Bicyclohumulenone, plagiochiline A, plagiochilide,plagiochilal B, menthanemonoterpenoids, triterpenoidal saponins, riccardinsA and B, sacullatal
28.	*Pallavicinia lyelli* (Plate 2: Figure 8)	Ascorbate peroxidase, δ-elemene, calamenene, Bicyclohumulenone, plagiochiline A, plagiochilide,plagiochilal B, menthanemonoterpenoids,triterpenoidal saponins, riccardins A and B, sacullatal
29.	*Philonotis fontana* (Plate 2: Figure 9)	p-hydroxycinnamic acid, Triterpenoidal saponins, p-hydroxycinnamic acid, 7–8-dihydroxycoumarin
30.	*Plagiochasma appendiculatum*	Prevent lipid peroxidation and increase antioxidant enzymes
31.	*Plagiochila* sp. (Plate 2: Figure 10)	Bicyclohumulenone, plagiochiline A, plagiochilide,plagiochilal B, menthanemonoterpenoids,triterpenoidal saponins, riccardins A and B, sacullatal
32.	*Plagiomnium* sp. (Plate 2: Figure 11)	Bicyclohumulenone, plagiochiline A, plagiochilide,plagiochilal B, menthanemonoterpenoids,triterpenoidal saponins, riccardins A and B, sacullatal
33.	*Platyhypnidium riparioides*	Phenolics
34.	*Polytrichastrum alpinum*	Benzonaphthoxanthenones (Ohioensins F and G)
35.	*Polytrichum formosum*	Phenolics
36.	*Porella platyphylla*	Custunolide, isoeremanthin, 3-β-hyderoxycostunolidecinnamolide
37.	*Rhodobryum roseum*	Prevents lipid peroxidation and augments antioxidants

38.	*Radula complanata*	Bibenzyl, 3-methoxy bibenzyl, 2-terpinine ethylbenzene
39.	*Rhodobryum giganteum*	Triterpenoidalsaponins, p-hydroxycinnamic acid,7-8-dihydroxycoumarin
40.	*Riccardia* sp. (Plate 2: Figure 12)	Bicyclohumulenone, plagiochiline A, plagiochilide,plagiochilal B, menthanem onoterpenoids,triterpenoidal saponins, riccardins A and B, sacullatal
41.	*Sanionia uncinata*	Antioxidant enzymes
42.	*Scapania parvitexta*	Subulatin
43.	*Sphagnum magellanicum*	Phenolics
44.	*Thudium tamariscinum*	Phenolics, terpenoids
45.	*Wiesnerella denudata*	Tulpinolide, costunolide, zaluzanin C & D, 2α acetoxy-zaluzanin

Plate 1

Figures 1-6: 1. *Chiloscyphus polyanthus*; 2. *Conocephalum conicum*; 3. *Diplophyllum albicans*; 4. *Dumortiera hirsuta*; 5. *Frullania tamarisci*; 6. *Marchantia polymorpha*.

Plate 2

Figures 7-12: 7. ***Mnium*** **sp.;** 8. ***Pallavicinia lyelli*****;** 9. ***Philonotis fontana*****;** 10. ***Plagiochila*** **sp.;** 11. ***Plagiomniuni*** **sp.;** 12. ***Riccardia*** **sp.**

3. Conclusion

Due to their unique thallus organization, phytoconstituents and defense responses, bryophytes have all the potential to be used in efficacious remedies to prevent and cure viral infections. These plants not only have antiviral activities but also provide natural antioxidants. Since they exist everywhere except the oceans, and can grow without any special need hence, readily available with low cost and can be used without any harmful effects on the human body. Therefore, in future they can be used as main reservoir of beneficial phytoconstituents to make natural pharmaceuticals and nutraceuticals with therapeutic utility against the viral infections.

The antioxidants which are naturally present in these plants have great potential to boost the immunity of human beings against a range a virus, including COVID-19 by quenching the free radicalsto protect the health status of cells. Increasing occurrences of viral diseases demand the use of natural therapeutic antioxidants as consistent dietetic complements for providing improved and effective healthcare. Earlier, the focus of the scientists was on the angiosperms but now there is need to explore the bryophytes second largest group of plants for the natural healthcare systems. Since nothing is created on this planet either without the need or with no benefit to human kind therefore these plants with rich storage of useful biomolecules can also offer a more competent resource of many phytoconstituents that could be used for innovative medication.

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Conflict of interest

The author declares that there are no conflicts of interest relevant to this article.

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