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## Review

## Emerging paradigms of viral diseases and paramount role of natural resources as antiviral agents



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## HIGHLIGHTS

- Viral diseases with high mortality rates are major public health threat globally.
- Antiviral drugs and vaccines against deadly diseases are of urgent demand.
- Medicines from natural resources have shown low side-effect to human.
- Plants, fungi, and microorganisms are recognized as potent antiviral agents.
- Drugs from natural resources as future antiviral therapy are suggested.

## GRAPHICAL ABSTRACT



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## ABSTRACT

In the current scenario, the increasing prevalence of diverse microbial infections as well as emergence and re-emergence of viral epidemics with high morbidity and mortality rates are major public health threat. Despite the persistent production of antiviral drugs and vaccines in the global market, viruses still remain as one of the leading causes of deadly human diseases. Effective control of viral diseases, particularly Zika virus disease, Nipah virus disease, Severe acute respiratory syndrome, Coronavirus disease, Herpes simplex virus infection, Acquired immunodeficiency syndrome, and Ebola virus disease remain promising goal amidst the mutating viral strains. Current trends in the development of antiviral drugs focus solely on testing novel drugs or repurposing drugs against potential targets of the viruses. Compared to synthetic drugs, medicines from natural resources offer less side-effect to humans and are often cost-effective in the productivity approaches. This review intends not only to emphasize on the major viral disease outbreaks in the past few decades and but also explores the potentialities of natural substances as antiviral traits to combat viral pathogens. Here, we spotlighted a

**Abbreviations:** AIDS, Acquired immunodeficiency syndrome; CHIKV, Chikungunya virus; CHMs, Chinese herbal medicine; CIN, Cervical intraepithelial neoplasia; COVID-19, Coronavirus disease 2019; DAA, Direct acting antiviral agents; ELISA, Enzyme-linked immunosorbent assay; EPS, Exopolysaccharides; EVD, Ebola virus disease; HA, Hemagglutinin; HAV, Hepatitis A virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; HPV, Human papilloma virus; HSV-1, Herpes simplex virus type-1; HSV-2, Herpes simplex virus type-2; MERS-CoV, Middle East Respiratory Syndrome-coronavirus; NA, Neuraminidase; NIV, Nipah virus; ORFs, Open reading frames; PCR, Polymerase chain reaction; RT-PCR, Reverse transcription-polymerase chain reaction; SARS, Severe acute respiratory syndrome; SARS-COV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; VZV, Varicella zoster virus; ZIKV, Zika virus.

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**1. Introduction**

Viral diseases are colossal threat to human and animal population. Emerging viral disease outbreaks have grown rapidly in the recent years and it has created great impact on human life, leading to the sudden increase in mortality rates. Over the past two decades, there have been seven disease epidemics that resulted in huge economic losses in the world, of which Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome (SARS), Nipah virus (NIV) disease, West Nile virus disease, Avian Influenza, and Rift Valley fever are caused by viruses. Three modes of viral disease occurrence have been identified such as a) infection to a new host with no transmission, b) spread out to local populations, and c) epidemic or constant host-to-host transmission (Parrish et al., 2008).

Viruses generally consist of DNA or RNA (single/double stranded or positive/negative stranded) as their genetic material which is surrounded by a lipoprotein/glycoprotein covering. Table 1 shows the classification of selected animal viruses with DNA/RNA genomes. Viruses invade host and employ the host metabolic processes as well as

generate many copies of viral proteins that produce individual virus. The viral strains eventually get adapted to the host's immune systems. Pre-vaccination was found to be more effective approach. The transmission of virus also depends on the contact of people in a population. Since the viral strains are mutated and are getting adapted, it is difficult to develop the vaccines (Alexander and Kobes, 2011). The antiviral drugs play a very important role in today's life by suppressing the viral transmission and helps in host surviving. Analyzing and understanding the kinetics and dynamics of antiviral drugs aid in controlling the virus during pandemics because the hosts may expose to the infection again. Antivirals are effective in cases where there are no vaccines available for viruses like Influenza virus (Pepin et al., 2013).

The degree of virus infection depends on the immunity of human. The immunocompromised hosts are at higher risk of viral infection, thereby creating the situation worse for those people (Ye et al., 2013). The drug usage should be studied properly to analyze the results. Administration of drugs is taken into consideration for predicting the dynamics during epidemic waves. The emergence of pandemic has made every country to contain stockpile of antiviral drugs. These drugs are

**Table 1**  
Classification of selected animal viruses with DNA/RNA genomes.

Type of viruses	DNA/RNA material	Family	Virus	Capsid shape	Envelope	Virion size (nm)	Length of genome
DNA viruses	dsDNA	Herpesviridae	HSV	Icosahedral	Yes	200	130–230 kbp
			VZV	Icosahedral	Yes	150–200	125 kb
RT viruses	Reverse transcribing	Papillomaviridae	HPV	Icosahedral	No	54–60	5–8 kbp
		Retroviridae	HIV	Icosahedral	Yes	90	9 kb
		Hepadnaviridae	HBV	Icosahedral	Yes	42	3 kbp
RNA viruses	(+) ssRNA	Coronaviridae	COVID-19	Spherical	Yes	120	27–32 kb
			SARS-CoV	Spherical	Yes	120	27–32 kb
			MERS-CoV	Spherical	Yes	120	27–32 kb
		Flaviviridae	Dengue	Icosahedral	Yes	45	11 kb
			ZIKV	Icosahedral	Yes	50	9.7–12 kb
			HCV	Icosahedral	Yes	50	10 kb
	(–) ssRNA	Picornaviridae	HAV	Icosahedral	No	27	7 kb
			Togaviridae	CHIKV	Icosahedral	Yes	70
		Filoviridae	Ebola virus	Helical	Yes	970	18–19 kb
			Paramyxoviridae	NIV	Helical	Yes	150
		Hantaviridae	Measles	Helical	Yes	120–150	15 kb
			Hanta virus	Helical	Yes	80–120	14 kb
			Orthomyxoviridae	Influenza virus	Helical	Yes	100

important because studies showed that these drugs can help in controlling future pandemic. Though it might not cure it, the rate of transmission can be controlled (Becker and Wang, 2011).

Antivirals in combination with other antimicrobials help to combat resistant strains (Villa et al., 2017). Similarly, direct acting antiviral agents (DAA) was very effective in treating hepatitis C virus (HCV) infection. The DAAs constitute a combination of simeprevir, paritaprevir, ritonavir, daclatasvir, ledipasvir, ombitasvir, sofosbuvir, and dasabuvir. The proper intake of food along with the drugs had a great effect (Talavera Pons et al., 2017). Antiviral drugs perform targeted therapy by interacting with viruses' target proteins and the host's immune system (Thomasy and Maggs, 2016). Despite the availability of plethora of antiviral drugs in the market, there is continuous effort by worldwide researchers to identify new therapeutic agents from un/less exploited resources. Those bioactive agents have revealed *in vitro* and *in vivo* antiviral potentialities against various groups of viruses. Bioactive agents from natural resources have established a great foundation for designing new therapeutic drugs. It is certainly essential to understand the nature, source of origin, and role of identified active agents as therapeutics. Considering this, the present comprehensive review overviews the effectiveness of antiviral components present in various natural sources (plants, fungi, and prokaryotes) in order to identify potential antiviral agents for developing alternative therapy in future.

## 2. Major viral diseases outbreaks: an overview

### 2.1. Zika virus (ZIKV) disease

Zika virus belongs to family Flaviviridae. The virus is transmitted through the bite of infected female mosquitoes, *Aedes aegypti* and *Aedes albopictus*. Flaviviruses in human can also lead to many diseases that include West Nile, dengue, yellow fever, tick-borne, and Japanese encephalitis. The route of transmission of ZIKV is through arthropod vectors, central nervous system injury, and hemorrhagic fevers. The infection of ZIKV during pregnancy results in birth defects in new born babies, a condition called microcephaly. In adults, it leads to temporary paralysis. In Flaviviridae family, all members have enveloped virus with single stranded RNA genome and possesses 3 structural proteins envelope, capsid, precursor membrane, and 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Patients in phase I and II clinical trials are vaccinated with DNA/mRNA vaccine. Symptoms of this infection include skin rashes, headache, joint pain, muscle pain, and fever. The major outbreak took place in Yap Island (2007), South America (2015–2016), and French Polynesia (2013–2014). Guillian-Barre syndrome and microcephaly are common neurological manifestations of this disease (Lin et al., 2018).

### 2.2. Nipah virus disease

Nipah virus can be transmitted to humans from animals like bats or pigs. It can also transmit through contaminated food or directly from people to people. It was first recognized in Malaysia (1999), the people who were in contact with sick pigs or contaminations of tissues. Transmission is through unprotective contact or secretions from pigs, and fruits contaminated with secretions of urine by infected fruit bats. Symptoms include fever, headache, myalgia, and acute encephalitis. Incubation period ranges from 4 to 14 days. The diagnosis includes reverse transcription-polymerase chain reaction (RT-PCR) from body fluids and enzyme-linked immunosorbent assay (ELISA). The fruit bats belonging to the family Pteropodidae are the host of NIV. It has also been reported in other animals such as horse, sheep, goats, cats, and dogs. It is a single stranded and non-segmented enveloped RNA virus. The NIV is second member of genus *Henipavirus* belonging to the family Paramyxoviridae. Prevention can be done by reducing overcrowding between animals and avoiding consumption of contaminating foods (Singh et al., 2019).

### 2.3. SARS-COV

Severe acute respiratory syndrome coronavirus (SARS-COV) belongs to family Coronaviridae and order Nidovirales. It causes respiratory or intestinal infections in humans and animals. It is positive sense single stranded RNA virus which has genome size about 30 kb with 14 functional open reading frames (ORFs). Their genome size is larger with respect to all other RNA viruses. Symptoms of this infection include cough, chilliness, myalgia, sore throat, rhinorrhea, breathlessness, and diarrhea. Serum test, RT-PCR, and ELISA are the most common tests performed for diagnosing the infected patients. There is no effective antiviral agent identified till date to control SARS-COV (Cheng et al., 2007).

### 2.4. Herpes genitalis

Herpes genitalis is a sexually transmitted infection caused by herpes simplex virus type-1 (HSV-1) or herpes simplex virus type-2 (HSV-2). They are enveloped DNA virus. The primary mode of transmission is by direct contact. There are some similarities between HSV-1 and HSV-2 based on type of epitopes and antigenic cross reactions. HSV-1 occurs in childhood and HSV-2 occurs during sexual contact. HSV-2 is commonly seen in females. Primary infection results in papular skin, lesion in mucous membrane, swelling in inflammatory regions in vulva, and dysuria. The recurrent infection includes fever, menstruation stress, abortion, and eye lesion. The diagnosis is done by swabbing the infected mucous membrane and then analyzed using polymerase chain reaction (PCR). Another diagnosis includes antibody detection of HSV infection.

Acyclovir, valacyclovir, and famciclovir are the first line drugs used for its treatment (Sauerbrei, 2016).

### 2.5. Measles virus

Measles is caused by Rubella virus. It mainly affects children and pregnant women. The virus belongs to the family Paramyxoviridae and holds single stranded negative sense RNA, encodes 6 structural proteins, and 2 non-structural proteins. Measles occurs only in humans and is transmitted by respiratory droplets, saliva, skin to skin contact, and touching contaminated surface. Incubation period of the virus is 14–18 days. Symptoms include maculopapular rashes, cough, conjunctivitis, fever, and diarrhea. Samples from throat, nasal, and urine are used for analyzing using PCR. Attenuated measles strain is used as a vaccine in the beginning stage of the infection (Kondamudi and Waymack, 2020).

### 2.6. Human papilloma virus (HPV)

Human papilloma virus disease is a sexually transmitted infection which causes cervical cancer and genital warts. Among various types of HPV, type 16 and 18 are responsible for causing cervical cancer and HPV 6 and 11 cause genital warts. It mostly affects woman and is transmitted through skin to skin contact and infects vagina or anal intercourse. Cervical cancer can be detected by papanicolaou testing; hence changes in squamous epithelium cells should be noted. The changes observed on the abnormal cells are referred as cervical intraepithelial neoplasia (CIN). Depending on the depth of the abnormal cells, it can be classified into 3 types (CIN-1, CIN-2, and CIN-3). CIN-1, CIN-2, and CIN-3 show mild, moderate, and severe dysplasia, respectively. For human papilloma virus, vaccine was developed against the type 6, 11, 16, and 18. It is prophylactic quadrivalent vaccine named gardasil. Another type of vaccine is bivalent vaccine, developed against HPV 16 and 18 (Braaten and Laufer, 2008).

### 2.7. Acquired immunodeficiency syndrome (AIDS)

AIDS is caused by human immunodeficiency virus (HIV). The virus infects the CD4+ T lymphocytes cells and results in catastrophic effect in the host. When the virus replication is increased it results in cardiovascular disease and infects other organs, resulting in kidney and liver damage. In some cases, tuberculosis plays the major role in activating the disease. Vaccines are developed using X-ray crystallography, cryo electron microscopy, and other technologies including probing the B-cell lineage and genome sequencing (Schwetz and Fauci, 2019).

### 2.8. Ebola virus disease (EVD)

Ebola virus belongs to family Filoviridae and is transmitted by fruit bats. It is transmitted by infected blood, airborne, and infection through droplet. The EVD can be diagnosed using blood samples, saliva, breast milk, semen, sweat, tears, stool, skin, vaginal, and rectal swabs. The transmission can also be oral such as by consuming uncooked animal food. The production of disease can be through tear, mucous membrane, and skin; which infects immune system and reaches lymph nodes, causing lymphadenopathy and hematogenous spread through liver and spleen resulting in failure of organs. Symptoms can be headache, dysphagia, malaise, dry cough, sore throat, nausea, vomiting, diarrhea, and conjunctival bleeding. Diagnosis is done by RT-PCR and ELISA test by the samples taken from infected persons. Currently, there is no antiviral drug for this virus (Hasan et al., 2019).

### 2.9. Chicken pox

Chicken pox is caused by varicella zoster virus (VZV) which is also responsible in causing herpes zoster or shingles. It is transmitted by

inhaling aerosol droplets from infected patient. Symptoms include small itchy blister that spreads over chest, back, and then spreads through face, resulting in fatigue, fever, headache, and pharyngitis lasty for seven days. It is diagnosed by PCR by the blister fluid samples. Vaccine was introduced in 1995 and it helps in the prevention of the infection (Ayoade and Kumar, 2020).

### 2.10. Hanta virus disease

Hanta virus causes hemorrhagic fever. It is also called as hanta virus cardio pulmonary syndrome, renal syndrome, and non-pathogenic prospects hill virus. It affects the function of kidney. The virus enters the host by interacting with cell surface integrin receptors and also uses alpha 5 beta 1 receptors to enter into the cell. The infection occurs by direct contact with infected rodents and inhaling virus through lungs. Hanta virus can be differentiated into many types such as Seoul virus from domestic rat, others are black creek canal virus, bayou virus etc. Symptoms include chillness, dizziness, headache, nausea, cough, vomiting, malaise, diarrhea, back pain, abdominal pain, and tachycardia. Diagnosis is based on positive serological test, blood samples detecting viral antigen, viral RNA sequences, serological assays, immunohistochemistry, and PCR. There is no antiviral drug for hanta virus but antipyretics and analgesic are used to control the disease (Mir, 2010).

### 2.11. COVID-19

Recent emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family Coronaviridae. It has created a great impact throughout the world by its pathogenic nature and named COVID-19 by World Health Organization. The infection was acquired from seafood market in Wuhan, China. The genome of coronavirus consists of positive single stranded RNA of approximately 27–32 kb. The virus has Nsp1–16 (non-structural proteins) genes and others that code for four structural proteins including the envelope protein (E), membrane protein (M), spike protein (S), and the nucleocapsid protein (N) (Schoeman and Fielding, 2019). Symptoms include cough, mild fever, breathlessness, and throat congestion. Detection of the SARS-CoV-2 can be done by RT-PCR. Although few drugs and traditional remedies have been reported to alleviate mild symptoms of COVID-19, there are no medicines or vaccines approved to cure the disease till date. Nevertheless, there are several clinical trials undertaken including antibiotics, vaccines, and natural products proposed for treatment purpose (Bimonte et al., 2020).

### 2.12. Dengue

Dengue and dengue hemorrhagic fever are caused by the virus that belongs to Flaviviridae family. Flaviviruses infect host by the intermediate vectors like mosquitoes (*Aedes aegypti*) or ticks. There are four distinct serotypes of dengue viruses (DEN-1, DEN-2, DEN-3, and DEN-4) (Gubler and Clark, 1995). Approximately 2.5 billion people are susceptible at risk for this epidemic disease. Clinically, this disease has an incubation period of 2–7 days and symptoms include rashes, anorexia, cold, flu, nausea, vomiting, and respiratory illness. Laboratory diagnosis includes immunoassay tests and PCR amplification. No vaccines or specific antiviral drugs are available for this disease.

### 2.13. Chikungunya

Chikungunya, an epidemic threat in the recent years is a mosquito-borne disease in the tropical regions. It is caused by Chikungunya virus (CHIKV), a pathogen of the genus *Alphavirus* and the family *Togaviridae*. These are otherwise known as arboviruses as they are arthropod-borne viruses. CHIKV is similar to other alphaviruses including Sindbis viruses and Ross River viruses. Three distinct genotypes including Asian, West African, and East Central South African have been

observed so far. CHIKV holds a positive sense single stranded RNA of ~12 kb genome length. The genome analysis revealed that the viral genome comprise two ORFs. The 5'ORF encodes the nsP1, nsP2, nsP3, and nsP4 non-structural proteins, and the 3'ORF encodes capsid (C), envelope (E1 and E2), and two peptides (E3 and 6K) (Nunes et al., 2015). The acute stage lasts for a week whereas the chronic stage lasts from months to years. The symptoms include fever, arthralgia, rarely causing cardiac, ophthalmic, and neurological disorders. Diagnostic assays include ELISA, IgM antibody levels, and PCR. Treatment includes anti-rheumatic drugs but no vaccines have been discovered yet.

#### 2.14. Influenza

Influenza viruses are significant due to its unavailing presence in the past centuries. The virus belongs to the family Orthomyxoviridae. Three forms namely A, B, and C infect human. Influenza A and B viruses cause relatively high morbidity and mortality compared to the C type. These are enveloped viruses that encompass segmented negative-sense single-stranded RNA. The gene structure contains surface glycoproteins, hemagglutinin (HA), and neuraminidase (NA). Based on the types of HA and NA, a total of 16 HA (H1–16) and 9 NA (N1–9) subtypes are identified in birds. Recent outbreaks in humans contain subtypes H1N1 and H3N2 that are reported to be endemic. The zoonotic spread from birds and swine includes H5N1, H7N9, and H9N2. These have the capabilities to mutate into new forms and produce severe pathological effects (Harris et al., 2017). Symptoms include rapid onset of fever, dry cough, headache, muscle and joint pain, and severe malaise. The diagnostic method comprises influenza-specific RNA by RT-PCR. Treatment includes NA and HA inhibitors with monoclonal antibodies (Nachbagauer and Krammer, 2017) and antiviral drugs.

#### 2.15. Middle East Respiratory Syndrome-coronavirus (MERS-CoV)

MERS-CoV is a zoonotic viral respiratory disease that has infected people with a high mortality rate of nearly 50% in the Middle East (first identified in Saudi Arabia in 2012). The disease is alleged to be contracted from infected camels. Coronaviruses possess enveloped single stranded RNA that is spherical in shape with glycoprotein projections. The genome shows presence of two ORFs namely ORF 1a and 1b coding for non-structural proteins. Structural proteins encode the spike (S), envelope (E), membrane (M), and nucleocapsid (N). Symptoms include mild respiratory disease to severe acute respiratory disease and death. Severe illness can lead to the respiratory failure and may weaken the immune systems, especially with those with renal diseases, cancer, lung diseases, and diabetes. RT-PCR assay has been used as a diagnostic tool to detect the virus. At present, no vaccine or precise treatment is available (Alagaili et al., 2014).

#### 2.16. Hepatitis viral disease

Hepatitis viruses are hepaciviruses that belong to Flaviviridae. These viruses possess a linear and positive sense single stranded RNA genome coding for nearly 10 proteins. There are 7 genotypes encountered till date (genotype 1 to 7). Hepatitis A virus (HAV), a member of hepatovirus is an endemic spread by fecal-oral route. Symptoms include necrosis and inflammation of the liver cells. It includes a positive sense RNA and the genome comprise of about 7500 (nucleotides). The incubation period is approximately 3–5 weeks. Hepatitis B virus (HBV) belongs to Hepadnaviridae family and includes dsDNA virus that replicates via reverse transcription (Stuyver et al., 2000). HCV is transmitted by blood-to-blood contacts and other blood/body fluid contaminants. This is an enveloped single-stranded RNA virus similar to flavivirus. It leads to complications such as liver cirrhosis, liver failure, and liver cancers such as hepatocellular carcinoma. Currently, no treatment is available for HCV infections.

### 3. Immune mechanisms in viral diseases

Immune system is a complex network of defence mechanism present in living organisms to fight the invading foreign microorganisms and provides protection from diseases. The immune system confers immunity to the organism by eliciting immune responses mediated by specialized immune cells and organs. Once the virus enters the host cells (cytopathic and non-cytopathic), it replicates, kills the infected cells, and invades other cells by releasing cellular contents (Münz et al., 2009).

Innate mechanism in human acts by the interaction of the virus particles with various receptors like endosomal Toll-like receptors, C-type lectin receptors, cytoplasmic retinoic acid-inducible gene I receptors, and Nod-like receptors. Once induced, these receptors produce cytokines and interferons. Following the action encountered by the innate cells like neutrophils and release of pro-inflammatory cytokines, special T cells get induced to respond to the invaders. These cells also persuade B cells to secrete antibodies, which form immune complexes. They further invoke cytotoxic T lymphocytes CD8+ to transfer to the infection site and kill infected cells. Antibody mediated immune responses ie. antigen-antibody complexes induce activation of complement cascade. HIV-1, human cytomegalovirus, and certain other viruses use the host complement control proteins into their virions that create cell lysis (Mengshol et al., 2010).

The complement system of the innate immunity includes several factors and cell surface proteins that invoke immune response to the pathogens (Carroll, 2004). Three pathways of complement system are i) classical pathway (viral antigens bound with IgM and IgG interact with C1q and activates 2 serine proteases C1r and C1s, that further cleaves C4 into C4a and C4b to form the C3 convertase-C4bC2a) ii) alternate pathway (triggered by the hydrolysis of C3 that binds to protease factor B. This is cleaved by Factor D to form Bb in order to end the formation of C3 convertase-C4bC2a), and iii) lectin pathway (antigenic substances initiate mannose-binding lectin (MBL) and the ficolins. It forms a complex with MBL-associated serine proteases and cleaves C4 and C2 proteins to form C3 convertase-C4bC2a). These pathways regulate and activate complement factors and unite to form the major C3 component involved in virus pathogenesis (Ricklin et al., 2010). The innate, complement, and the adaptive immune responses are interlinked and are activated by the varying mechanisms, depending on the type of infecting viral particles leading to reduced pathogenesis, regulate inflammatory conditions, and modulating adaptive responses (Fig. 1).

### 4. Antivirals from natural sources

Recent researches in etiology have made better understanding of viral diseases. There is a continuous search of natural drugs to target viral proteins. Only limited chemicals are available for treating emerging viral diseases which is a major disadvantage. Therefore, there is an urgent need to unravel the potential antiviral metabolites from varying natural sources.

#### 4.1. Medicinal plants

Medicinal plants produce a variety of bioactive constituents that have the abilities to inhibit the replication cycle of various types of DNA or RNA viruses like HIV, HSV, Influenza virus, Human rhinovirus, Hepatitis B and C virus (HBV and HCV), and Dengue virus. Throughout the globe, medicinal plants act as important components to relieve from various ailments like bacterial, viral, and other infections. To mention a few, bioflavonoids such as Naringin (grape), daidzein (soybean), quercetin (foods and fruits such as green and black tea, apple, onion, citrus, tomato, and some other plants), and hesperetin (citrus) have been reported to fight dengue virus replication (Zandi et al., 2011).

Extracts of plants like *Rosa nutkana* and *Amelanchier alnifolia* were found active against enteric coronavirus (Jassim and Naji, 2003).

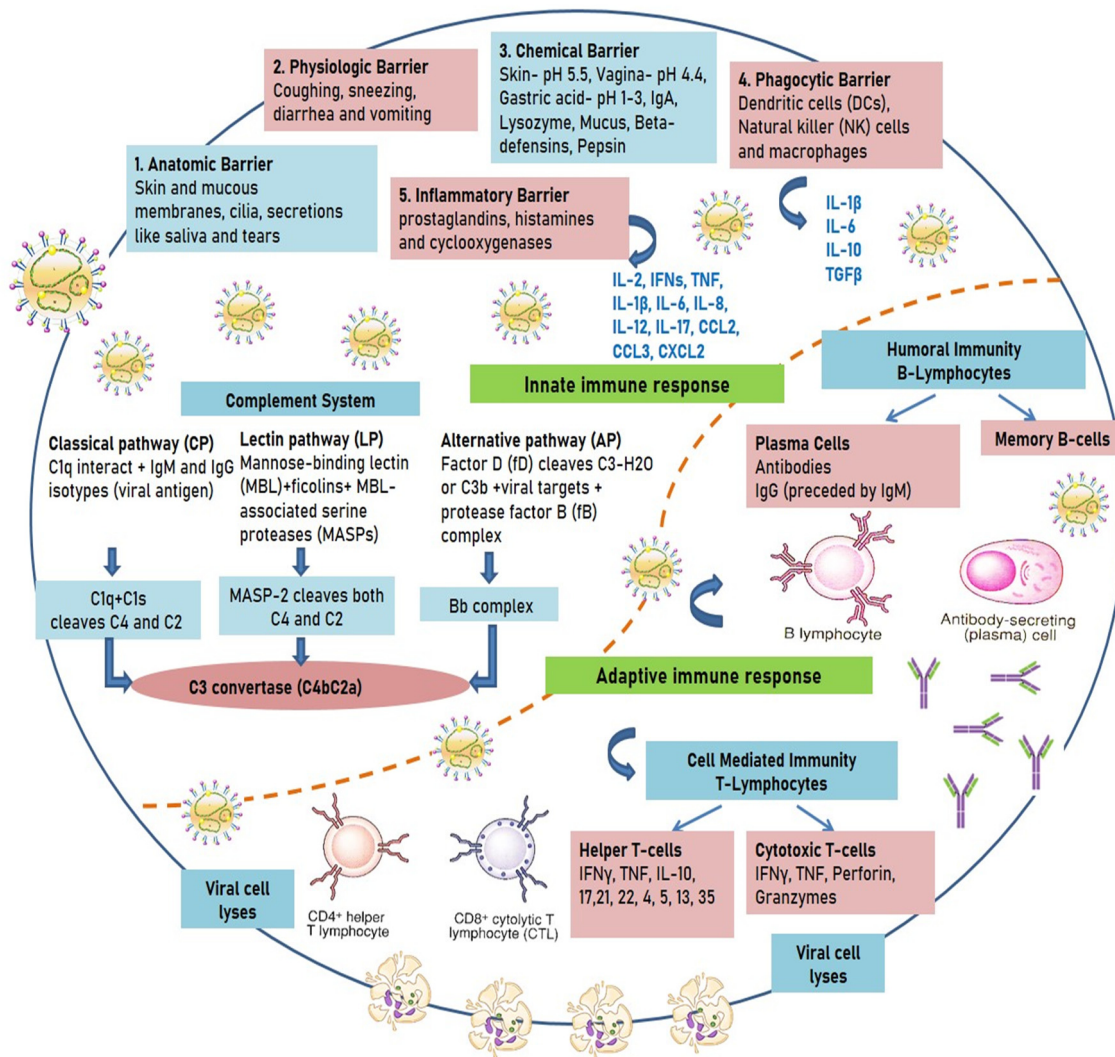


Fig. 1. Immune responses against viral infections.

Significant compound glycyrrhizin, found in *Glycyrrhiza glabra*, has antiviral activity against many viruses such as HBV, HCV, HIV, and HSV infections. Lycorine isolated from *Lycoris radiata* showed strong anti-SARS-CoV activity. The hot water extracts of *Stevia rebaudiana* blocked entry of various infectious serotypes of Human Rhinovirus into the permissive cells by an anionic polysaccharide with uronic acid as a major sugar constituent (Mishra et al., 2013).

Essential oils (eucalyptus oil, tea tree oil, and thyme oil) and monoterpenes like isoborneol proved antiviral activities against HSV-1 by inhibiting glycosylation of viral proteins (Astani et al., 2010). Silymarin (from the seeds of *Silybum marianum*) and catechin (present in green tea extract) inhibited HCV and also displayed anti-inflammatory and immunomodulatory actions (Calland et al., 2012). Table 2 illustrates antiviral properties of various plants associated metabolites against deadly viruses.

#### 4.2. Fungi

Fungi are excellent sources of bioactive metabolites, possessing antiviral properties (Table 3). The first antiviral metabolite from fungi *Stachybotrys* sp. was tested against H1N1 Influenza virus (Moghadamtousi et al., 2015). Compounds isolated from *Penicillium* sp. were tested for antiviral properties. Trypiplepyrazinol acted as an inhibitor against HIV-1 and HCV. (+)-neocitreoviridin showed anti-influenza A virus activity. 3- $\beta$ -hydroxyergosta-

8,14,24(28)-trien-7-one expressed anti-HIV and anti-influenza A activities (Li et al., 2019). Fungi associated compounds such as physcion, neoehinulin D, and dihydroauroglaucin inhibited replication of Influenza A virus (Bovio et al., 2019).

A sulphated polysaccharide from *Agaricus brasiliensis* against HSV-1 and 2, two proteins namely neutral protein bound polysaccharide, acidic protein bound polysaccharide, and triterpenes and laccases of *Ganoderma lucidum* exhibited anti-HIV-1 protease activity and anti-HIV-1 reverse transcriptase activity (Bishop et al., 2015). GFAHP, a protein from *Grifola frondosa* inhibited replication of HSV-1 (Hassan et al., 2015). *Alternaria* sp. ZJ-2008003, extracted from *Sarcophyton* sp. produced tetrahydroaltersolanols C-F and dihydrosolanol A and alterporriols N-R. Tetrahydroaltersolanol C and alterporriol Q showed antiviral activities against the porcine reproductive and respiratory syndrome virus. 11a-Dehydroxyisoterreulactone A from *Aspergillus terreus* possessed weak antiviral activity against HSV-1 virus. Aspergilli peptides D and E showed inhibitory activities towards HSV-1. Asperterrestide A displayed antiviral activity against H1N1 and H3N2 Influenza virus. *Aspergillus* sp. derived from *Muricella abnormalis*, on fermentation yielded 22-O-(N-methyl-L-valyl)-21-epiaflaquinolone B. It exhibited antiviral activity against human respiratory syncytial virus. Isobutyrolactone II, obtained from another strain of *Aspergillus* sp. expressed strong antiviral activity towards HSV-1 (Liu et al., 2020).

The metabolites halovirs A-E isolated from the marine fungus *Scytalidium* sp. demonstrated antiviral activity against HSV type-1 and

**Table 2**  
Antiviral traits of medicinal plants associated metabolites.

Name of the compound	Plant	Active against	References
Alkaloids and nitrogenated compounds			
Actinophnine	<i>Actinodaphne hookeri</i>	HSV-1	Montanha et al. (1995)
Atropine	<i>Atropa belladonna</i> L.	Enveloped virus	Yamazaki and Tagaya (1980)
Biopterin	<i>Crithidia fasciculata</i>	Antiviral activity	Tschesche et al. (1962)
Buchapine	<i>Euodia roxburghiana</i>	HIV-1	Manske and Brossi (1985)
Camptothecin	<i>Ophiorrhiza mungos</i>	Herpes virus	Tafur et al. (1976)
Canavanin	<i>Carnavalia ensiformis</i> L.	Influenza virus	Pilcher et al. (1955)
Caffeine	<i>Theobroma cacao</i> L. and <i>Coffea</i> sp.	Coxsackie-virus, Herpes, Poliovirus, vaccinia, and influenza virus	Yamazaki and Tagaya (1980)
Caribine	<i>Hymenocallis arenola</i>	Antiviral activity	Manske and Brossi (1987)
Carinatine	<i>Zephyranthes carinata</i>	Antiviral activity	Manske and Brossi (1987)
Chelidonine	<i>Chelidonium majus</i> L.	Herpes virus and influenza virus	Manske and Brossi (1987)
Cordycepin	<i>Aspergillus nidulans</i> Eidam Wint. <i>Cordyceps militaris</i>	Picornavirus, poliovirus, vaccinia, newcastle disease virus, Herpes simplex, and influenza viruses	Kaij-a-Kamb et al. (1992)
Cryptopleurine	<i>Bochneria cylindrica</i> L. Sw. and <i>Cryptocarya pleurosperma</i>	HSV-1	Cordell (1981); Manske and Brossi (1989)
O-demethyl-buchenavianine	<i>Buchenavia capitata</i>	HIV	Vlietinck et al. (1997)
Emetine	<i>Cephaelis ipecacuanha</i> A. Rich.	Pseudorabies and Herpes virus	Hanish et al. (1966)
Fagaronine	<i>Fagara zanthoxyloides</i> Lam	Retrovirus	Manske and Brossi (1988)
Harmaline, Harmine	<i>Peganum harmala</i>	HSV-1	Rashan (1990)
Hypoxanthine	<i>Beta vulgaris</i>	Antiviral activity	Mifflin (1981)
Lycorine	<i>Clivia miniata</i>	Antiviral activity	Leven et al. (1983)
Michellamines D, Michellamines F	<i>Ancistrocladus korupensis</i> D. Thomas and Gereau	HIV	Hallock et al. (1997)
10-Methoxycamptothecin	<i>Camptotheca acuminata</i> Descene	Adenovirus, Herpes, and vaccinia viruses	Clemens (1977)
Odorinol	<i>Aglaiia roxburghiana</i> Miq. var. <i>Beddomei</i>	Ranikhet disease virus	Phillipson and Zenk (1980)
Oliverine	<i>Polyathia oliveri</i>	HSV-1	Montanha et al. (1995)
Oxostephanine	<i>Stephania japonica</i>	HSV-1	Montanha et al. (1995)
Pachystaudine	<i>Pachypodanthium staudti</i>	HSV-1	Montanha et al. (1995)
Papaverine	<i>Papaver somniferum</i>	CMV, measles, HIV	Manske and Brossi (1990)
Psychotrine	<i>Cephaelis acuminata</i>	HIV-1	Manske and Brossi (1985)
Schumannificine	<i>Schumanniphyton magnificum</i>	HIV and HSV	Vlietinck et al. (1997)
Taspine	<i>Croton lechleri</i> M.	Avian myeloblastosis virus, Rauscher virus, and Simian sarcoma virus	Manske and Brossi (1990)
Homonojirimycin, Deoxymanojirimycin	<i>Omphalea diandra</i>	Homonojirimycin is an inhibitor of several a-glucosidases, Deoxymanojirimycin is an inhibitor of glycoprocessing mannosidase	Kite et al. (1988)
Aranotin, Gliotoxin	<i>Arachniotus aureus</i> (Eidam) Schoeter	Coxsackievirus A 21, poliovirus, rhinovirus, influenza virus, and para-influenza virus type 3	Becker (1980); Miller et al. (1968)
Ochropamine and epi-16-Ochropamine	<i>Cabucula erythrocarpa</i> Vatke Mar	Influenza virus	Manske and Brossi (1990)
(+)-Glucine fumarate, (+)-N-Methylaurotetanine, (+)-Isoboldine, and (-)-Nuciferine HCl	<i>Corydalis cava</i> , <i>Glaucium flavum</i> , <i>Peumus boldo</i>	HSV and picornaviridae	Boustie et al. (1998)
Castanospermine, Australine	<i>Castanospermum australe</i>	HIV	Foder and Colasanti (1985)
Leurocristina, Periformylone, Perivine, and Vincalucoblastine	<i>Catharanthus roseus</i> L. G. Don. and C. lanceus Pich	Leurocristina-Mengovirus extracellular virucidal, poliovirus, vaccinia, and influenza viruses Periformylone -poliovirus type 3-Perivine - vaccinia Polio extracellular virucidal activity Vincalucoblastine - poliovirus vaccinia, and influenza virus	Farnsworth et al. (1968)
Columbamine, Berberine, and Palmitine	Annonaceae, <i>Berberis vulgaris</i> , menispermaceae and Papaveraceae	HIV-1	Manske and Brossi (1990)
Narciclasine, Lycoricidine, Pancratistatin, 7-deoxypancratistatin, Acetatos, Isonarciclasine, cis-Dihydronarciclasine, Lycorines, and Pretazettine	<i>Narcissus poeticus</i> L., Lycorine was isolated from <i>Clivia miniata</i> Regel	Flaviviruses, bunyaviruses, and Poliomyelitis virus	Gabrielsen et al. (1992); Leven et al. (1982)
Buxamine E and Cyclobuxamine H	<i>Buxus sempervirens</i>	HIV-1 reverse transcriptase	Hiller (1987)
Triptonines A and Triptonines B	<i>Tripterygium hypoglaucom</i> and <i>Tripterygium wilfordii</i>	HIV	Duan et al. (2000)
5-hydroxynoracronycine and Acrimarine F	Citrus plants	Epstein-Barr virus	Takemura et al. (1995)
Fagaronine, Columbamine, and Fulvoplumierin	<i>Plumeria rubra</i> L.	HIV-1 reverse transcriptase	Tan et al. (1991)
$\beta$ -carbolines, furanoquinolines, indolizidines, swainsonine, and castanospermine	<i>Swainsona canescens</i> , <i>Astragalus lentiginosus</i> , <i>Castanospermum australe</i> , <i>Aglaiia roxburghiana</i>	DNA viruses	Hudson (1990); Sydiskis et al. (1991); Asano et al. (1996); Erdelmeier et al. (1996); Marchetti et al. (1996)
Coumarins			
Calmolide A	<i>Calophyllum lanigerum</i>	HIV	Murray et al. (1982)
Coriandrin	<i>Coriandrum sativus</i>	HIV	Towers (1989)
Inophyllum B and Inophyllum P	<i>Calophyllum inophyllum</i> Linn.	HIV-1 reverse transcriptase	Patil et al. (1993)
Soulatrolide	<i>Calophyllum teysmanii</i>	HIV	Murray et al. (1982)
Glycoumarin and Licopyranocoumarin	<i>Glycyrrhiza glabra</i>	HIV	Vlietinck et al. (1997)

(continued on next page)



Table 2 (continued)

Name of the compound	Plant	Active against	References
<b>Flavonoids</b>			
Acacetin 7-o-(6"-rhamnopyranosyl)- $\beta$ -D-glucopyranoside)	<i>Chrysanthemum morifolium</i> Ramar (Compositae)	HIV	Qi-Hu et al. (1994)
Apigenin	Widely distributed in the plant kingdom	Herpes virus	Béládi et al. (1977)
3,3'-Dimethoxyquercetin	<i>Euphorbia grantii</i> Oliv. and <i>Veronia amygdalina</i> Del. (Compositae)	Picornaviruses and vesicular stomatitis virus	Van Hoof et al. (1989); Rwangabo et al. (1986)
Fisetin inactivates	<i>Rhus</i> spp.	Pseudorabies virus	Béládi et al. (1977)
O-Glucosyl-7-methyl-5-genistein	<i>Ulex europaeus</i> L.	HSV	Swallow et al. (1975)
Glycosil-7-O-luteolin	<i>Matricaria inodora</i> L. (Compositae)	HSV and poliomyelitis	Suganda et al. (1983)
Hesperetin	<i>Citrus</i> spp. (lemons and sweet oranges)	Vesicular stomatitis	Harborne (1988)
Isoquercitrin	<i>Waldsteinia fragarioides</i> Michx.	HSV-1 virus	Karam and Shier (1992)
Justicidin B	<i>Phyllanthus acuminatus</i>	Cytomegalovirus and Sindbis virus	Ingham (1983)
Kaemferol 3-methyl ether; and Isokaempferide	<i>Solanum sarrachoides</i>	Antiviral activity	Harborne (1988)
Luteolin	Widely distributed in the plant kingdom	Pseudorabies virus	Béládi et al. (1977)
Luteolin-7-O-glucoside	<i>Matricaria inodora</i> L. (Compositae)	HSV and poliovirus	Béládi et al. (1977)
Morin	<i>Chlorophora tinctoria</i> L. Gaud	Pseudorabies virus	Béládi et al. (1977)
Naringin	<i>Citrus paradisi</i> Macfad.	Vesicular stomatitis virus	Wacker and Eilmes (1978)
Pachypodol (quercetin 3,7,3'-trimethyl ether)	<i>Begonia glabra</i>	Antiviral activity	Cody et al. (1986)
Pelargonidin	<i>Pelargonium</i> sp.	Enveloped viruses	Béládi et al. (1977)
Quercetin	<i>Chenopodium quinoa</i>	Potato virus X	French and Towers (1992)
Quercetin 3-methyl ether	Found as the aglycone in the leaves of Compositae	Antiviral activity	Cody et al. (1986)
Quercetin 3-O-(2"-galloyl)- $\beta$ -D-galactopyranoside	<i>Acer okamotoanum</i> Nakai	HIV-1 integrase	Kim et al. (1998)
Quercetagenin	Found in the flowers of many spp. of Compositae	Rauscher murine leukemia and HIV	Cody et al. (1986)
Rutin	<i>Fagopyrum esculentum</i> Moench	Pseudorabies and vesicular stomatitis virus	Béládi et al. (1977)
Taxifolin	<i>Acacia catechu</i>	Antiviral activity	Harborne (1988)
Volkensiflavone	<i>Rhus succedania</i> L.	Influenza B virus	Lin et al. (1997); Lin et al. (1999)
<b>Ternatin and Melaternatin</b>	<i>Evodia madagascariensis</i> Baker	HSV-1, HSV-2, adenovirus type 2, poliovirus type 2, and VSV type 2	Simões et al. (1990)
Afromosin and Formononetin	<i>Wisteria brachybotrys</i> Sieb	Epstein-Barr virus early antigen	Konoshima et al. (1989)
Axillarin, Chrysofenol B, and Chrysofenol C	<i>Chrysofenol B</i> and <i>Chrysofenol C</i>	Rhinovirus	Tsuchiya et al. (1985)
Lophirone F, Azobechalcone, and Isolophirachalcone	<i>Lophira alata</i>	Epstein-Barr virus early antigen induction test	Murakami et al. (1992)
Centaurein and Jacein	<i>Centaurea nigra</i> L.	Herpes virus and poliovirus	Kaij-a-Kamb et al. (1992)
5,7,3,3',4,5-Hexahydroxyflavone, and 5,7,4'-Trihydroxy-3-glycosylflavone	<i>Befaria cinnamomea</i>	HIV-1	Mahmood et al. (1993)
Agathisflavone, Robustaflavone, Hinokiflavone, Amentoflavone, and Morelloflavone	<i>Rhus succedanea</i> L. and <i>Garcinia multiflora</i> Champ	HIV-1 reverse transcriptase	Lin et al. (1997)
3-O-Methylcalopocarpin, Licoisoflavanone, Glyasperin	<i>Erythrina lysistemon</i> Hutch	HIV	McKee et al. (1997)
Macluraxanthone B, Macluraxanthone C, and Dihydrocudraflavone B	<i>Maclura tinctoria</i>	HIV	Groweiss et al. (2000)
7-O-Methyl-glabranine	<i>Tephrosia madrensis</i>	Dengue virus	Sanchez et al. (2000)
Wogonin	<i>Scutellaria baicalensis</i>	HBV	Huang et al. (2000)
Samarangenin B and Myricetin	<i>Limonium sinense</i>	HSV-1 replication	Lin et al. (2000)
<b>Lignans</b>			
Dihydroanhydrodopodrhizol	<i>Bursera schlectendalii</i>	HSV-1	Ayres and Loike (1990)
Diphyllin apioside-5-acetate, justicidin A and B, diphyllin, and diphyllin apioside	<i>Justicia procumbens</i> var. <i>leucantha</i>	Vesicular stomatitis virus	Asano et al. (1996)
Lignine guaiacyl derivative	<i>Pinus nigra</i> Arnold	HIV	Eberhardt and Young (1996)
Deoxypodophyllotoxin, 4'-Dimethylpodophyllotoxin, Podophyllotoxin acetate, Epidophyllotoxin acetate, and $\beta$ -Peltatin A methyl ether	<i>Juniperus sabina</i>	HSV-1 and vesicular stomatitis virus	Feliciano et al. (1993)
Podophyllotoxin, $\beta$ -Peltatin, Deoxypodophyllotoxin, Picropodophyllotoxin, and $\alpha$ -Peltatin	<i>Podophyllum peltatum</i>	Measles and HSV-1 viruses	McKee et al. (1997); Bedows and Hatfield (1982)
Kadsulignan L, Kadsulignan M, and Kadsulignan N	<i>Kadsura coccinea</i>	HIV	Liu and Li (1995)
Justicidins A, Justicidins B, Diphyllin, Actigenin, and Trachelogenin	<i>Forsythia intermedia</i> and <i>Ipomoea cairica</i>	HIV-1	Vlietinck et al. (1998)
Schizarin B and taiwanschirin D	<i>Kadsura matsudai</i>	HBV virus	Kuo et al. (2001)
Rhinacanthin E and rhinacanthin F	<i>Rhinacanthus nasutus</i>	Influenza virus type A	Kernan et al. (1997)
<b>Miscellaneous compounds</b>			
Calcium elenolate	<i>Olea europaea</i> L.	Antiviral activity	Swallow et al. (1975)
Castelanone	<i>Castela tweedii</i>	Oncogenic Rous sarcoma virus	Rembold (1989)
Chaparrinone	<i>Quassia undulata</i>	Oncogenic Rous sarcoma virus	Rembold (1989)
Cochinolide	<i>Homalium cochinchinesis</i>	HSV-1 and -2	Ishikawa et al. (1998)
Curdlan sulphate, Dextran sulphate, and Dextrin sulphate	Dextran sulphate - <i>Viola yedoensis</i> , Dextrin sulphate - <i>Prunella vulgaris</i> and Curdlan sulphate - <i>Alternanthera philoxeroides</i> (Amarantaceae)	HIV	Vlietinck et al. (1998)
Glaucarubolone	<i>Quassia simarouba</i>	Oncogenic Rous sarcoma virus	Rembold (1989)
D-glucosamine	<i>Dahlis</i> sp., <i>Glycine max</i> (L.) Merr and <i>Phaeseolus aureus</i> Roxb.	Fowl plague, Sindbis and Semliki Forest virus, RNA viruses, HSV, pox virus, NDV-inhibits para influenza 3, and measles	Kaluza et al. (1972)

Table 2 (continued)

Name of the compound	Plant	Active against	References
Glucans 1 and Glucans 2 Pentagalloylglucose	<i>Nicotiana tabacum</i> <i>Paeonia albiflora</i> Pallas	Antiviral activity HSV	Rouhier et al. (1995) Kaij-a-Kamb et al. (1992)
Monoterpenoids, diterpenoids and sesquiterpenoids Alloaromadendrol glycosides	<i>Calendula arvensis</i> L.	Vesicular stomatitis virus and rhinovirus (HRV type 1B)	Tommasi et al. (1990)
Arbotristosides A,B,C Carnosolic acid and Carnosol	<i>Nyctanthes arbor-tristis</i> <i>Rosmarinus officinalis</i> L.	EMCV and SFV HIV protease inhibitors	Rathore et al. (1990) Pariš et al. (1993)
Celaforin A-1, Celaforin B-2, Celaforin B-3, Celaforin C-1, Celaforin D-1, Celaforin D-2, and Celaforin D-3 12-Deoxyphorbol-13(3E,5E-decadienoate)	<i>Celastrus stephanotiifolius</i> Makino	Epstein-Barr virus	Takaishi et al. (1993)
Euglobal T1	<i>Excoecaria agallocha</i>	HIV	Erickson et al. (1995)
Euglobal 1, Euglobal 2, and Euglobal 3	<i>Eucalyptus tereticornis</i> Sm.	Epstein-Barr virus	Kokumai et al. (1991)
Halnanolide	<i>Eucalyptus grandis</i> <i>Banisteria caapi</i>	Epstein-Barr virus Influenza virus A (WS), Newcastle diseases virus, Japanese B encephalitis virus (AZ), and vaccina virus	Takasaki et al. (1990) Cracker and Simon (1986)
Liangshanin B and Liangshanin D Nimbinen	<i>Rabdosia liangshanica</i> C.Y. Limonoids found in plants of the order Rutales	Hepatitis virus Antiviral activity	Fenglei et al. (1989) Champagne et al. (1992)
Sclerocarpic acid Scoparic acid A, Scoparic acid B, Scoparic acid C, and Scopadulcis acid B	<i>Glyptopetalum sclerocarpum</i> <i>Scoparia dulcis</i>	HSV 1 and 2 HSV 1	Sotaphun et al. (1999) Hayashi et al. (1988); Hayashi et al. (1990)
Dolabellane Safficinolide and Sageone	<i>Dolabella californica</i> <i>Salvia officinalis</i>	Influenza and adenovirus viruses Vesicular stomatitis virus	Piattelli et al. (1995) Tada et al. (1994)
Tripterifordin	<i>Triterygium wilfordii</i> Hook	HIV	Chen et al. (1992)
Arennoside, Geniposidic acid, Geniposidic, and Gardenoside	<i>Genipa americana</i> L.	Antiviral activity	Ueda et al. (1991)
Xylopinic acid 12-O-Acetylphorbol-13-Decanoate and 12-O-Decanoylphorbol-13-(2- methyl butyrate)	<i>Xylopiya</i> sp. <i>Croton tiglium</i>	HIV HIV-1	Fuller et al. (1996) El-Mekawy et al. (2000)
Phenolic 2-O-Caffeoyl-(+)-allohydroxycitric 2,6-Dihydroxymethoxyisobutylrophenone and 4,6-Dihydroxymethoxyisobutylrophenone	<i>Spondias mombin</i> <i>Kunzea ericoides</i> A. Rich.	Coxsackie and HSV Antiviral activity	Corthout et al. (1992) Bloor (1992)
Eugenin or Ellagitannin	<i>Syzygium aromaticum</i> Merr <i>Paeonia suffruticosa</i>	HSV	Takechi and Tanaka (1982); Takechi and Tanaka (1981)
Gentisic acid Gossypol	<i>Citrus cultivars, Vitus vinifera</i> <i>Gossypium herbaceum</i> L.	Antiviral activity Herpes parainfluenza 3 and influenza viruses	Van Sumere (1989) Harborne and Baxter (1993)
Guttiferone A,B,C,D, and E	<i>Symphonia globulifera, Garcinia livinstonei, Garcinia ovalifolia and Clusia rosea</i>	HIV	Gustafson et al. (1992)
Mallotojaponin and Mallotochromene Peltalol A	<i>Mallotus japonicum</i> <i>Pothomorphe peltata</i>	HIV HIV-1	Van Sumere (1989) Van Sumere (1989)
Pentagalloyl-βD-glucose	<i>Nuphar japonicum</i>	HIV	Porter (1989)
Polyphenolic complex	<i>Geranium sanguineum</i> L.	Neuramidase activity of different influenza virus H1N1, H2N2, and H3N2	Serkedjieva and Manolova (1992)
Salicin and Salireposide Δ-9-Tetrahydrocannabinol	<i>Populus trichocarpa</i> <i>Cannabis sativa</i> L.	Poliomyelitis and Semliki forest virus HSV-1, HSV-2	Van Hoof et al. (1989) Blevins and Dumić (1980)
Woodorien	<i>Woodwardia orientalis</i>	HSV-1 and poliovirus	Xu et al., 2010
Silymarin and Cyanidol	<i>Silybum marianum</i>	Acute viral hepatitis	Swallow et al. (1975)
Dibalanocarpol and Balanocarpol	<i>Hopea malibato</i> Foxw	HIV	Hatano et al. (1988)
3,5-di-O-Galloylquinic acid, 3,4,5-tri-O-Caffeoylquinic acid, and 1,3,4-tri-O-Galloylquinic acid	<i>Guiera senegalensis</i> and <i>Securidata longipedunculata</i>	HIV	Van Sumere (1989)
(+)-Nortrachelogenin, Genkwanol A, Wilkstro B, and Daphnodorin B	<i>Wikstroemia indica</i> C. A. Meyer	HIV-1	Hu et al. (2000)
1,3,4,5-tetra-O-Galloylquinic acid	<i>Lepidobotrys staudtii</i> Engl.)	HIV-1 and HIV-2	Bokesch et al. (1996)
Phenylpropanoids Caffeic acid	<i>Coffea arabica</i>	Influenza virus, HSV, vaccinia, and polio viruses	Mølgaard and Ravn (1988)
Chlorogenic acid 3-Methyl-but-2-enyl caffeate	<i>Coffea arabica</i> <i>Populus nigra</i> L.	Poliiovirus Antiviral activity	Mølgaard and Ravn (1988) Amoros et al. (1994)
Usneoidone E, and Usneoidone Z	Brown seaweed <i>Cystoseira usneoides</i>	Antiviral activity	Urones et al. (1992)
Verbacoside, Isoverbacoside, Luteoside A, and Luteoside B	<i>Markhamia lutea</i> Seemann ex Baillor	Respiratory syncytial virus	Kernan et al. (1998)
Magnolol, Honokiol, and Monoterpenylmagnolol	<i>Magnolia officinalis</i> Rehd. et Wils	Epstein-Barr virus early antigen	Konoshima et al. (1991)
Quinones Conocurvone	<i>Conospermum incurvum</i>	HIV-1 reverse transcriptase	Decosterd et al. (1993)
Juglone	<i>Juglans nigra</i> ; <i>Hypericum triquetrifolium</i>	HSV-1 virus and retrovirus	Berg and Labiade (1989)
Pseudohypericin	<i>Hypericum triquetrifolium</i>	Retrovirus	Berg and Labiade (1989)
Rhinacanthin C and Rhinacanthin D	<i>Rhinacanthus nasutus</i> (L) Kurz	Cytomegalovirus	Sendt et al. (1996)
Hypericin and Pseudohypericin	<i>Hypericum perforatum</i>	Retroviruses	Hudson et al. (1993)

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Table 2 (continued)

Name of the compound	Plant	Active against	References
Tannins			
Agrimoniin	<i>Agrimonia pilosa</i>	Avian myeloblastosis virus	Porter (1989)
Coriariin A	<i>Coriaria japonica</i>	HIV	Porter (1989)
Procyanidin B2	<i>Rubus idaeus</i>	HIV	Porter (1989)
Camellin B, Gemin D, Chebulagic acid, and Nobotanin B	Chebulagic acid was isolated from <i>Terminalia chebula</i> , gemin D from <i>Geum japonicum</i> , nobotanin B from <i>Tibouchina semicandra</i>	HIV	Vlietinck et al. (1998)
Thiophenes and polyacetylenes			
Sidoresmin A	<i>Sirodesmiun diversum</i>	Rhinoviruses	Swallow et al. (1975)
Thiarubine-A	<i>Chaenactis douglasii</i>	Cytomegalovirus and Sindbis virus	Hudson et al. (1986a)
$\alpha$ -Terthienyl ( $\alpha$ -T) ACBP-thiophene	<i>Bidens pilosa</i> , thiophene-A - <i>Chaenactis douglasii</i> , $\alpha$ -Terthienyl and ACBP-thiophene - <i>Tagetes patula</i>	Sindbis virus	Hudson et al. (1986b)
Allyl methyl tiosulfinate, Methyl allyl tiosulfinate, Ajoene, and Allicin	Garlic, <i>Allium sativa</i> L.	HSV, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2	Weber et al. (1992)
Phenylheptatriene (PHT), Thiophene-A, Erysolin, and Sulforaphen	<i>Cardaria draba</i> L. Desv.	Mengovirus and newcastle disease virus	Kajj-a-Kamb et al. (1992)
Triterpenoids			
$\beta$ -Aescin	<i>Aesculus hippocastranum</i> L.	Influenza viruses	Hiller (1987)
Arjunolic acid	<i>Cochlospermum tinctorium</i> A. Rich.	EBV-EA	Diallo et al. (1989)
Chikusetsusaponin	<i>Panax japonicus</i> C.A. Mayer	HIV	Hasegawa et al. (1994)
Cucurbitacin F, 23,24-Dihydrocucurbitacin F, 15-oxo-23, 24-Cucurbitacin F, and 15-oxo-Cucurbitacin F	<i>Cowania mexicana</i>	Epstein-Barr virus	Konoshima et al. (1993)
Digitoxin	<i>Digitalis purpurea</i> L.	Poliovirus	Koch and Gyorgy (1969)
Eichlerianic acid	<i>Cowania Mexicana</i>	Herpes virus type 1	Hiller (1987)
Ganoderiol F and Ganodermanontriol	<i>Ganoderma lucidum</i>	HIV-1	El-Mekawy et al. (1998)
Gleditsia saponin C	<i>Gleditsia japonica</i> Miquel and <i>Gymnocladus chinensis</i> Baillon	HIV	Konoshima et al. (1995)
Gymnocladus saponin G and Glycyrrhizic acid	<i>Glycyrrhiza glabrata</i> L.	HSV 1, vaccinia virus, newcastle disease virus, and vesicular stomatitis virus	Hatano et al. (1988)
3-O-Glucose(1-3) [arabinose 1-4]-glucose-xyloside of 23-hydroxy-protoprimumagenin A 3-O-Glucose(1-3) [arabinose 1-4]-glucose-xyloside of 23-hydroxyproto-primulagenin A	<i>Anagallis arvensis</i>	HSV 1 and poliovirus	Amoros and Girre (1987)
Gymnemic acid	<i>Gymnema sylvestre</i>	Anti-influenza activity	Rao and Cochran (1974)
24-Hydroxydammaran-20,25-dien-3-one	<i>Chisocheon macrophyllum</i>	Epstein-Barr virus	Inada et al. (1993)
1 $\beta$ -Hydroxyaleuritic acid 3-p-hydroxy-benzoate (3 $\beta$ -hydroxyolean-12-en-23,28 dioic acid 23-o-[[ $\beta$ -D-glucopyranosyl-28-o-[[ $\beta$ -D-glucopyranosyl(1-3)]] $\beta$ -D-gluco-pyranosyl(1-6)]] $\beta$ -D-galactopy-ranoside	<i>Maprounea Africana</i> and <i>Gypsophila capillaris</i>	HIV-1 reverse transcriptase HSV	Pengsuparp et al. (1995) Elgamal et al. (1995)
Isofouqueierol	<i>Fouquieria splendens</i> Engelm	HSV	Gyorgy and Koch (1969)
Lancilactones C	<i>Kadsura lancilimba</i>	HIV	Chen et al. (1999)
Lanatoside D	<i>Digitalis lanata</i> Ehrh.	Influenza, Herpes and vaccinia viruses	Koch and Sandor (1969)
Methyl ester of wistariasaponin D, Methyl ester of wistariasaponin G, and Methyl ester of dehydrosoyasaponin	<i>Wistaria brachybotrys</i> Sieb	Epstein-Barr	Konoshima et al. (1989)
Nigranoic acid (22E)-5 $\beta$ -24-Norcholest-22-ene-3 $\alpha$ ,4 $\alpha$ ,11 $\beta$ ,21-tetrol,3,2,1-disulfate	<i>Schisandra sphaerandra</i> Stapf. <i>Ophioplocus januarii</i> Luetken	HIV Respiratory syncytial and polio viruses	Sun et al. (1996) Roccatagliata et al. (1996)
Ouabain	<i>Acokanthera ouabaio</i> Cathel.	Newcastle disease virus	Becher (1976)
Saikosaponin-A	<i>Bupleurum falcatum</i> L.	Influenza virus	Hiller (1987)
Salaspermic acid	<i>Tritergium wilfordii</i> Hook	HIV	Hiller (1987)
Saponin 2	<i>Anagallis arvensis</i> L.	Herpes virus and poliovirus	Koch and Sandor (1969)
Shoeric acid	<i>Strophanthus kombe</i> Oliv	Herpes virus	Kajj-a-Kamb et al. (1992)
Strophanthin G	<i>Strophanthus kombe</i> Oliv.	Influenza, Herpes and vaccinia viruses	Kajj-a-Kamb et al. (1992)
Suberosol	<i>Polyalthia suberosa</i> Roxburgh Thwaites	HIV	Li et al. (1993)
3-O-trans-Caffeoyltormentic acid	<i>Eriobotrya japonica</i> Lindl.)	Rhinovirus infection	Tommasi et al. (1992)
Wistariasaponins A, Wistariasaponins B, and Wistariasaponins C	<i>Wistaria brachybotrys</i> Sieb	Epstein-Barr virus	Konoshima et al. (1989)
Zingibroside R1	<i>Panax zingiberensis</i>	HIV	Hasegawa et al. (1994)
2 $\alpha$ -19 $\alpha$ -Dihydroxy-3-oxo-12-ursen-28-oic-acid, and Mastinic acid	<i>Geum japonicum</i>	HIV	Hiller (1987)
Proscillaridin A and Scillarenin	<i>Urginea scilla</i> Steinh	Influenza, HSV, vaccinia virus, and picornaviruses	Koch and Sandor (1969)
Betulinic acid and Platanic acid	<i>Syzygium claviflorum</i> (Roxb.) Wall	HIV	Fujioka et al. (1994)
Oleanolic acid and Pomolic acid, Alphitolic acid, Asiantic acid, and Betulinic acid	Oleanolic acid ( <i>Prosopis glandulosa</i> , Torr), pomolic acid, alphitolic acid ( <i>Rosa woodsii</i> Lindl.), arjunolic acid, asiantic acid, betulinic acid ( <i>Syzygium claviflorum</i> Wall)	HIV	Kashiwada et al. (1998)
Dammaradienol, Dammaradienol II, Dammarenolic	<i>Balanocarpus heimii</i> King	Herpes virus	Swallow et al. (1975)

Table 2 (continued)

Name of the compound	Plant	Active against	References
acid, Hydroxydammarone I, Hydroxyhopanone, Hydroxyoleanolic acid, and Ursonic acid	<i>Xanthoceras sorbifolia</i> Bunge	HIV-1	Ma et al. (2000)
Epigallocatechin-(4 $\beta$ -8,2 $\beta$ -O-7)-epicatechin, 3-Oxotirucalla-7-24-dien-21oic acid. And Oleanolic acid			
1- $\beta$ -hydroxyaleuritic acid-3-p-hydroxybenzoate	<i>Maprounea africana</i>	Reverse transcriptase inhibitors	Cos et al. (2008)
Escin	<i>Aesculus chinensis</i> Bge.	HIV	Yang et al. (1999); Xiu-Wuei et al. (1999)
Proteins and peptides			
Trichobitacin	<i>Trichosanthes kirilowii</i>	HIV	Mishra et al. (2013)
Pokeweed antiviral proteins (PAP) (MRK29, MAP30 and GAP31)	<i>Phytolacca Americana</i> , <i>Momordica charantia</i> , <i>Gelonium multiflorum</i>	HIV-1	Rajamohan et al. (1999)
Panaxagin	<i>Panax ginseng</i>	HIV-1 reverse transcriptase	Ng and Wang (2001)
Kalata B1,B2	<i>Oldenlandia affinis</i>	HIV	Craik et al. (2012)
Cyruilin A,B	<i>Chassalia parviflora</i>	HIV	Gustafson et al. (1994)
Lunatusin	<i>Phaseolus lunatus</i>	Antiviral activity	Wong and Ng (2005)
Vulgarinin	<i>Phaseolus vulgaris</i>	Antiviral activity	Jack and Tzi (2005)
Cicerin and Arietin	<i>Cicer arietinum</i>	Antiviral activity	Ye et al. (2002); De Souza et al. (2011)
Peptidasa-Mitogenic	<i>Brassica napus</i>	ND-Not determined	Yust (2004)
Phaseococcin	<i>Phaseolus coccineus</i>	HIV	Kuczer et al. (2010)
Sesquin	<i>Vigna sesquipedalis</i>	HIV	Hultmark et al. (2005)

type-2 (Youssef et al., 2019). Equisetin from *Fusarium heterosporum*, Phomasetin from *Phoma* sp., Integric acid from *Xylaria* sp., and Oxoglyantrypine, Norquinadolone A and Tryptoquivaline extracted from *Clostridium* sp. possessed antiviral activities against HIV.

#### 4.3. Algae

Table 4 shows antiviral attributes of algal metabolites and polysaccharides. Griffithsin and Scytovirin isolated from red and blue-green algae, respectively inhibited HCV (Takebe et al., 2013). The former is also a prominent HIV inhibitor (Besednova et al., 2019). Group I diterpenes like 8 $\alpha$ ,11-dihydroxy-pachydiol A, 8 $\beta$ -hydroxy pachydiol A from *Dictyota* sp. and diterpenes of Group II including Acetoxypachydiol, 3 $\beta$ -actoxydilophol obtained from *Dictyota plectens* showed weak antiviral activity. Dolabelladienols A-B extracted from *Dictyota pfaffii* displayed strong antiviral properties. Bicyclic diterpenes, Crenulidanes from Da-1, and AcDa-1 obtained from *D. menstrualis* inhibited HIV replication process (Chen et al., 2018).

Fucoidan, a polysaccharide from the marine alga, *Cladosiphon okamuranus* prevented dengue virus infection (Teixeira et al., 2014). The effect is specific on retroviruses by using heparan sulphate as primary viral receptors (Besednova et al., 2019). Carrageenan, from *Gigartina skottsbergii* inhibited Influenza virus, HIV, HPV, HSV-1, HSV-2, and dengue virus. Galactan from red algae like *Callophyllis variegata* and *Agardhiella tenera* possessed antiviral properties against HIV, HSV-1, -2, Dengue virus, and Hepatitis A virus. Alginate from brown algae inhibited Hepatitis B, Influenza A, and HIV. Fucan from brown algae like *Adenocytis utricularis* and *Undaria pinnatifida* expressed antiviral activities against HIV, HSV, Sindbis virus, and Vesicular Stomatitis Indiana virus. The extract of red alga, *Schizymenia pacifica* exhibited antiviral properties against HIV (Ahmadi et al., 2015).

Calcium spirulan, isolated from *Spirulina platensis* blocked replication of HSV-1, HIV-1, Influenza A, measles, and mumps virus. Extract of *Spirulina maxima* reduced HSV-2 infection. Cyanovirin-N, a protein produced by blue-green alga *Nostoc ellipsosporum* stopped HSV-1 entry into cells by preventing fusion with HSV-1 glycoproteins (Kim et al., 2011). Nostoflan, extracted from *Nostoc flagelliforme* showed antiviral activities against HSV-1, HSV-2, and Influenza A virus (Thuan et al., 2019). Dieckol isolated from *Ecklonia cava* prevented cleavage of SARS-CoV 3CL protein and stopped viral replication (Koirala et al., 2017). Ulvan, from *Ulva armoricana* has been identified to have antiviral properties (Xu et al., 2017). Laminarans or laminarins have been found to

play the role of HIV reverse transcriptase and avoid absorption of HIV onto human lymphocytes (Besednova et al., 2019).

#### 4.4. Bacteria

Therapeutic agents from natural resources, particularly bacteria are considered pivotal alternatives of commercially available synthetic drugs. Advancements in genomic technology (identify secondary metabolite gene clusters) and analytical techniques (isolation and purification of compounds) have led the drug discovery approaches to identify novel compounds with antiviral ability. Few noteworthy antiviral drugs isolated so far include surfactins from *Bacillus subtilis* which display antiviral activities against HSV (Ongena and Jacques, 2008).

Representatives of exopolysaccharides (EPS) producing strains of the genera *Streptococcus*, *Lactococcus*, *Lactobacillus*, *Leuconostoc*, *Pediococcus*, and *Weissella* have been well studied for immunostimulating properties. The EPSs extracted from lactic acid bacteria of the genera *Pediococcus*, *Leuconostoc*, and *Lactobacillus* significantly proved to produce anti-adenovirus effects in cell line studies (Biliavska et al., 2019). Other microbial metabolites like spongouridine, spongothymidine, statins, myriocin, NA255, and cyclosporine were reported to have antiviral activities against HSV1,2, HBV, HIV, influenza virus, HCV, and coronaviruses (Nkongolo et al., 2014). Antiviral attributes of bacteria associated bioactive compounds are summarized in Table 5.

#### 4.5. Actinomycetes

Actinomycetes are present in various environments and are active in the microbial communities. The secondary metabolites of these organisms are potential antiviral agents (Table 6). Xiamycin and its methyl ester of *Streptomyces* sp. GT2002/1503 showed selective anti-HIV-1 activity (Xu et al., 2014). The compound (4S)-4-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide, identified from *Streptomyces* sp. Smu03 possessed antiviral property over a broad range of Influenza A virus (Li et al., 2018). Antimycin A from *Streptomyces kaviengensis* inhibited RNA virus families like *Togaviridae*, *Picornaviridae*, *Bunyaviridae*, and western equine encephalitis virus. AhmpatininiBu from *Streptomyces* sp. CCCC 202950 and 4862F from *Streptomyces albosporus* I03A-04862 inhibited HIV-1 protease. Narasin from *Streptomyces aureofaciens* prohibited post-entry stages of viral replication during Dengue virus infection (Teixeira et al., 2014). Other antivirals include daptomycin from *Streptomyces roseosporus* (Jakubiec-Krzesniak et al., 2018), diffusomycin from

**Table 3**  
Fungal metabolites against viral pathogens.

Name of the compound	Organisms	Active against	References
Aphidicolin	<i>Cephalosporium aphidicola</i>	HSV 1 and 2	Hanson (1972)
Hyalodendrin A	<i>Penicillium turbatu</i>	Polio, Coxsackie viruses	Becher (1976)
Stachyobrisphenone B, Grisephenone A, and 3,6,8-Trihydroxy-1-methylxanthone	<i>Stachybotrys</i> sp.	Enterovirus-71	Qin et al. (2014)
Halovirs A–E and Simplicilliumtide J	<i>Scytalidium</i> sp.	HSV	Rowley et al. (2003); Youssef et al. (2019)
11a-dehydroxyisoterreulactone A, Arisugacin A, Isobutyrolactone II, and Aspernolide A	<i>Aspergillus terreus</i> SCGAF0162	HSV	Nong et al. (2014)
Balticolid	Ascomycetous strain 222	HSV	Shushni et al. (2011)
Equisetin	<i>Fusarium heterosporum</i>	HIV	Shushni et al. (2011)
Phomasetin	<i>Phoma</i> sp.	HIV	Singh et al. (1999)
Integric acid	<i>Xylaria</i> sp.	HIV	Rowley et al. (2004)
Stachyflin	<i>Stachybotrys</i> sp. RF-7260	Influenza virus	Minagawa et al. (2002)
Oxoglyantrypine, Norquinadoline A, Deoxynortryptoquivaline, Deoxytryptoquivaline, Tryptoquivaline, and Quinadoline B	<i>Cladosporium</i> sp.	Influenza virus	Peng et al. (2013)
Cladosin C	<i>Cladosporium sphaerospermum</i> 2005-01-E3	Influenza virus	Wu et al. (2014)
(Z)-5-(Hydroxymethyl)-2-(6'-methylhept-2'-en-2'-yl)-phenol, Diorcinol, and IFV Cordyol C	<i>A. sydowii</i> ZSDS1-F6	Influenza virus	Wang et al. (2014)
Rubrolide S	<i>A. terreus</i> OUCMDZ-1925	Influenza virus	Zhu et al. (2013)
Asperterrestide A	<i>A. terreus</i> SCGAF0162	Influenza virus	He et al. (2013)
Isoaspulvinone E, Aspulvinone E, and Pulvic acid	<i>A. terreus</i> Gwq-48	Influenza virus	Gao et al. (2013)
Emerimidine A and Emerimidine B	<i>Emericella</i> sp. (HK-ZJ)	Influenza virus	Zhang et al. (2011)
Purpurquinone B, Purpurquinone C, Purpuresters A, and TAN-931	<i>P. purpurogenum</i> JS03-21	Influenza virus	Wang et al. (2011)
Sorbiccatechol A and Sorbiccatechol B	<i>P. chrysogenum</i> PJX-17	Influenza virus	Peng et al. (2014)
Tetrahydroaltersolanol C and Alterporriol Q	<i>Alternaria</i> sp. ZJ-2008003	Porcine reproductive and respiratory syndrome	Zheng et al. (2012)
Sansalvamide A (43)	<i>Fusarium</i> sp.	Molluscum contagiosum virus	Hwang et al. (1999)
22-O-(N-Me-L-valyl)-21-epiaflaquinolone B (44)	<i>Aspergillus</i> sp. XS-20090B15	Respiratory syncytial virus	Prieto and Castro (2005)
Extracts	<i>Agaricus subrufescens</i>	HSV-1	Bruggemann et al. (2006)
GFAHP	<i>Grifola frondosa</i>	HSV	Gu et al. (2007)
Beta-glucan-protein	<i>Agaricus subrufescens</i>	HSV	Yamamoto et al. (2013)
Aurenitol	<i>Chaetomium coarctatum</i>	Influenza A (H3N2)	Sacramento et al. (2015)
Extracts	<i>Lentinula edodes</i>	HPV	Rincão et al. (2012)
Polysaccharopeptide	<i>Trametes versicolor</i>	HIV	Collins and Ng (1997)
Polysaccharides	<i>Agaricus subrufescens</i>	HPV	Faccin et al. (2007)
Extracts	<i>Trametes versicolor</i>	Influenza, HSV	Krupodorova et al. (2014)
Adenosine	<i>Cordyceps militaris</i>	HIV protease	Jiang et al. (2011)
Velutin	<i>Flammulina velutipes</i>	HIV-reverse transcriptase	Wang and Ng (2001)
4.5 kDa protein	<i>Russula paludosa</i>	HIV protease	Wang et al. (2007)
Ganoderic acid	<i>Ganoderma lucidum</i>	HIV protease and HBV	Min et al. (1998)
Brefeldin A	<i>Penicillium</i> sp. FKI-7127	Dengue viruses, ZIKV, and Japanese encephalitis virus	Raekiansyah et al. (2017)
Ganodermediol, applanoxidic acid G triterpenoids, and lucidadiol	<i>Ganoderma pfeifferi</i> Bres.	Influenza virus type A and HSV-1	Mothana et al. (2003)
Cordycepin (also named 3'-deoxyadenosine)	<i>Cordyceps militaris</i>	Influenza viral, HIV-1 RT, Epstein-Barr virus, and Rota virus	Yong et al. (2018)
Ganodermic acids are A, AM1, B, β, C1, C2, C6, D, Df, DM, E, F, G, H, J, K, Mc, Me, Nf, Mk, N, P, R, S, Sz, T, TR, TQ, X, and Y	<i>Ganoderma lucidum</i>	HIV-1 and HBV	Hsu and Yen (2014)
Hispidin and hispolon	<i>Inonotus hispidus</i> (Bull.) P. Karst.	Influenza virus type A and type B	Li and Wang (2006)
PSK Krestin and PSP	<i>Trametes versicolor</i>	HIV-1	Mlinaric et al. (2005)
Velutin and Flammulin proteins	<i>Flammulina velutipes</i>	HIV-1 reverse transcriptase	Wang and Ng (2001)
Trypitypyrazinol, (+)-neocitreoviridin, and 3β-hydroxyergosta-8,14,24 (28)-trien-7-one	<i>Penicillium</i> sp.	HIV-1, HCV, and Influenza	Li et al. (2019)
Physson, Neoehinulin D, and Dihydroauroglaucin	<i>Eurotium chevalieri</i>	Influenza A virus	Bovio et al. (2019)
Isobutyrolactone II	<i>Aspergillus</i> sp.	HSV-1	Liu et al. (2020)

*Streptomyces* sp. KBFP-2025 (Vil et al., 2019), and Sinefungin from *Streptomyces griseolus* and *Streptomyces incarnatus* NRRL 8089 (Chen et al., 2017).

#### 4.6. Endophytic bacteria

Endophytes are a group of bacteria and fungi which live inside the host without damaging them. Metabolites obtained from endophytes possess antiviral properties (Table 7). Xiamycin A, a distinguished compound extracted from *Bruguiera gymnorrhiza* mangrove plant, demonstrated selective anti-HIV activity (Christina et al., 2013).

#### 4.7. Lichens

Lichens are symbiotic organisms between fungi and algae. Nearly 1100 bioactive metabolites have been isolated from 18,500 lichens, but still numerous organisms are yet to be discovered from different environments. These metabolites generally belong to the classes of polyketides, phenols, terpenoids or quinines. Several research studies indicated the antiviral activities of metabolites (Table 8), such as (+)-usnic acid, sekikaic acid, and anthraquinones against arenaviruses, respiratory syncytial virus, and HSV type 1 (Boustie and Grube, 2005; Stocker-Wörgötter, 2008; Zambare and Christopher, 2012; Lai et al., 2013).

**Table 4**  
Algal metabolites and polysaccharides with antiviral activities.

Antiviral polysaccharide	Organism	Virus	References
Carrageenan	Red alga, <i>Gigartina skottsbergii</i>	Influenza virus, HSV-1, HSV-2, HPV, HRV, and HIV	Vera et al. (2011)
Galactan	Red algae, <i>Callophyllis variegata</i> , <i>Agardhiella tenera</i> , <i>Schizymenia binderi</i> , <i>Cryptonemia crenulata</i>	HSV-1, HSV-2, HIV-1, HIV-2, and HAV	Estevez et al. (2001)
Alginate	Brown algae, <i>Laminaria hyperborea</i> , <i>Laminaria digitata</i> , <i>Laminaria japonica</i> , <i>Ascophyllum nodosum</i> , <i>Macrocystis pyrifera</i>	HIV, IAV, and HBV	Jiang et al. (2003)
Fucan	Brown algae, <i>Adenocytis utricularis</i> , <i>Undaria pinnatifida</i> , <i>Stoechospermum marginatum</i> , <i>Cystoseira indica</i> , <i>Cladosiphon okamuranus</i> , <i>Fucus vesiculosus</i>	HSV-1, HSV-2, HCMV, VSV, Sindbis virus, and HIV-1	Patankar et al. (1993)
Laminaran	Brown algae, <i>Fucus vesiculosus</i> , <i>Saccharina longiciruris</i> , <i>Ascophyllum nodosum</i>	HIV	Rioux et al. (2010)
Naviculan	Diatom, <i>Navicula directa</i>	HSV-1 and HSV-2	Lee et al. (2006)
p-KG03	Microalga, <i>Gyrodinium impudicum</i>	Influenza A virus	Kim et al. (2012)
A1 and A2	Microalga, <i>Cochlodinium polykrikoides</i>	Influenza A and B viruses, RSV-A, RSV-B, and parainfluenza-2	Hasui et al. (1995)
Calcium spirulan	Blue-green alga, <i>Arthrospira platensis</i>	HSV-1, measles, mumps, influenza, polio, Coxsackie, HIV-1	Hayashi et al. (1996)
Nostaflan	Blue-green alga, <i>Nostoc flagelliforme</i>	HSV-1, HSV-2, influenza A virus, and human cytomegalovirus	Kanekiyo et al. (2007)
Sea algae extract	Red alga, <i>Schizymenia pacifica</i>	HIV	Nakashima et al. (1987a)
Sea weed extract	<i>Acrosiphonia coalita</i> Scagel, Garbary, Golden et Hawkes	HSV-1 and Sindbis virus	Hudson et al. (1999)
Sea weed extract	<i>Enteromorpha linza</i> (Linnaeus) J.C. Agardh	HSV-1 and Sindbis virus	Hudson et al. (1999)
Sea weed extract	<i>Ulva</i> sp.	HSV-1 and Sindbis virus	Kim et al. (1997)
Sea weed extract	<i>Corallina vancouveriensis</i> Yendo	HSV-1 and Sindbis virus	Hudson et al. (1999)
Sea weed extract	<i>Analipus japonicus</i> (Harvey) Wynne	HSV-1	Baba et al. (1988)
Sea weed extract	<i>Egria menziesii</i>	HSV-1 and Sindbis virus	Baba et al. (1988)
Sea weed extract	<i>Gracilaria pacifica</i> Abbott	HSV-1 and Sindbis virus	Taylor et al. (1996)
Sea weed extract	<i>Nereocystis luetkeana</i> (Mertens) Postels et Ruprecht	HSV-1	Anani et al. (2000)
Sea weeds	<i>Postelsia palmaeformis</i> Ruprecht	HSV-1	Towers et al. (1997)
PLE extracts (hexane, ethanol and water)	<i>Haematococcus pluvialis</i>	HSV-1	Santoyo et al. (2011)
PLE extracts (hexane, ethanol and water)	<i>Dunaliella salina</i>	HSV-2	Santoyo et al. (2011)
Cyanovirin	<i>Nostoc</i> sp.	Influenza A (H1N1)	Smee et al. (2008)
$\beta$ -1,3 glucan	<i>Chlorella vulgaris</i>	Immune stimulator	Spolaore et al. (2006)
AcDa-1	<i>Dictyota menstrualis</i>	HIV	Pereira et al. (2004)
SAE (sea algal extract)	Red alga, <i>Schizymenia pacifica</i>	HSV-1 and HSV-2	Nakashima et al. (1987a, 1987b)
Griffithsin and Scytovirin	Blue-green algae	HCV and HIV inhibitor	Takebe et al. (2013); Besednova et al. (2019)
Group I diterpenes like 8 $\alpha$ ,11-Dihydroxy-pachydictyol A, 8 $\beta$ -Hydroxy pachydictyol A	<i>Dictyota</i> sp.	HIV	Chen et al. (2018)
Group II including Acetoxypachydiol, 3 $\beta$ -acetoxydilophol	<i>Dictyota plectens</i>	HIV	Chen et al. (2018)
Dolabelladienols A-B	<i>Dictyota paffii</i>	HIV	Chen et al. (2018)
Bicyclic diterpenes, Crenulidanes from Da-1 and AcDa-1	<i>D. menstrualis</i>	HIV	Chen et al. (2018)
Fucoidan	<i>Cladosiphon okamuranus</i>	HIV	Teixeira et al. (2014)
Extract	Red alga, <i>Schizymenia pacifica</i>	HIV	Ahmadi et al. (2015)
Dieckol	<i>Ecklonia cava</i>	SARS-CoV	Koirala et al. (2017)
Ulvan	<i>Ulva armoricana</i>	HIV-reverse transcriptase	Xu et al. (2017); Besednova et al. (2019)

## 5. Complementary and herbal preparations as future therapy

### 5.1. Indian medicinal plants, Ayurvedic, and Unani systems

Plants are a potential source of antiviral agents. In India, herbal medicines have proved to intensify therapeutic effects against several viral infections like Dengue virus, HBV, HCV, HSV, HIV, and Influenza virus. These natural agents inhibit viral replication and synthesis. These indigenous plants stand alone in Indian tradition and have been recognized worldwide for its beneficial healing effects (Ballabh and Chaurasia, 2007; Pandey et al., 2008).. Some of the common medicinal plants used are shown in Fig. 2.

An Indian Government initiative, Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) held by the Ministry of Health and Family Welfare, 2014 provides education, awareness, and enhances research to use natural resources that can fight several life threatening diseases. Ayurvedic medicine has been in use since two thousand years. Over 700 herbal drugs were recorded in Ayurveda with reported clinical effects categorised into 50 drug classifications. Also, Unani is recognized as traditional medicine producer, showing therapeutic effects against many infectious diseases. Both the Ayurvedic and Unani systems of medicine have recorded several preparations like decoctions, powders, and liquids of potential plants with immunomodulatory and antiviral properties (Subhose et al., 2005; Patwardhan et al., 2005; Weeks, 2020).

**Table 5**  
Antiviral compounds from bacteria.

Name of the compound	Organisms	Active against	References
Sulfangolid C, soraphen F, epothilon D, and spirangien B, and Kulkenon	<i>Sorangium cellulosum</i>	HIV	Zander et al. (2012)
Rhizopodin	<i>Myxococcus stipitatus</i>	HIV	Martinez et al. (2013)
Thiangazole, phenalamide A1, and phenoxan	<i>Polyangium species</i>	HIV	Jurkiewicz et al. (1992)
Aetheramide A and aetheramide B (10b)	<i>Aetherobacter</i>	HIV	Trowitzsch-Kienast et al. (1992)
Ratjadon A (11) and $\alpha$ -pyrone	<i>Sorangium cellulosum</i>	HIV	Gerth et al. (1995)
Myxochelins A-F	<i>Angiococcus disciformis</i>	Human cytomegalovirus	Miyanaaga et al. (2009)
Nannochelin A-C	<i>Nannocystis exedens</i>	Human cytomegalovirus	Kunze et al. (1992)
Hyalachelin A-C	<i>Hyalangium minutum</i>	Human cytomegalovirus	Nadmid et al. (2014)
Chondramide A-D	<i>genus Chondromyces</i>	EVD	Reichenbach (1988)
Noricumazol A-C	<i>Sorangium cellulosum</i>	EVD	Kunze et al. (1991)
Labindole A and B, 3-chloro-9H-carbazole, 4-hydroxymethyl-quinoline, and Soraphen A	<i>Labilithrix luteola</i>	HCV	Mulwa et al. (2018)
Lanyamycin	<i>Sorangium cellulosum</i>	HCV	Gentzsch et al. (2011)
Surfactin	<i>Bacillus amyloliquefaciens</i>	Antiviral activity	Koumoutsis et al. (2004)
Bacitracin	<i>Bacillus licheniformis</i>	Antiviral activity	Konz et al. (1997)
Lichenysin	<i>Bacillus licheniformis</i>	Antiviral activity	Veith et al. (2004)
Locillomycin	<i>Bacillus subtilis</i> 1	Antiviral activity	Luo et al. (2015)
Macrolactin A	<i>B. subtilis</i>	HSV	Gustafson et al. (1989)
Exopolysaccharides (EPSs)	<i>Pediococcus, Leuconostoc, Lactobacillus</i>	Human adenovirus	Liubov et al. (2019)

Due to changing lifestyles and requirements for nutrition and immunity to overcome growing infections complementary and herbal medicine can act as best alternatives for chemical drugs. Nutraceutical components and ethnopharmacological preparations play a very important role to fight against viral infections (Kamboj, 2000). India is the largest manufacturer of traditional health products and formulations

from medicinal plants. Herbal medicines and other nutrients from food are provided as dietary supplements in the form of pills, capsules, powders, solids or liquid (processed forms). They act as antioxidants, vitamin, and mineral supplements, also alleviate health against respiratory diseases, strengthen the immune system, and protect against the common cold (Mukherjee and Wahile, 2006).

**Table 6**  
Actinobacterial metabolites against viral pathogens.

Name of the compound	Organism	Active against	References
9-Methyl strptimidone	<i>Streptomyces</i> sp. S-885	Poliovirus	Swallow et al. (1975)
Rifampin	<i>Streptomyces mediterranei</i>	Vaccinia and pox viruses	De Clercq (1973)
Novobiocin	<i>Streptomyces spheroides</i> (Actinomycetales)	Antiviral activity	Murray et al. (1982)
Guanine-7-N-oxide	<i>Streptomyces</i> sp.	Rhabdovirus and infectious pancreatic necro virus	Nakagawa et al. (1985)
Antimycin A1a	<i>Streptomyces kaviengensis</i>	Western equine encephalitis virus	Raveh et al. (2013)
Xiamycins C-E	<i>Streptomyces</i> sp. #HK18	Porcine epidemic diarrhea virus, and HIV	Kim et al. 2016; Xu et al. (2014)
Pentapeptide 4862F-N,N,N-(trimethylated)-Tyr-L-Leu-L-Val-L-Leu-(dehydrated)-His	<i>Streptomyces albosporus</i> I03A-04862	HIV-1	Liu et al. (2012)
4-amino-3-hydroxy-5-(4-methoxyphenyl) pentanoic acid	<i>Streptomyces</i> sp. CPCC 202950	HIV-1	Chen et al. (2018)
Daptomycin and Nanchangmycin	<i>Streptomyces nanchangensis, Streptomyces roseosporus</i>	ZIKV	Barrows et al. (2016); Pascoalino et al. (2016); Rausch et al. (2017)
Chartreusin	<i>Streptomyces chartreusis</i>	Influenza A	Miyakawa et al. (1958)
Mannose specific pradimicin-A (PRMA)	<i>Actinomadura hibisca</i>	HIV	Tanabe-Tochikura et al. (1990)
Actinohivin	<i>Longispora albida</i> gen. nov, sp. nov	HIV	Chiba et al. (2004); Takahashi et al. (2005)
Benzastatin C, a 3-chloro-tetrahydroquinolone alkaloid	<i>Streptomyces nitrosporeus</i>	HSV-1, HSV-2, and vesicular stomatitis virus	Lee et al. (2007)
JBIR-68	<i>Streptomyces</i> sp. RI18	Influenza virus	Takagi et al. (2010)
Methylelaioaphylin	<i>Streptomyces melanosporofaciens</i>	Newcastle disease virus	Lee et al. (2011)
Furan-2-yl acetate (C6H6O3)	<i>Streptomyces VITSDK1</i> spp.	Fish nodavirus	Suthindhiran et al. (2011)
Di-n-octyl phthalate and bis (2-methylheptyl) phthalate	<i>Streptomyces parvus</i>	HCV	Elnaby et al. (2016)
Fattiviracin A1	<i>Streptomyces microflavus</i>	Antiviral activity	Yokomizo et al. (1998)
Musacin C	<i>Streptomyces griseovirdis</i>	Antiviral activity	Schneider et al. (1996)
MM461156	<i>Actinomadura pelletieri</i>	Antiviral activity	Ashton et al. (1990)
FK 506	<i>Streptomyces tsukubaensis</i>	Antiviral activity	Reis et al. (2006)
Benzastatin C	<i>Streptomyces nitrosporeus</i>	Antiviral activity	Kuzuyama and Seto (2003); Lee et al. (2007)
(4S)-4-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide	<i>Streptomyces</i> sp. Smu03	Influenza A virus	Li et al. (2018)
Ahmpatinini Bu	<i>Streptomyces</i> sp. CPCC 202950	HIV-1	Teixeira et al. (2014)
4862F	<i>Streptomyces albosporus</i> I03A-04862	HIV-1	Teixeira et al. (2014)
Narasin	<i>Streptomyces aureofaciens</i>	Dengue virus	Teixeira et al. (2014)

**Table 7**  
Endophytes derived metabolites with antiviral activities.

Name of the compound	Organism	Active against	References
Bis (2-methylheptyl) phthalate	Actinomycetes - leaves of <i>Pongamia pinnata</i>	White spot syndrome virus	Rameshthangam and Ramasamy (2007)
Xiamycin A	<i>Streptomyces</i> sp. GT 2002/1503	HIV	Ding et al. (2010)
Cytotoxic acids A and B	<i>Cytonaema</i> sp.	Human cytomegalovirus	Bhardwaj and Agrawal (2014)
Valinomycin	<i>Streptomyces tsusimaensis</i>	Coronavirus	Alvin et al. (2014)
Alttoxins	<i>Alternaria tenuissima</i> QUE1Se	HIV-1 virus	Bashyal et al. (2014)
Aspernidine (A, B), dehydroaustin, emeriphenolicins (A, D), austinol, emerimidine (A, B), austin, and acetoxyl dehydroaustin	<i>Emericella</i> sp. (HK-ZJ)	Influenza A virus (H1N1)	Zhang et al. (2009)
2-(Furan-2-yl)-6-(2S,3S,4-trihydroxybutyl) pyrazine	<i>Jishengella endophytica</i> 161,111	Influenza A virus (H1N1)	Wang et al. (2014)

### 5.2. Chinese herbal medicine (CHMs)

CHMs contain several plant products and preparations which play a tremendous role in treating various ailments (Fig. 3). They help to regulate body temperature and detoxify chemical substances in our body. Xiaoqinglong decoction mixture is used in China for respiratory ailments such as asthma, cough, and chronic obstructive pulmonary disease. The mixture consists of wild ginger (Xixin, *Asari Radix* et *Rhizoma*), *Pinellia ternata* (Banxia, *Pinelliae Rhizoma*), Licorice root (Gancao, *Glycyrrhizae Radix* et *Rhizoma*), Chinese Magnoliavine Fruit (Wuweizi, *Schisandrae Chinensis Fructus*), dried ginger (Ganjiang, *Zingiberis Rhizoma*), Cassia Twig (Guizhi, *Ramulus Cinnamomi*), Chinese Ephedra herb (mahuang, *Ephedrae Herba*), and white peony root (Baishao, *Paeoniae Radix Alba*). This herbal extract exhibited antiviral activity against drug-resistant H1N1 virus (Zhen et al., 2018).

Extracts of *Scutellaria baicalensis* contain flavonoids such as 5,7,4'-trihydroxy-8-methoxyflavone, baicalein, and 5,7,8,4'-tetrahydroxyflavone. These extracts showed antiviral properties that inhibited the neuraminidase activity of Sendai virus and Influenza A H5N1 (Hou and Lu, 2009). *Houttuynia cordata* Thunb is a traditional Chinese medicine used for treating pneumonia and lung-related ailments. It is also found active against SARS-CoV (Lau et al., 2018).

### 5.3. Other traditional medicines

Maoto is a Japanese herbal medicine used for upper respiratory tract infection. Maoto constitutes extracts obtained from *Ephedra* herb, Apricot kernel, Cinnamon bark, and *Glycyrrhiza* root. Maoto expressed antiviral effect against Influenza virus PR8 and H1N1 by inhibiting the V-ATPase present in the endosome and lysosome membranes, thereby preventing the uncoating of the virus and its entry into the cytoplasm (Masui et al., 2017).

Korean Red Ginseng is used as traditional medicine in East Asian countries as it has enhanced pharmacological properties as compared with

fresh ginseng (the root of *Panax ginseng*) because of the steaming process against Respiratory syncytial virus, Rhinovirus, Influenza virus, HIV, Hepatitis virus, Norovirus, Rotavirus, Enterovirus, and Coxsackievirus (Im et al., 2016).

### 5.4. Enhancing immunity via nutrition

A healthy immune system is the necessity in today's world to combat emerging pathogenic infections. Fig. 4 enlists common nutraceuticals to improve immunity against viral pathogens. Vitamins are the best source of nutrient supplements readily available in plants, fresh fruits, and vegetables. Vitamin C and D hamper speedy recovery of common cold, cough, sore throats, etc., while other vitamins like A, B6, K, and E strengthen the immune system by enhancing inflammatory responses and speed up the biochemical pathways involved in viral destruction. Minerals like zinc, copper, iron, and potassium inhibit pro-inflammatory cytokines and enable the differentiation of T-lymphocytes (Patel et al., 2019). In addition to micronutrients, probiotics not only metabolize food but also wipe out pathogens from the hosts. Herbal home remedies like preparation of decoctions with garlic, ginger, turmeric, pepper, and onions increase flu fighting responses and boost the immune system (Kang et al., 2013; Curtis et al., 2017).

## 6. Conclusions and future perspectives

Newly emerging viral diseases are serious threat to human health. Recent impact of viral disease outbreaks like COVID-19, SARS, EVD, ZIKV disease, NIV disease, and Influenza viruses have emphasized new drug designing and vaccine development. Though synthetic molecules are available for viral infections, traditional medicines or novel drug formulations from different natural sources benefit better with low complications. Natural resources viz. medicinal plants, bacteria, and fungi have been identified as promising producers of plethora of alkaloids, coumarins, phenolics, flavonoids, lignans, terpenoids, tannins, and

**Table 8**  
Antiviral metabolites from lichens.

Name of the compound	Organism	Active against	References
Protolichesterinic acid	<i>Cetraria islandica</i>	HIV reverse transcriptase	Van Sumere (1989)
Swertifrancheside	<i>Swertia franchetiana</i>	HIV-1 reverse transcriptase	Pengsuparp et al. (1995)
Physodalic acid, physodic acid; 3-hydroxy physodic acid, and isophysodic acid	<i>Hypogymnia physodes</i>	Influenza	Pavlovic et al. (2013)
Atranorin and fumarprotocetraric acid	<i>Cladonia furcata</i> , <i>Cladonia pyxidata</i> and <i>Cladonia rangiferina</i>	Influenza	Kosanić et al. (2014)
Usnic acid and derivatives	<i>Cetraria islandica</i> and <i>Vulpicida canadensis</i>	Influenza A viruses (H1N1 and H3N2)	Sokolov et al. (2014); Shtro et al. (2014); Shtro et al. (2015)
α-Methylene-γ-lactone	<i>Lichen Cetraria islandica</i>	HIV-1 reverse transcriptase	Pengsuparp et al. (1995)
Depsidone salazinic acid	<i>Parmelia saxatilis</i> (L.) Ach.	Antiviral activity	Omarsdottir et al. (2006)
Benzyl depside alectorialic acid	<i>Alectoria nigricans</i> (Ach.) Nyl.	Antiviral activity	Omarsdottir et al. (2006)
Antraquinones, bianthrone, and hypericin derivatives	<i>Parmelia perlata</i>	HSV-1	Cohen et al. (1996)
Sekikaic acid	<i>Ramalina farinacea</i>	Respiratory syncytial virus	Lai et al. (2013)



Allium sativa	Phyllanthus	Allium cepa	Haldina cordifolia
Aloe barbadensis	Zingiber officinalis	Hypericummysorensense	Holarrhena pubescens
Alstonia venenata	Magnifera indica	Hypericum hookerianum	Oroxylum indicum
Amaranthus tricolor	Banbusa vulgaris	Berberis tinctoria	Vitex negundo
Annona reticulata	Momordica charantia	Mahonia leschenaultii	Woodfordia fruticosa
Anodendron paniculatum	Zea mays	Boerhavia diffusa	Andrographis paniculata
Azadirachta indica	Nicotiana tabacum	Tagetes minuta	Cajanus cajan
Bacopa monnieri	Helitropium indium	Leucas lavandulaefolia	Phyllanthus emblica
Bauhinia purpurea	Psidium guajava	Argemone mexicana	Ocimum americanum
Centella asiatica	Terminalia superb	Eclipta prostrata	Cynodon dactylon
Chenopodium murale	Solanum trilobatum	Flacourtia indica	Tinospora cordifolia
Lawsonia inermis	Hibiscus vitifolius	Glycosmis pentaphylla	

**(a)**

Ayurvedha	Unani	Decoctions used in Unani
Azadirachta indica A. Juss	Swertiachirata karst	Cydonia oblonga
Acorus calamus Linn.	Cichorium intybus Linn.	Zizyphus jujube Linn.
Vitex negundo Linn.	Artemisia absinthium Linn.	Cordia myxa Linn.
Boswellia serrata Roxb.	Trachysperm umammi sprague	Cinnamomum zeylanicum
Commiphora wightii Arn.	Borage officinalis Linn.	Viola odorata Linn.
Curcuma longa	Azadirachta indica A. Juss.	Borago officinalis Linn.
Punica granatum	Cyperus scariosus R. Br.	Papaver somniferum
Ocimum sanctum		Hyoscyamus niger
Nyctanthes arbortristis		Papaver somniferum
Carica papaya		Myrtus communis
Holarrhena antidysentrica		Lactuca sativa
Phyllanthus urinaria Linn.		Rosa damascene
Euphorbia jolkini Bioss		

**(b)**

**Fig. 2. (a)** Indian medicinal plants reported to treat viral diseases such as Measles, Poliomyelitis, Herpes, Influenza, Hepatitis, HIV, Chickenpox, and Yellow fever. **(b)** Plant extract formulations prepared by Ayurvedic and Unani medicines to combat viral diseases.

peptides which have shown tremendous abilities as antiviral agents and suggested their role in the development of ideal antiviral drugs in future. Indian medicinal plants and Ayurveda have shown

beneficial effects against diversified groups of viral diseases. In addition, CHMs and Unani medicines contained several plant products and preparations which played a tremendous role in treating various

<p><b>Corona Virus</b>                  Bupleurum spp. (Chái Hú)                  Scrophularia scorodonia (Xuán Shēn)                  Lycoris radiata (Shí Suàn)                  Artemisia annua (Huáng Huā Hāo),                  Pyrrosia lingua (Shí Wěi)                  Lindera aggregata (Wū Yào)                  Isatis indigotica (Bān Lán Gēn)                  Torreya nucifera (Fěi)                  Houttuynia cordata (Yú Xīng Cǎo)</p>	<p><b>Influenza Virus</b>                  elderberry (Jiē Gǔ Mù;                  Sambucus nigra)                  dandelion ( Pú Gōng Yīng;                  Taraxacum officinale)                  homoisoflavonoids from                  Caesalpinia sappan (Sū Mù)</p> <p><b>Other medications</b>                  Ocimum basilicum (Luó Lè)                  Woodfordia fruticosa flowers                  (Xiā Zǐ Huā)                  Artemisia apiacea (Qing Hao)                  Fructus arctii (Niu Bang Zi)                  Uncaria tomentosa (Gou Teng)                  Gastrodia elata (Tian Ma)                  P. ginseng (Ren Shen)                  Aconiti carmichaeli (Fu Zi)</p>	<p><b>Hepatitis B Virus</b>                  Piper longum ( Jiǎ Jù)                  Xiao-Chai-Hu-Tang (Xiǎo Chái Hú Tang),                  Bupleurum species (Chái Hú),                  Polygonum cuspidatum sieb. et zucc                  (Hǔ Zhàng)</p> <p><b>Hepatitis C Virus</b>                  Silybum marianum</p>
<p><b>Measles Virus</b>                  Rhus succedanea (Yě Qī) Garcinia                  multiflora                  Olinia rochetiana (Olkirenyi) Warburgia                  ugandensis (Osokonoi)</p>		<p><b>Respiratory Syntitial Virus</b>                  Lophatherum gracile (Dàn Zhú Yè)                  Sheng-Ma-Ge-Gen-Tang ( Shēng                  Má Gé Gēn Tang), its major                  component herb Cimicifuga foetida                  L. (Shēng Má),.</p>
<p><b>Human Immunodeficiency Virus</b>                  Artemisia annua (Huáng Huā Hāo)</p>		<p><b>Dengue Virus</b>                  Terminalia chebula (Hē Zǐ)</p>
<p><b>Sheng-Ma-Ge-Gen-Tang (SMGGT)</b> is a Chinese formula, consisting of four herbal medicines: Rhizoma Cimicifu-gae (Sheng Ma), P. lobata (Ge Gen), Glycyrrhiza uralen-sis (Gan Cao), and Raeonia lactiflora (Shao Yao)</p>	<p><b>Pu Di Lan</b> is prepared as oral tablets or a liquid, and mainly consists of Taraxacum mongolicum (Pu Gong Ying), S. baicalensis (Huang Qin), Corydalis bungeana Turcz. (Ku Di Ding), and Baphicacanthis cusiae Rhizoma et Radix (Ban Lan Gen).</p>	

**Fig. 3.** Chinese herbal medicines used for treating viral infections.

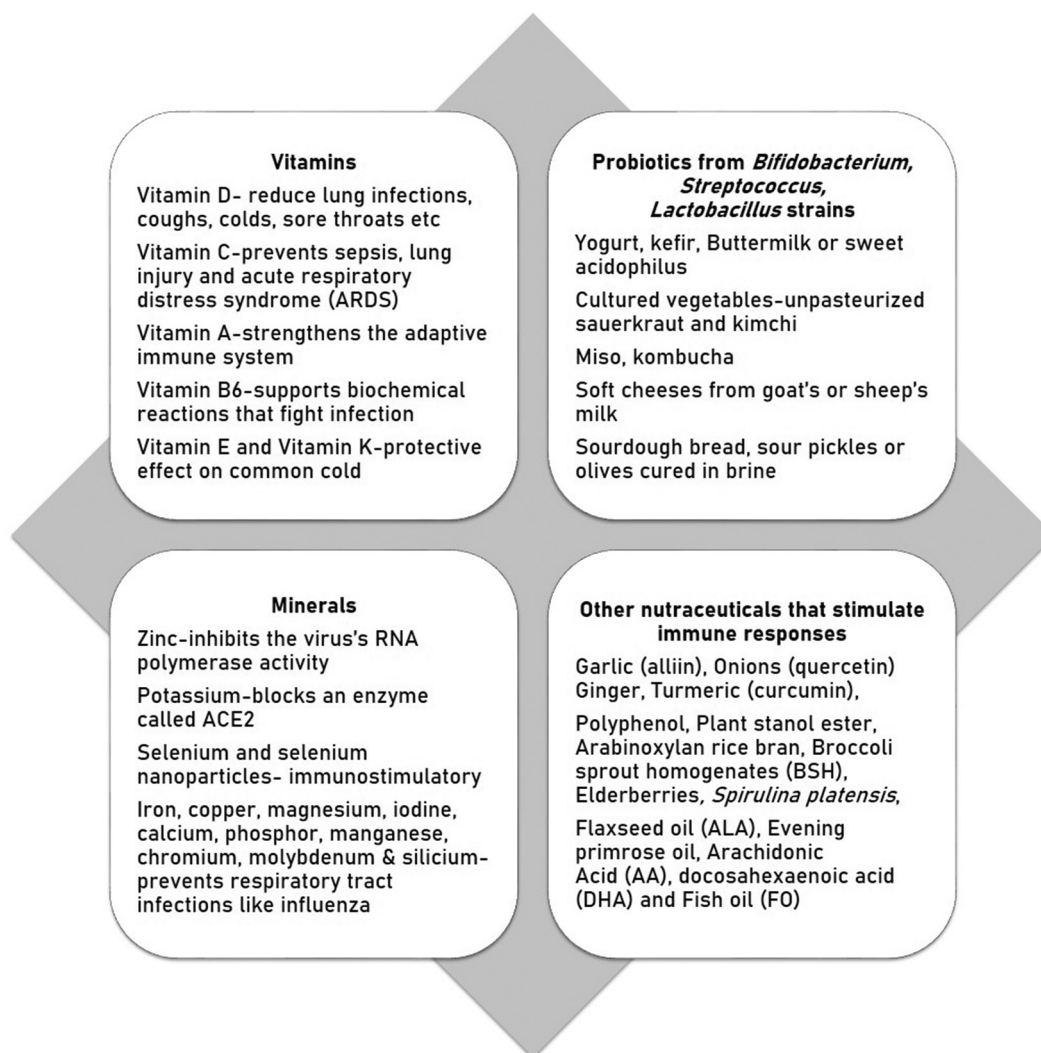


Fig. 4. Nutraceuticals to improve immunity.

ailments. These evidences led to investigate further the field of pharmacology in order to strengthen the constant warning of emerging and re-emerging viral infections and develop a state of preparedness in the world. However, plethora of natural resources still requires in depth pharmacological investigations in terms of suggesting their profound roles as therapeutics.

#### CRedit authorship contribution statement

**R. Sagaya Jansi:** Investigation, Writing - original draft. **Ameer Khusro:** Investigation, Writing - original draft. **Paul Agastian:** Conceptualization, Writing - original draft. **Ahmed Alfarhan:** Conceptualization, Resources, Supervision. **Naif Abdullah Al-Dhabi:** Writing - review & editing, Supervision. **Mariadhas Valan Arasu:** Writing - review & editing, Resources. **Rajkrishnan Rajagopal:** Writing - review & editing, Resources. **Damia Barcelo:** Conceptualization, Writing - review & editing, Supervision. **Amal Al-Tamimi:** Resources, Writing - review & editing.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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