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Exploring the role of phytochemicals as biopharmaceuticals targeting Acute Respiratory Distress Syndrome (ARDS) virus: An Overview

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ABSTRACT

ALI (Acute lung injury) and its more fatal form ARDS (acute respiratory distress syndrome) together represent a broad spectrum of lung diseases, which are characterized by the abrupt onset of pulmonary inflammation with fluid filled alveoli resulting in hypoxia. With the advancement of several diagnostic tools, especially discovery of multiplex RT-PCR, increased the chance to investigate the involvement of different respiratory viruses in causing ARDS. There are several different viruses responsible for ARDS and among them few are capable of causing pandemic. Influenza viruses such as H5N1 and H1N1 causing pandemic in 2009. Also among different corona viruses, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and most recently a novel betacoronavirus strain, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been identified. Till date, the therapy against virus induced ARDS has not been optimized. Naturally existing phytochemicals and plant biotechnology could offer prospective solutions for the treatment against virus induced ARDS by developing inhibitors, low-cost vaccines and antibodies, which could not only be useful for treatment but could also be used for diagnosis. In this present COVID-19 pandemic, use of plant based therapeutic approach has already been adopted by several pharma companies to treat ARDS and there are several molecules currently under clinical trials with encouraging results. This review provides detailed outlook on ARDS pandemic causing viruses, pathophysiology of viruses and role of phytochemicals and plantibodies as anti-viral agent. Further, it summarizes list of phytochemicals and their mode of action in these pathogenic viruses.

Keywords: ARDS, Pulmonary viral infections, pathophysiology, SARS-CoV-2, Influenza, Phytochemicals.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinically defined pulmonary edema mainly arises due to a pulmonary inflammation, but does not involves cardiovascular system. According to European Society of Intensive Care Medicine in 2012 ARDS is classified in three categories mild, moderate and severe.[1,2] High viral loads in lung can cause ARDS, chiefly by causing localized disease (pneumonia) and/or systemic disease (sepsis, sepsis syndrome and septic).[3] Viral induced lung damage can be broadly categorized into two classes: respiratory viruses, such as coronavirus, influenza virus induced community-acquired viral disease,[4] and Herpes simplex virus (HSV) or cytomegalovirus (CMV) induced nosocomial viral infection.[5,6] Community-acquired-pneumonia is most frequently caused by the influenza, rhinovirus and several strains of coronavirus.[7,8] However in the last couple of decades five different viruses were foundto be responsible for major outbreak in pandemic scale causing acute respiratory failure and ARDS, which includes influenza viruses[9,10] and three different strains of betacoronaviruses.[11-13] However the scariest pandemic (COVID-19) spread recently in December, 2019 by thesevere acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2, belongs to the family *Coronaviridae* in the order *Nidovirales*.[10,14] One common feature associated with SARS-CoV-2 & other related coronaviruses is initial low level of inflammatory response coupled with sudden burst of pro-inflammatory cytokines at the later time points. In fact, all the severe cases of COVID-19 have been associated with excessive or uncontrolled levels of cytokines resulting in hyper inflammation, ARDS and mortality. This phenomenon commonly referred to as 'Cytokine storms' are a common complication not only in case of COVID-19 but also in severe cases of SARS & MERS.[15] According to the latest data by World Health Organization (WHO), up to the September, 2020, the number of confirmed cases in world reached 36,996,501 of which 1,069,476 were dead. Still the mortality graph isrising at a very fast-erpace. This precarious situation is added up by the unavailabilityof vaccines or drug to protect human race against this epidemic. In the current situation when COVID-19 pathogenesis was poorly understood it is better to reuse the drugs/vaccines which are currently in hand.

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Purified natural products, traditional herbal medicines and genetically engineered plants constitute a rich resource for novel antiviral biopharmaceuticals. For the last three decades, plant derived products become essential for the development of drugs, antibodies and vaccines against various pathogenic diseases including viral infections.[16-18] Several natural compounds already shown high potential of anti-viral efficiency against different strains of influenza virus and coronavirus including Severe acute respiratory corona virus (SARS-CoV)and Middle Eastern respiratory corona virus (MERS-CoV).[17,19] However literature survey has also established the role of plant based substances as anti-inflammatory drugs, which proves useful to control delayed cytokine surge in different organs associated with influenza and corona virus infection[20,21] and as SARS-CoV-2 shares much of a sequence homology and pattern of transmission and viral entry into the host cell with other corona viruses and influenza viruses, use of these plant based substances could be found valuable in treatment against SARS-CoV-2 infection. This review first tried to explain the similar immune pathogenesis mechanisms of ALI and ARDS causing viruses (SARS-COV-2 and other coronaviruses and influenza viruses). Secondly, this article also explainsthe anti-viral potentials of different phytochemicals, discussing their anti-inflammatory properties with no or less side effects. We enlisted available plant based treatment against ARDS caused by influenza viruses along different corona viruses with a special reference to the recent research progress in SARS-CoV-2 research and the knowledge from researches on ARDS.

EPIDEMIOLOGY OF VIRUSES CAUSING ARDS

ARDS basically consists of a wide range of diseases having severe infections both at pulmonary or extra-pulmonary regions. These infections may include one of the most common contagious form; Community-acquired pneumonia (CAP). ARDS may also be caused by viral infections of the lungs, ultimately resulting in tissue damages in the pulmonary and extra-pulmonary region.[3] CAP is one of the most common cause of developing ARDS and involvement of various respiratory viruses are recognized in patients with severe CAP and ARDS problems.[22-24] In 5-10% cases of CAP, various strains of respiratory viruses are found to be responsible,[4,25] among which influenza viruses and rhinoviruses are predominant.[4,5] Other than these viruses, several seasonal respiratory viruses or pandemic viruses also caused viral pneumonia and ARDS,[26] which are discussed below.

Respiratory viruses causing Seasonal outbreak

Seasonal viruses, which causes CAP most commonly include Respiratory Syncytial Virus (RSV), non-pandemic influenza, rhinoviruses, parainfluenza, adenovirus, coronaviruses, and human meta-pneumovirus(hMPV).These viruses cause up to 10% and in some case studies contributing up to 40% of the viral-induced seasonal outbreaks.[4,25,27] Among these outbreaks, influenza and rhinoviruses can cause severe pneumonia, which could lead to ARDS.[28,29] There are several subtypes of influenza & corona viruses, which are determined by presence of envelope glycoproteins having either hemagglutinins (HA) or neuraminidase (NA) enzyme activity[30] or variations in the functional sites of receptor-binding domain (RBD) of the surface spike protein.[31] High mutational ratesand recurrent genetic rearrangements in these viral proteins contribute to the increasing antigenic variabilityin these virus stains, resulting in new pandemic strains.

Respiratory viruses causing pandemic outbreaks

Over the past decade, five different viruses were accountable for acute respiratory failures and ARDS, which became pandemic are: severe acute respiratory syndrome corona virus (SARS-CoV) in 2002, two influenza virus strains – avian influenza A H5N1 & influenza A H1N1 2009, the Middle East respiratory syndrome corona virus (MERS-CoV) in June, 2012 a novel beta-coronavirus strain severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) most recently in 2019 (Figure 1).[26]

Severe acute respiratory syndrome corona virus (SARS-CoV)

SARS-CoV was first recognized in in Guangdong, China, in November, 2002 and then spread fast globally to 29 different countries, resulting in more than 9.6% mortality[32] with initial symptoms of shortness of breath and damage in the lung tissues, confirmed by chest X-rays in almost all the patients.[32,33] 20–30% of the SARS patients required ICU facility and a large number of them required mechanical ventilation (MV) to counter ARDS.[33-36] SARS patients are treated with a combination therapy of ribavirin, protease inhibitors, and INF that. However, none of these drug treatments was effective. Thus health personals mostly depend on good supportive care.[37]

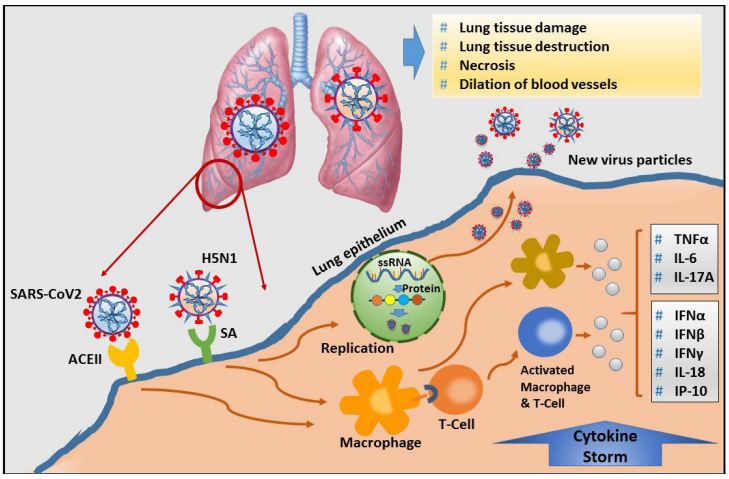

Figure 1 Schematic representation of the pathophysiology of acute respiratory distress syndrome (ARDS) and cytokine storm with possible effects. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; H5N: Avian influenza; ACEII: Angiotensin-converting enzyme 2; SA: Sialic acid receptors. Following entry of SARS-CoV-2/H5N1 into the host, the virus uses its spike protein to bind to ACE2/SA receptors, invading the respiratory airway epithelial cells, causing damage to the upper respiratory epithelium. Subsequently its releases pro-inflammatory cytokines and interleukins like IL-6, IL-18, TNF-α, IFN-γ and several other factors that can further trigger inflammation (Inflammasome activation) especially in the lower respiratory tract. Activation of macrophages also takes place to amplify the inflammatory cascade resulting in cytokine storm syndrome Excessive cytokine release resulting in damage and destruction of the lung tissue leading to widespread damage of blood capillaries in the lungs

Influenza viruses- avian influenza A H5N1 and influenza A H1N1:

Severe pneumonia caused by avian influenza A virus-H5N1quickly progressed to ARDS with a high case-fatality rate (nearly 60%).[38,39] Symptoms for H5N1 infection in humans are mostly nonspecific, including fever, headache, vomiting, diarrhea, dyspnea, cough, etc. But in majority the pneumonia rapidly causes ARDS mostly in aged people (>65year. However disease spread occurs due to avian to human transmission not due to human to human transmission.[38,39] Majority of Patients are treated with high-dose oseltamivir (300 mg daily) for 10 days period and for oseltamivir-resistant H5N1 strain zanamivir used intravenously. In 2009, the influenza A H1N1 virus outbreak induces multiple clinical syndromes like afebrile upper respiratory illness, fulminant viral pneumonia affecting mostly children and young adults.[40] Symptoms for H1N1 infection in humans are mostly diffuse viral pneumonitis associated with severe hypoxemia and ARDS.[9,40] Short incubation (24 hrs) period and rapid disease progression occurred in most of the cases. Viral infection detected in the entire respiratory tract. Like H5N1 oseltamivir and zanamivir used to treat patients with a good success rate.[9,40-42]

Middle East respiratory syndrome coronavirus (MERS-CoV)

After a decade In June 2012, the first MERS case reported in Jeddah, Saudi Arabia. Nearly similar clinical symptoms are observed in MERS case which is characterized by progressive acute pneumonia. It affected all most all the age groups with a slight predominance for patients aged between 40 to 50 years. MERS-CoV continues to infect humans sporadically in clusters of communities, and also via nosocomial infections in the Middle East regions. As of Feb 29, 2020, 2494 new cases of MERS-CoV infection have been registered worldwide with a mortality rate of 34·0%, majority from countries in Middle-East regions.[43]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

The current worldwide epidemic started from end of 2019 by novel Coronaviruses belong to the family *Coronaviridae* in the order *Nidovirales*[44] Being a close relative of SARS-CoV and MERS-CoV this beta-coronavirus has shown similar symptom like fever, non-productive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia in the upper respiratory tract which rapidly leads to ARDS.[45] SARS-CoV-2 has mortality rate (~3%), with a much higher transmissibility (it spread to >200 countries, within a period of three months).[46] Still the numbers are increasing in a very high rate.

PATHOPHYSIOLOGY OF THE HUMAN RESPIRATORY VIRUSES CAUSING ARDS

Emergence of several zoonotic viruses appeared to be serious risk for the human population by the beginning of this century. Among them recurring appearance of different human respiratory viruses are much prevalent like SARS-CoV, avian influenza A H5N1, influenza A H1N1, MERS-CoV, SARS-CoV-2. All these viruses cause respiratory disease with clinical manifestation varies from mild to even fatal cases of ARDS. The outcome of these viral infections are mostly common, which can be studied by comparing and associating their pathophysiology. In general these viruses regulate a set of variable host factors, thus affecting host immune response, leading to the acute lung injury (ALI), severe pneumonia and ARDS. Understanding the pathophysiology of influenza and coronaviruses will provide valuable information for the

development of vaccine/therapeutic drugs against these viral infections.

Pathophysiology of Influenza viruses

Influenza A viruses infection involve a wide variety of disease spectrum in respiratory tract, ranging from mild upper respiratory symptoms to acute respiratory failure and ARDS.[47] Infection with influenza viruses results in some common and nonspecific symptoms like fever, dyspnea, cough, diarrhea, etc. along with severe conditions like acute respiratory failure and ARDS.[39] This severe hypoxemic respiratory failure and ARDS were also hallmarks of the 2009 influenza pandemic, which ultimately leads to the ICU admissions for most of the patients.[40] Reports stated that there is a correlation between viral load and the severity of the respiratory infection with an enlarged risk of the requirement of mechanical ventilation facility.[48] Influenza viruses mainly targets alveolar epithelial cells, which are the preliminary defense layer to protect against respiratory infections.[49] Histological studies revealed that influenza A (H1N1) virus infection is associated with diffuse alveolar damage with inflammation, leading to fibrosis and edema in the lung tissue along with uniform distribution of viral antigens throughout the lung parenchyma.[50] Early exposure of the virus to the alveolar macrophages results in the advancement of the disease, damaging the gas exchange to allow exposure of viruses to the endothelial cells.[51] Disintegration of this fragile layer leads to the huge production of pro-inflammatory cytokine upon viral antigen exposure to the endothelial layer that further stimulates the host derived innate and adaptive immune responses.[52] The viral infection further targets innate immune pathways, amplifyingpro-inflammatory signals and contribute to the formation of inflammasome. This also stimulates secretion of IL-1β and IL-18 secretion that has been associated in numerous studies as influenza-associated pathology.[53] Following cytokine and chemokine release, neutrophil and inflammatory monocytes are recruited to the alveolar tissue, leading to the tissue-damage by producing Matrix metalloproteinase(MMPs) and by secreting extracellular traps (NETs).[54,55]

This inflammatory response is initiated with the recognition of the pathogen-associated molecular pattern (PAMP) from the virus by the host pattern recognition receptors (PRRs) of innate immune cells,[56] releasing huge amount of pro-inflammatory cytokines[57] from the host cells, sometimes denoted as "cytokine storm".[58] Activation of PRRs further stimulates c-Jun N-terminal kinase (JNK), which induce translocation of NF-kB to the nucleus to produce pro-inflammatory cytokines.[59] This inflammatory circuit further escalates cytokine storm.[60] Severe cytokine storm is markedlyrelated with higher levels of pro-inflammatory cytokines such as interferons (IFNs),[61,62] tumor necrosis factors (TNFs),[63] interleukins (ILs),[59] and chemokines, identified in ARDS patients.[38] Also, chemokines sped up the process of tissue damage by specific chemotactic activities that recruited monocytes and T-lymphocytes to migrate into the site of inflammation.[64] These chemotactic activities are aided by several proteins like IL-8, monocyte chemoattractant protein MCP-1, interferon-induced protein (IP)-10, macrophage inflammatory protein (MIP)-1, and monokines induced by IFN-c (MIG), which were found abnormally elevated in severe H5N1 influenza infection, in which IL-8 and MCP-1 were mostly dominant.[65] Both CD4 and CD8 T cells are also responsible for the lethal lung injury associated with influenza infection in humans. This injury can be triggered by the interaction between antigen-specific CD8 T cells and the influenza HA antigen.[66] ARDSassociated with influenza infection can also be characterized by the early secretion of CD4 T cell mediated Th1 and Th17 cytokines.[67]

Pathophysiology of Corona viruses

Gross pathology of the SARS-CoV, MERS-CoV, SARS-CoV-2 and other human corona virus infection exhibits a variable degree of consolidation, edema, congestion of the lungs, along with diffuse alveolar damage (DAD) at the respiratory tract. Although the severity of the infection leads to the ARDS, which depends on the viral loads and exposure. The corona virus infection also leads to the fibrosis in the alveolar epithelial cells, hemorrhage and also stimulates inflammatory cells like monocytes, macrophages, lymphocytes and neutrophils to infiltrate in alveolar wall and lamina.[68-71] Similar to the Influenza virus cases, the development of ARDS in the more severe form of viral infections with SARS-CoV, MERS-CoV or SARS-CoV-2 in human cases may be related to several factors like induction of cytokines, chemokine etc. The severe corona virus induced pulmonary damage may be endorsed due to an excessive host immune response mediated by the production of pro-inflammatory cytokines like type I IFNs, IL-12, IL-6 etc.[45,72,73] In the blood of SARS-CoV, MERS-CoV or SARS-CoV-2 infected patients with ARDS condition, the level of different chemokines such as IP-10, MCP-1, CXCL-1, CXCL2, and IL-8 etc. also get up-regulated.[73-75] Literature survey also stated that, the elevated levels of cytokine and chemokine in corona virus infected patients are associated with the increasing accumulation of neutrophils and monocytes in the patients' lung tissues and peripheral blood, suggesting that these cells may play a role in ARDS pathophysiology.[76-78] The high

level of cytokine and chemokine rapidly attract many inflammatory cells, such as neutrophils and monocytes, resulting in extreme infiltration of the cells into lung and thus causing severe damage to the lung tissue or triggering ARDS. Pulmonary recruitment of these cells along with lymphopenia (a rapid decrease of CD4+ and CD8+ T cells) is also a hallmark of SARS-CoV-2 infection as more than 80% of patients with SARS-CoV-2 infection showing this condition.[78,79] Presence of high amount of neutrophils and other inflammatory cells causes ARDS by secreting excessive proteases and reactive oxygen species.[80,81] This affects the efficiency of gas exchange through alveoli, causing difficulty in breathing, hypoxia and also increases the chance of secondary infection in the lungs.[82,83] The elevated levels of cytokines, chemokine, and increasing infiltration of inflammation together can cause septic shock and multi-organ failure, along with myocardial damage and circulatory failure in extreme cases.[84-86]

DEVELOPMENT OF PROPHYLACTIC AND THERAPEUTIC TREATMENTS AGAINST ARDS

Presently, there is no specific treatment for virus induced ALI or it's more severe form:ARDS. Although, corticosteroids have been used for the treatment of ALI for several years. But it didn't show promising results in clinical trials and have been found with several side effects in corticosteroids treated patients with ALI.[87,88] Other clinically used anti-inflammatory drugs also been reported having several disadvantages, which includes adverse effects and a high cost. Thus the use of plant based vaccines and therapeutic drugs for the treatment of ALI/ARDS could fill up this gap. Several phytochemicals have been traditionally used for the treatment against inflammation and have shown promising results with less or zero side effects.[46,89]

'Antiviral agent' against ARDS

Nearly 40% of currently available drugs came from phytochemical resources either directly utilizing phytochemicals or a synthesized product.[90] The term 'antiviral agent' indicates all those compounds (other than vaccine and antibody) which can provide a protective or therapeutic effect to viral infected host.According to World Health Organization (WHO) majority of people from underdeveloped countries dependent on cheap phytochemical as their medicinal source. In this context, some of the medicinal plants and their respective compounds used for the treatment against virus induced ALI/ARDS are summarized in Table 1.

Search against potential antiviral phytochemical can be carried either through random screening of phytochemicals or based on traditional knowledge, practices and Ethno-pharmacology. However it was found that the second approach is more successful than the previous one.[91] From long agemedicinal plants were successfully used against various respiratory and immunological disorders (like bronchial asthma, cold, cough etc.).[92] Different plants derived compounds are already reported for their antiviral activity against ARDS causing virus. Lists of antiviral compounds are summarized in Table 2.

Vaccines against ARDS

A vaccine is a therapeutic preparation usually administered for developing active immunity for an infectious disease. Now a day's, molecular farming is utilized where plants are used as bioreactors to produce vaccines.[93] Efficient mass scale synthesis of genetically engineered proteins, decreasing contamination risk, easy and cheap purification method remains the major advantages for this plant based biopharmaceuticals production.[94] Plant vaccine candidates against swine influenza,rabies,andhepatitisB are already entered in clinical trial. To fight against ARDS causing virus several approaches has been adoptedto develop vaccine (Table 2). Although none of them are available till now in the market but many of have entered in the clinical trials (Table 3).[18] In the current COVID-19 scenario the need of plant based vaccine escalated several times. The knowledge of previous plant vaccines helps to reach that goal quickly and efficiently.

Plants are also genetically engineered to form human antibodies or part of antibodies and subsequently used as a vaccine for therapeutic cause and the term "Plantibodies" has been created to describe these products. It is considered as an effective technique as plants have already been proven to produce wide varieties of proteins that are free of mammalian toxins and pathogens.

The global pandemic caused due to COVID-19 virus has prompted the scientific community to divulge all their available resources to battle against the pathogen. In this respect several companies and research groups have started developing antibodies against COVID-19 in search of a vaccine.. Medicago Inc. reported successful production of VLPs against S protein of SARS-CoV-2 virus in huge capacity in a transient expression system (www.medicago.com/en/pipeline/). Many other companies like iBioinc. (www.ibioinc.com/pipeline), Nomad (www.nomadbioscience.com/), Ventria (ventria.com/), Greenovation Biopharmaceuticals (www.greenovation.com/), protalix (ww.protalix.com) along with

Table 1 Phytochemicals derived from medicinal plants and their mode of action

Virus	Medicinal plant	Plant product	Mode of action	Reference
SARS-CoV	*Lycoris radiate*	Lycorine, isolated fromLycoris radiate	NA	[95]
	Glycyrrhiza glabra	Glycyrrhizin	NA	[96]
	Houttuynia cordata	Aquous extract of whole plant	Inhibiting the viral 3CL protease and blocking the activity of viral RNA-dependent RNApolymerase2	[97]
	Boenninghauseniasessilicarpa	Leptodactylone	NA	[98]
	Hippeastrum hybrid	Lectins (Agglutinins:mannoses pecific) present in diaminopropane extract	inhibiting viral attachment and another target at end of replication cycle	[99]
	Galanthus nivalis			
	Narcissus pseudonarcissus			
	Lycoris radiata			
	Allium porrum			
	Allium ursinum			
	Cymbidium hybrid			
	Listera ovata			
	Epipactis helleborine			
	Tulipa hybrid	Lectins (GlcNAc-specific) present in diaminopropane extract		
	Morus nigra	Gal-specific present in diaminopropane extract		
	Nicotiana tabacum	Lectins (Man/Glc-specific) present in diaminopropane extract		
	Urtica dioica	Lectins(Gal/GalNAc- specific) present in diaminopropane extract		
	Morus nigra	Lectins (GalNAc(>Gal)specific) present in diaminopropane extract		
	Cladastris lutea	Lectins (GalNAcα(1.3)Gal>Gal NAc>) present in diaminopropane extract		
	Polygonatum multiflorum	Lectins(Gal-specific) present in diaminopropane extract		
	Iris hybrid	Lectins (Man/GalNAc- specific) present in diaminopropane extract		
	Artemisia annua	95% EtOH extract ofWhole plant	NA	[95]
	Pyrrosia lingua	Chloroform extract ofleaf	NA	
	Lindera aggregate	95% EtOH extract ofroot	NA	
	Lycoris radiata	lycorine	NA	
SARS-CoV BJ01	*Galla chinensis*	Luteolin Tetra-O- galloyl-β-Dglucose	By binding with S2 subunit and preventingentry	[100]
SARS-CoV FFM1	*Toona sinensis*	Water extract of leaf	Inhibits ofviral growth	[101]
	Laurus nobilis	Essential oils present in β-ocimene, 1,8-cineole, α-pinene, β- pinene	Inhibits of viral replication	[102]
	Thuja orientalis	Essential oils present in α-pinene, δ-3-carene,α-cedrol	Inhibits of viralreplication	
SARS-CoV (Hong Kong strain)	*Cibotium barometz*	75% ethanol extract of of whole plant	Inhibis 3CLpro and viral replication	[103]
	Gentiana scabra			
	Dioscorea batatas			
	Cassia tora			
	Taxillus chinensis			

Table 1 ***Continues***

Virus	Medicinal plant	Plant product	Mode of action	Reference
SARS-CoV PUMC01 F5	*Cinnamomi sp.*	Procyanidin A2	Play roles in Early stage inhibition of viral entry (clathrin-dependententocytosis pathway)	[104]
SARS- CoV Sprotein	*Rheum officinale*	Emodin	Inhibisbinding of S protein toACE2	[105]
	Polygonum multiflorum	Emodin	Inhibis binding of S protein toACE2	
SARS-CoV 3CLpro	*Isatis indigotica*	Sinigrin, Indigo, β-sitosterol, Aloe-emodin and Hesperetin	Inhibis 3CLpro	[106]
	Rheum palmatum	Possiblyanthraquinones	Inhibis 3CLpro	[107]
	Salvia miltiorrhiza	Tanshinone IIA,Tanshinone IIB, Methyl tanshinonate, Cryptotanshinone, Tanshinone I, Dihydrotanshinone Iand Rosmariquinone	NA	[108]
	Torreya nucifera	Amentoflavone,Bilobetin, Ginkgetin, Sciadopitysin	NA	[109]
	Salvia miltiorrhiza	Tanshinone IIA,Tanshinone IIB, Methyl tanshinonate, Cryptotanshinone, Tanshinone I, Dihydrotanshinone Iand Rosmariquinone	NA	[108]
SARS-CoV PLpro	*Broussonetia papyrifera*	3'-(3-methylbut-2-enyl)- 3',4,7- trihydroxyflavane	Inhibis SARS- CoV Plpro.	
	Psoralea corylifolia	Bavachinin, Neobavaisoflavone, Isobavachalcone, 4'-O- methylbavachalcone, Psoralidin andCorylifol A	Inhibis SARS- CoV Plpro.	[110]
	Paulownia tomentosa	Tomentin (A-E)	Inhibis SARS-CoV Plpro.	[111]
MARS-CoV	*Broussonetia papyrifera*	Kazinol F, Broussochalcone A	Inhibis MARS-CoVPlpro.	[112]
Influenza virus	*Sambucus nigra*	Extract of fruit	A randomized, double-blinded A randomized, double-blindedan efficient, safe and cost-effective treatment for influenza	[113]
	Allium oreoprasum *Androsace strigilosa* *Bergenia ligulata* *Nerium indicum*	Methanolic and methanolic-aqueous extracts	influenza surface glycoprotein hemagglutinin (HA) is a potential target for antiviral drugs because of its key roles in the initial stages of infection: receptor binding and the fusion of virus and cellmembranes	[114]
	Asparagus filicinus	steroidal saponins,furostanol glycosides, furostanosides	NA	[115]
	Chaenomeles sinensis	high molecular weightpolyphenols	NA	[114]
	Myrica rubra	ethanol extract	NA	
	Verbascum Thapsus	methanolic andmethanolic-aqueous extracts	NA	[115]
	Berginia ligulata	Plant extract	NA	[116]
	Caesalpinea sappan	Sappan chalcones	NA	[117]
	Gardenia sp.	Plant extract	NA	[118]
	Glycyrrhiza glabra	Glycyrrhizin	NA	[96]
	Neerium indicum	Plant extract	NA	[116]
	Punica granatum	Plant extract	NA	[119]

Table 1 ***Continues***

Virus	Medicinal plant	Plant product	Mode of action	Reference
Influenza virus A	*Asparagus filicinus Buch.-Ham. ex D.Don. (Asparagaceae)*	Methanolic and methanolic-aqueous extracts	Influenza surface glycoprotein hemagglutinin (HA) is a potential target for antiviral drugs because of its key rolesin the initial stages of infection: receptor binding and the fusion of virus and cellmembranes	[114]
	Astilbe rivularis			
	Verbascum thapsus L. (Scrophulariaceae)			
	Bergenia ciliata	Polyphenols containing methanolic-aqueous extracts	NA	
Influenza B virus	*Scutellaria baicalensis(Lamiaceae)*	Flavonoids: baicalein,baicalin, and wogonin	NA	[114]
	Prunus mume (Rosaceae)	Lectin-like molecule(s)isolated from the fruit-juice	NA	
H3N2	*Hypericum japonicum(Hypericaceae)*	Ethanol extract	NA	[120]
H1N1	*Alpinia officinarium*	Diaryl heptanoids	NA	[118]
	Andrographis paniculata	Andrographolide	NA	[121]
	Ephedra sinica	Catechin[c]	NA	[122]
	Pandanus amaryllifoius	Pandanin	NA	[123]
	Prunus mume	Lectin-like molecule(s)isolated from the fruit-juice	NA	[114]
	Curcuma longa	Plant extract		[124]
	Sambucus nigra	Plant extract		
H5N1	*Andrographis paniculata*	Plant extract		
H3N2	*Prunus mume*	Lectin-like molecule(s) isolated from the fruit-juice	NA	[114]
	Scutellaria baicalensis	Flavonoids: baicalein,baicalin, and wogonin	NA	
H3N3	*Elsholtzia rugulosa*	apigenin, luteolin, apiin, galuteolin and luteolin 3'-glucuronylacid methyl ester	NA	
Respiratory syncytial virus	*Blumea laciniata*	Polyphenols	NA	[125]
	Elephantopus scaber		NA	
	Laggera pterodonta		NA	
	Mussaenda pubescens		NA	
	Schefflera octophylla		NA	
	Scutellaria indica	Flavonoids: baicalein,baicalin, and wogonin	NA	
	Selaginella sinensis	Amentoflavone,IC50 of5.5 µg/ml	NA	[114]
	Barleria prionitis	Iridoids	NA	
	Glycyrrhiza glabra	Glycyrrhizin	NA	[96]
	Wickstroemia indica	Daphnoretin	NA	[126]
	Ageratum conyzoides	Polyphenols	NA	[125]
	Clausena lansium		NA	
	Emilia sonchifolia		NA	
	Evodia lepta		NA	
	Kyllinga brevifolia		NA	
	Rostellularia procumbens		NA	
	Rostellularia procumbens		NA	
	Wedelia prostrata		NA	

Table 1 *Continues*

Virus	Medicinal plant	Plant product	Mode of action	Reference
Newcastl e	*Avicennia marina*	Methanolic extract	NA	[127]
	Nigelia sativa	Plant extract	NA	
	Zizyphus spira-christi	Plant extract	NA	
Adenovir us	*Artimisai princepsvar. orientalis*	hot water (HW) extract	NA	[114]
	Ardisia squamulosa	hot water extract	NA	
	Boussingaultia gracilis varpseudobaselloides	hot water (HW) extract	NA	
	Serissa japonica	hot water (HW) extract	NA	
	Ocimum basilicum	Apigenin, Linalool, andUrolic Acid	NA	

Table 2 **Classified phytochemicals targeting ARDS causing viruses**

Phytochemicals	Bioactivity	Targeting ARDS Virus	Reference
Lycorine	Ribonucleoprotein complex inhibit viral replication	H5N1	[128]
		HCoV-OC43, MERS-CoV	[129]
Mannose specific Lectins	Lectins bind N-Glycosylation sites on Spike Protein inhibiting viral attachment	RSV, H1N1, H5N1	[130]
		SARS-CoV	[99]
Procyanin A2	Interact with sialic acid binding site of Hemagglutinin.	H5N1, H1N1	[131]
	Target clathrin mediated endocytic pathways	SARS-CoV	[96]
Emodin	In IAVs, it induce anti-inflammatory pathway Nrf2.	H5N1, H1N1, H3N2	[132]
	In CoVs, it binds and inhibit Spike protein with ACE-II receptor.	SARS-CoVs	[97]
Sinigrin	Anti-inflammatory role by inhibiting TNF-α	H5N1, H1N1, H3N2	[133]
	Targeted inhibition of 3C-Like proteases	SARS-CoVs	[98]
Tanshinone	Targeted inhibition of 3C-Like proteases	SARS-CoVs	[100]
Kazinol F	Targeted inhibition of 3C-like and papain-like (nsp3) proteases	SARS-CoVs	[112]
Tomentin A	Targeted inhibition papain-like (nsp3) proteases	SARS-CoVs	[111]
Baicalein	Inhibit neuraminidase activity of influenza virus	HINI,	[134]
	Targeted inhibition of 3C-Like proteases	SARS-CoVs	[135]

Table 3 **List of plantibodies designed against ARDS viruses**

Target Virus	Target protein and Vaccines type	Major Advantages	Reference
SARS-CoV-1	S protein; multiepitope vaccines	Expressed of SARS-CoV-1 Spike protein (S1) N-terminal fragment in stably transformed tomato and low- nicotine tobacco plants. This helped to induce IgA and IgG responses in mice.Process allows inheritable antigen production and seed bank generation;	[136]
SARS-CoV-1	S protein; multiepitope vaccines	Expressed GFP tagged partial SARS- CoV-1 S protein (amino acids 1-658) was in transiently transformed tobacco leaves and stably transformed in both tobacco and lettuce. No immunizationassays were performed.Expressed SARS-CoV-1 nucleo protein transformed Nicotianabenthamiana. This helped to induce high levels of IgG1 and IgG2a in mice along with up regulation of IFN-γ and IL-10 in splenocytes.This transient nuclear genome transformation approach helps in rapid production and quick implementation atthe industrial level.	[137-139]

Table 3 ***Continue***

Target Virus	Target protein and Vaccines type	Major Advantages	Reference
SARS-CoV-1	multiepitope vaccines	Expressed GFP tagged partial SARS- CoV-1 S protein (amino acids 1-658) was in transplastomic tobacco plants. This transplastomic technology provideshigher productivity, biosafety (as transgene inherited maternally only) etc.	[136,140]
H1N1 A/California/0 7/2009(pdmH1N1) strain	Haemagglutinin (HA);VLP vaccines	Intramuscular (i.m.) immunization in mice twice through combination of i.m. priming and (intranasal) i.n. boosting. High levels of antibodies titers found. Less amount of virus particle detected in lung homogenate with comparison toinactivated influenza vaccine (IIV) group.	[141]
H1N1 A/California/0 7/2009(H1/Cal) strain H3N2 A/Victoria/361/11 (H3/ Vic) strain	Haemagglutinin (HA); VLP vaccines	In a Phase II clinical trial,due to single dose immunization (Alhydrogel as an adjuvant) homologous and heterologous antigen-specific CD4+ T cells were generated along with formation of cytokines like IFN-γ, IL-2, and/or TNF- α.	[142]
H1N1 A/California/0 7/2009 strain	Haemagglutinin (HA); VLP vaccines	The plant-made VLPs were isolated, subjected to endosomal processing and cross-presentation. In vivo evaluation done in human monocyte-derived macrophages.	[143]
H1N1 A/California/0 7/2009 strain	Haemagglutinin (HA); VLP vaccines	Better Tcell response found due to administration of plant-made vaccine to mice than inactivated H1N1 vaccine (IIV) along with higher CD4+ (TNF-α, IFN-γ) and CD8+ (IFN-γ) responses.	[144]
H1N1 A/California/7/ 09 strain; H5N1 A/Indonesia/5/ 05 strain	Haemagglutinin (HA); VLP vaccines	Upon exposure of plant-made VLPs to mice and human dendritic cells better in activation of CD4+ and CD8+ T cells recorded along with vitro higher IL-6, IL-10, and TNFα and CD83 expression. assays were performed using mouse and human DCs.	[145]
H1N1 A/California/7/ 2009strain; H5N1 A/Indonesia/5/ 05 strain	Haemagglutinin (HA); VLP vaccines	Upon exposure of plant-made VLPs to mouse dendritic cells interaction with activated antigen-presenting cells similar to the wild type virus.	[146]

different academic institutions are also working in the field of molecular farming (S R Mendoza, 2020).

CONCLUSION

Outbreak of covid-19 has led to a worldwide emergency situation to develop an antidote. In this scenario,development of plant vaccine, discovery of a phytochemical antiviral agent or repurposing of the traditional plant-based antiviral drugs can combat the virus in an urgent basis. Even in presence of advanced supportive treatment ARDS still is a threat to health professionals due to its high patient morbidity and mortality along with high cost treatment. Natural phytochemicals are always a vital source of antiviral chemical compounds and already shown much promise as potential antiviral compounds against ARDS caused by viruses. The information regarding extract, antiviral compounds, vaccine, derived from plant consolidate in this review may be useful for ARDS treatment caused by SARS-CoV-2. The knowledge of compounds like Leptodactylone, Lectins, Glycyrrhizin, Lycorine, Luteolin and Tetra-O-galloyl-β-D-glucose, etc.could accelerate drug discovery or vaccines development to fight against SARS-CoV-2 induced ARDS. Along with this development formation of monoclonal plantibody may provide another treatment process by substituting convalescent plasma transfusion method in a much less expensive and safer approach.

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CONFLICT OF INTEREST

Author's declare no conflict of interest.

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