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Review

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

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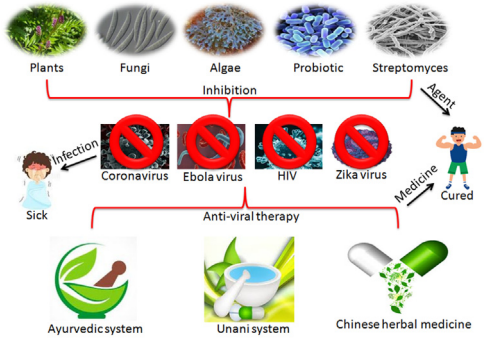
## HIGHLIGHTS

- 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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Natural sources
Viral diseases

comprehensive overview of antiviral components present in varied natural sources, including plants, fungi, and microorganisms in order to identify potent antiviral agents for developing alternative therapy in future.



**Contents**



## 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 |
| | | Papillomaviridae | HPV | Icosahedral | No | 54–60 | 5–8 kbp |
| RT viruses | Reverse transcribing | 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 |
| | | Picornaviridae | HAV | Icosahedral | No | 27 | 7 kb |
| | | Togaviridae | CHIKV | Icosahedral | Yes | 70 | 12 kb |
| | (−) ssRNA | Filoviridae | Ebola virus | Helical | Yes | 970 | 18–19 kb |
| | | Paramyxoviridae | NIV | Helical | Yes | 150 | 18 kb |
| | | | Measles | Helical | Yes | 120–150 | 15 kb |
| | | Hantaviridae | Hanta virus | Helical | Yes | 80–120 | 14 kb |
| | | Orthomyxoviridae | Influenza virus | Helical | Yes | 100 | 14 kb |

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 *Henipavius* 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 Coronaviride 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, chillness, 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 conjuctival 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 lasy 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 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).

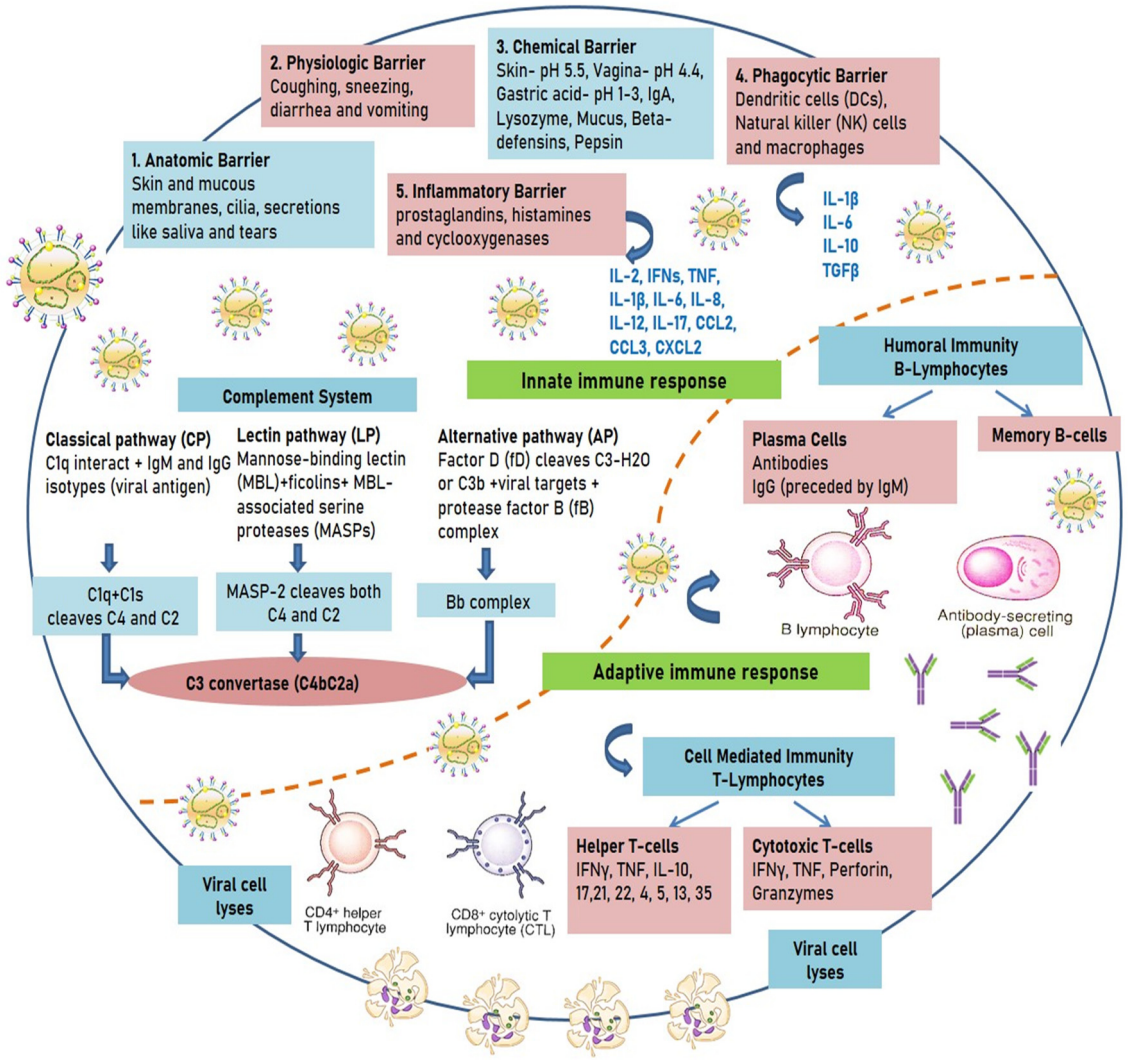


**Fig. 1.** Immune responses against viral infections.

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

(continued on next page)

**Table 2** (*continued*)

| Name of the compound | Plant | Active against | References |
|---|---|---|---|
| Flavonoids | | | |
| Acacetin 7-o-(6″-rhamnopyranosyl) β-D-glucopyra-noside) | *Chrysanthemum morifolium* Ramar (Compositae) | HIV | Qi-Hu et al. (1994) |
| Apigenin | Widely distributed in the plant kingdom | Herpes virus | Béládi et al. (1977) |
| 3,3′ Dimethoxyquercetin | *Euphorbia grantii* Oliv. and *Veronia amygdalina* Del. (Compositae) | Picornaviruses and vesicular stomatitis virus | Van Hoof et al. (1989); Rwangabo et al. (1986) |
| Fisetin inactivates | *Rhus* spp. | Pseudorabies virus | Béládi et al. (1977) |
| *O*-Glucosyl-7-methyl-5-genistein | *Ulex europaeus* L. | HSV | Swallow et al. (1975) |
| Glycosil-7-*O*-luteolin | *Matricaria inodora* L. (Compositae) | HSV and poliomelytis | Suganda et al. (1983) |
| Hesperetin | *Citrus* spp. (lemons and sweet oranges) | Vesicular stomatitis | Harborne (1988) |
| Isoquercitrin | *Waldsteinia fragarioides* Michx. | HSV-1 virus | Karam and Shier (1992) |
| Justicidin B | *Phyllanthus acuminatus* | Cytomegalovirus and Sindbis virus | Ingham (1983) |
| Kaemferol 3-methyl ether; and Isokaempferide | *Solanum sarrachoides* | Antiviral activity | Harborne (1988) |
| Luteolin | Widely distributed in the plant kingdom | Pseudorabies virus | Béládi et al. (1977) |
| Luteolin-7-*O*-glucoside | *Matricaria inodora* L. (Compositae) | HSV and poliovirus | Béládi et al. (1977) |
| Morin | *Chlorophora tinctoria* L. Gaud | Pseudorabies virus | Béládi et al. (1977) |
| Naringin | *Citrus paradisi* Macfad. | Vesicular stomatitis virus | Wacker and Eilmes (1978) |
| Pachypodol (quercetin 3,7,3′-trimethyl ether) | *Begonia glabra* | Antiviral activity | Cody et al. (1986) |
| Pelargonidin | *Pelargonium* sp. | Enveloped viruses | Béládi et al. (1977) |
| Quercetin | *Chenopodium quinoa* | 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)-β-D-galactopyranoside | *Acer okamotoanum* Nakai | HIV-1 integrase | Kim et al. (1998) |
| Quercetagetin | Found in the flowers of many spp. of Compositae | Rauscher murine leukemia and HIV | Cody et al. (1986) |
| Rutin | *Fagopyrum esculentum Moench* | Pseudorabies and vesicular stomatitis virus | Béládi et al. (1977) |
| Taxifolin | *Acacia catechu* | Antiviral activity | Harborne (1988) |
| Volkensiflavone | *Rhus succedania* L. | Influenza B virus | Lin et al. (1997); Lin et al. (1999) |
| Ternatin and Melaternatin | *Evodia madagascariensis Baker* | HSV-1, HSV-2, adenovirus type 2, poliovirus type 2, and VSV type 2 | Simões et al. (1990) |
| Afromosin and Formononetin | *Wisteria brachybotrys* Sieb | Epstein-Barr virus early antigen | Konoshima et al. (1989) |
| Axillarin, Chrysosphenol B, and Chrysosplenol C | *Chrysosplenium tosaense* | Rhinovirus | Tsuchiya et al. (1985) |
| Lophirone F, Azobechalcone, and Isolophirachalcone | *Lophira alata* | Epsein-Barr virus early antigen induction test | Murakami et al. (1992) |
| Centaurein and Jacein | *Centaurea nigra* 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 | *Befaria cinnamomea* | HIV-1 | Mahmood et al. (1993) |
| Agathisflavone, Robustaflavone, Hinokiflavone, Amentoflavone, and Morelloflavone | *Rhus succedanea* L. and *Garcinia multiflora* Champ | HIV-1 reverse transcriptase | Lin et al. (1997) |
| 3-*O*-Methylcalopocarpin, Licoisoflavanone, Glyasperin | *Erythrina lysistemon* Hutch | HIV | McKee et al. (1997) |
| Macluraxanthone B, Macluraxanthone C, and Dihydrocudraflavone B | *Maclura tinctoria* | HIV | Groweiss et al. (2000) |
| 7-*O*-Methyl-glabranine | *Tephrosia madrensis* | Dengue virus | Sanchez et al. (2000) |
| Wogonin | *Scutellaria baicalensis* | HBV | Huang et al. (2000) |
| Samarangenin B and Myricetin | *Limonium sinense* | HSV-1 replication | Lin et al. (2000) |
| Lignans | | | |
| Dihydroanhydropodorhizol | *Bursera schletchtendalii* | HSV-1 | Ayres and Loike (1990) |
| Diphyllin apioside-5-acetate, justicidin A and B, diphyllin, and diphyllin apioside | *Justicia procumbens* var. *leucantha* | Vesicular stomatitis virus | Asano et al. (1996) |
| Lignine guaiacyl derivative | *Pinus nigra* Arnold | HIV | Eberhardt and Young (1996) |
| Deoxypodophyllotoxin, 4′-Dimethylpodophyllotoxin, Podophyllotoxin acetate, Epidophyllotoxin acetate, and β-Peltatin A methyl ether | *Juniperus sabina* | HSV-1 and vesicular stomatitis virus | Feliciano et al. (1993) |
| Podophyllotoxin, β-Peltatin, Deoxypodophyllotoxin, Picropodophyllotoxin, and α-Peltatin | *Podophyllum peltatum* | Measles and HSV-1 viruses | McKee et al. (1997); Bedows and Hatfield (1982) |
| Kadsulignan L, Kadsulignan M, and Kadsulignan N | *Kadsura coccinea* | HIV | Liu and Li (1995) |
| Justicidins A, Justicidins B, Diphyllin, Actigenin, and Trachelogenin | *Forsythia intermedia* and *Ipomoea cairica* | HIV-1 | Vlietinck et al. (1998) |
| Schizarin B and taiwanschirin D | *Kadsura matsudai* | HBV virus | Kuo et al. (2001) |
| Rhinacanthin E and rhinacanthin F | *Rhinacanthus nasutus* | Influenza virus type A | Kernan et al. (1997) |
| Miscellaneous compounds | | | |
| Calcium elenolate | *Olea europaea* L. | Antiviral activity | Swallow et al. (1975) |
| Castelanone | *Castela tweediei* | Oncogenic Rous sarcoma virus | Rembold (1989) |
| Chaparrinone | *Quassia undulata* | Oncogenic Rous sarcoma virus | Rembold (1989) |
| Cochinolide | *Homalium cochinchinesis* | HSV-1 and -2 | Ishikawa et al. (1998) |
| Curdlan sulphate, Dextran sulphate, and Dextrin sulphate | Dextran sulphate - *Viola yedoensis*, Dextrin sulphate - *Prunella vulgaris* and Curdlan sulphate - *Alternanthera philoxeroides* (Amarantaceae) | HIV | Vlietinck et al. (1998) |
| Glaucarubolone | *Quassia simarouba* | Oncogenic Rous sarcoma virus | Rembold (1989) |
| D-glucosamine | *Dahlis* sp., *Glycine* max (L.) Merr and Phaeseolus aureus 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 | *Nicotania tabacum* | Antiviral activity | Rouhier et al. (1995) |
| Pentagalloylglucose | *Paeonia albiflora* Pallas | HSV | Kaij-a-Kamb et al. (1992) |
| Monoterpenoids, diterpenoids and sesquiterpenoids | | | |
| Alloaromadendrol glycosides | *Calendula arvensis* L. | Vesicular stomatitis virus and rhinovirus (HRV type 1B) | Tommasi et al. (1990) |
| Arbotristosides A,B,C | *Nyctanhes arbor-tristis* | EMCV and SFV | Rathore et al. (1990) |
| Carnosolic acid and Carnosol | *Rosmarinus officinalis* L. | HIV protease inhibitors | Pariš et al. (1993) |
| Celafolin A-1, Celaforin B-2, Celaforin B-3, Celaforin C-1, Celaforin D-1, Celaforin D-2, and Celaforin D-3 | *Celastrus stephanotiifolius* Makino | Epstein-Barr virus | Takaishi et al. (1993) |
| 12-Deoxyphorbol-13(3E,5E-decadienoate) | *Excoecaria agallocha* | HIV | Erickson et al. (1995) |
| Euglobal T1 | *Eucalyptus tereticornis* Sm. | Epstein-Barr virus | Kokumai et al. (1991) |
| Euglobal 1, Euglobal 2, and Euglobal 3 | *Eucalyptus grandis* | Epstein-Barr virus | Takasaki et al. (1990) |
| Halnanolide | *Banisteria caapi* | Influenza virus A (WS), Newcastle diseases virus, Japanese B encephalitis virus (AZ), and vaccina virus | Cracker and Simon (1986) |
| Liangshanin B and Liangshanin D | *Rabdosia liangshanica* C.Y. | Hepatitis virus | Fenglei et al. (1989) |
| Nimbinen | Limonoids found in plants of the order Rutales | Antiviral activity | Champagne et al. (1992) |
| Sclerocarpic acid | *Glyptopetalum sclerocarpum* | HSV 1 and 2 | Sotanaphun et al. (1999) |
| Scoparic acid A, Scoparic acid B, Scoparic acid C, and Scopadulcis acid B | *Scoparia dulcis* | HSV 1 | Hayashi et al. (1988); Hayashi et al. (1990) |
| Dolabellane | *Dolabella californica* | Influenza and adenovirus viruses | Piattelli et al. (1995) |
| Safficinolide and Sageone | *Salvia officinalis* | Vesicular stomatitis virus | Tada et al. (1994) |
| Tripterifordin | *Triterygium wilfordii* Hook | HIV | Chen et al. (1992) |
| Arennoside, Geniposidic acid, Geniposidic, and Gardenoside | *Genipa americana* L. | Antiviral activity | Ueda et al. (1991) |
| Xylopinic acid | *Xylopia* sp. | HIV | Fuller et al. (1996) |
| 12-*O*-Acetylphorbol-13-Decanoate and 12-O-Decanoylphorbol-13-(2- methyl butyrate) | *Croton tiglium* | HIV-1 | El-Mekkawy et al. (2000) |
| Phenolic | | | |
| 2-*O*-Caffeoyl-(+)-allohydroxycitric | *Spondias mombin* | Coxsackie and HSV | Corthout et al. (1992) |
| 2,6-Dihydroxymethoxyisobutylrophenone and 4,6-Dihydroxymethoxyisobutylrophenone | *Kunzea ericoides* A. Rich. | Antiviral activity | Bloor (1992) |
| Eugenin or Ellagitanin | *Syzyium aromatica* Merr *Paeonia suffruticosa* | HSV | Takechi and Tanaka (1982); Takechi and Tanaka (1981) |
| Gentisic acid | *Citrus cultivars*, *Vitus vinifera* | Antiviral activity | Van Sumere (1989) |
| Gossypol | *Gossypium herbaceum* L. | Herpes parainfluenza 3 and influenza viruses | Harborne and Baxter (1993) |
| Guttiferone A,B,C,D, and E | *Symphonia globulifera*, *Garcinia livinstonei*, *Garcinia ovalifolia* and *Clusia rosea* | HIV | Gustafson et al. (1992) |
| Mallotojaponin and Mallotochromene | *Mallotus japonicum* | HIV | Van Sumere (1989) |
| Peltalol A | *Pothomorpha peltata* | HIV-1 | Van Sumere (1989) |
| Pentagalloyl-βD-glucose | *Nuphar japonicum* | HIV | Porter (1989) |
| Polyphenolic complex | *Geranium sanguineum* L. | Neuraminidase activity of different influenza virus HINI, H2N2, and H3N2 | Serkedjieva and Manolova (1992) |
| Salicin and Salireposide | *Populus trichocarpa* | Poliomyelitis and Semliki forest virus | Van Hoof et al. (1989) |
| Δ-9-Tetrahydrocannabinol | *Cannabis sativa* L. | HSV-1, HSV-2 | Blevins and Dumic (1980) |
| Woodorien | *Woodwardia orientalis* | HSV-1 and poliovirus | Xu et al., 2010 |
| Silymarin and Cyanidol | *Silybum marianum* | Acute viral hepatitis | Swallow et al. (1975) |
| Dibalanocarpol and Balanocarpol | *Hopea malibato* 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 | *Guiera senegalensis* and *Securidata longipedunculata* | HIV | Van Sumere (1989) |
| (+)-Nortrachelogenin, Genkwanol A, Wilkstrol B, and Daphnodorin B | *Wikstroemia indica* C. A. Meyer | HIV-1 | Hu et al. (2000) |
| 1,3,4,5-tetra-*O*-Galloylquinic acid | *Lepidobotrys staudtii* Engl.) | HIV-1 and HIV-2 | Bokesch et al. (1996) |
| Phenylpropanoids | | | |
| Caffeic acid | *Coffea arabica* | Influenza virus, HSV, vaccinia, and polio viruses | Mølgaard and Ravn (1988) |
| Chlorogenic acid | *Coffea arabica* | Poliovirus | Mølgaard and Ravn (1988) |
| 3-Methyl-but-2-enyl caffeate | *Populus nigra* L. | Antiviral activity | Amoros et al. (1994) |
| Usneoidone E, and Usneoidone Z | Brown seaweed *Cystoseira usneoides* | Antiviral activity | Urones et al. (1992) |
| Verbacoside, Isoverbacoside, Luteoside A, and Luteoside B | *Markhamia lutea* Seemann ex Baillor | Respiratory syncytial virus | Kernan et al. (1998) |
| Magnolol, Honokiol, and Monoterpenylmagnolol | *Magnolia officinalis* Rehd. et Wils | Epstein-Barr virus early antigen | Konoshima et al. (1991) |
| Quinones | | | |
| Conocurvone | *Conospermun incurvum* | HIV-1 reverse transcriptase | Decosterd et al. (1993) |
| Juglone | *Juglans nigra*; Hypericum triquetrifolium | HSV-1 virus and retrovirus | Berg and Labiade (1989) |
| Pseudohypericin | *Hypericum triquetrifolium* | Retrovirus | Berg and Labiade (1989) |
| Rhinacanthin C and Rhinacanthin D | *Rhinacanthus nasutus* (L) *Kurz* | Cytomegalovirus | Sendl et al. (1996) |
| Hypericin and Pseudohypericin | *Hypericum perforatum* | Retroviruses | Hudson et al. (1993) |

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**Table 2** (*continued*)

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

**Table 2** (*continued*)

| Name of the compound | Plant | Active against | References |
|---|---|---|---|
| acid, Hydroxydammarenone I, Hydroxyhopanone, Hydroxyoleanolic acid, and Ursonic acid | | | |
| Epigallocatechin-(4β-8,2β-*O*-7)-epicatechin, 3-Oxotirucalla-7–24-dien-21oic acid. And Oleanolic acid | *Xanthoceras sorbifolia Bunge* | HIV-1 | Ma et al. (2000) |
| 1-J3-hydroxyaleuritolic acid-3-p-hydroxybenzoate | *Maprounea africana* | Reverse transcriptase inhibitors | Cos et al. (2008) |
| Escin | *Aesculus chinensis* Bge. | HIV | Yang et al. (1999); Xiu-Wuei et al. (1999) |
| Proteins and peptides | | | |
| Trichobitacin | *Trichosanthes kirilowii* | HIV | Mishra et al. (2013) |
| Pokeweed antiviral proteins (PAP) (MRK29, MAP30 and GAP31) | *Phytolacca Americana*, *Momordica charantia*, *Gelonium multiflorum* | HIV-1 | Rajamohan et al. (1999) |
| Panaxagin | *Panax ginseng* | HIV-1 reverse transcriptase | Ng and Wang (2001) |
| Kalata B1,B2 | *Oldenlandia affinis* | HIV | Craik et al. (2012) |
| Cyrulin A,B | *Chassalia parviflora* | HIV | Gustafson et al. (1994) |
| Lunatusin | *Phaseolus lunatus* | Antiviral activity | Wong and Ng (2005) |
| Vulgarinin | *Phaseolus vulgaris* | Antiviral activity | Jack and Tzi (2005) |
| Cicerin and Arietin | *Cicer arietinum* | Antiviral activity | Ye et al. (2002); De Souza et al. (2011) |
| Peptidesa-Mitogenic | *Brassica napus* | ND-Not determined | Yust (2004) |
| Phaseococcin | *Phaseolus coccineus* | HIV | Kuczer et al. (2010) |
| Sesquin | *Vigna sesquipedalis* | 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, Norquinadoline 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 8α,11-dihydroxy-pachydictyol A, 8β-hydroxy pachydictyol A from *Dictyota* sp. and diterpenes of Group II including Acetoxypachydiol, 3β-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 variegate* 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 (4*S*)-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. CPCC 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 | *Cephalosporium aphidicola* | HSV 1 and 2 | Hanson (1972) |
| Hyalodendrin A | *Penicillium turbatu* | Polio, Coxsackie viruses | Becher (1976) |
| Stachybogrisephenone B, Grisephenone A, and 3,6,8-Trihydroxy-1-methylxanthone | *Stachybotrys* sp. | Enterovirus-71 | Qin et al. (2014) |
| Halovirs A–E and Simplicilliumtide J | *Scytalidium* sp. | HSV | Rowley et al. (2003); Youssef et al. (2019) |
| 11a-dehydroxyisoterreulactone A, Arisugacin A, Isobutyrolactone II, and Aspernolide A | *Aspergillus terreus* SCSGAF0162 | HSV | Nong et al. (2014) |
| Balticolid | *Ascomycetous* strain 222 | HSV | Shushni et al. (2011) |
| Equisetin | *Fusarium heterosporum* | HIV | Shushni et al. (2011) |
| Phomasetin | *Phoma* sp. | HIV | Singh et al. (1999) |
| Integric acid | *Xylaria* sp. | HIV | Rowley et al. (2004) |
| Stachyflin | *Stachybotrys* sp. RF-7260 | Influenza virus | Minagawa et al. (2002) |
| Oxoglyantrypine, Norquinadoline A, Deoxynortryptoquivaline, Deoxytryptoquivaline, Tryptoquivaline, and Quinadoline B | *Cladosporium* sp. | Influenza virus | Peng et al. (2013) |
| Cladosin C | *Cladosporium sphaerospermum 2005-01-E3* | Influenza virus | Wu et al. (2014) |
| (Z)-5-(Hydroxymenthyl)-2-(6′)-methylhept-2′-en-2′-yl)-phenol, Diorcinol, and IFV Cordyol C | A. sydowii ZSDS1-F6 | Influenza virus | Wang et al. (2014) |
| Rubrolide S | *A. terreus* OUCMDZ-1925 | Influenza virus | Zhu et al. (2013) |
| Asperterrestide A | *A. terreus SCSGAF0162* | Influenza virus | He et al. (2013) |
| Isoaspulvinone E, Aspulvinone E, and Pulvic acid | *A. terreus* Gwq-48 | Influenza virus | Gao et al. (2013) |
| Emerimidine A and Emerimidine B | *Emericella* sp. (HK-ZJ) | Influenza virus | Zhang et al. (2011) |
| Purpurquinone B, Purpurquinone C, Purpuresters A, and TAN-931 | *P. purpurogenum* JS03-21 | Influenza virus | Wang et al. (2011) |
| Sorbicatechol A and Sorbicatechol B | *P. chrysogenum* PJX-17 | Influenza virus | Peng et al. (2014) |
| Tetrahydroaltersolanol C and Alterporriol Q | Alternaria sp. ZJ-2008003 | Porcine reproductive and respiratory syndrome | Zheng et al. (2012) |
| Sansalvamide A (43) | Fusarium sp. | Molluscum contagiosum virus | Hwang et al. (1999) |
| 22-O-(N-Me-L-valyl)-21-epiaflaquinolone B (44) | Aspergillus sp. XS-20090B15 | Respiratory syncytial virus | Prieto and Castro (2005) |
| Extracts | *Agaricus subrufescens* | HSV-1 | Bruggemann et al. (2006) |
| GFAHP | *Grifola frondosa* | HSV | Gu et al. (2007) |
| Beta-glucan-protein | *Agaricus subrufescens* | HSV | Yamamoto et al. (2013) |
| Aurenitol | *Chaetomium coarctatum* | Influenza A (H3N2) | Sacramento et al. (2015) |
| Extracts | *Lentinula edodes* | HPV | Rincão et al. (2012) |
| Polysaccharopeptide | *Trametes versicolor* | HIV | Collins and Ng (1997) |
| Polysaccharides | *Agaricus subrufescens* | HPV | Faccin et al. (2007) |
| Extracts | *Trametes versicolor* | Influenza, HSV | Krupodorova et al. (2014) |
| Adenosine | *Cordyceps militaris* | HIV protease | Jiang et al. (2011) |
| Velutin | *Flammulina velutipes* | HIV-reverse transcriptase | Wang and Ng (2001) |
| 4.5 kDa protein | *Russula paludosa* | HIV protease | Wang et al. (2007) |
| Ganoderic acid | Ganoderma lucidum | HIV protease and HBV | Min et al. (1998) |
| Brefeldin A | *Penicillium* sp. FKI-7127 | Dengue viruses, ZIKV, and Japanese encephalitis virus | Raekiansyah et al. (2017) |
| Ganodermadiol, applanoxidic acid G triterpenoids, and lucidadiol | *Ganoderma pfeifferi* Bres. | Influenza virus type A and HSV-1 | Mothana et al. (2003) |
| Cordycepin (also named 3′-deoxyadenosine) | *Cordyceps militaris* | Influenza viral, HIV-1 RT, Epstein-Barr virus, andRota 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 | *Ganoderma lucidum* | HIV-1 and HBV | Hsu and Yen (2014) |
| Hispidin and hispolon | *Inonotus hispidus* (Bull.) P. Karst. | Influenza virus type A and type B | Li and Wang (2006) |
| PSK Krestin and PSP | *Trametes versicolor* | HIV-1 | Mlinaric et al. (2005) |
| Velutin and Flammulin proteins | *Flammulina velutipes* | HIV-1 reverse transcriptase | Wang and Ng (2001) |
| Trypilepyrazinol, (+)-neocitreoviridin, and 3β-hydroxyergosta-8,14,24 (28)-trien-7-one | *Penicillium* sp. | HIV-1, HCV, and Influenza | Li et al. (2019) |
| Physcion, Neoechinulin D, and Dihydroauroglaucin | *Eurotium chevalieri* | Influenza A virus | Bovio et al. (2019) |
| Isobutyrolactone II | *Aspergillus* 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, *Gigartina skottsbergii* | Influenza virus, HSV-1, HSV-2, HPV, HRV, and HIV | Vera et al. (2011) |
| Galactan | Red algae, *Callophyllis variegate*, *Agardhiella tenera*, *Schizymenia binderi*, *Cryptonemia crenulata* | HSV-1, HSV-2, HIV-1, HIV-2, and HAV | Estevez et al. (2001) |
| Alginate | Brown algae, *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, *Macrocystis pyrifera* | HIV, IAV, and HBV | Jiang et al. (2003) |
| Fucan | Brown algae, *Adenocytis utricularis*, *Undaria pinnatifida*, *Stoechospermum marginatum*, *Cystoseira indica*, *Cladosiphon okamuranus*, *Fucus vesiculosus* | HSV-1, HSV-2, HCMV, VSV, Sindbis virus, and HIV-1 | Patankar et al. (1993) |
| Laminaran | Brown algae, *Fucus vesiculosus*, *Saccharina longicruris*, *Ascophyllum nodosum* | HIV | Rioux et al. (2010) |
| Naviculan | Diatom, *Navicula directa* | HSV-1 and HSV-2 | Lee et al. (2006) |
| p-KG03 | Microalga, *Gyrodinium impudicum* | Influenza A virus | Kim et al. (2012) |
| A1 and A2 | Microalga, *Cochlodinium polykrikoides* | Influenza A and B viruses, RSV-A, RSV-B, and parainfluenza-2 | Hasui et al. (1995) |
| Calcium spirulan | Blue-green alga, *Arthrospira platensis* | HSV-1, measles, mumps, influenza, polio, Coxsackie, HIV-1 | Hayashi et al. (1996) |
| Nostaflan | Blue-green alga, *Nostoc flagelliforme* | HSV-1, HSV-2, influenza A virus, and human cytomegalovirus | Kanekiyo et al. (2007) |
| Sea algae extract | Red alga, *Schizymenia pacifica* | HIV | Nakashima et al. (1987a) |
| Sea weed extract | *Acrosiphonia coalita* Scagel, Garbary, Golden et Hawkes | HSV-1 and Sindbis virus | Hudson et al. (1999) |
| Sea weed extract | *Enteromorpha linza* (Linnaeus) J.C. Agardh | HSV-1 and Sindbis virus | Hudson et al. (1999) |
| Sea weed extract | *Ulva* sp. | HSV-1 and Sindbis virus | Kim et al. (1997) |
| Sea weed extract | *Corallina vancouveriensis* Yendo | HSV-1 and Sindbis virus | Hudson et al. (1999) |
| Sea weed extract | *Analipus japonicus* (Harvey) Wynne | HSV-1 | Baba et al. (1988) |
| Sea weed extract | *Egregia menziesii* | HSV-1 and Sindbis virus | Baba et al. (1988) |
| Sea weed extract | *Gracilaria pacifica* Abbott | HSV-1 and Sindbis virus | Taylor et al. (1996) |
| Sea weed extract | *Nereocystis luetkeana* (Mertens) Postels et Ruprecht | HSV-1 | Anani et al. (2000) |
| Sea weeds | *Postelsia palmaeformis* Ruprecht | HSV-1 | Towers et al. (1997) |
| PLE extracts (hexane, ethanol and water) | *Haematococcus pluvialis* | HSV-1 | Santoyo et al. (2011) |
| PLE extracts (hexane, ethanol and water) | *Dunaliella salina* | HSV-2 | Santoyo et al. (2011) |
| Cyanovirin | *Nostoc* sp. | Influenza A (H1N1) | Smee et al. (2008) |
| β-1,3 glucan | *Chlorella vulgaris* | Immune stimulator | Spolaore et al. (2006) |
| AcDa-1 | *Dictyota menstrualis* | HIV | Pereira et al. (2004) |
| SAE (sea algal extract) | Red alga, Schizymenia pacifca | 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 8α,11-Dihydroxy-pachydictyol A, 8β-Hydroxy pachydictyol A | *Dictyota* sp. | HIV | Chen et al. (2018) |
| Group II including Acetoxypachydiol, 3β-actoxydilophol | *Dictyota plectens* | HIV | Chen et al. (2018) |
| Dolabelladienols A-B | *Dictyota pfaffii* | HIV | Chen et al. (2018) |
| Bicyclic diterpenes, Crenulidanes from Da-1 and AcDa-1 | *D. menstrualis* | HIV | Chen et al. (2018) |
| Fucoidan | *Cladosiphon okamuranus* | HIV | Teixeira et al. (2014) |
| Extract | Red alga, *Schizymenia pacifica* | HIV | Ahmadi et al. (2015) |
| Dieckol | *Ecklonia cava* | SARS-CoV | Koirala et al. (2017) |
| Ulvan | *Ulva armoricana* | 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 | *Sorangium cellulosum* | HIV | Zander et al. (2012) |
| Rhizopodin | *Myxococcus stipitatus* | HIV | Martinez et al. (2013) |
| Thiangazole, phenalamide A1, and phenoxan | *Polyangium species* | HIV | Jurkiewicz et al. (1992) |
| Aetheramide A and aetheramide B (10b) | *Aetherobacter* | HIV | Trowitzsch-Kienast et al. (1992) |
| Ratjadon A (11) and α-pyrone | *Sorangium cellulosum* | HIV | Gerth et al. (1995) |
| Myxochelins A-F | *Angiococcus disciformis* | Human cytomegalovirus | Miyanaga et al. (2009) |
| Nannochelin A-C | *Nannocystis exedens* | Human cytomegalovirus | Kunze et al. (1992) |
| Hyalachelin A-C | *Hyalangium minutum* | Human cytomegalovirus | Nadmid et al. (2014) |
| Chondramide A-D | *genus Chondromyces* | EVD | Reichenbach (1988) |
| Noricumazol A-C | *Sorangium cellulosum* | EVD | Kunze et al. (1991) |
| Labindole A and B, 3-chloro-9H-carbazole, 4-hydroxymethyl-quinoline, and Soraphen A | *Labilithrix luteola* | HCV | Mulwa et al. (2018) |
| Lanyamycin | *Sorangium cellulosum* | HCV | Gentzsch et al. (2011) |
| Surfactin | *Bacillus amyloliquefaciens* | Antiviral activity | Koumoutsi et al. (2004) |
| Bacitracin | *Bacillus licheniformis* | Antiviral activity | Konz et al. (1997) |
| Lichenysin | *Bacillus licheniformis* | Antiviral activity | Veith et al. (2004) |
| Locillomycin | *Bacillus subtilis1* | Antiviral activity | Luo et al. (2015) |
| Macrolactin A | *B. subtilis* | HSV | Gustafson et al. (1989) |
| Exopolysaccharides (EPSs) | *Pediococcus*, *Leuconostoc*, *Lactobacillus* | 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 | *Streptomyces* sp. *S-885* | Poliovirus | Swallow et al. (1975) |
| Rifampin | *Streptomyces mediterranei* | Vaccinia and pox viruses | De Clercq (1973) |
| Novobiocin | *Streptomyces spheroids* (*Actinomycetales*) | Antiviral activity | Murray et al. (1982) |
| Guanine-7-N-oxide | *Streptomyces* sp. | Rhabdovirus and infectious pancreatic necrovirus | Nakagawa et al. (1985) |
| Antimycin A1a | *Streptomyces kaviengensis* | Western equine encephalitis virus | Raveh et al. (2013) |
| Xiamycins C-E | *Streptomyces* 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 | *Streptomyces albosporus I03A-04862* | HIV-1 | Liu et al. (2012) |
| 4-amino-3-hydroxy-5-(4-methoxyphenyl) pentanoic acid | *Streptomyces* sp. *CPCC 202950* | HIV-1 | Chen et al. (2018) |
| Daptomycin and Nanchangmycin | *Streptomyces nanchangensis*, *Streptomyces roseosporus* | ZIKV | Barrows et al. (2016); Pascoalino et al. (2016); Rausch et al. (2017) |
| Chartreusin | *Streptomyces chartreusis* | Influenza A | Miyakawa et al. (1958) |
| Mannose specific pradimicin-A (PRMA) | *Actinomadura hibisca* | HIV | Tanabe-Tochikura et al. (1990) |
| Actinohivin | *Longispora albida* gen. nov, sp. nov | HIV | Chiba et al. (2004); Takahashi et al. (2005) |
| Benzastatin C, a 3-chloro-tetrahydroquinolone alkaloid | *Streptomyces nitrosporeus* | HSV-1, HSV-2, and vesicular stomatitis virus | Lee et al. (2007) |
| JBIR-68 | *Streptomyces sp. RI18* | Influenza virus | Takagi et al. (2010) |
| Methylelaiophylin | *Streptomyces melanosporofaciens* | Newcastle disease virus | Lee et al. (2011) |
| Furan-2-yl acetate (C6H6O3) | *Streptomyces VITSDK1* spp. | Fish nodavirus | Suthindhiran et al. (2011) |
| Di-n-octyl phthalate and bis (2-methylheptyl) phthalate | *Streptomyces parvus* | HCV | Elnaby et al. (2016) |
| Fattiviracin A1 | *Streptomyces microflavus* | Antiviral activity | Yokomizo et al. (1998) |
| Musacin C | *Streptomyces griseovirdis* | Antiviral activity | Schneider et al. (1996) |
| MM461156 | *Actinomadura pelletieri* | Antiviral activity | Ashton et al. (1990) |
| FK 506 | *Streptomyces tsukubaensis* | Antiviral activity | Reis et al. (2006) |
| Benzastatin C | *Streptomyces nitrosporeus* | Antiviral activity | Kuzuyama and Seto (2003); Lee et al. (2007) |
| (4*S*)-4-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide | *Streptomyces* sp. *Smu03* | Influenza A virus | Li et al. (2018) |
| Ahmpatinini Bu | *Streptomyces sp. CPCC 202950* | HIV-1 | Teixeira et al. (2014) |
| 4862F | *Streptomyces albosporus I03A-04862* | HIV-1 | Teixeira et al. (2014) |
| Narasin | *Streptomyces aureofaciens* | 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 *Pongamia pinnata* | White spot syndrome virus | Rameshthangam and Ramasamy (2007) |
| Xiamycin A | *Streptomyces* sp. GT 2002/1503 | HIV | Ding et al. (2010) |
| Cytonic acids A and B | *Cytonaema* sp. | Human cytomegalovirus | Bhardwaj and Agrawal (2014) |
| Valinomycin | *Streptomyces tsusimaensis* | Coronavirus | Alvin et al. (2014) |
| Altertoxins | *Alternaria tenuissima* QUE1Se | HIV-1 virus | Bashyal et al. (2014) |
| Aspernidine (A, B), dehydroaustin, emeriphenolicins (A, D), austinol, emerimidine (A, B), austin, and acetoxy dehydroaustin | *Emericella sp.* (HK-ZJ) | Influenza A virus (H1N1) | Zhang et al. (2009) |
| 2-(Furan-2-yl)-6-(2S,3S,4-trihydroxybutyl) pyrazine | *Jishengella endophytica* 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), Liquorice 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 Infuenza 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 | *Cetraria islandica* | HIV reverse transcriptase | Van Sumere (1989) |
| Swertifrancheside | *Swertia franchetiana* | HIV-1 reverse transcriptase | Pengsuparp et al. (1995) |
| Physodalic acid, physodic acid; 3-hydroxy physodic acid, and isophysodic acid | *Hypogymnia physodes* | Influenza | Pavlovic et al. (2013) |
| Atranorin and fumarprotocetraric acid | *Cladonia furcata*, *Cladonia pyxidata* and *Cladonia rangiferina* | Influenza | Kosanić et al. (2014) |
| Usnic acid and derivatives | *Cetraria islandica* and *Vulpicida canadensis* | Influenza A viruses (H1N1 and H3N2) | Sokolov et al. (2014); Shtro et al. (2014); Shtro et al. (2015) |
| α-Methylene-γ-lactone | *Lichen Cetraria islandica* | HIV-1 reverse transcriptase | Pengsuparp et al. (1995) |
| Depsidone salazinic acid | *Parmelia saxatilis* (L.) Ach. | Antiviral activity | Omarsdottir et al. (2006) |
| Benzyl depside alectorialic acid | *Alectoria nigricans* (Ach.) Nyl. | Antiviral activity | Omarsdottir et al. (2006) |
| Anthraquinones, bianthrones, and hypericin derivatives | *Parmelia perlata* | HSV-1 | Cohen et al. (1996) |
| Sekikaic acid | *Ramalina farinacea* | Respiratory syncytial virus | Lai et al. (2013) |

| | | | |
|---|---|---|---|
| Allium sativa | Phyllanthus | Allium cepa | Haldina cordifolia |
| Aloe barbadensis | Zingiber officinalis | Hypericummysorense | 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 indiucm | 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

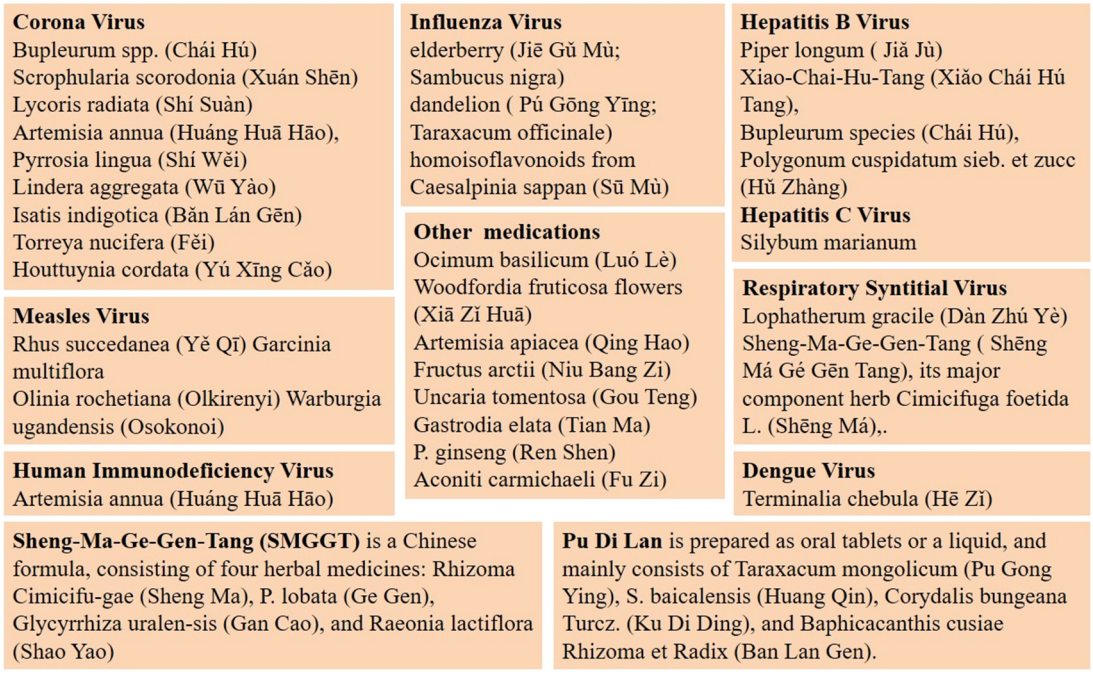


**Fig. 3.** Chinese herbal medicines used for treating viral infections.

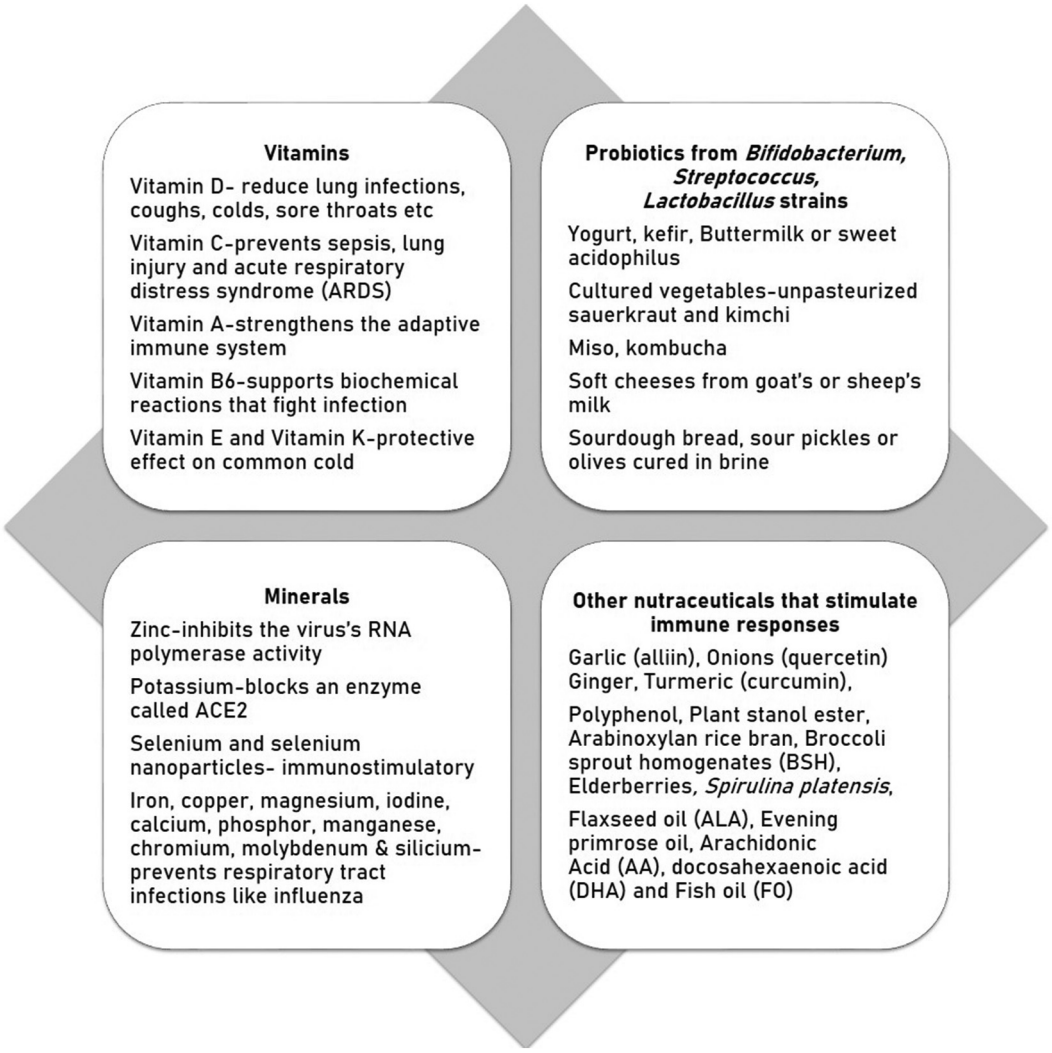


**Fig. 4.** Nutraceuticals to improve immunity.

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. **Rajakrishnan 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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## References

Ahmadi, A., Zorofchian Moghadamtousi, S., Abubakar, S., Zandi, K., 2015. Antiviral potential of algae polysaccharides isolated from marine sources: a review. Biomed. Res. Int., 825203 https://doi.org/10.1155/2015/825203.

Alagaili, A.N., Briese, T., Mishra, N., Kapoor, V., Sameroff, S.C., Burbelo, P.D., de Wit, E., Munster, V.J., Hensley, L.E., Zalmout, I.S., Kapoor, A., Epstein, J.H., Karesh, W.B., Daszak, P., Mohammed, O.B., Lipkin, W.I., 2014. Middle East Respiratory Syndrome Coronavirus infection in dromedary camels in Saudi Arabia. MBio 5 (2). https://doi.org/10.1128/mbio.01002-14.

Alexander, M.E., Kobes, R., 2011. Effects of vaccination and population structure on influenza epidemic spread in the presence of two circulating strains. BMC Public Health 11 (Suppl. 1), S8. https://doi.org/10.1186/1471-2458-11-S1-S8.

Alvin, A., Miller, K.I., Neilan, B.A., 2014. Exploring the potential of endophytes from medicinal plants as sources of antimycobacterial compounds. Microbiol. Res. 169 (7–8), 483–495. https://doi.org/10.1016/j.micres.2013.12.009.

Amoros, M., Girre, R.L., 1987. Structure of two antiviral triterpene saponins from *Anagallis arvensis*. Phytochemistry 26 (3), 787–791. https://doi.org/10.1016/s0031-9422(00)84787-1.

Amoros, M., Lurton, E., Boustie, J., Girre, L., Sauvager, F., Cormier, M., 1994. Comparison of the anti-Herpes Simplex Virus activities of propolis and 3-methyl-but-2-enyl caffeate. J. Nat. Prod. 57 (5), 644–647. https://doi.org/10.1021/np50107a013.

Anani, K., de Souza, C., Akpagana, K., Tower, G.H.N., Arnason, J.T., Gbeassor, M., Hudson, J.B., 2000. Investigation of medicinal plants of Togo for antiviral and antimicrobial

activities. Pharm. Biol. 38 (1), 40–45. https://doi.org/10.1076/1388-0209(200001)38:1;1-b;ft040.
Asano, J., Chiba, K., Tada, M., Yoshii, T., 1996. Antiviral activity of lignans and their glycosides from *Justicia procumbens*. Phytochemistry 42 (3), 713–717. https://doi.org/10.1016/0031-9422(96)00024-6.
Ashton, R.J., Kenig, M.D., Luk, K., Planterose, D.N., Scott-Wood, G., 1990. Mm 46115, a new antiviral antibiotic from *Actinomadura pelletieri*. Characteristics of the producing cultures, fermentation, isolation, physico-chemical and biological properties. J. Antibiot. 43 (11), 1387–1393. https://doi.org/10.7164/antibiotics.43.1387.
Astani, A., Reichling, J., Schnitzler, P., 2010. Comparative study on the antiviral activity of selected monoterpenes derived from essential oils. Phytother. Res. 24 (5), 673–679. https://doi.org/10.1002/ptr.2955.
Ayoade, F., Kumar, S., 2020. Varicella zoster (chickenpox) [updated 2019 Dec 16]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.https://www.ncbi.nlm.nih.gov/books/NBK448191/.
Ayres, D.C., Loike, J.D., 1990. Lignans. Cambridge University Press https://doi.org/10.1017/cbo9780511983665.
Baba, M., Snoeck, R., Pauwels, R., de Clercq, E., 1988. Sulfated polysaccharides are potent and selective inhibitors of various enveloped viruses, including herpes simplex virus, cytomegalovirus, vesicular stomatitis virus, and human immunodeficiency virus. Antimicrob. Agents Chemother. 32 (11), 1742–1745. https://doi.org/10.1128/aac.32.11.1742.
Ballabh, B., Chaurasia, O.P., 2007. Traditional medicinal plants of cold desert Ladakh-used in treatment of cold, cough and fever. J. Ethnopharmacol. 112 (2), 341–345. https://doi.org/10.1016/j.jep.2007.03.020.
Barrows, N.J., Campos, R.K., Powell, S.T., Prasanth, K.R., Schott-Lerner, G., Soto-Acosta, R., Galarza-Muñoz, G., McGrath, E.L., Urrabaz-Garza, R., Gao, J., Wu, P., Menon, R., Saade, G., Fernandez-Salas, I., Rossi, S.L., Vasilakis, N., Routh, A., Bradrick, S.S., Garcia-Blanco, M.A., 2016. A screen of FDA-approved drugs for inhibitors of Zika virus infection. Cell Host and Microbe 20 (2), 259–270. https://doi.org/10.1016/j.chom.2016.07.004.
Bashyal, B.P., Wellensiek, B.P., Ramakrishnan, R., Faeth, S.H., Ahmad, N., Gunatilaka, A.A.L., 2014. Altertoxins with potent anti-HIV activity from *Alternaria tenuissima* QUE1Se, a fungal endophyte of *Quercus emoryi*. Bioorganic and Medicinal Chemistry 22 (21), 6112–6116. https://doi.org/10.1016/j.bmc.2014.08.039.
Becher, Y., 1976. Monographs in Virology: Antiviral Drugs; Mode of Action and Chemotherapy of Viral Infection of Man. Springer Verlag, and Wien, New York, pp. 144–148.
Becker, Y., 1980. Antiviral agents from natural sources. Pharmacol. Ther. 10 (1), 119–159. https://doi.org/10.1016/0163-7258(80)90011-x.
Becker, N.G., Wang, D., 2011. Can antiviral drugs contain pandemic influenza transmission? PLoS One 6 (3), e17764. https://doi.org/10.1371/journal.pone.0017764.
Bedows, E., Hatfield, G.M., 1982. An investigation of the antiviral activity of *Podophyllum peltatum*. J. Nat. Prod. 45 (6), 725–729. https://doi.org/10.1021/np50024a015.
Béládi, I., Pusztai, R., Mucsi, I., Bakay, M., Gábor, M., 1977. Activity of some flavonoids against viruses. Ann. N. Y. Acad. Sci. 284 (1 Third Conference), 358–364. https://doi.org/10.1111/j.1749-6632.1977.tb21971.x.
Berg, A.J.J., Labiade, R.P., 1989. Methods in plants biochemistry. In: Harborne JB, Plant Phenolic London, Academic Press. Blevins RD, Dumic MP (1980): the effect of D-9-tetrahydrocannabinol on herpes simplex virus replication. J. Gen. Virol. 49, 427–431.
Besednova, N.N., Zvyagintseva, T.N., Kuznetsova, T.A., Makarenkova, I.D., Smolina, T.P., Fedyanina, L.N., Kryzhanovsky, S.P., Zaporozhets, T.S., 2019. Marine algae metabolites as promising therapeutics for the prevention and treatment of HIV/AIDS. Metabolites 9 (5), 87. https://doi.org/10.3390/metabo9050087.
Bhardwaj, A., Agrawal, P., 2014. A review fungal endophytes: as a store house of bioactive compound. World J. Pharm. Pharm. Sci. 3, 228–237.
Biliavska, L., Pankivska, Y., Povnitsa, O., Zagorodnya, S., 2019. Antiviral activity of exopolysaccharides produced by lactic acid bacteria of the genera *Pediococcus*, *Leuconostoc* and *Lactobacillus* against human adenovirus type 5. Medicina 55, 519. https://doi.org/10.3390/medicina55090519.
Bimonte, S., Crispo, A., Amore, A., Celentano, E., Cuomo, A., Cascella, M., 2020. Potential antiviral drugs for SARS-Cov-2 treatment: preclinical findings and ongoing clinical research. In Vivo 34, 1597–1602. http://doi.org/10.21873/invivo.11949.
Bishop, K.S., Kao, C.H.J., Xu, Y., Glucina, M.P., Paterson, R.R.M., Ferguson, L.R., 2015. From 2000 years of *Ganoderma lucidum* to recent developments in nutraceuticals. Phytochemistry 114, 56–65. https://doi.org/10.1016/j.phytochem.2015.02.015.
Blevins, R.D., Dumic, M.P., 1980. The effect of -9-tetrahydrocannabinol on Herpes Simplex Virus replication. J. Gen. Virol. 49 (2), 427–431. https://doi.org/10.1099/0022-1317-49-2-427.
Bloor, S.J., 1992. Antiviral phloroglucinols from New Zealand Kunzea species. J. Nat. Prod. 55 (1), 43–47. https://doi.org/10.1021/np50079a006.
Bokesch, H.R., McKee, T.C., Currens, M.J., Gulakowski, R.J., McMahon, J.B., Cardellina, J.H., Boyd, M.R., 1996. HIV-inhibitory gallotannins from *Lepidobotrys staudtii*. Nat. Prod. Lett. 8 (2), 133–136. https://doi.org/10.1080/10575639608043252.
Boustie, J., Grube, M., 2005. Lichens-a promising source of bioactive secondary metabolites. Plant Genetic Resources 3 (2), 273–287. https://doi.org/10.1079/pgr200572.
Boustie, J., Stigliani, J.L., Montanha, J., Amoros, M., Payard, M., Girre, L., 1998. Antipoliovirus structure-activity relationships of some aporphine alkaloids. J. Nat. Prod. 61 (4), 480–484. https://doi.org/10.1021/np970382v.
Bovio, E., Garzoli, L., Poli, A., Luganini, A., Villa, P., Musumeci, R., McCormack, G.P., Cocuzza, C.E., Gribaudo, G., Mehiri, M., Varese, G.C., 2019. Marine fungi from the sponge *Grantia compressa*: biodiversity, chemodiversity, and biotechnological potential. Marine Drugs 17 (4), 220. https://doi.org/10.3390/md17040220.
Braaten, K.P., Laufer, M.R., 2008. Human Papillomavirus (HPV), HPV-related disease, and the HPV vaccine. Rev. Obstet. Gynecol. 1 (1), 2–10.
Bruggemann, R., Matsuo Orlandi, J., Benati, F.J., Faccin, L.C., Mantovani, M.S., Nozawa, C., Linhares, R.E.C., 2006. Antiviral activity of *Agaricus blazei* Murrill ss. Heinem extract against human and bovine herpesviruses in cell culture. Braz. J. Microbiol. 37 (4), 561–565. https://doi.org/10.1590/s1517-83822006000400029.
Calland, N., Dubuisson, J., Rouillé, Y., Séron, K., 2012. Hepatitis C virus and natural compounds: a new antiviral approach? Viruses 4 (10), 2197–2217. https://doi.org/10.3390/v4102197.
Carroll, M.C., 2004. The complement system in regulation of adaptive immunity. Nat. Immunol. 5 (10), 981–986. https://doi.org/10.1038/ni1113.
Champagne, D.E., Koul, O., Isman, M.B., Scudder, G.G.E., Neil Towers, G.H., 1992. Biological activity of limonoids from the rutales. Phytochemistry 31 (2), 377–394. https://doi.org/10.1016/0031-9422(92)90003-9.
Chen, K., Shi, Q., Fujioka, T., Zhang, D.C., Hu, C.Q., Jin, J.Q., Kilkuskie, R.E., Lee, K.H., 1992. Anti-AIDS agents, 4. Tripterifordin, a novel anti-HIV principle from *Tripterygium wilfordii*: isolation and structural elucidation. J. Nat. Prod. 55 (1), 88–92. https://doi.org/10.1021/np50079a013.
Chen, D.F., Zhang, S.-X., Wang, H.K., Zhang, S.-Y., Sun, Q.Z., Cosentino, L.M., Lee, K.H., 1999. Novel anti-HIV Lancilactone C and related triterpenes from *Kadsura lancilimba*. J. Nat. Prod. 62 (1), 94–97. https://doi.org/10.1021/np980291d.
Chen, S., Kinney, W.A., Van Lanen, S., 2017. Nature's combinatorial biosynthesis and recently engineered production of nucleoside antibiotics in *Streptomyces*. World J. Microbiol. Biotechnol. 33 (4). https://doi.org/10.1007/s11274-017-2233-6.
Chen, J., Li, H., Zhao, Z., Xia, X., Li, B., Zhang, J., Yan, X., 2018. Diterpenes from the marine algae of the genus *Dictyota*. Marine Drugs 16 (5), 159. https://doi.org/10.3390/md16050159.
Cheng, V.C., Lau, S.K., Woo, P.C., Yuen, K.Y., 2007. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin. Microbiol. Rev. 20 (4), 660–694. https://doi.org/10.1128/CMR.00023-07.
Chiba, H., Inokoshi, J., Nakashima, H., Ōmura, S., Tanaka, H., 2004. Actinohivin, a novel anti-human immunodeficiency virus protein from an actinomycete, inhibits viral entry to cells by binding high-mannose type sugar chains of gp120. Biochem. Biophys. Res. Commun. 316 (1), 203–210. https://doi.org/10.1016/j.bbrc.2004.02.036.
Christina, A., Christapher, V., Bhore, S.J., 2013. Endophytic bacteria as a source of novel antibiotics: an overview. Pharmacogn. Rev. 7 (13), 11–16. https://doi.org/10.4103/0973-7847.112833.
Clemens, M.J., 1977. Chemoprophylaxis and Virus Infections of Respiratory Tract II. Chemical Rubber Co. Press, Cleveland, Ohio, pp. 189–190.
Cody, V., Middleton, E., Harborne, J.B., 1986. Plant Flavonoids in Biology and Medicine. Alan R Liss, New York.
Cohen, P.A., Hudson, J.B., Towers, G.H.N., 1996. Antiviral activities of anthraquinones, bianthrones and hypericin derivatives from lichens. Experientia 52 (2), 180–183. https://doi.org/10.1007/bf01923366.
Collins, R.A., Ng, T.B., 1997. Polysaccharopeptide from *Coriolus versicolor* has potential for use against human immunodeficiency virus type 1 infection. Life Sci. 60 (25). https://doi.org/10.1016/s0024-3205(97)00294-4 PL383–PL387.
Cordell, G.A., 1981. Introduction to Alkaloids: A Biogenetic Approach. Wiley, New York.
Corthout, J., Pieters, L., Claeys, M., Berghe, D.V., Vlietinck, A., 1992. Antiviral caffeoyl esters from *Spondias mombin*. Phytochemistry 31 (6), 1979–1981. https://doi.org/10.1016/0031-9422(92)80344-e.
Cos, P., Maes, L., Vlietinck, A., Pieters, L., 2008. Plant-derived leading compounds for chemotherapy of human immunodefiency virus (HIV) infection – an update (1998–2007). Planta Med. 74 (11), 1323–1337. https://doi.org/10.1055/s-2008-1081314.
Cracker, L.E., Simon, J., 1986. Herbs, Spices, and Medicinal Plants2. Harwarth Press, Inc, New York, p. 22.
Craik, D.J., Swedberg, J.E., Mylne, J.S., Cemazar, M., 2012. Cyclotides as a basis for drug design. Expert Opin. Drug Discovery 7 (3), 179–194. https://doi.org/10.1517/17460441.2012.661554.
Curtis, L.J., Bernier, P., Jeejeebhoy, K., Allard, J., Duerksen, D., Gramlich, L., Laporte, M., Keller, H.H., 2017. Costs of hospital malnutrition. Clin. Nutr. 36 (5), 1391–1396. https://doi.org/10.1016/j.clnu.2016.09.009.
De Clercq, E., 1973. Selective Inhibitors of Viral Functions. Chemical Rubber Co. Press, Cleveland, Ohio, pp. 78–82.
De Souza, A.D.R., Medeiros, A.C., De Souza, M., Wink, I.R., Siqueira, M.B.C., Ferreira, L., Fernandes, M.P., Loayza Hidalgo, I.L.D.S., Torres, 2011. Evaluation of the impact of exposure to pesticides on the health of the rural population: vale do Taquari, State of Rio Grande do Sul (Brazil). CiênciaSaúdeColetiva 16, 3519–3528.
Decosterd, L., Parsons, I., Gustafson, K., Cardellina, J., McMahon, J., Cragg, G., Murata, Y., Pannell, L., Steiner, J., Clardy, J., Boyd, M., 1993. Isolation, structure and synthesis of Conocurvone, a potent, novel HIV-inhibitory naphthoquinone trimer from *Conospermum* species. Planta Med. 59 (S 1), A581. https://doi.org/10.1055/s-2006-959777.
Diallo, B., Vanhaelen, M., Vanhaelen-Fastré, R., Konoshima, T., Kozuka, M., Tokuda, H., 1989. Studies on inhibitors of skin-tumor promotion. Inhibitory effects of triterpenes from *Cochlospermum tinctorium* on Epstein-Barr virus activation. J. Nat. Prod. 52 (4), 879–881. https://doi.org/10.1021/np50064a039.
Ding, L., Münch, J., Goerls, H., Maier, A., Fiebig, H.-H., Lin, W.H., Hertweck, C., 2010. Xiamycin, a pentacyclic indolosesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. Bioorganic and Medicinal Chemistry Letters 20 (22), 6685–6687. https://doi.org/10.1016/j.bmcl.2010.09.010.
Duan, H., Takaishi, Y., Imakura, Y., Jia, Y., Li, D., Cosentino, L.M., Lee, K.H., 2000. Sesquiterpene alkaloids from *Tripterygium hypoglaucum* and *Tripterygium wilfordii*: a new class of potent anti-HIV agents. J. Nat. Prod. 63 (3), 357–361. https://doi.org/10.1021/np990281s.
Eberhardt, T., Young, R., 1996. Assessment of the anti-HIV activity of a pine cone isolate. Planta Med. 62 (01), 63–65. https://doi.org/10.1055/s-2006-957801.

Elgamal, M.H.A., Soliman, H.S.M., Karawya, M.S., Mikhova, B., Duddeck, H., 1995. Isolation of triterpene saponins from *Gypsophila capillaris*. Phytochemistry 38 (6), 1481–1485. https://doi.org/10.1016/0031-9422(94)00900-e.

El-Mekkawy, S., Meselhy, M.R., Nakamurame, N., Tezuka, Y., Hattori, M., Kakiuchi, N., Shimotohno, K., Kawahata, T., Otake, T., 1998. Anti-HIV-1 and anti-HIV-1-protease substances from *Ganoderma lucidum*. Phytochemistry 49 (6), 1651–1657. https://doi.org/10.1016/s0031-9422(98)00254-4.

El-Mekkawy, S., Meselhy, M.R., Nakamura, N., Hattori, M., Kawahata, T., Otake, T., 2000. Anti-HIV-1 phorbol esters from the seeds of *Croton tiglium*. Phytochemistry 53 (4), 457–464. https://doi.org/10.1016/s0031-9422(99)00556-7.

Elnaby, A.H., Abo-Elala, G., Abdel-Raouf, U., Abd-elwahab, A., Hamed, M., 2016. Antibacterial and anticancer activity of marine *Streptomyces parvus*: optimization and application. Biotechnol. Biotechnol. Equip. 30 (1), 180–191.

Erdelmeier, C., Cinatl, J., Rabenau, H., Doerr, H., Biber, A., Koch, E., 1996. Antiviral and antiphlogistic activities of *Hamamelis virginiana* bark. Planta Med. 62 (03), 241–245. https://doi.org/10.1055/s-2006-957868.

Erickson, K.L., Beutler, J.A., Cardellina, J.H., McMahon, J.B., Newman, D.J., Boyd, M.R., 1995. A novel phorbol ester from *Excoecaria agallocha*. J. Nat. Prod. 58 (5), 769–772. https://doi.org/10.1021/np50119a020.

Estevez, J.M., Ciancia, M., Cerezo, A.S., 2001. DL-galactan hybrids and agarans from gametophytes of the red seaweed *Gymnogongrus torulosus*. Carbohydrate Res. 331, 27–41. https://doi.org/10.1016/S0008-6215(01)00015-5.

Faccin, L.C., Benati, F., Rincão, V.P., Mantovani, M.S., Soares, S.A., Gonzaga, M.L., Nozawa, C., Carvalho Linhares, R.E., 2007. Antiviral activity of aqueous and ethanol extracts and of an isolated polysaccharide from *Agaricus brasiliensis* against poliovirus type 1. Lett. Appl. Microbiol. 45 (1), 24–28. https://doi.org/10.1111/j.1472-765x.2007.02153.x.

Farnsworth, N.R., Svoboda, G.H., Blomster, R.N., 1968. Antiviral activity of selected *Catharanthus* alkaloids. J. Pharm. Sci. 57 (12), 2174–2175. https://doi.org/10.1002/jps.2600571235.

Feliciano, A., Gordaliza, M., del Corral, J., Castro, M., García-Grávalos, M., Ruiz-Lázaro, P., 1993. Antineoplastic and antiviral activities of some cyclolignans. Planta Med. 59 (03), 246–249. https://doi.org/10.1055/s-2006-959660.

Fenglei, Z., Yunlong, X., Handong, S., 1989. Diterpenoids constituents of *Rabdosia liangshanica*. Phytochemistry 28, 1671–1674.

Foder, G.B., Colasanti, B., 1985. Alkaloids, Chemical and Biological Perspectives. 3. Wiley, New York, pp. 1–90.

French, C.J., Towers, G.H.N., 1992. Inhibition of infectivity of potato virus X by flavonoids. Phytochemistry 31 (9), 3017–3020. https://doi.org/10.1016/0031-9422(92)83438-5.

Fujioka, T., Kashiwada, Y., Kilkuskie, R.E., Cosentino, L.M., Ballas, L.M., Jiang, J.B., Janzen, W.P., Chen, I.-S., Lee, K.H., 1994. Anti-AIDS agents, 11. Betulinic acid and platanic acid as anti-HIV principles from *Syzigium claviflorum*, and the anti-HIV activity of structurally related triterpenoids. J. Nat. Prod. 57 (2), 243–247. https://doi.org/10.1021/np50104a008.

Fuller, R.W., Cardellina, J.H., Boyd, M.R., 1996. HIV-inhibitory natural products. Diterpene carboxylic acid from fruits of *Xylopia* sp.1. Nat. Prod. Lett. 8 (3), 169–172. https://doi.org/10.1080/10575639608044890.

Gabrielsen, B., Monath, T.P., Huggins, J.W., Kefauver, D.F., Pettit, G.R., Groszek, G., Hollingshead, M., Kirsi, J.J., Shannon, W.M., Schubert, E.M., DaRe, J., Ugarkar, B., Ussery, M.A., Phelan, M.J., 1992. Antiviral (RNA) activity of selected amaryllidaceae isoquinoline constituents and synthesis of related substances. J. Nat. Prod. 55 (11), 1569–1581. https://doi.org/10.1021/np50089a003.

Gao, W., Sun, Y., Chen, S., Zhang, J., Kang, J., Wang, Y., Wang, H., Xia, G., Liu, Q., Kang, Y., 2013. Mushroom lectin enhanced immunogenicity of HBV DNA vaccine in C57BL/6 and HBsAg-transgenic mice. Vaccine 31 (18), 2273–2280. https://doi.org/10.1016/j.vaccine.2013.02.062.

Gentzsch, J., Hinkelmann, B., Kaderali, L., Irschik, H., Jansen, R., Sasse, F., Frank, R., Pietschmann, T., 2011. Hepatitis C virus complete life cycle screen for identification of small molecules with pro- or antiviral activity. Antivir. Res. 89 (2), 136–148. https://doi.org/10.1016/j.antiviral.2010.12.005.

Gerth, K., Schummer, D., Höfle, G., Irschik, H., Reichenbach, H., 1995. Ratjadon: a new antifungal compound from *Sorangium cellulosum* (Myxobacteria) production, physicochemical and biological properties. J. Antibiot. 48 (9), 973–976. https://doi.org/10.7164/antibiotics.48.973.

Groweiss, A., Cardellina, J.H., Boyd, M.R., 2000. HIV-inhibitory prenylated xanthones and flavones from Macluratinctoria. J. Nat. Prod. 63 (11), 1537–1539. https://doi.org/10.1021/np000175m.

Gu, C.Q., Li, J.W., Chao, F., Jin, M., Wang, X.-W., Shen, Z.Q., 2007. Isolation, identification and function of a novel anti-HSV-1 protein from *Grifola frondosa*. Antivir. Res. 75 (3), 250–257. https://doi.org/10.1016/j.antiviral.2007.03.011.

Gubler, D.J., Clark, G.G., 1995. Dengue/dengue hemorrhagic fever: the emergence of a global health problem. Emerg. Infect. Dis. 1 (2), 55–57. https://doi.org/10.3201/eid0102.952004.

Gustafson, K., Roman, M., Fenical, W., 1989. The macrolactins, a novel class of antiviral and cytotoxic macrolides from a deep-sea marine bacterium. J. Am. Chem. Soc. 111 (19), 7519–7524. https://doi.org/10.1021/ja00201a036.

Gustafson, K.R., Blunt, J.W., Munro, M.H.G., Fuller, R.W., McKee, T.C., Cardellina, J.H., McMahon, J.B., Cragg, G.M., Boyd, M.R., 1992. The guttiferones, HIV-inhibitory benzophenones from *Symphonia globulifera*, *Garcinia livingstonei*, *Garcinia ovalifolia* and *Clusia rosea*. Tetrahedron 48 (46), 10093–10102. https://doi.org/10.1016/s0040-4020(01)89039-6.

Gustafson, K.R., Sowder, R.C., Henderson, L.E., Parsons, I.C., Kashman, Y., Cardellina, J.H., McMahon, J.B., Buckheit, R.W., Pannell, L.K., Boyd, M.R., 1994. Circulins A and B. Novel human immunodeficiency virus (HIV)-inhibitory macrocyclic peptides from the tropical tree *Chassalia parvifolia*. J. Am. Chem. Soc. 116 (20), 9337–9338. https://doi.org/10.1021/ja00099a064.

Gyorgy, E., Koch, A., 1969. Heart glycosides in poliovirus host cell interaction. Effect of the time of addition on stimulatory or inhibitory action. Acta Microbiology 16, 197–202.

Hallock, Y.F., Manfredi, K.P., Dai, J.R., Cardellina, J.H., Gulakowski, R.J., McMahon, J.B., Schäffer, M., Stahl, M., Gulden, K.-P., Bringmann, G., François, G., Boyd, M.R., 1997. Michellamines D—F, new HIV-inhibitory dimeric naphthylisoquinoline alkaloids, and korupensamine E, a new antimalarial monomer, from *Ancistrocladus korupensis*. J. Nat. Prod. 60 (7), 677–683. https://doi.org/10.1021/np9700679.

Hanish, J., Vajda, G., Liona, B., 1966. The mode of action of emetine. *Acta* chirurgica Academiae Scientiarum Hungaricae 7, 51–54.

Hanson, J.R., 1972. Chemistry of Terpenes and Terpenoids. Academic Press, New York, p. 155.

Harborne, J.B., 1988. The Flavonoids: Advances in Research Since 1980. London Chapman and Hall.

Harborne, J.B., Baxter, H., 1993. Phytochemical Dictionary a Handbook of Bioactive Compounds from Plants. Burgess Science Press Basingstoke, London, pp. 12–567.

Harris, K.A., Freidl, G.S., Munoz, O.S., von Dobschuetz, S., De Nardi, M., Wieland, B., Koopmans, M.P.G., Stärk, K.D.C., van Reeth, K., Dauphin, G., Meijer, A., de Bruin, E., Capua, I., Hill, A.A., Kosmider, R., Banks, J., Stevens, K., van der Werf, S., Enouf, V., Breed, A.C., 2017. Epidemiological risk factors for animal Influenza A viruses overcoming species barriers. Eco Health 14 (2), 342–360. https://doi.org/10.1007/s10393-017-1244-y.

Hasan, S., Ahmad, S.A., Masood, R., Saeed, S., 2019. Ebola virus: a global public health menace: a narrative review. Journal of Family Medicine and Primary Care 8 (7), 2189–2201. https://doi.org/10.4103/jfmpc.jfmpc_297_19.

Hasegawa, H., Matsumiya, S., Uchiyama, M., Kurokawa, T., Inouye, Y., Kasai, R., Ishibashi, S., Yamasaki, K., 1994. Inhibitory effect of some triterpenoid saponins on glucose transport in tumor cells and its application to *in vitro* cytotoxic and antiviral activities. Planta Med. 60 (03), 240–243. https://doi.org/10.1055/s-2006-959467.

Hassan, S.T.S., Masarčíková, R., Berchová, K., 2015. Bioactive natural products with antiherpes simplex virus properties. J. Pharm. Pharmacol. 67 (10), 1325–1336. https://doi.org/10.1111/jphp.12436.

Hasui, M., Matsuda, M., Okutani, K., Shigeta, S., 1995. *In vitro* antiviral activities of sulfated polysaccharides from a marine microalga (*Cochlodinium polykrikoides*) against human immunodeficiency virus and other enveloped viruses. Int. J. Biol. Macromol. 17 (5), 293–297. https://doi.org/10.1016/0141-8130(95)98157-T.

Hatano, T., Yasuhara, T., Miyamoto, K., Okuda, T., 1988. Anti-human immunodeficiency virus phenolics from licorice. Chem. Pharm. Bull. 36 (6), 2286–2288. https://doi.org/10.1248/cpb.36.2286.

Hayashi, K., Niwayama, S., Hayashi, T., Nago, R., Ochiai, H., Morita, N., 1988. *In vitro* and *in vivo* antiviral activity of scopadulcic acid B from *Scoparia dulcis*, Scrophulariaceae, against herpes simplex virus type 1. Antivir. Res. 9 (6), 345–354. https://doi.org/10.1016/0166-3542(88)90036-8.

Hayashi, T., Hayashi, K., Uchida, K., Niwayama, S., Morita, N., 1990. Antiviral agents of plant origin. II. Antiviral activity of scopadulcic acid B derivatives. Chem. Pharm. Bull. 38 (1), 239–242. https://doi.org/10.1248/cpb.38.239.

Hayashi, K., Hamada, J., Hayashi, T., 1996. A screening strategy for selection of anti-HSV-1 and anti-HIV extracts from algae. Phytother. Res. 10 (3), 233–237. https://doi.org/10.1002/(sici)1099-1573(199605)10:3<233::aid-ptr824>3.0.co;2-w.

He, F., Bao, J., Zhang, X.Y., Tu, Z.C., Shi, Y.M., Qi, S.H., 2013. Asperterrestide A, a cytotoxic cyclic tetrapeptide from the marine-derived fungus *Aspergillus terreus* SCSGAF0162. J. Nat. Prod. 76 (6), 1182–1186. https://doi.org/10.1021/np300897v.

Hiller, K., 1987. In: Hostettmann, K., Lea, P.J. (Eds.), New results on the structure and biological activity of triterpenoid saponins. Clarendon Press, Oxford, pp. 167–168.

Hou, E.C., Lu, Y.X., 2009. Primary hepatocarcinoma treated by traditional Chinese medicine combined with transcatheter arterial chemoembolization. Zhongguo Zhongxiyi Jiehe Zazhi 29, 225–227.

Hsu, C.L., Yen, G.C., 2014. Ganoderic acid and lucidenic acid (triterpenoid). The Enzymes. Elsevier, pp. 33–56 https://doi.org/10.1016/b978-0-12-802215-3.00003-3.

Hu, K., Kobayashi, H., Dong, A., Iwasaki, S., Yao, X., 2000. Antifungal, antimitotic and anti-HIV-1 agents from the roots of *Wikstroemia indica*. Planta Med. 66 (6), 564–567. https://doi.org/10.1055/s-2000-8601.

Huang, R.L., Chen, C.C., Huang, H.L., Chang, C.G., Chen, C.F., Chang, C., Hsieh, M.T., 2000. Anti-Hepatitis B virus effects of wogonin isolated from *Scutellaria baicalensis*. Planta Medica, 66(8), 694–698. doi:/https://doi.org/10.1055/s-2000-9775.

Hudson, J., Graham, E., Fong, R., Finlayson, A., Towers, G., 1986a. Antiviral properties of thiarubrine-a, a naturally occurring polyine. Planta Med. 52 (01), 51–54. https://doi.org/10.1055/s-2007-969068.

Hudson, J., Graham, E., Chan, G., Finlayson, A., Towers, G., 1986b. Comparison of the antiviral effects of naturally occurring thiophenes and polyacetylenes. Planta Med. 52 (06), 453–457. https://doi.org/10.1055/s-2007-969252.

Hudson, J.B., Harris, L., Towers, G.H.N., 1993. The importance of light in the anti-HIV effect of hypericin. Antivir. Res. 20 (2), 173–178. https://doi.org/10.1016/0166-3542(93)90006-5.

Hudson, J.B., Kim, J.H., Lee, M.K., Hong, Y.K., DeWreede, R.E., 1999. Multiple antiviral activities in extracts of seaweeds from British Columbia. Pharm. Biol. 37 (4), 300–306. https://doi.org/10.1076/phbi.37.4.300.5804.

Hultmark, D., Steiner, H., Rasmuson, T., Boman, H.G., 2005. Insect immunity. Purification and properties of three inducible bactericidal proteins from hemolymph of immunized pupae of *Hyalophora cecropia*. Eur. J. Biochem. 106 (1), 7–16. https://doi.org/10.1111/j.1432-1033.1980.tb05991.x.

Hwang, Y., Rowley, D., Rhodes, D., Gertsch, J., Fenical, W., Bushman, F., 1999. Mechanism of inhibition of a poxvirus topoisomerase by the marine natural product Sansalvamide A. Mol. Pharmacol. 55 (6), 1049–1053. https://doi.org/10.1124/mol.55.6.1049.

Ieven, M., Vlietinick, A.J., Berghe, D.A. Vanden, Totte, J., Dommisse, R., Esmans, E., Alderweireldt, F., 1982. Isolation of alkaloids from *Clivia miniata* regel (Amaryllidaceae). J. Nat. Prod. 45 (5), 564–573. https://doi.org/10.1021/np50023a009.

Im, K., Kim, J., Min, H., 2016. Ginseng, the natural effectual antiviral: protective effects of Korean Red Ginseng against viral infection. Journal of Ginseng Research 40 (4), 309–314. https://doi.org/10.1016/j.jgr.2015.09.002.

Inada, A., Somekawa, M., Murata, H., Nakanishi, T., Tokuda, H., Nishino, H., Iwashima, A., Darnaedi, D., Murata, J., 1993. Structures and inhibitory effects on Epstein-Barr virus activation of triterpenoids from leaves of *Chisocheton macrophyllus* King. Chem. Pharm. Bull. 41 (3), 617–619. https://doi.org/10.1248/cpb.41.617.

Ingham, J.L., 1983. Naturally occurring isoflavonoids (1855–1981). Fortschritte der Chemie Organischer Naturstoffe/Progress in the Chemistry of Organic Natural Products. Springer Vienna, pp. 1–266 https://doi.org/10.1007/978-3-7091-8703-6_1.

Ishikawa, T., Nishigaya, K., Uchikoshi, H., Chen, I.S., 1998. Cochinolide, a new γ-alkylidene bicyclic butenolide with antiviral activity, and its β-glucopyranoside from *Homaliumcochin chinensis*. J. Nat. Prod. 61 (4), 534–537. https://doi.org/10.1021/np970341z.

Jack, H.W., Tzi, B.N., 2005. Vulgarinin, a broad-spectrum antifungal peptide from haricot beans (*Phaseolus vulgaris*). Int. J. Biochem. Cell Biol. 37, 1626–1632.

Jakubiec-Krzesniak, K., Rajnisz-Mateusiak, A., Guspiel, A., Ziemska, J., Solecka, J., 2018. Secondary metabolites of actinomycetes and their antibacterial, antifungal and antiviral properties. Pol. J. Microbiol. 67 (3), 259–272. https://doi.org/10.21307/pjm-2018-048.

Jassim, S.A.A., Naji, M.A., 2003. Novel antiviral agents: a medicinal plant perspective. J. Appl. Microbiol. 95 (3), 412–427. https://doi.org/10.1046/j.1365-2672.2003.02026.x.

Jiang, B., Xu, X., Li, L., Yuan, W., 2003. Study on '911' anti-HBV effect in HepG2 2115 cells culture. Modern Preventive Medicine 30, 517–518.

Jiang, Y., Wong, J.H., Fu, M., Ng, T.B., Liu, Z.K., Wang, C.R., Li, N., Qiao, W.T., Wen, T.Y., Liu, F., 2011. Isolation of adenosine, iso-sinensetin and dimethylguanosine with antioxidant and HIV-1 protease inhibiting activities from fruiting bodies of *Cordyceps militaris*. Phytomedicine 18 (2–3), 189–193. https://doi.org/10.1016/j.phymed.2010.04.010.

Jurkiewicz, E., Jansen, R., Kunze, B., Trowitzsch-Kienast, W., Forche, E., Reichenbach, H., Höfle, G., Hunsmann, G., 1992. Three new potent HIV-1 inhibitors from Myxobacteria. Antivir. Chem. Chemother. 3 (4), 189–193. https://doi.org/10.1177/095632029200300401.

Kaij-a-Kamb, M., Amoros, M., Girre, L., 1992. Search for new antiviral agent of plant origin. Pharm. Acta Helv. 67, 130–147.

Kaluza, G., Scholtissek, C., Rott, R., 1972. Inhibition of the multiplication of enveloped RNA-viruses by glucosamine and 2-deoxy-D-glucose. J. Gen. Virol. 14 (3), 251–259. https://doi.org/10.1099/0022-1317-14-3-251.

Kamboj, V.P., 2000. Herbal medicine. Curr. Sci. 8 (1), 35–39.

Kanekiyo, K., Hayashi, K., Takenaka, H., Lee, J.B., Hayashi, T., 2007. Anti-Herpes Simplex Virus target of an acidic polysaccharide, Nostoflan, from the edible blue-green alga *Nostoc flagelliforme*. Biol. Pharm. Bull. 30 (8), 1573–1575. https://doi.org/10.1248/bpb.30.1573.

Kang, E.J., Kim, S.Y., Hwang, I.-H., Ji, Y.J., 2013. The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies. Korean Journal of Family Medicine 34 (1), 2–10. https://doi.org/10.4082/kjfm.2013.34.1.2.

Karam, M., Shier, T., 1992. Isolation and characterization of an antiviral flavonoid from *Waldsteinia fragarioides*. J. Nat. Prod. 55, 1525–1527.

Kashiwada, Y., Wang, H.K., Nagao, T., Kitanaka, S., Yasuda, I., Fujioka, T., Yamagishi, T., Cosentino, L.M., Kozuka, M., Okabe, H., Ikeshiro, Y., Hu, C.-Q., Yeh, E., Lee, K.H., 1998. Anti-HIV activity of oleanolic acid, pomolic acid, and structurally related triterpenoids1. J. Nat. Prod. 61 (9), 1090–1095. https://doi.org/10.1021/np9800710.

Kernan, M.R., Sendl, A., Chen, J.L., Jolad, S.D., Blanc, P., Murphy, J.T., Stoddart, C.A., Nanakorn, W., Balick, M.J., Rozhon, E.J., 1997. Two new lignans with activity against influenza virus from the medicinal plant *Rhinacanthus nasutus*. J. Nat. Prod. 60 (6), 635–637. https://doi.org/10.1021/np960613i.

Kernan, M.R., Amarquaye, A., Chen, J.L., Chan, J., Sesin, D.F., Parkinson, N., Ye, Z., Barrett, M., Bales, C., Stoddart, C.A., Sloan, B., Blanc, P., Limbach, C., Mrisho, S., Rozhon, E.J., 1998. Antiviral phenylpropanoid glycosides from the medicinal plant *Markhamia lutea*. J. Nat. Prod. 61 (5), 564–570. https://doi.org/10.1021/np9703914.

Kim, J.H., Huang, A.M., Bannister, K., Choi, T.J., Towers, G.H.N., DeWreede, R.E., Hudson, J.B., Jin, H., Hong, Y.K., 1997. Biological activities of seaweed extracts from British Columbia, Canada, and Korea. Can. J. Bot. 75 (10), 1656–1660. https://doi.org/10.1139/b97-878.

Kim, H.J., Woo, E.R., Shin, C.G., Park, H., 1998. A new flavonol glycoside gallate ester from *Acer okamotoanum* and its inhibitory activity against human immunodeficiency virus-1 (HIV-1) integrase. J. Nat. Prod. 61 (1), 145–148. https://doi.org/10.1021/np970171q.

Kim, S.K., Vo, T.S., Ngo, D.H., 2011. Potential application of marine algae as antiviral agents in medicinal foods. Marine Medicinal Foods - Implications and Applications, Macro and Microalgae. Elsevier, pp. 245–254 https://doi.org/10.1016/b978-0-12-387669-0.00019-3.

Kim, M., Yim, J.H., Kim, S.-Y., Kim, H.S., Lee, W.G., Kim, S.J., Kang, P.-S., Lee, C.-K., 2012. *In vitro* inhibition of influenza A virus infection by marine microalga-derived sulfated polysaccharide p-KG03. Antivir. Res. 93 (2), 253–259. https://doi.org/10.1016/j.antiviral.2011.12.006.

Kite, G.C., Fellows, L.E., Fleet, G.W.J., Liu, P.S., Scofield, A.M., Smith, N.G., 1988. α-Homonojirimycin [2,6-dideoxy-2,6-imino-d-glycero-l-gulo-heptitol] from *Omphalea diandra* L.: isolation and glucosidase inhibtion. Tetrahedron Lett. 29 (49), 6483–6485. https://doi.org/10.1016/s0040-4039(00)82379-5.

Koch, A., Gyorgy, E., 1969. Heart glycosides in poliovirus host cell interaction. I. Effect of digitoxin and digitoxin and their aglucons on one step growth curves. Acta. Microbiology 16, 189–196.

Koch, A., Sandor, G., 1969. Heart glycosides in poliovirus host cell interaction III. Chemical Structure and Activity. Acta Microbiology 16, 245–251.

Koirala, P., Jung, H.A., Choi, J.S., 2017. Recent advances in pharmacological research on *Ecklonia* species: a review. Arch. Pharm. Res. 40 (9), 981–1005. https://doi.org/10.1007/s12272-017-0948-4.

Kokumai, M., Konoshima, T., Kozuka, M., Haruna, M., Ito, K., 1991. Euglobal T1, a new Euglobal from *Eucalyptus tereticornis*. J. Nat. Prod. 54 (4), 1082–1086. https://doi.org/10.1021/np50076a025.

Kondamudi, N.P., Waymack, J.R., Measles. (updated 2019 Nov 20). In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2020 Jan-. https://www.ncbi.nlm.nih.gov/books/NBK448068/.

Konoshima, T., Kozuka, M., Haruna, M., Ito, K., Kimura, T., Tokuda, H., 1989. Studies on the constituents of leguminous plants. XII. The structures of new triterpenoid saponins from *Wistaria brachybotrys* SIEB. et ZUCC. Chem. Pharm. Bull. 37 (10), 2731–2735. https://doi.org/10.1248/cpb.37.2731.

Konoshima, T., Kozuka, M., Tokuda, H., Nishino, H., Iwashima, A., Haruna, M., Ito, K., Tanabe, M., 1991. Studies on inhibitors of skin tumor promotion, IX. Neolignans from *Magnolia officinalis*. J. Nat. Prod. 54 (3), 816–822. https://doi.org/10.1021/np50075a010.

Konoshima, T., Takasaki, M., Kozuka, M., Haruna, M., Ito, K., Estes, J.R., Lee, K.H., 1993. Constituents of rosaceous plants. I. Structures of new Triterpenoids from *Cowania mexicana*. Chem. Pharm. Bull. 41 (9), 1612–1615. https://doi.org/10.1248/cpb.41.1612.

Konoshima, T., Yasuda, I., Kashiwada, Y., Cosentino, L.M., Lee, K.H., 1995. Anti-AIDS agents, 21. Triterpenoid saponins as anti-HIV principles from fruits of *Gleditsia japonica* and *Gymnocladus chinesis*, and a structure-activity correlation. J. Nat. Prod. 58 (9), 1372–1377. https://doi.org/10.1021/np50123a006.

Konz, D., Klens, A., Schörgendorfer, K., Marahiel, M.A., 1997. The bacitracin biosynthesis operon of *Bacillus licheniformis* ATCC 10716: molecular characterization of three multi-modular peptide synthetases. Chem. Biol. 4 (12), 927–937. https://doi.org/10.1016/s1074-5521(97)90301-x.

Kosanić, M., Ranković, B., Stanojković, T., Rančić, A., Manojlović, N., 2014. Cladonia lichens and their major metabolites as possible natural antioxidant, antimicrobial and anticancer agents. LWT Food Sci. Technol. 59 (1), 518–525. https://doi.org/10.1016/j.lwt.2014.04.047.

Koumoutsi, A., Chen, X.-H., Henne, A., Liesegang, H., Hitzeroth, G., Franke, P., Vater, J., Borriss, R., 2004. Structural and functional characterization of gene clusters directing nonribosomal synthesis of bioactive cyclic lipopeptides in *Bacillus amyloliquefaciens* strain FZB42. J. Bacteriol. 186 (4), 1084–1096. https://doi.org/10.1128/jb.186.4.1084-1096.2004.

Krupodorova, T., Rybalko, S., Barshteyn, V., 2014. Antiviral activity of *Basidiomycete mycelia* against influenza type A (serotype H1N1) and herpes simplex virus type 2 in cell culture. Virol. Sin. 29 (5), 284–290. https://doi.org/10.1007/s12250-014-3486-y.

Kuczer, M., Dziubasik, K., Midak-Siewirska, A., Zahorska, R., Łuczak, M., Konopińska, D., 2010. Studies of insect peptides alloferon, any -GS and their analogues. Synthesis and antiherpes activity. J. Pept. Sci. 16 (4), 186–189. https://doi.org/10.1002/psc.1219.

Kunze, B., Trowitzsch-Kienast, W., Höfle, G., Reichenbach, H., 1992. Nannochelins A, B and C, new iron-chelating compounds from *Nannocystis exedens* (myxobacteria). Production, isolation, physico-chemical and biological properties. J. Antibiot. 45 (2), 147–150. https://doi.org/10.7164/antibiotics.45.147.

Kuo, Y.H., Li, S.Y., Huang, R.L., Wu, M.-D., Huang, H.C., Lee, K.H., 2001. Schizarin B, C, D, and E, four new lignans from Kadsuramatsudai and their antihepatitis activities. J. Nat. Prod. 64 (4), 487–490. https://doi.org/10.1021/np000261m.

Kuzuyama, T., Seto, H., 2003. Diversity of the biosynthesis of the isoprene units. Nat. Prod. Rep. 20 (2), 171–183. https://doi.org/10.1039/b109860h.

Lai, D., Odimegwu, D., Esimone, C., Grunwald, T., Proksch, P., 2013. Phenolic compounds with *in vitro* activity against respiratory syncytial virus from the Nigerian lichen *Ramalina farinacea*. Planta Med. 79 (15), 1440–1446. https://doi.org/10.1055/s-0033-1350711.

Lau, S.K.P., Zhang, L., Luk, H.K.H., Xiong, L., Peng, X., Li, K.S.M., He, X., Zhao, P.S.-H., Fan, R.Y.Y., Wong, A.C.P., Ahmed, S.S., Cai, J.P., Chan, J.F.W., Sun, Y., Jin, D., Chen, H., Lau, T.C.K., Kok, R.K.H., Li, W., Woo, P.C.Y., 2018. Receptor usage of a novel bat lineage C betacoronavirus reveals evolution of Middle East Respiratory Syndrome-related coronavirus spike proteins for human dipeptidyl peptidase 4 binding. J. Infect. Dis., 218 (2), 197–207. doi:/https://doi.org/10.1093/infdis/jiy018.

Lee, J.B., Hayashi, K., Hirata, M., Kuroda, E., Suzuki, E., Kubo, Y., Hayashi, T., 2006. Antiviral sulfated polysaccharide from *Navicula directa*, a diatom collected from deep-sea water in Toyama Bay. Biol. Pharm. Bull. 29 (10), 2135–2139. https://doi.org/10.1248/bpb.29.2135.

Lee, J.G., Yoo, I.D., Kim, W.G., 2007. Differential antiviral activity of Benzastatin C and its dechlorinated derivative from *Streptomyces nitrosporeus*. Biol. Pharm. Bull. 30 (4), 795–797. https://doi.org/10.1248/bpb.30.795.

Lee, S.D., Lee, D.W., Ko, Y.H., 2011. *Marmoricola korecus* sp. nov. Int. J. Syst. Evol. Microbiol. 61 (7), 1628–1631. https://doi.org/10.1099/ijs.0.025460-0.

Leven, M., Van den Berghe, D., Vlietinck, A.J., 1983. Plant antiviral agents. Planta Med. 49, 109–114.

Li, Y.Q., Wang, S.F., 2006. Anti-hepatitis B activities of ganoderic acid from *Ganoderma lucidum*. Biotechnol. Lett. 28 (11), 837–841. https://doi.org/10.1007/s10529-006-9007-9.

Li, H.Y., Sun, N.-J., Kashiwada, Y., Sun, L., Snider, J.V., Cosentino, L.M., Lee, K.H., 1993. Anti-AIDS agents, 9. Suberosol, a new C31Lanostane-type triterpene and anti-HIV principle from *Polyalthia suberosa*. J. Nat. Prod. 56 (7), 1130–1133. https://doi.org/10.1021/np50097a017.

Li, F., Chen, D., Lu, S., Yang, G., Zhang, X., Chen, Z., Fan, S., Wu, S., He, J., 2018. Anti-influenza A viral butenolide from *Streptomyces* sp. Smu03 inhabiting the intestine of *Elephas maximus*. Viruses 10 (7), 356. https://doi.org/10.3390/v10070356.

Li, J., Wang, Y., Hao, X., Li, S., Jia, J., Guan, Y., Peng, Z., Bi, H., Xiao, C., Cen, S., Gan, M., 2019. Broad-spectrum antiviral natural products from the marine-derived *Penicillium* sp. IMB17-046. Molecules (Basel, Switzerland) 24 (15), 2821. https://doi.org/10.3390/molecules24152821.

Lin, Y.M., Anderson, H., Flavin, M.T., Pai, Y.H.S., Mata-Greenwood, E., Pengsuparp, T., Pezzuto, J.M., Schinazi, R.F., Hughes, S.H., Chen, F.C., 1997. *In vitro* anti-HIV activity of biflavonoids isolated from *Rhus succedanea* and *Garcinia multiflora*. J. Nat. Prod. 60 (9), 884–888. https://doi.org/10.1021/np9700275.

Lin, Y.M., Flavin, M.T., Schure, R., Chen, F.C., Sidwell, R., Barnard, D.I., Huffmann, J.H., Kern, E.R., 1999. Antiviral activities of biflavonoids. Planta Med. 65 (2), 120–125. https://doi.org/10.1055/s-1999-13971.

Lin, L.C., Kuo, Y.C., Chou, C.J., 2000. Anti-Herpes Simplex Virus Type-1 flavonoids and a new flavanone from the root of *Limonium sinense*. Planta Med. 66 (04), 333–336. https://doi.org/10.1055/s-2000-8540.

Lin, H.H., Yip, B.S., Huang, L.M., Wu, S.C., 2018. Zika virus structural biology and progress in vaccine development. Biotechnol. Adv. 36 (1), 47–53. https://doi.org/10.1016/j.biotechadv.2017.09.004.

Liu, J.S., Li, L., 1995. Kadsulignans L-N, three dibenzocyclooctadiene lignans from *Kadsura coccinea*. Phytochemistry 38 (1), 241–245. https://doi.org/10.1016/0031-9422(94)00557-a.

Liu, X., Gan, M., Dong, B., Zhang, T., Li, Y., Zhang, Y., Fan, X., Wu, Y., Bai, S., Chen, M., Yu, L., Tao, P., Jiang, W., Si, S., 2012. 4862F, a new inhibitor of HIV-1 protease, from the culture of *Streptomyces* I03A-04862. Molecules (Basel, Switzerland) 18 (1), 236–243. https://doi.org/10.3390/molecules18010236.

Liu, Z., Frank, M., Yu, X., Yu, H., Tran-Cong, N.M., Gao, Y., Proksch, P., 2020. Secondary metabolites from marine-derived fungi from China. Progress in the Chemistry of Organic Natural Products. vol. 111. Springer International Publishing, pp. 81–153. https://doi.org/10.1007/978-3-030-37865-3_2.

Luo, C., Liu, X., Zhou, X., Guo, J., Truong, J., Wang, X., Zhou, H., Li, X., Chen, Z., 2015. Unusual biosynthesis and structure of Locillomycins from *Bacillus subtilis* 916. Appl. Environ. Microbiol. 81 (19), 6601–6609. https://doi.org/10.1128/AEM.01639-15.

Ma, C., Nakamura, N., Hattori, M., Kakuda, H., Qiao, J., Yu, H., 2000. Inhibitory effects on HIV-1 protease of constituents from the wood of *Xanthocerassor bifolia*. J. Nat. Prod. 63 (2), 238–242. https://doi.org/10.1021/np9902441.

Mahmood, N., Pizza, C., Aquino, R., De Tommasi, N., Piacente, S., Colman, S., Burke, A., Hay, A.J., 1993. Inhibition of HIV infection by flavanoids. Antivir. Res. 22 (2–3), 189–199. https://doi.org/10.1016/0166-3542(93)90095-z.

Manske, R.F., Brossi, A., 1985. The Alkaloids 24. Academic Press, London, pp. 153–154.

Manske, R.F., Brossi, A., 1987. The Alkaloids 15. Academic Press, London, pp. 83–164.

Manske, R.F., Brossi, A., 1988. The Alkaloids 18. Academic Press, London, pp. 99–216.

Manske, R.F., Brossi, A., 1989. The Alkaloids 34. Academic Press, London, pp. 211–239.

Manske, R.F., Brossi, A., 1990. The Alkaloids 36. Academic Press, London, pp. 135–170.

Marchetti, M., Pisani, S., Pietropaolo, V., Seganti, L., Nicoletti, R., Degener, A., Orsi, N., 1996. Antiviral effect of a polysaccharide from *Sclerotium glucanicum* towards Herpes Simplex Virus Type 1 infection. Planta Med. 62 (04), 303–307. https://doi.org/10.1055/s-2006-957889.

Martinez, J.P., Hinkelmann, B., Fleta-Soriano, E., Steinmetz, H., Jansen, R., Diez, J., Frank, R., Sasse, F., Meyerhans, A., 2013. Identification of myxobacteria-derived HIV inhibitors by a high-throughput two-step infectivity assay. Microb. Cell Factories 12, 85. https://doi.org/10.1186/1475-2859-12-85.

Masui, S., Nabeshima, S., Ajisaka, K., Yamauchi, K., Itoh, R., Ishii, K., Soejima, T., Hiromatsu, K., 2017. Maoto, a traditional Japanese herbal medicine, inhibits uncoating of influenza virus. Evidence-Based Complementary and Alternative Medicine: ECAM, 1062065 https://doi.org/10.1155/2017/1062065.

McKee, T.C., Bokesch, H.R., McCormick, J.L., Rashid, M.A., Spielvogel, D., Gustafson, K.R., Alavanja, M.M., Cardellina, J.H., Boyd, M.R., 1997. Isolation and characterization of new anti-HIV and cytotoxic leads from plants, marine, and microbial organisms. J. Nat. Prod. 60 (5), 431–438. https://doi.org/10.1021/np970031g.

Mengshol, J.A., Golden-Mason, L., Arikawa, T., Smith, M., Niki, T., McWilliams, R., Randall, J.A., McMahan, R., Zimmerman, M.A., Rangachari, M., Dobrinskikh, E., Busson, P., Polyak, S.J., Hirashima, M., Rosen, H.R., 2010. A crucial role for Kupffer cell-derived galectin-9 in regulation of T cell immunity in hepatitis C infection. PLoS One 5 (3), e9504. https://doi.org/10.1371/journal.pone.0009504.

Mifflin, B.J., 1981. Biochemistry of Plants 5. Academic Press, New York, p. 345.

Miller, P.A., Milstrey, K.P., Trown, P.W., 1968. Specific inhibition of viral ribonucleic acid replication by gliotoxin. Science 159 (3813), 431–432. https://doi.org/10.1126/science.159.3813.431.

Min, B.S., Nakamura, N., Miyashiro, H., Bae, K.W., Hattori, M., 1998. Triterpenes from the spores of *Ganoderma lucidum* and their inhibitory activity against HIV-1 protease. Chem. Pharm. Bull. 46 (10), 1607–1612. https://doi.org/10.1248/cpb.46.1607.

Minagawa, K., Kouzuki, S., Yoshimoto, J.U.N., Kawamura, Y., Tani, H., Iwata, T., Terui, Y., Nakai, H., Yagi, S., Hattori, N., Fujiwara, T., Kamigauchi, T., 2002. Stachyflin and Acetylstachyflin, novel anti-influenza A virus substances, produced by *Stachybotrys* sp. RF-7260. Isolation, structure elucidation and biological activities. J. Antibiot. 55 (2), 155–164. https://doi.org/10.7164/antibiotics.55.155.

Mir, M.A., 2010. Hantaviruses. Clin. Lab. Med. 30 (1), 67–91. https://doi.org/10.1016/j.cll.2010.01.004.

Mishra, K.P., Sharma, N., Diwaker, D., Ganju, L., Singh, S.B., 2013. Plant derived antivirals: a potential source of drug development. Journal of Virology and Antiviral Research 2, 2–9.

Miyakawa, T., Anzai, O., Shimizu, N., 1958. Studies on antiviral antibiotics from streptomyces. Japanese Journal of Microbiology 2 (1), 53–62. https://doi.org/10.1111/j.1348-0421.1958.tb00052.x.

Miyanaga, S., Sakurai, H., Saiki, I., Onaka, H., Igarashi, Y., 2009. Synthesis and evaluation of myxochelin analogues as antimetastatic agents. Bioorganic and Medicinal Chemistry 17 (7), 2724–2732. https://doi.org/10.1016/j.bmc.2009.02.040.

Mlinaric, A., Kac, J., Pohleven, F., 2005. Screening of selected wood-damaging fungi for the HIV-1 reverse transcriptase inhibitors. Acta Pharma. 55, 69–79.

Moghadamtousi, S.Z., Nikzad, S., Kadir, H.A., Abubakar, S., Zandi, K., 2015. Potential antiviral agents from marine fungi: an overview. Marine Drugs 13 (7), 4520–4538. https://doi.org/10.3390/md13074520.

Mølgaard, P., Ravn, H., 1988. Evolutionary aspects of caffeoyl ester distribution in dicotyledons. Phytochemistry 27 (8), 2411–2421. https://doi.org/10.1016/0031-9422(88)87005-5.

Montanha, J., Amoros, M., Boustie, J., Girre, L., 1995. Anti-herpes virus activity of aporphine alkaloids. Planta Med. 61 (05), 419–424. https://doi.org/10.1055/s-2006-958128.

Mothana, R.A.A., Awadh Ali, N.A., Jansen, R., Wegner, U., Mentel, R., Lindequist, U., 2003. Antiviral lanostanoid triterpenes from the fungus *Ganoderma pfeifferi*. Fitoterapia 74 (1–2), 177–180. https://doi.org/10.1016/s0367-326x(02)00305-2.

Mukherjee, P.K., Wahile, A., 2006. Integrated approaches towards drug development from Ayurveda and other Indian system of medicines. J. Ethnopharmacol. 103 (1), 25–35. https://doi.org/10.1016/j.jep.2005.09.024.

Mulwa, L.S., Jansen, R., Praditya, D.F., Mohr, K.I., Wink, J., Steinmann, E., Stadler, M., 2018. Six heterocyclic metabolites from the myxobacterium *Labilithrix luteola*. Molecules (Basel, Switzerland) 23 (3), 542. https://doi.org/10.3390/molecules23030542.

Münz, C., Lünemann, J.D., Getts, M.T., Miller, S.D., 2009. Antiviral immune responses: triggers of or triggered by autoimmunity? Nat. Rev. Immunol. 9 (4), 246–258. https://doi.org/10.1038/nri2527.

Murakami, A., Tanaka, S., Ohigashi, H., Hirota, M., Irie, R., Takeda, N., Tatematsu, A., Koshimizu, K., 1992. Possible anti-tumour promoters: BI- and tetraflavonoids from *Lophira alata*. Phytochemistry 31 (8), 2689–2693. https://doi.org/10.1016/0031-9422(92)83612-3.

Murray, R.D.H., Mendez, J., Brown, L., 1982. The Natural Coumarins. Wiley, Chichester.

Nachbagauer, R., Krammer, F., 2017. Universal influenza virus vaccines and therapeutic antibodies. Clin. Microbiol. Infect. 23 (4), 222–228. https://doi.org/10.1016/j.cmi.2017.02.009.

Nadmid, S., Plaza, A., Lauro, G., Garcia, R., Bifulco, G., Müller, R., 2014. Hyalachelins A–C, unusual siderophores isolated from the terrestrial myxobacterium *Hyalangium minutum*. Org. Lett. 16 (16), 4130–4133. https://doi.org/10.1021/ol501826a.

Nakagawa, A., Tomoda, H., Hao, M., Okano, K., Iwai, Y., Omura, S., 1985. Antiviral activities of pentalenolactones. J. Antibiot. 38 (8), 1114–1115. https://doi.org/10.7164/antibiotics.38.1114.

Nakashima, H., Kido, Y., Kobayashi, N., Motoki, Y., Neushul, M., Yamamoto, N., 1987a. Antiretroviral activity in a marine red alga: reverse transcriptase inhibition by an aqueous extract of *Schizymenia pacifica*. J. Cancer Res. Clin. Oncol. 113 (5), 413–416. https://doi.org/10.1007/bf00390034.

Nakashima, H., Kido, Y., Kobayashi, N., Motoki, Y., Neushul, M., Yamamoto, N., 1987b. Purification and characterization of an avian myeloblastosis and human immunodeficiency virus reverse transcriptase inhibitor, sulfated polysaccharides extracted from sea algae. Antimicrob. Agents Chemother. 31 (10), 1524–1528. https://doi.org/10.1128/aac.31.10.1524.

Ng, T.B., Wang, H., 2001. Panaxagin, a new protein from Chinese ginseng possesses antifungal, anti-viral, translation-inhibiting and ribonuclease activities. Life Sci. 68 (7), 739–749. https://doi.org/10.1016/s0024-3205(00)00970-x.

Nkongolo, S., Ni, Y., Lempp, F.A., Kaufman, C., Lindner, T., Esser-Nobis, K., Lohmann, V., Mier, W., Mehrle, S., Urban, S., 2014. Cyclosporin A inhibits hepatitis B and hepatitis D virus entry by cyclophilin-independent interference with the NTCP receptor. J. Hepatol. 60 (4), 723–731. https://doi.org/10.1016/j.jhep.2013.11.022.

Nong, X.H., Wang, Y.F., Zhang, X.Y., 2014. Territrem and butyrolactone derivatives from a marine-derived fungus *Aspergillus terreus*. Mar. Drugs 12, 6113–6124. https://doi.org/10.3390/md12126113.

Nunes, M.R.T., Faria, N.R., de Vasconcelos, J.M., Golding, N., Kraemer, M.U.G., de Oliveira, L.F., Azevedo, R.S.S., da Silva, D.E.A., da Silva, E.V.P., da Silva, S.P., Carvalho, V.L., Coelho, G.E., Cruz, A.C.R., Rodrigues, S.G., Vianez Jr., J.L.S.G., Nunes, B.T.D., Cardoso, J.F., Tesh, R.B., Hay, S.I., Vasconcelos, P.F.C., 2015. Emergence and potential for spread of Chikungunya virus in Brazil. BMC Med. 13, 102. https://doi.org/10.1186/s12916-015-0348-x.

Omarsdottir, S., Olafsdottir, E.S., Freysdottir, J., 2006. Immunomodulating effects of lichen-derived polysaccharides on monocyte-derived dendritic cells. Int. Immunopharmacol. 6 (11), 1642–1650. https://doi.org/10.1016/j.intimp.2006.06.006.

Ongena, M., Jacques, P., 2008. Bacillus lipopeptides: versatile weapons for plant disease biocontrol. Trends Microbiol. 16 (3), 115–125. https://doi.org/10.1016/j.tim.2007.12.009.

Pandey, M.M., Rastogi, S., Rawat, A.K.S., 2008. Indian herbal drug for general healthcare: an overview. The Internet Journal of Alternative Medicine 6 (1), 3.

Pariš, A., Štrukelj, B., Renko, M., Turk, V., Pukl, M., Umek, A., Korant, B.D., 1993. Inhibitory effect of carnosolic acid on HIV-1 protease in cell-free assays. J. Nat. Prod. 56 (8), 1426–1430. https://doi.org/10.1021/np50098a031.

Parrish, C.R., Holmes, E.C., Morens, D.M., Park, E.C., Burke, D.S., Calisher, C.H., Laughlin, C.A., Saif, L.J., Daszak, P., 2008. Cross-species virus transmission and the emergence of new epidemic diseases. Microbiol. Mol. Biol. Rev. 72 (3), 457–470. https://doi.org/10.1128/MMBR.00004-08.

Pascoalino, B.S., Courtemanche, G., Cordeiro, M.T., Gil, L.H.V.G., Freitas-Junior, L., 2016. Zika antiviral chemotherapy: identification of drugs and promising starting points for drug discovery from an FDA-approved library. F1000Research 5, 2523. https://doi.org/10.12688/f1000research.9648.1.

Patankar, M.S., Oehninger, S., Barnett, T., Williams, R.L., Clark, G.F., 1993. A revised structure for fucoidan may explain some of its biological activities. J. Biol. Chem. 268 (29), 21770–21776.

Patel, N., Penkert, R.R., Jones, B.G., Sealy, R.E., Surman, S.L., Sun, Y., Tang, L., DeBeauchamp, J., Webb, A., Richardson, J., Heine, R., Dallas, R.H., Ross, A.C., Webby, R., Hurwitz, J.L., 2019. Baseline serum vitamin A and D levels determine benefit of oral vitamin A&D

supplements to humoral immune responses following pediatric influenza vaccination. Viruses 11 (10), 907. https://doi.org/10.3390/v11100907.
Patil, A.D., Freyer, A.J., Eggleston, D.S., Haltiwanger, R.C., Bean, M.F., Taylor, P.B., Caranfa, M.J., Breen, A.L., Bartus, H.R., 1993. The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from the Malaysian tree, *Calophyllum inophyllum* Linn. J. Med. Chem. 36 (26), 4131–4138. https://doi.org/10.1021/jm00078a001.
Patwardhan, B., Warude, D., Pushpangadan, P., Bhatt, N., 2005. Ayurveda and traditional Chinese medicine: a comparative overview. Evid. Based Complement. Alternat. Med. 2 (4), 465–473. https://doi.org/10.1093/ecam/neh140.
Pavlovic, V., Stojanovic, I., Jadranin, M., Vajs, V., Djordjević, I., Smelcerovic, A., Stojanovic, G., 2013. Effect of four lichen acids isolated from *Hypogymnia physodes* on viability of rat thymocytes. Food Chem. Toxicol. 51, 160–164. https://doi.org/10.1016/j.fct.2012.04.043.
Peng, J., Lin, T., Wang, W., Xin, Z., Zhu, T., Gu, Q., Li, D., 2013. Antiviral alkaloids produced by the mangrove-derived fungus *Cladosporium* sp. PJX-41. J. Nat. Prod. 76 (6), 1133–1140. https://doi.org/10.1021/np400200k.
Peng, J., Zhang, X., Du, L., Wang, W., Zhu, T., Gu, Q., Li, D., 2014. Sorbicatechols A and B, antiviral Sorbicillinoids from the marine-derived fungus *Penicillium chrysogenum* PJX-17. J. Nat. Prod. 77 (2), 424–428. https://doi.org/10.1021/np400977e.
Pengsuparp, T., Cai, L., Constant, H., Fong, H.H.S., Lin, L.Z., Kinghorn, A.D., Pezzuto, J.M., Cordell, G.A., Ingolfsdöttir, K., Wagner, H., Hughes, S.H., 1995. Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. J. Nat. Prod. 58 (7), 1024–1031. https://doi.org/10.1021/np50121a006.
Pepin, K.M., Riley, S., Grenfell, B.T., 2013. Effects of influenza antivirals on individual and population immunity over many epidemic waves. Epidemiol. Infect. 141 (2), 366–376. https://doi.org/10.1017/S0950268812000477.
Pereira, H., Leaoferreira, L., Moussatche, N., Teixeira, V., Cavalcanti, D., Costa, L., Diaz, R., Frugulhetti, I., 2004. Antiviral activity of diterpenes isolated from the Brazilian marine alga *Dictyota menstrualis* against human immunodeficiency virus type 1 (HIV-1). Antivir. Res. 64 (1), 69–76. https://doi.org/10.1016/s0166-3542(04)00122-6.
Phillipson, J.D., Zenk, M.H., 1980. Indole and Biogenetically Related Alkaloids. Academic Press, London.
Piattelli, M., Tringali, C., Neri, P., Rocco, C., 1995. Stereochemistry and conformation of dolabellane diterpenes: an NMR and molecular mechanics study. J. Nat. Prod. 58 (5), 697–704. https://doi.org/10.1021/np50119a007.
Pilcher, K.S., Soike, K.F., Smith, V.H., Trosper, F., Folston, B., 1955. Inhibition of multiplication of Lee influenza virus by canavanine. Exp. Biol. Med. 88 (1), 79–86. https://doi.org/10.3181/00379727-88-21498.
Porter, L.J., 1989. Tannins. Methods in Plant Biochemistry. Elsevier, pp. 389–419 https://doi.org/10.1016/b978-0-12-461011-8.50017-2.
Prieto, C., Castro, J.M., 2005. Porcine reproductive and respiratory syndrome virus infection in the boar: a review. Theriogenology 63 (1), 1–16. https://doi.org/10.1016/j.theriogenology.2004.03.018.
Qi-Hu, C., Chen, K., Shi, Q., Kilkuskie, R., Chi-Cheng, Y., Lee, Y.J., 1994. Anti-AIDS agent 10. Acacetin-7-O-β-D-galactopyranoside, an anti-HIV principle from *Chrysanthemum morifolium* and a structure-activity correlation with some related flavonoids. J. Nat. Prod. 57, 42–51.
Qin, C., Lin, X., Lu, X., Wan, J., Zhou, X., Liao, S., Tu, Z., Xu, S., Liu, Y., 2014. Sesquiterpenoids and xanthones derivatives produced by sponge-derived fungus *Stachybotry* sp. HH1 ZSDS1F1-2. J. Antibiot. 68 (2), 121–125. https://doi.org/10.1038/ja.2014.97.
Raekiansyah, M., Mori, M., Nonaka, K., Agoh, M., Shiomi, K., Matsumoto, A., Morita, K., 2017. Identification of novel antiviral of fungus-derived brefeldin A against dengue viruses. Tropical Medicine and Health 45, 32. https://doi.org/10.1186/s41182-017-0072-7.
Rajamohan, F., Venkatachalam, T.K., Irvin, J.D., Uckun, F.M., 1999. Pokeweed antiviral protein isoforms PAP-I, PAP-II, and PAP-III depurinate RNA of human immunodeficiency virus (HIV)-1. Biochem. Biophys. Res. Commun. 260 (2), 453–458. https://doi.org/10.1006/bbrc.1999.0922.
Rameshthangam, P., Ramasamy, P., 2007. Antiviral activity of bis(2-methylheptyl)phthalate isolated from *Pongamia pinnata* leaves against White Spot syndrome virus of *Penaeus monodon* Fabricius. Virus Res. 126 (1–2), 38–44. https://doi.org/10.1016/j.virusres.2007.01.014.
Rao, G.S., Cochran, K.W., 1974. Antiviral activity of triterpenoid saponins containing acylated b-amyrin aglycones. J. Pharm. Sci. 63, 471–473.
Rashan, L.J., 1990. *In vitro* study of the antiviral activity of some b-carboline alkaloids. Fitoterapia LXI 153–155.
Rathore, A., Rivastava, V., Srivastava, K.C., Tandon, J.S., 1990. Iridoid glucosides from Nyctanthes arbor-tristis. Phytochemistry 29 (6), 1917–1920. https://doi.org/10.1016/0031-9422(90)85040-m.
Rausch, K., Hackett, B.A., Weinbren, N.L., Reeder, S.M., Sadovsky, Y., Hunter, C.A., Schultz, D.C., Coyne, C.B., Cherry, S., 2017. Screening bioactives reveals nanchangmycin as a broad spectrum antiviral active against Zika virus. Cell Rep. 18 (3), 804–815. https://doi.org/10.1016/j.celrep.2016.12.068.
Raveh, A., Delekta, P.C., Dobry, C.J., Peng, W., Schultz, P.J., Blakely, P.K., Tai, A.W., Matainaho, T., Irani, D.N., Sherman, D.H., Miller, D.J., 2013. Discovery of potent broad spectrum antivirals derived from marine actinobacteria. PLoS One 8 (12), e82318. https://doi.org/10.1371/journal.pone.0082318.
Reichenbach, H., 1988. Myxobacteria: a source of new antibiotics. Trends Biotechnol. 6 (6), 115–121. https://doi.org/10.1016/0167-7799(88)90100-x.
Reis, S.A., Moussatche, N., Damaso, C.R.A., 2006. FK506, a secondary metabolite produced by *Streptomyces*, presents a novel antiviral activity against Orthopoxvirus infection in cell culture. J. Appl. Microbiol. 100 (6), 1373–1380. https://doi.org/10.1111/j.1365-2672.2006.02855.x.
Rembold, H., 1989. The azadirachtins- their potential for insect control. Economic and Medicinal Plant Research. Elsevier, pp. 57–72 https://doi.org/10.1016/b978-0-12-730064-1.50007-0.
Ricklin, D., Hajishengallis, G., Yang, K., Lambris, J.D., 2010. Complement: a key system for immune surveillance and homeostasis. Nat. Immunol. 11 (9), 785–797. https://doi.org/10.1038/ni.1923.
Rincão, V.P., Yamamoto, K.A., Ricardo, N.M.P.S., Soares, S.A., Meirelles, L.D.P., Nozawa, C., Linhares, R.E.C., 2012. Polysaccharide and extracts from *Lentinula edodes*: structural features and antiviral activity. Virol. J. 9, 37. https://doi.org/10.1186/1743-422X-9-37.
Rioux, L.-E., Turgeon, S.L., Beaulieu, M., 2010. Structural characterization of laminaran and galactofucan extracted from the brown seaweed *Saccharina longicruris*. Phytochemistry 71 (13), 1586–1595. https://doi.org/10.1016/j.phytochem.2010.05.021.
Roccatagliata, A.J., Maier, M.S., Seldes, A.M., Pujol, C.A., Damonte, E.B., 1996. Antiviral sulfated steroids from the ophiuroid *Ophioplocus januarii*. J. Nat. Prod. 59 (9), 887–889. https://doi.org/10.1021/np960171a.
Rouhier, P., Kopp, M., Begot, V., Bruneteau, M., Fritig, B., 1995. Structural features of fungal β-D-glucans for the efficient inhibition of the initiation of virus infection on *Nicotiana tabacum*. Phytochemistry 39 (1), 57–62. https://doi.org/10.1016/0031-9422(94)00852-k.
Rowley, D.C., Kelly, S., Kauffman, C.A., Jensen, P.R., Fenical, W., 2003. Halovirs A-E, new antiviral agents from a marine-derived fungus of the genus *Scytalidium*. ChemInform 35 (6). https://doi.org/10.1002/chin.200406159.
Rowley, D.C., Kelly, S., Kauffman, C.A., Jensen, P.R., Fenical, W., 2004. Synthesis and structure–activity relationships of the halovirs, antiviral natural products from a marine-derived fungus. Bioorganic and Medicinal Chemistry 12 (18), 4929–4936. https://doi.org/10.1016/j.bmc.2004.06.044.
Rwangabo, P., Laekeman, G., Claeys, M., Totté, J., Pieters, L., Berghe, D., Herman, A., Vlietinck, A., 1986. Phytochemical- and pharmacological investigation of the biologically active fraction from the flowers of *Vernonia amygdalina*. Planta Med. 52 (06), 547–548. https://doi.org/10.1055/s-2007-969351.
Sacramento, C.Q., Marttorelli, A., Fintelman-Rodrigues, N., de Freitas, C.S., de Melo, G.R., Rocha, M.E.N., Kaiser, C.R., Rodrigues, K.F., da Costa, G.L., Alves, C.M., Santos-Filho, O., Barbosa, J.P., Souza, T.M.L., 2015. Aureonitol, a fungi-derived tetrahydrofuran, inhibits influenza replication by targeting its surface glycoprotein hemagglutinin. PLoS One 10 (10), e0139236. https://doi.org/10.1371/journal.pone.0139236.
Sanchez, I., Gomez-Garibay, F., Taboada, J., Ruiz, B.H., 2000. Antiviral effect of flavonoids on the dengue virus. Phytother. Res. 14 (2), 89–92. https://doi.org/10.1002/(sici)1099-1573(200003)14:2<89::aid-ptr569>3.0.co;2-c.
Santoyo, S., Jaime, L., Plaza, M., Herrero, M., Rodriguez-Meizoso, I., Ibañez, E., Reglero, G., 2011. Antiviral compounds obtained from microalgae commonly used as carotenoid sources. J. Appl. Phycol. 24 (4), 731–741. https://doi.org/10.1007/s10811-011-9692-1.
Sauerbrei, A., 2016. Herpes genitalis: diagnosis, treatment and prevention. Geburtshilfe Frauenheilkd. 76 (12), 1310–1317. https://doi.org/10.1055/s-0042-116494.
Schneider, A., Späth, J., Breiding-Mack, S., Zeeck, A., Grabley, S., Thiericke, R., 1996. New cineromycins and musacins obtained by metabolite pattern analysis of *Streptomyces griseoviridis* (FH-S 1832). II. Structure elucidation. J. Antibiot. 49 (5), 438–446. https://doi.org/10.7164/antibiotics.49.438.
Schoeman, D., Fielding, B.C., 2019. Coronavirus envelope protein: current knowledge. Virol. J. 16 (1), 69. https://doi.org/10.1186/s12985-019-1182-0.
Schwetz, T.A., Fauci, A.S., 2019. The extended impact of human immunodeficiency virus/AIDS research. J. Infect. Dis. 219 (1), 6–9. https://doi.org/10.1093/infdis/jiy441.
Sendl, A., Chen, J.L., Jolad, S.D., Stoddart, C., Rozhon, E., Kernan, M., Nanakorn, W., Balick, M., 1996. Two new naphthoquinones with antiviral activity from *Rhinacanthus nasutus*. J. Nat. Prod. 59 (8), 808–811. https://doi.org/10.1021/np9601871.
Serkedjieva, J., Manolova, N., 1992. Plant polyphenolic complex inhibits the reproduction of influenza and herpes simplex viruses. Plant Polyphenols. Springer, US, pp. 705–715 https://doi.org/10.1007/978-1-4615-3476-1_42.
Shtro, A.A., Zarubaev, V.V., Luzina, O.A., Sokolov, D.N., Kiselev, O.I., Salakhutdinov, N.F., 2014. Novel derivatives of usnic acid effectively inhibiting reproduction of influenza A virus. Bioorg. Med. Chem. 22 (24), 6826–6836. https://doi.org/10.1016/j.bmc.2014.10.033.
Shtro, A.A., Zarubaev, V.V., Luzina, O.A., Sokolov, D.N., Salakhutdinov, N.F., 2015. Derivatives of usnic acid inhibit broad range of influenza viruses and protect mice from lethal influenza infection. Antiviral Chemistry and Chemotherapy 24 (3–4), 92–98. https://doi.org/10.1177/2040206616636992.
Shushni, M.A.M., Singh, R., Mentel, R., Lindequist, U., 2011. Balticolid: a new 12-membered macrolide with antiviral activity from an ascomycetous fungus of marine origin. Marine Drugs 9 (5), 844–851. https://doi.org/10.3390/md9050844.
Simões, C.M.O., Amoros, M., Girre, L., Gleye, J., Fauvel, M.T., 1990. Antiviral activity of ternatin and meliternatin, 3-methoxyflavones from species of Rutaceae. J. Nat. Prod. 53 (4), 989–992. https://doi.org/10.1021/np50070a036.
Singh, S.B., Zink, D., Polishook, J., Valentino, D., Shafiee, A., Silverman, K., Felock, P., Teran, A., Vilella, D., Hazuda, D.J., Lingham, R.B., 1999. Structure and absolute stereochemistry of HIV-1 integrase inhibitor integric acid. A novel eremophilane sesquiterpenoid produced by a *Xylaria* sp. Tetrahedron Lett. 40 (50), 8775–8779. https://doi.org/10.1016/s0040-4039(99)01878-x.
Singh, R.K., Dhama, K., Chakraborty, S., Tiwari, R., Natesan, S., Khandia, R., Munjal, A., Vora, K.S., Latheef, S.K., Karthik, K., Singh Malik, Y., Singh, R., Chaicumpa, W., Mourya, D.T., 2019. Nipah virus: epidemiology, pathology, immunobiology and advances in diagnosis, vaccine designing and control strategies - a comprehensive review. The Veterinary Quarterly 39 (1), 26–55. https://doi.org/10.1080/01652176.2019.1580827.
Smee, D.F., Bailey, K.W., Wong, M.-H., O'Keefe, B.R., Gustafson, K.R., Mishin, V.P., Gubareva, L.V., 2008. Treatment of influenza A (H1N1) virus infections in mice and ferrets with cyanovirin-N. Antivir. Res. 80 (3), 266–271. https://doi.org/10.1016/j.antiviral.2008.06.003.
Sokolov, D.N., Kiselev, O.I., Salakhutdinov, N.F., 2014. Bioorganic and medicinal chemistry novel derivatives of usnic acid effectively inhibiting reproduction of influenza A virus. Bioorganic and Medicinal Chemistry 22 (24), 6826–6836.

Sotanaphun, U., Lipipun, V., Suttisri, R., Bavovada, R., 1999. A new antiviral and antimicrobial sesquiterpene from *Glyptopetalum sclerocarpum*. Planta Med. 65 (03), 257–258. https://doi.org/10.1055/s-2006-960472.

Spolaore, P., Joannis-Cassan, C., Duran, E., Isambert, A., 2006. Commercial applications of microalgae. J. Biosci. Bioeng. 101 (2), 87–96. https://doi.org/10.1263/jbb.101.87.

Stocker-Wörgötter, E., 2008. Metabolic diversity of lichen-forming ascomycetous fungi: culturing, polyketide and shikimate metabolite production, and PKS genes. Nat. Prod. Rep. 25 (1), 188–200. https://doi.org/10.1039/b606983p.

Stuyver, L., Rossau, R., Zoulim, F., Fried, M., De Gendt, S., Schinazi, R.F., Van Geyt, C., 2000. A new genotype of hepatitis B virus: complete genome and phylogenetic relatedness. J. Gen. Virol. 81 (1), 67–74. https://doi.org/10.1099/0022-1317-81-1-67.

Subhose, V., Srinivas, P., Narayana, A., 2005. Basic principles of pharmaceutical science in Ayurveda. Bulletin of the Indian Institute of History of Medicine 35 (2), 83–92.

Suganda, A.G., Amoros, M., Girre, L., Fauconnier, B., 1983. Effets Inhibiteurs de Quelques Extraites Bruts et Semi Purifiés de Plantes Indigènes Françaises sur la Multiplication de l'Herpesvirus Humain 1 et du Poliovirus Humain 2 en Culture Cellulaire. J. Nat. Prod. 46 (5), 626–632. https://doi.org/10.1021/np50029a006.

Sun, H., Qiu, S., Lin, L., Wang, Z., Lin, Z., Pengsuparp, T., Pezzuto, J.M., Fong, H.H.S., Cordell, G.A., Farnsworth, N.R., 1996. Nigranoic acid, a triterpenoid from *Schisandra sphaerandra* that inhibits HIV-1 reverse transcriptase. J. Nat. Prod. 59 (5), 525–527. https://doi.org/10.1021/np960149h.

Suthindhiran, K., Sarath Babu, V., Kannabiran, K., Ishaq Ahmed, V.P., Sahul Hameed, A.S., 2011. Anti-fish nodaviral activity of furan-2-yl acetate extracted from marine *Streptomyces* spp. Nat. Prod. Res. 25 (8), 834–843. https://doi.org/10.1080/14786419.2010.530599.

Swallow, D.L., Sc, M.A., Fric, P., 1975. Antiviral agents. Prog. Drug Res. 22, 267–270.

Sydiskis, R.J., Owen, D.G., Lohr, J.L., Rosler, K.H., Blomster, R.N., 1991. Inactivation of enveloped viruses by anthraquinones extracted from plants. Antimicrob. Agents Chemother. 35 (12), 2463–2466. https://doi.org/10.1128/aac.35.12.2463.

Tada, M., Okuno, K., Chiba, K., Ohnishi, E., Yoshii, T., 1994. Antiviral diterpenes from *Salvia officinalis*. Phytochemistry 35 (2), 539–541. https://doi.org/10.1016/s0031-9422(00)94798-8.

Tafur, S., Nelson, Y., DeLong, D., Gordon, H., 1976. Antiviral components of *Ophiorrhiza mungos*. Lloydia 39, 261–262.

Takagi, M., Motohashi, K., Nagai, A., Izumikawa, M., Tanaka, M., Fuse, S., Doi, T., Iwase, K., Kawaguchi, A., Nagata, K., Takahashi, T., Shin-ya, K., 2010. Anti-influenza virus compound from *Streptomyces* sp. RI18. Org. Lett. 12 (20), 4664–4666. https://doi.org/10.1021/ol102007d.

Takahashi, A., Inokoshi, J., Chiba, H., Omura, S., Tanaka, H., 2005. Essential regions for antiviral activities of actinohivin, a sugar-binding anti-human immunodeficiency virus protein from an actinomycete. Arch. Biochem. Biophys. 437 (2), 233–240. https://doi.org/10.1016/j.abb.2005.03.017.

Takaishi, Y., Ohshima, S., Nakano, K., Tomimatsu, T., Tokuda, H., Nishino, H., Iwashima, A., 1993. Structures of Sesquiterpene polyol esters from *Celastrus stephanotiifolius* with potential tumor-promotion inhibitory activity. J. Nat. Prod. 56 (6), 815–824. https://doi.org/10.1021/np50096a003.

Takasaki, M., Konoshima, T., Shingu, T., Tokuda, H., Nishino, H., Iwashima, A., Kozuka, M., 1990. Structures of euglobal-G1, -G2, and -G3 from *Eucalyptus grandis*, three new inhibitors of Epstein- Barr virus activation. Chem. Pharm. Bull. 38 (5), 1444–1446. https://doi.org/10.1248/cpb.38.1444.

Takebe, Y., Saucedo, C.J., Lund, G., Uenishi, R., Hase, S., Tsuchiura, T., Kneteman, N., Ramessar, K., Tyrrell, D.L.J., Shirakura, M., Wakita, T., McMahon, J.B., O'Keefe, B.R., 2013. Antiviral lectins from red and blue-green algae show potent *in vitro* and *in vivo* activity against hepatitis C virus. PLoS One 8 (5), e64449. https://doi.org/10.1371/journal.pone.0064449.

Takechi, M., Tanaka, Y., 1981. Purification and characterization of antiviral substance from the bud of *Syzygium aromatica*. Planta Med. 42 (05), 69–74. https://doi.org/10.1055/s-2007-971548.

Takechi, M., Tanaka, Y., 1982. Antiviral substances from the root of *Paeonia* species. Planta Med. 45 (08), 252–253. https://doi.org/10.1055/s-2007-971387.

Takemura, Y., Ju-ichi, M., Ito, C., Furukawa, H., Tokuda, H., 1995. Studies on the inhibitory effects of some acridone alkaloids on Epstein-Barr virus activation. Planta Med. 61 (04), 366–368. https://doi.org/10.1055/s-2006-958104.

Talavera Pons, S., Boyer, A., Lamblin, G., Chennell, P., Châtenet, F.-T., Nicolas, C., Sautou, V., Abergel, A., 2017. Managing drug-drug interactions with new direct-acting antiviral agents in chronic hepatitis C. Br. J. Clin. Pharmacol. 83 (2), 269–293. https://doi.org/10.1111/bcp.13095.

Tan, G.T., Pezzuto, J.M., Kinghorn, A.D., Hughes, S.H., 1991. Evaluation of natural products as inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. J. Nat. Prod. 54 (1), 143–154. https://doi.org/10.1021/np50073a012.

Tanabe-Tochikura, A., Tochikura, T.S., Yoshida, O., Oki, T., Yamamoto, N., 1990. Pradimicin A inhibition of human immunodeficiency virus: attenuation by mannan. Virology 176 (2), 467–473. https://doi.org/10.1016/0042-6822(90)90016-k.

Taylor, R.S.L., Manandhar, N.P., Hudson, J.B., Towers, G.H.N., 1996. Antiviral activities of Nepalese medicinal plants. J. Ethnopharmacol. 52 (3), 157–163. https://doi.org/10.1016/0378-8741(96)01409-2.

Teixeira, R.R., Pereira, W.L., Oliveira, A.F.C., da Silva, A.M., de Oliveira, A.S., da Silva, M.L., da Silva, C.C., de Paula, S.O., 2014. Natural products as source of potential dengue antivirals. Molecules (Basel, Switzerland) 19 (6), 8151–8176. https://doi.org/10.3390/molecules19068151.

Thomasy, S.M., Maggs, D.J., 2016. A review of antiviral drugs and other compounds with activity against feline herpesvirus type 1. Vet. Ophthalmol. 19 Suppl 1 (Suppl. 1), 119–130. https://doi.org/10.1111/vop.12375.

Thuan, N.H., An, T.T., Shrestha, A., Canh, N.X., Sohng, J.K., Dhakal, D., 2019. Recent advances in exploration and biotechnological production of bioactive compounds in three cyanobacterial genera: *Nostoc*, *Lyngbya*, and *Microcystis*. Frontiers in Chemistry 7, 604. https://doi.org/10.3389/fchem.2019.00604.

Tommasi, N., Pizza, C., Conti, C., Orsi, N., Stein, M.L., 1990. Structure and in vitro antiviral activity of sesquiterpene glycosides from Calendula arvensis. J. Nat. Prod. 53, 830–835.

Tommasi, N., De Simone, F., Pizza, C., Mahmood, N., Moore, P., Conti, C., Orsi, N., Stein, M., 1992. Constituents of *Eriobotrya japonica*. A study of their antiviral propierties. J. Nat. Prod. 55, 1067–1073.

Towers, G.H.N., 1989. Photosensitisers from plants and their photodynamic action. Prog. Phytochem. 6, 183–189.

Towers, G.H.N., Page, J., Hudson, J.B., 1997. New aspects of light-mediated activities of natural products from plants and fungi. Curr. Org. Chem. 1, 395–414.

Trowitzsch-Kienast, W., Forche, E., Wray, V., Reichenbach, H., Jurkiewicz, E., Hunsmann, G., Höfle, G., 1992. Antibiotika aus Gleitenden Bakterien, 45. Phenalamide, neue HIV-1-inhibitor en ausMyxococcus stipitatus Mx s40. Liebigs Annalen Der Chemie 7, 659–664. https://doi.org/10.1002/jlac.1992199201112.

Tschesche, R., Hess, B., Ziegler, I., Machleidt, H., 1962. Über Pteridine, XVII. Trennung von synthetischem Biopterin und Isobiopterin. Justus Liebigs Annalen Der Chemie 658 (1), 193–201. https://doi.org/10.1002/jlac.19626580117.

Tsuchiya, Y., Shimizu, M., Hiyama, Y., Itoh, K., Hashimoto, Y., Nakayama, M., Horie, T., Morita, N., 1985. Antiviral activity of natural occurring flavonoids *in vitro*. Chem. Pharm. Bull. 33 (9), 3881–3886. https://doi.org/10.1248/cpb.33.3881.

Ueda, S., Iwahashi, Y., Tokuda, H., 1991. Production of anti-tumor-promoting iridoid glucosides in *Genipa americana* and its cell cultures. J. Nat. Prod. 54 (6), 1677–1680. https://doi.org/10.1021/np50078a032.

Urones, J.G., Basabe, P., Marcos, I.S., Pineda, J., Lithgow, A.M., Moro, R.F., Brito Palma, F.M.S., Arau'jo, M.E.M., Gravalos, M.D.G., 1992. Meroterpenes from *Cystoseira usneoides*. Phytochemistry 31 (1), 179–182. https://doi.org/10.1016/0031-9422(91)83031-f.

Van Hoof, L., Totté, J., Corthout, J., Pieters, L.A., Mertens, F., Vanden Berghe, D.A., Vlietinck, A.J., Dommisse, R., Esmans, E., 1989. Plant antiviral agents, VI. Isolation of antiviral phenolic glucosides from populus cultivar beaupre by droplet counter-current chromatography. J. Nat. Prod. 52 (4), 875–878. https://doi.org/10.1021/np50064a038.

Van Sumere, C.F., 1989. Phenols and phenolic acids. Methods in Plant Biochemistry. Elsevier, pp. 29–73 https://doi.org/10.1016/b978-0-12-461011-8.50008-1.

Vera, J., Castro, J., Gonzalez, A., Moenne, A., 2011. Seaweed polysaccharides and derived oligosaccharides stimulate defense responses and protection against pathogens in plants. Marine Drugs 9 (12), 2514–2525. https://doi.org/10.3390/md9122514.

Vil, V., Terent'ev, A.O., Al Quntar, A.A.A., Gloriozova, T.A., Savidov, N., Dembitsky, V.M., 2019. Oxetane-containing metabolites: origin, structures, and biological activities. Appl. Microbiol. Biotechnol. 103 (6), 2449–2467. https://doi.org/10.1007/s00253-018-09576-z.

Villa, T.G., Feijoo-Siota, L., Rama, J.L.R., Ageitos, J.M., 2017. Antivirals against animal viruses. Biochem. Pharmacol. 133, 97–116. https://doi.org/10.1016/j.bcp.2016.09.029.

Vlietinck, A.J., Bruyne, D., Berghe, V., 1997. Plant substances as antiviral agents. In: Atta-ur-Rahman (Ed.), Current Organic Chemistry, Natural Product Chemistry Issue. Benthem Science Publishers, The Netherlands, pp. 320–326.

Vlietinck, A., De Bruyne, T., Apers, S., Pieters, L., 1998. Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection. Planta Med. 64 (02), 97–109. https://doi.org/10.1055/s-2006-957384.

Wacker, A., Eilmes, H.G., 1978. Antivirale wirkung von pffanzeninhaltsstoffen. Arzneimittelforschung. Drug Research 28, 347–349.

Wang, H., Ng, T.B., 2001. Isolation and characterization of velutin, a novel low-molecular-weight ribosome-inactivating protein from winter mushroom (*Flammulina velutipes*) fruiting bodies. Life Sci. 68 (18), 2151–2158. https://doi.org/10.1016/s0024-3205(01)01023-2.

Wang, J., Wang, H.X., Ng, T.B., 2007. A peptide with HIV-1 reverse transcriptase inhibitory activity from the medicinal mushroom *Russula paludosa*. Peptides 28 (3), 560–565. https://doi.org/10.1016/j.peptides.2006.10.004.

Wang, H., Wang, Y., Wang, W., Fu, P., Liu, P., Zhu, W., 2011. Anti-influenza virus polyketides from the acid-tolerant fungus *Penicillium purpurogenum* JS03-21. J. Nat. Prod. 74 (9), 2014–2018. https://doi.org/10.1021/np2004769.

Wang, P., Kong, F., Wei, J., Wang, Y., Wang, W., Hong, K., Zhu, W., 2014. Alkaloids from the mangrove-derived actinomycete *Jishengella endophytica* 161111. Marine Drugs 12 (1), 477–490. https://doi.org/10.3390/md12010477.

Weber, N., Andersen, D., North, J., Murray, B., Lawson, L., Hughes, B., 1992. In vitro virucidal effects of *Allium sativum* (garlic) extract and compounds. Planta Med. 58 (05), 417–423. https://doi.org/10.1055/s-2006-961504.

Weeks, J., 2020. Call to action: announcing the traditional, complementary and integrative health and medicine COVID-19 support registry. J. Altern. Complement. Med. 26 (4), 256–258. https://doi.org/10.1089/acm.2020.29083.jjw.

Wong, J.H., Ng, T.B., 2005. Lunatusin, a trypsin-stable antimicrobial peptide from lima beans (*Phaseolus lunatus* L.). Peptides 26 (11), 2086–2092. https://doi.org/10.1016/j.peptides.2005.03.004.

Wu, G., Sun, X., Yu, G., Wang, W., Zhu, T., Gu, Q., Li, D., 2014. Cladosins A–E, hybrid polyketides from a deep-sea-derived fungus, *Cladosporium sphaerospermum*. J. Nat. Prod. 77 (2), 270–275. https://doi.org/10.1021/np400833x.

Xiu-Wuei, Y., Jing, Z., Yu-Xin, C., Xue-Hui, L., Chao-Mei, M., Masao, H., Li-He, Z., 1999. Anti-HIV-1 protease triterpenoid saponins from the seeds of *Aesculus chinensis*. J. Nat. Prod. 62, 1510–1513.

Xu, H.X., Kadota, S., Kurokawa, M., Shiraki, K., Matsumoto, T., Namba, T., 2010. ChemInform abstract: isolation and structure of woodorien, a new glucoside having antiviral activity, from Woodwardia orientalis. ChemInform 25 (19). https://doi.org/10.1002/chin.199419253.

Xu, D.B., Ye, W.W., Han, Y., Deng, Z.X., Hong, K., 2014. Natural products from mangrove actinomycetes. Marine Drugs 12 (5), 2590–2613. https://doi.org/10.3390/md12052590.

Xu, S.Y., Huang, X., Cheong, K.L., 2017. Recent advances in marine algae polysaccharides: isolation, structure, and activities. Marine Drugs 15 (12), 388. https://doi.org/10.3390/md15120388.

Yamamoto, K.A., Galhardi, L.C.F., Rincão, V.P., Soares, S. de A., Vieira, Í.G.P., Ricardo, N.M.P.S., Nozawa, C., Linhares, R.E.C., 2013. Antiherpetic activity of an *Agaricus brasiliensis* polysaccharide, its sulfated derivative and fractions. Int. J. Biol. Macromol. 52, 9–13. https://doi.org/10.1016/j.ijbiomac.2012.09.029.

Yamazaki, Z., Tagaya, I., 1980. Antiviral effects of atropine and caffeine. J. Gen. Virol. 50 (2), 429–431. https://doi.org/10.1099/0022-1317-50-2-429.

Yang, X.W., Zhao, J., Cui, Y.X., Liu, X.H., Ma, C.M., Hattori, M., Zhang, L.H., 1999. Anti-HIV-1 protease triterpenoid saponins from the seeds of *Aesculus chinensis*. J. Nat. Prod. 62 (11), 1510–1513. https://doi.org/10.1021/np990180u.

Ye, X.E., Ng, T.B., Rao, P.F., 2002. Cicerin and arietin, novel chickpea peptides, with different antifungal potencies. Peptides 23, 817–822. https://doi.org/10.1016/s0196-9781(02)00005-0.

Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2013. Occupational pesticide exposures and respiratory health. Int. J. Environ. Res. Public Health 10 (12), 6442–6471. https://doi.org/10.3390/ijerph10126442.

Yokomizo, K., Miyamoto, Y., Nagao, K., Kumagae, E., Habib, E.-S.E., Suzuki, K., Harada, S., Uyeda, M., 1998. Fattiviracin A1, a novel antiviral agent produced by *Streptomyces microflavus* strain no. 2445. II. Biological properties. J. Antibiot. 51 (11), 1035–1039. https://doi.org/10.7164/antibiotics.51.1035.

Yong, T., Chen, S., Xie, Y., Chen, D., Su, J., Shuai, O., Jiao, C., Zuo, D., 2018. Cordycepin, a characteristic bioactive constituent in *Cordyceps militaris*, Ameliorates hyperuricemia through URAT1 in hyperuricemic mice. Front. Microbiol. 9, 58. https://doi.org/10.3389/fmicb.2018.00058.

Youssef, F.S., Ashour, M.L., Singab, A.N.B., Wink, M., 2019. A comprehensive review of bioactive peptides from marine fungi and their biological significance. Marine Drugs 17 (10), 559. https://doi.org/10.3390/md17100559.

Yust, M., 2004. Rapeseed protein hydrolysates: a source of HIV protease peptide inhibitors. Food Chem. 87 (3), 387–392. https://doi.org/10.1016/j.foodchem.2003.11.020.

Zambare, V.P., Christopher, L.P., 2012. Biopharmaceutical potential of lichens. Pharm. Biol. 50 (6), 778–798. https://doi.org/10.3109/13880209.2011.633089.

Zander, W., Irschik, H., Augustiniak, H., Herrmann, M., Jansen, R., Steinmetz, H., Gerth, K., Kessler, W., Kalesse, M., Höfle, G., Müller, R., 2012. Sulfangolids, macrolide sulfate esters from *Sorangium cellulosum*. Chem. Eur. J. 18 (20), 6264–6271. https://doi.org/10.1002/chem.201100851.

Zandi, K., Teoh, B.T., Sam, S.S., Wong, P.F., Mustafa, M.R., Abubakar, S., 2011. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol. J. 8, 560. https://doi.org/10.1186/1743-422X-8-560.

Zhang, Y., Mu, J., Feng, Y., Kang, Y., Zhang, J., Gu, P.J., Wang, Y., Ma, L.F., Zhu, Y.-H., 2009. Broad-spectrum antimicrobial epiphytic and endophytic fungi from marine organisms: isolation, bioassay and taxonomy. Marine Drugs 7 (2), 97–112. https://doi.org/10.3390/md7020097.

Zhang, G., Sun, S., Zhu, T., Lin, Z., Gu, J., Li, D., Gu, Q., 2011. Antiviral isoindolone derivatives from an endophytic fungus *Emericella* sp. associated with *Aegiceras corniculatum*. Phytochemistry 72 (11−12), 1436–1442. https://doi.org/10.1016/j.phytochem.2011.04.014.

Zhen, G., Jing, J., Fengsen, L., 2018. Traditional Chinese medicine classic herbal formula Xiaoqinglong decoction for acute exacerbation of chronic obstructive pulmonary disease: a systematic review protocol. Medicine 97 (52), e13761. https://doi.org/10.1097/MD.0000000000013761.

Zheng, C.J., Shao, C.L., Guo, Z.Y., Chen, J.F., Deng, D.S., Yang, K.L., Chen, Y.Y., Fu, X.M., She, Z.G., Lin, Y.C., Wang, C.Y., 2012. Bioactive hydroanthraquinones and anthraquinone dimers from a soft coral-derived *Alternaria* sp. fungus. J. Nat. Prod. 75 (2), 189–197. https://doi.org/10.1021/np200766d.

Zhu, T., Chen, Z., Liu, P., Wang, Y., Xin, Z., Zhu, W., 2013. New rubrolides from the marine-derived fungus *Aspergillus terreus* OUCMDZ-1925. J. Antibiot. 67 (4), 315–318. https://doi.org/10.1038/ja.2013.135.