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

R. Sagaya Jansi a, Ameer Khusro b, Paul Agastian b,*, Ahmed Alfarhan c,*, Naif Abdullah Al-Dhabi c, Mariadhas Valan Arasu c, Rajakrishnan Rajagopalan c, Damia Barcelo d, Amal Al-Tamimi e

a Department of Bioinformatics, Stella Maris College, Chennai, India
b Department of Plant Biology and Biotechnology, Loyola College, Chennai, India
c Department of Botany and Microbiology, College of Science, King Saud University, Riyadh, Saudi Arabia
d Water and Soil Research Group, Department of Environmental Chemistry, IDAEA-CSIC, JORDI GIRONA 18-26, 08034 Barcelona, Spain
e Ecology Department, College of Science, Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia

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.

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; 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.

⁎ Corresponding authors.
E-mail addresses: agastian@loyoloacollege.edu (P. Agastian), alfarhan@ksu.edu.sa (A. Alfarhan).

https://doi.org/10.1016/j.scitotenv.2020.143539
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1. Introduction

Viral diseases are colossal threat to human and animal population. Emerging viral disease outbreaks have grown rapidly in the recent years and it has created great impact on human life, leading to the sudden increase in mortality rates. Over the past two decades, there have been seven disease epidemics that resulted in huge economic losses in the world, of which Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome (SARS), Nipah virus (NIV) disease, West Nile virus disease, Avian Influenza, and Rift Valley fever are caused by viruses. Three modes of viral disease occurrence have been identified such as a) infection to a new host with no transmission, b) spread out to local populations, and c) epidemic or constant host-to-host transmission (Parish 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
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 on treatment. The DAAs were approved in the EU in January 2016. 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 on treatment. The DAAs were approved in the EU in January 2016.

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 newborn 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 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). There are no effective antiviral agents identified till date to control SARS-COV (Cheng et al., 2007).

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 unprotected 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. There has been reported in other animals such as horse, sheep, goats, cats, and dogs. It is a single stranded and non-segmented enveloped RNA virus. The NIV is second member of genus Henipavirus belonging to the family Paramyxoviridae. Prevention can be done by reducing overcrowding between animals and avoiding consumption of contaminating foods (Singh et al., 2019).

2.3. SARS-COV

Severe acute respiratory syndrome coronavirus (SARS-COV) belongs to family 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 popular 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.

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 kb      |
|                 |                  | VZV    | Icosahedral | Yes       | 150–200  | 125 kb          |
|                 |                  | Papillomaviridae | HPV   | Icosahedral  | No        | 54–60           | 5–8 kb          |
| RT viruses      | Reverse transcribing | Retroviridae | HIV   | Icosahedral  | Yes       | 90              | 9 kb            |
|                 |                  | Hepadnaviridae | HBV   | Icosahedral  | Yes       | 42              | 3 kb            |
| RNA viruses     | (+) ssRNA        | Coronavirusidae | COVID-19 | Spherical | Yes       | 120             | 27–32 kb        |
|                 |                  | SARS-CoV | Icosahedral  | Yes       | 120      | 27–32 kb        |
|                 |                  | MERS-CoV | Icosahedral  | 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           |
|                 |                  | Filoviridae | Ebola virus | Helical   | Yes       | 970             | 18–19 kb        |
|                 |                  | Paramyxoviridae | NIV   | Helical   | Yes       | 150             | 18 kb           |
|                 |                  |             | Measles | Helical   | Yes       | 120–150         | 15 kb           |
|                 |                  |             | Hantavirus | Helical   | Yes       | 80–120          | 14 kb           |
|                 |                  | Orthomyxoviridae | Influenza virus | Helical   | Yes       | 100             | 14 kb           |
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 papaniculou testing; hence changes in squamous epithelium cells should be noted. The changes observed on the abnormal cells are referred as cervical intraepithelial neoplasia (CIN). Depending on the depth of the abnormal cells, it can be classified into 3 types (CIN-1, CIN-2, and CIN-3). CIN-1, CIN-2, and CIN-3 show mild, moderate, and severe dysplasia, respectively. For human papilloma virus, vaccine was developed against the type 6, 11, 16, and 18. It is prophylactic quadrivalent vaccine named gardasil. Another type of vaccine is bivalent vaccine, developed against HPV 16 and 18 (Braaten and Laufer, 2008).

2.7. Acquired immunodeficiency syndrome (AIDS)

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

2.8. Ebola virus disease (EVD)

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

2.9. Chicken pox

Chicken pox is caused by varicella zoster virus (VZV) which is also responsible in causing herpes zoster or shingles. It is transmitted by inhaling aerosol droplets from infected patient. Symptoms include small itchy blister that spreads over chest, back, and then spreads through face, resulting in fatigue, fever, headache, and pharyngitis lary 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 glycoprotein projections, hemagglutinin (HA), and neuraminidase (NA). Based on the types of HA and NA, a total of 16 HA (H1–H6) 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 hepatocircuses 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 such as 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 viros 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-C4b2a) 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-C4b2a), 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-C4b2a). 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 alnifoíía were found active against enteric coronavirus (Jassim and Naji, 2003).
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. Trypiplepyrazinol 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 phycsin, neoechinulin D, and dihydroauraglaucin 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. 11α-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 22-0-(N-methyl-L-valyl)-21-epiaflaquinolone B. It exhibited antiviral activity against human respiratory syncytial virus. Isobutylarolactone 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|                                         |                                                         |                                                 |
| Acynoniphrine                        | Actinodaphne hookeri                    | HSV-1                                                   | Montanha et al. (1995)                          |
| Atropine                            | Atropa belladonna L.                    | Enveloped virus                                         | Yamazaki and Tagaya (1980)                      |
| Biopeterin                          | Cithidia fasciculata                    | Antiviral activity                                       | Tschescie et al. (1962)                         |
| Buchapnine                           | Euodia roxburghiana                     | HIV-1                                                   | Manske and Brossi (1985)                        |
| Campyptothecin                       | Ophiromizna mungos                      | Herpes virus                                             | Tafur et al. (1976)                            |
| Canavanin                            | Carnaavia ensiformis L.                 | Influenza virus                                          | Piicher et al. (1955)                          |
| Caffeine                            | Theobroma cacao L. and Coffea sp.       | Cossackie-virus, Herpes, Poliovirus, vaccinia, and influenza virus | Yamazaki and Tagaya (1980)                      |
| Carinabe                            | Hymenocallis arecolana                  | Antiviral activity                                       | Manske and Brossi (1987)                        |
| Carnicline                          | Zephyranthes carinata                   | Antiviral activity                                       | Manske and Brossi (1987)                        |
| Chelidonine                          | Chelodium majus L.                      | Herpes virus and influenza virus                         | Manske and Brossi (1987)                        |
| Cordycepil                          | Aspergillus nidulans Eidam Wint.       | Picornavirus, poliovirus, vaccinia, newcastle disease virus, Herpes simplex, and influenza viruses | Kaj-a-Kamb et al. (1992)                       |
| Cryptopetelelin                      | Bocherna cylindrica L. Sw. and          | HSV-1                                                   | Cordell (1981); Manske and Brossi (1989)       |
| O-demethyl-buchenavianine           | Buchenavia capita                       | HIV                                                     | Vlietinck et al. (1997)                         |
| Emetine                             | Cephalis ipecuauhina A. Rich.           | Pseudorabies and Herpes virus                           | Hanish et al. (1966)                           |
| Ectoparasite                        | Peganum harmala                         | HSV-1                                                   | Manske and Brossi (1988)                        |
| Harmoline                           | Pegurn harmala                          | HSV-1                                                   | Rashan (1990)                                  |
| Hypoxanthine                        | Beta vulgaris                           | Antiviral activity                                       | Mifflin (1981)                                 |
| Lycoris                            | Clivia miniatia                         | Antiviral activity                                       | Leven et al. (1983)                            |
| Michellamines D, Michellamines F    | Anacstrocalus korupensis D. Thomas and G cane | HIV                                                      | Hallock et al. (1997)                          |
| 10-Methoxycaumptothecin             | Camptocere acaumata Descene             | Adenovirus, Herpes, and vaccinia viruses                 | Clements (1977)                                |
| Odorinol                           | Aglaia roxburghiana Miq. var. Beddomeii | Ranikhet disease virus                                   | Phillipson and Zenk (1980)                      |
| Oliverine                           | Polyuthia oliveri                       | HSV-1                                                   | Montanha et al. (1995)                         |
| Oxetanshaline                       | Stephania japonica                      | HSV-1                                                   | Montanha et al. (1995)                         |
| Pachystaudine                       | Pachyphodium lamari                      | Retrovirus                                              | Montanha et al. (1995)                         |
| Papaverine                          | Papaver somniferum                      | CMV, measles, HSV                                       | Manske and Brossi (1990)                        |
| Psychotrine                         | Cephaelis acuminata                    | HIV-1                                                   | Manske and Brossi (1985)                        |
| Schumannilicte                      | Schummannilchytton 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)                        |
| Homonojiromycin, Deoxymanojirimycin | Omphalea diandria                      | Homonojiromycin is an inhibitor of several a-glucosidases, Deoxymanojirimycin is an inhibitor of glycoprocessing mannosidase | Kite et al. (1988)                             |
| Aranotin, Gliotoxin                  | Arachniotus aureus (Eidam) Schoeter     | Cossackie-virus A21, poliovirus, rhinovirus, influenza virus, and para-influenza virus type 3 | Becker (1980); Miller et al. (1968)             |
| Ochopamine and epi-16-Ochopamine    | Cabucula erythrocera Vatke Mar           | Influenza virus                                          | Manske and Brossi (1990)                        |
| (+)-Glaucine fumarate, (+)-N-Methylaurotetanine, | Corydalis cava, Glaucium flavum, | HSV and picornaviridae                                   | Bousie et al. (1998)                           |
| (+)-Isoboldine, and (-)-Nuciferine HCl | Pachyphodium lamari                      | HSV-1                                                   | Manske and Brossi (1990)                        |
| Castanospermine, Australe           | Catharanthus roseus L. G. Don. and C. lancues Pich | HIV and HSV and HSV-1 reverse transcriptase | Foder and Colasant (1985)                      |
| Leucrocinela, Perifomyline, Perivine, and Vincaulecoalbstatine | Catharanthus roseus L. G. Don. and C. lancues Pich | HIV and HSV and HSV-1 reverse transcriptase | Farnsworth et al. (1968)                       |
| Columbamine, Berberine, Palmitine   | Annonacea, Berbis vulgaris, menispermacae and Papaveracea | HIV-1                                                   | Manske and Brossi (1990)                        |
| Narcissine, Lycoricith, Pancratistatin, | Narcissus poeticus L. Lycorine was isolated from Clivia miniata Regel | HIV-1 reverse transcriptase | Gabrielsen et al. (1992); leven et al. (1982) |
| 7-deoxyxoparanitstatin, Acetats, Isosuferinacate, cis-Dihydroracineacine, Lycorines, and Pretazetamine | Aglaia roxburghiana Miq. var. Beddomeii | HIV-1 reverse transcriptase | Hiller (1987)                                   |
| Buxameone E and Clusobuxame H       | Buxus sempervirens                      | HIV-1 reverse transcriptase                               | Duan et al. (2000)                             |
| Triptonines A and Triptonines B     | Tripterygium hypoglaucum and Tripterygium wollofri | HIV-1 reverse transcriptase | Takanura et al. (1995)                          |
| 5-hydroxyxoparanacrine and Acimarine F | Plumeria rubra L.                        | Epstein-Barr virus                                       | Tan et al. (1991)                              |
| Fagamarone, Columbamine, and Fulvopulmerin | Swithine canescens, Astragalus lentinosus, Castanospernum australe, Aglaia roxburghiana | HIV-1 reverse transcriptase | Hudson (1990); Sydskis et al. (1991); Asano et al. (1996); Erdelmeier et al. (1996); Marchetti et al. (1996) |
| 1-carbolines, foranoquinolines, indolizidines, swainsonine, and castanospermine | Plumeria rubra L.                        | DNA viruses                                              | Take et al. (1995)                             |
| Coumarins                           | Calmidolide A                           | HIV                                                     | Murray et al. (1982)                           |
| Coriandrin                          | Coriandrum sativus                      | HIV                                                     | Towers (1989)                                  |
| Inophyllum B and Inophyllum P       | Calphylum inophyllum Linn.              | HIV-1 reverse transcriptase                               | Patil et al. (1993)                            |
| Soulatokeide                         | Calphylum triytsmani                    | HIV                                                     | Murray et al. (1982)                           |
| Glycycoumarin and Licopyranocoumarin | Glycrythia glabra                       | HIV                                                     | Vlietinck et al. (1997)                        |

(continued on next page)
Table 2 (continued)

| Name of the compound | Plant | Active against | References |
|----------------------|-------|----------------|------------|
| Flavonoids           |       |                |            |
| Acetatin 7-o-(6'-rhamnopyranosyl) | Chrysanthemum morifolium Ramar (Compositae) | HIV | Qi-Hu et al. (1994) |
| [4'-D-glucopyra-no-side] | | | |
| Apigenin             | Chrysanthemum morifolium Ramar (Compositae) | HIV | Qi-Hu et al. (1994) |
| 3,3'-Dimethoxyquercetin | Euphorbia granitsi Oltv. and Veronica amygdalina Del. (Compositae) | Herpes virus | Béládi et al. (1977) |
| Fisetin inactives    | Ulex europaeus L. | Pseudorabies virus | Swallow et al. (1975) |
| 0-Glucosyl-7-methyl-5-genistein | Matricaria inodora L. (Compositae) | HSV | Suganda et al. (1983) |
| Hesperetin           | Citrus spp. (lemons and sweet oranges) | Pseudorabies virus | Béládi et al. (1977) |
| Isoquercetin         | W. H. | Pseudorabies virus | Béládi et al. (1977) |
| Justicidin B         | Solanum sarrachoides | HSV-1 virus | Karam and Shier (1992) |
| Kaempferol          | Phytoanthus acuminatus | Cytomegalovirus and Sindbis virus | Ingham (1983) |
| 3,3'-Dimethyl ether; and Isoaekampferide | | Antiviral activity | Harborne (1988) |
| Luteolin             | Citrus parads MacFad. | Vesicular stomatitisis | Harborne (1988) |
| Quercetin            | Begonia glabra | Enveloped viruses | Béládi et al. (1977) |
| Quercetin 3-methyl ether | | Enveloped viruses | Béládi et al. (1977) |
| Quercetin 3-O-(2'-galloyl)-3'-D-galactopyranoside | Acer okamotoanum Nakai | HIV-1 integrase | Kim et al. (1998) |
| Quercetagenin        | Rhus succedanum L. | Pseudorabies and vesicular stomatitisis virus | Béládi et al. (1977) |
| Rutin                | Acacia catechu | Antiviral activity | Rauscher murine leukemia and HIV | Cody et al. (1986) |
| Taxifolin            | Maclura tinctoria | HIV | Liu et al. (1997); Liu et al. (1999) |
| Volkensiflavone      | Acacia catechu | Influenza B virus | Lee et al. (1997) |
| Ternatin and Melaternatins | 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, Chrysosplenium B, and Chrysosplenium C | Chrysosplenium tansae | Rhinovirus | Tsuichiya et al. (1985) |
| Lophirome F, Azobeclachone, and Isolophirachalcone | Lophira alata | Epine-Barr virus early antigen induction test | Murakami et al. (1992) |
| Centaurein and Jacein | Centaurea nigra L. | Herpes virus and poliovirus | Kaji-a-Kamb et al. (1992) |
| 5,5',3',4',5',5'-Hexahydroxyflavonse, and 5,7',4'-Trihydroxy-3'-glicosylflavone | Befaria cinnamomea | HIV-1 | Mahmood et al. (1993) |
| Agathisflavone, Robustaflavone, Hinokiflavone, Amentotiflavone, and Morelloflavone | | HIV-1 reverse transcriptase | Lin et al. (1997) |
| 3-O-Methylcalpocarpin, Licoisoflavane, Glyasper in | Erythrina lysistemon Hutch | HIV | McKeel et al. (1997) |
| Macluraxanthone A, Macluraxanthone C, and Macluraxanthone B | Maclura tinctoria | HIV | Groweiss et al. (2000) |
| 7-O-Methyl-glaranine | Tephrros madrens | Dengue virus | Sanchez et al. (2000) |
| Wogonin             | Scutellaria baicalensis | HBV | Huang et al. (2000) |
| Samarangin B and Myricetin | Limonium sinense | HSV-1 replication | Lin et al. (2000) |
| Lignans             | Bursera schlachetdandi | HSV-1 | Ayres and Loike (1990) |
| Dihydroxydiphenyldihorizol | Justicia procumbens var. leucantha | Herpesvirus stomatitis virus | Asano et al. (1996) |
| Diphyllyl diphenylasate-5-acetate, justicidin A and B, and diphyllyl diphenyl asipside | Pinus nigra Arnold | HIV | Eberhardt and Young (1996) |
| Lignane guaiacyl derivative | Juniperus sabina | HSV-1 and vesicular stomatitisis virus | Feliciano et al. (1993) |
| Deoxyxopophyllotolitoxin, 4'-Dimethylpodophyllotoxin, Podophyllotoxin acetate, Epipodophyllotoxin acetate, and 4'-Peltatin A methyl ether | Podophyllotin | Measles and HSV-1 viruses | McKeel et al. (1997); Bedows and Harfield (1982) |
| Podophyllotoxin, 4'-Peltatin, Deoxyxopophyllotoxin, Picropodophyllotoxin, and α-Peltatin | Podophyllum peltatum | Measles and HSV-1 viruses | McKeel et al. (1997); Bedows and Harfield (1982) |
| Kadsilignan L, Kadsilignan M, and Kadsilignan N | Kadsilignan coccinea | HIV | Liu and Li (1995) |
| Justicidin A, Justicidins B, Diphyllyl, Actigenin, and Trachelenolign | Forsythia intermedia and Ipomoea cafrica | HSV-1 | Vliegheinck et al. (1998) |
| Schizzarin B and taiwanschirin D | Kadsilignan matsudai | HIV | Liu and Li (1995) |
| Rhinacanthin F | Rhinacanthin matsudai | HSV-1 | Vliegheinck et al. (1998) |
| Miscellaneous compounds | Kadsilignan matsudai | HSV-1 | Vliegheinck et al. (1998) |
| Calcium elenolate | Kadsilignan matsudai | HSV-1 | Vliegheinck et al. (1998) |
| Castelanone | Olea europea L. | Antiviral activity | Swallow et al. (1975) |
| Champanirone | Castela tierdlet | Oncogenic Rous sarcoma virus | Rembold (1989) |
| Cochinolide | Quassia andulata | Oncogenic Rous sarcoma virus | Rembold (1989) |
| Curdian sulphate, Dextran sulphate, and Dextrin sulphate | Homolium cochinnichesis | HSV-1 and -2 | Ishikawa et al. (1998) |
| Glacarubolone and D-glucosamine | Dextrin sulphate - Violoidocontinis, Dextrin sulphate - Prunella vulgaris and Curdian sulphate - Alternanthera philoxeroides (Amaranaceae) | HIV | Vliegheinck et al. (1998) |
| D-glucosamine | Quassia simaruba | Oncogenic Rous sarcoma virus | Rembold (1989) |
| | Dahlia sp. | Fowl plague, Sindbis and Semliki Forest virus | Rauh et al. (1972) |
| | Glycine max (L.) Merr and Phaseoles aureus Roxb. | RNA viruses, HSV, pox virus, NDV-inhibits para influenza 3, and measles | Rauh et al. (1972) |
| Name of the compound | Plant | Active against | References |
|----------------------|-------|----------------|------------|
| Glucans 1 and Glucans 2 | Nicotiana tabacum | Antiviral activity | Routhier et al. (1995) |
| Pentagalloylglucose | Paeonia abloom Pallas | HCV | Kaj-i-Kamb et al. (1992) |
| Monoterpenoids, diterpenoids and sesquiterpenoids | Calendula arvensis L. | Vesicular stomatitis virus and rhinovirus (HRV type 1B) | Tommasi et al. (1990) |
| Alloaromandrol glycosides | Nyctanthes arbor-tristis | EMCV and SPV | Rathore et al. (1990) |
| Arbitrosides A,B,C | Rosmarinus officinalis L. | HIV protease inhibitors | Paril et al. (1993) |
| Carnosolic acid and Carnosol | Celastrus stephanotifolius Makino | Epstein-Barr virus | Takaiishi et al. (1993) |
| Cefalolin A-1, Cefalolin B-2, Cefalolin B-3, Cefalolin C-1, Cefalolin D-1, Cefalolin D-2, and Cefalolin D-3 | Exococcarea agallocha | HIV | Erickson et al. (1995) |
| Eudoglophora orientalis | Eucalyptus tereticornis Sm. | Epstein-Barr virus | Kokumai et al. (1991) |
| Littoral study TGL | Euphorbus grandis | Epstein-Barr virus | Takakasi et al. (1990) |
| Halanolide | Banisteria caapi | Influenza virus A (WS), Newcastle diseases virus, Japanese B encephalitis virus (AZ), and vaccina virus | Cracker and Simon (1986) |
| Liangshanbin B and Liangshanin D | Rhabdosia liangshanica C.Y. | Hepatitis virus | Fenglei et al. (1989) |
| Rutales | Limonoids found in plants of the order | Antiviral activity | Champagne et al. (1992) |
| Scleroacrid acid | Glycytopetallum scolocrum | HSV 1 and 2 | Satyanaphun 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 | Dolobella californica | Influenza and adenovirus viruses | Piattelli et al. (1995) |
| Saffinolide and Saegeone | Salvia officinalis | Vesicular stomatitis virus | Tada et al. (1994) |
| Triterpenoids | Tritygium wilfordii Hook | HIV | Chen et al. (1992) |
| Aromoside, 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-Acetylphloroglucinol-13-Decanoate and 12-O-Denoxylphloroglucinol-13-(2-methyl butyrate) | Croton tigium | HIV-1 | El-Mekkawy et al. (2000) |
| Phenolic | 2-O-Caffeoyl-(+)-allohydroxy citric | Spondias mombin | Coxsackie and HSV | Corthouth et al. (1992) |
| 2,6-Dihydroxymethoxysuberylphenone and 4,6-Dihydroxymethoxybutylphenone | Scoparic acid A, Scoparic acid B | Antiviral activity | Bloor (1992) |
| Eugenol or Ellagitannin | Syzygium aromaticum | HSV | Sotanaphun et al. (1999) |
| Gentisic acid | Mentha suaveolens | HSV 1 and 2 | Hayashi et al. (1988); Hayashi et al. (1990) |
| Gossypol | Vaccinium corymbosum | HSV 1 | Hayashi et al. (1988); Hayashi et al. (1990) |
| Gutierrezine A,B,C,D, and E | Symphonia globulisera, Garcinia invintonei, Garcinia ovalifolia and Chusia rosea | Antiviral activity | Van Sunvere (1989) |
| Mallotus japonicum and Mallotocromerone | Mallotus japonicus | HIV | Van Sunvere (1989) |
| Peltal A | Pothomorpha peltata | HIV-1 | Van Sunvere (1989) |
| Pentagalloyl-1D-glucose | Nuphar japonicum | HIV | Porter (1989) |
| Pentagalloylglucose | Geranium sanguineum | Neuraminidase activity of different influenza virus HIN, H2N2, and H3N2 | Sankajeeva and Manolova (1992) |
| Salicin and Salicropinosides | Populus trichocarpa | Poliovirions and Semliki forest virus | Van Hoof et al. (1989) |
| A-9-Tetrahydrocannabinol | Cannabis sativa L | HSV-1, HSV-2 | Blevins and Dunic (1980) |
| Woodoriens | Syzygium aromaticum | HSV-1 and poliovirus | Xu et al., 2010 |
| Silymarin and Cyanidol | Syzygium macrocarpum | Acute viral hepatitis | Swallow et al. (1975) |
| Diocarapapin and Balanocarapin | Syzygium cordatum | HIV | Hatano et al. (1988) |
| 3,5-di-O-Allyloxyquinic acid, 3,4,5-tri-O-Caffeoylquinic acid, and 1,3,4,5-tetra-O-Allyloxyquinic acid | Wistostrea indica C. A. Meyer | HIV-1 | Van Sunvere (1989) |
| (+)-Norotrichelogenin, Genkwonol A, Wilkstrol B, and Daphnomorin B | Lepidobotrya staudtii Engl. | HIV-1 and HIV-2 | Hu et al. (2000) |
| 1,3,4,5-tetra-O-Allyloxyquinic acid | Lepidobotrya staudtii Engl. | HIV-1 and HIV-2 | Bokesch et al. (1996) |
| Phenylpropanoids | Coffea arabica | Influenza virus, HSV, vaccinia, and polio viruses | Melgaard and Ravn (1988) |
| Caffeic acid | Coffea arabica | Poliovirus | Melgaard and Ravn (1988) |
| Chlorogenic acid | Populus nigra L | Antiviral activity | Amoros et al. (1994) |
| 3-Methyl-buty-2-enyl caffeate | Populus nigra L | Antiviral activity | Urones et al. (1992) |
| Unsineoide E, and Unsineoide Z | Brown seaweed Cystoseira usneoides | Respiratory syncytial virus | Kernan et al. (1998) |
| Verbascoside, Isoverascoside, Luteoside A, and Luteoside B | Markhumia lutea | Respiratory syncytial virus | Kernan et al. (1998) |
| Magnolol, Honokiol, and Monoterpenyllagnol | Magnolia officinalis | Epstein-Barr virus early antigen | Konoshima et al. (1991) |
| Quinones | Conodurum incurvum | HIV-1 reverse transcriptase | Decosterd et al. (1993) |
| Juglone | Juglans nigra; Hypericum triquetrifolium | HSV-1 virus and retrovirus | Berg and Labade (1989) |
| Pseudoacaprin | Hypericum triquetrifolium | Retrovirus | Berg and Labade (1989) |
| Rhinacanthin C and Rhinacanthin D | Hypericum nasutus (L.) Kurz | Cytomegalovirus | Sendil et al. (1996) |
| Hypericin and Pseudohypericin | Hypericum perforatum | Retroviruses | Hudson et al. (1993) |
| Name of the compound | Plant | Active against | References |
|----------------------|-------|----------------|------------|
| Tannins | | | |
| Aragominin | | Avian myeloblastosis virus | Porter (1989) |
| Cortarain A | | HIV | Porter (1989) |
| Procyandin B2 | | HIV | Porter (1989) |
| Camellin B, Gemin D, Chebulagic acid, and Nobotanin B | Chebulagic acid was isolated from Terminalia chebula, gemin D from Geum japonicium, nobotanin B from Tisboichina semicandra | HIV | Vlietinck et al. (1998) |
| Thiophenes and polyacetylenes | | | |
| Sideresmin A | | Rhinovirus | Swallow et al. (1975) |
|α-Terthieryl (α-T) ACPB-thiophene | | Cytomegalovirus and Sindbis virus | Hudson et al. (1986a), Hudson et al. (1986b) |
| Allyl methyl tiosulfinate, Methyl allyl tiosulfinate, Ajoene, and Allicin | | Sindbis virus | Hudson et al. (1986b) |
| Phyllanthrin (PHT), Thiophene-A, Erysoin, and Sulfouraphen | | HSV, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2 | Weber et al. (1992) |
| Triterpenoids | | | |
| 3-α-Aescin | | Influenza viruses | Hiller (1987) |
| Arjunolic acid | | EBV-EA | Dallal et al. (1989) |
| Chukisetinosaponin | | HIV | Hasegawa et al. (1994) |
| Cucurbitacin F, 23,24-Dihydrocucurbitacin F, 15-oxo-23, 24-Cucurbitacin F, and 15-oxo-Cucurbitacin F | | Epstein-Barr virus | Konoshima et al. (1993) |
| Diterpenoids | | | |
| Echlerianic acid | | Poliovirus | Koch and Gyorgy (1969) |
| Genaderol F and Genaderonmantriol | | Herpes virus type 1 | Hiller (1987) |
| Gleditsia japonica | | HIV-1 | El-Mekkawy et al. (1998) |
| Gleditsia saponin C | | HIV | Konoshima et al. (1995) |
| Gymnocyclus saponin G and Glycyrrhizic acid | | HSV 1, vaccinia virus, newcastle disease virus, and vesicular stomatitis virus | Hatano et al. (1988) |
| 3-0-Glucose (1-3) [arabinose 1-4]-glucose-xyloside of 3-0-Hydroxy-protoprimulagenin A 3-O-Glucose (1-3) [arabinose 1-4]-glucose-xyloside of 23-hydroxyprotoprimulagenin A | | HSV 1 and poliovirus | Amoros and Girre (1987) |
| Gymnemic acid | | Anti-influenza activity | Rao and Cochran (1974) |
| 24-Hydroxydammannan-20,25-dien-3-one | | Epstein-Barr virus | Inada et al. (1993) |
| 3’β-Hydroxyauricolic acid 3-β-hydroxy-benzoate | | HIV-1 reverse transcriptase | Pengsuparp et al. (1995) |
| (23-0) [β-0-glucopyranosyl-28-o-[β-0-glucopyranosyl (1-6)]β-D-galactopyranosyl (1-3)][arabinose 1-3]-D-glucopyranosyl (1-6)] | | HSV | Elgamal et al. (1995) |
| Isoflouqueisierol | | HSV | Gyorgy and Koch (1969) |
| Lanclactone C | | HIV | Chen et al. (1999) |
| Lanatoside D | | Influenza, Herpes and vaccinia viruses | Koch and Sandor (1969) |
| Methyl ester of wistariasaponin D, Methyl ester of wistariasaponin G, and Methyl ester of dehydrosoyasaponin | | Epstein-Barr virus | Konoshima et al. (1989) |
| Nigranic acid | | HIV | Sun et al. (1996) |
| (22E)-5β-24-Norcholest-22-ene-3 α,4α,11 | | Respiratory syncytial and polio viruses | Roccagallati et al. (1996) |
| Oubain | | | |
| Saikosaponin-A | | Newcastlde disease virus | Becher (1976) |
| Salaspanic acid | | Influenza virus | Hiller (1987) |
| Saponin 2 | | HIV | Hiller (1987) |
| Shoeric acid | | Herpes virus and poliovirus | Kaj‐a‐Kamb et al. (1992) |
| Strophantin G | | Herpes virus | Koch and Sandor (1969) |
| Suberosol | | Influenza, Herpes and vaccinia viruses | Kaj‐a‐Kamb et al. (1992) |
| 3-O-Runs-Caffeoylortentorien | 3-O-Runs-Caffeoylortentorien | HIV | Li et al. (1993) |
| Wistariasaponin A, Wistariasaponin B, and Wistariasaponin C | | Rhinovirus infection | Tommasi et al. (1992) |
| Zingibroside R1 | | | |
| 2x-19a-Dihydroxy-3-oxo-12-ursen-28-oic-acid, and Mastinic acid | | | |
| Proxilariosidin A and Scillarenin | | | |
| Betulinic acid and Platanic acid | | Influenza, HSV, vaccinia virus, and picornaviruses | Koch and Sandor (1969) |
| Oleandric acid and Pomolic acid, Alphitolic acid, Asianic acid, and Betulinic acid | | | |
| Dammaradienol, Dammaradienol II, Dammarenolic | | Herpes virus | Fujikawa et al. (1994) |
| Dammaradienol, Dammaradienol II, Dammarenolic | | | |
Table 2 (continued)

| Name of the compound | Plant | Active against | References |
|----------------------|-------|----------------|------------|
| acid, Hydroxyspirulanone I, Hydroxyphapanone, Hydroxyspirulanone, Hydroxyspirulanone, Hydroxyspirulanone, Hydroxyspirulanone, Hydroxyspirulanone, | Xanthoceras sorbifolia Bunge | HIV-1 | Ma et al. (2000) |
| Epigallocatechin-(4â€‘â€‘8,2)-O-7-epicatechin, 3-Oxotricacalla-7â€‘20-dien-21oic acid. And Oleolic acid | | | |
| 1-J3-hydroxyeulearotic acid-3-p-hydroxybenzoate | Escin | | |
| Proteins and peptides | | Reverse transcriptase inhibitors | |
| Trichobactin | Trichosanthes kirilowii | HIV | Miska et al. (2013) |
| Pokeweed antiviral proteins (PAP) (MRK29, MAP30 and GAP31) | Phytoallca Americana, Monordica 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) |
| Lunatursin | Phaseolus lunatus | Antiviral activity | Wong and Ng (2005) |
| Vulgarinin | Phaseolus vulgaris | Antiviral activity | Jack and Ti (2005) |
| Cicerin and Arierin | Cicer arietinum | Antiviral activity | Ye et al. (2002); De Souza et al. (2011) |
| Peptidesa-Mitogenic | Brassica napus | ND-Not determined | Yast (2004) |
| Phaseococcin | Phaseolus coccineus | HIV | Kuczera et al. (2010) |
| Sesquin | Vigna sesquispes | HIV | Hulmark et al. (2005) |

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 8ox,11-dihydroxy-pachydictyol A, 8â€‘hydroxy pachydictyol A from Dicytota sp. and diterpenes of Group II including Acetoxychidodiol, 3â€‘-actoxydilophol obtained from Dicytota pliectens showed weak antiviral activity. Dolabelladienols A-B extracted from Dicytota pfludii displayed strong antiviral properties. Bicyclic diterpenes, Crenulidalens from Da-1, and AcDa-1 obtained from D. menestraulis 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 Callanpyllis varigate and Agardhiella tenera possessed antiviral properties against HIV, HSV-1, -2, Dengue virus, and Hepatitis A virus. Alginate from brown algae inhibited Hepatitis B, HIV, and A virus. Fucan from brown algae like Adenocystis utricularis and Undaria pinnatifida expressed antiviral activities against HIV, HSV, Sindbis virus, and Vesicular Stomatitis Indiana virus. The virus of red alga, Schizymenia pacifica exhibited antiviral properties against HIV (Ahmadi et al., 2015).

Calcium spirulin, 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 armoricanus 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 activity. 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, Pedicoccocus, and Weissella have been well studied for immunostimulating properties. The EPSs extracted from lactic acid bacteria of the genera Pedicoccus, Leuconostoc, and Lactobacillus significantly proved to produce anti-adeno virus effects in cell line studies (Bilavisk 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 Streptomycyes sp. GT2002/1503 showed selective anti-HIV-1 activity (Xu et al., 2014). The compound (4S)-4-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide, identified from Streptomycyes sp. Smu03 possessed antiviral property over a broad range of Influenza A virus (Li et al., 2018). Antimycin C from Streptomycyes kaviiensisis inhibited RNA virus families like Togaviridae, Picornaviridae, Bunaviridae, and western equine encephalitis virus. AhmpatininiBu from Streptomycyes sp. CPC 202950 and 4862F from Streptomycyes albusporus I03A-04862 inhibited HIV-1 protease. Narasin from Streptomycyes aureofaciens prohibited post-entry stages of viral replication during Dengue virus infection (Teixeira et al., 2014). Other antivirals include daptoycin from Streptomycyes roseoporus (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 turbata                      | Polio, Coxsackie viruses                             | Becher (1976) |
| Stachybotrys A             | Stachybotrys sp.                         | Enterovirus-71                                      | Qin et al. (2014) |
| 3,6,8-Trihydroxy-1-methylbenzanthone | Sclerotium sp.                          | HSV                                                 | Rowley et al. (2003); Youssef et al. (2019) |
| Halovir 1                   | Aspergillus terreus SCGAF0162             | 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) |
| Intergic acid              | Xylohypha sp.                            | HIV                                                 | Rowley et al. (2004) |
| Stachyphil                 | Stachybotrys sp. RF-7260                 | Influenza virus                                     | Minagawa et al. (2002) |
| Oxoglycantrypine, Norquinadoline A, Deoxynortryptoquiline, Deoxynortryptoquiline, Trypotoxine, and Quinadoline B | Cladosporium sp.                            | Influenza virus                                     | Peng et al. (2013) |
| Cladosin C                 | Cladosporium sporaespermum              | Influenza virus                                     | Wu et al. (2014) |
| (2-)–5-(Hydroxymethyl)-2-(6‘)-methylhept–2‘-en–2‘-yl)-phenol, Dichiorin, and HIV Cordyl C | A. sydowii 2SDS1-F6                          | Influenza virus                                     | Wang et al. (2014) |
| Rubridole S                | A. terreus OUCMDZ-1925                   | Influenza virus                                     | Zhu et al. (2013) |
| Aspergesterol A            | A. terreus SCGAF0162                     | Influenza virus                                     | Gao et al. (2013) |
| Isoaspulvinone E           | A. terreus Cqgw-48                       | Influenza virus                                     | Gao et al. (2013) |
| Emerinamide A              | Emericella sp. (HK-ZJ)                   | Influenza virus                                     | Zhang et al. (2011) |
| Purpurquinone B            | P. purpurigenum JS03-21                  | Influenza virus                                     | Wang et al. (2011) |
| Sorbitacetate B            | P. chrysogenum PJK-17                    | Influenza virus                                     | Peng et al. (2014) |
| Tetracydroalerosol A       | Alternaria sp. 22-2008003                | Purine reproductive and respiratory syndrome        | Zheng et al. (2012) |
| Sansalvamite A (43)        | Fusarium sp.                            | Molluscum contagiosum virus                          | Hwang et al. (1999) |
| 22-O-([N-Me-L-valyl]-21-epiaflquinoline | Aspergillus sp. XS-20090B15            | Respiratory syncytial virus                         | Prieto and Castro (2005) |
| B (44)                    | Extracts                                 |                                                     |             |
| GFAHP                      | Agaricus subfurescens                    | HSV-1                                               | Bruggemann et al. (2006) |
| Beta-glucan-protein        | Gliophora frondosa                      | HSV                                                 | Gu et al. (2007) |
| Aureniol                   | Agaricus subfurescens                    | HSV                                                 | Yamamoto et al. (2013) |
| Lentinula edodes           | Chaetomium cinereum                      | Influenza A (HIN2)                                  | Sacramento et al. (2015) |
| Trametes versicolor        | Trametes versicolor                      | HPV                                                 | Collins and Ng (1997) |
| Polyaccharide              | Agaricus subfurescens                    | HPV                                                 | Facchin et al. (2007) |
| Cordyceps militaris        | Cordyceps militaris                      | Influenza, HSV                                       | Krupodora et al. (2014) |
| 4.5 kDa protein            | Cordyceps militaris                      | HIV protease                                         | Jiang et al. (2011) |
| Ganoderin acid             | Ganoderma lucidum                       | HIV reverse transcriptase                            | Wang and Ng (2001) |
| Brefeldi A                 | Penicillium sp. PKI-7127                 | Dengue viruses, ZIKV, and Japanese encephalitis virus | Min et al. (1998) |
| Ganodermic acid G triterpenoids, and lucidicol | Ganoderma gelphiif Bres.                | Influenza virus type A and HSV-1                   | Mathona et al. (2003) |
| Cordycepin (also named 3-deoxyadenosine) | Cordyceps militaris                     | Influenza viral, HIV-1 RT, Epstein-Barr virus, and Rota virus | Yong et al. (2018) |
| Ganodermic acids are A, AM1, B, j, C1, C2,C5, D, DF, DM, E, F, G, H,JK, MC, Me, Me, MK, N, P, R, S, T, TR, TQ, X, and Y | Ganoderma lucidum | HIV-1 and HBV | Hsa and Yen (2014) |
| Hsp20 and hispolon         | Innotus hispidus (Bull.) P. Karst.       | Influenza virus type A and type B                    | Li and Wang (2005) |
| PKS Kreston and P5P        | Trametes versicolor                      | HIV-1                                               | Milinari et al. (2005) |
| Velutin and Flammunin proteins | Flammulina velutipes                      | HIV-1 reverse transcriptase                         | Wang and Ng (2001) |
| Trypipelleazolin, (+)-neocreticoargin, and 3’-hydroxyergosta-8,14,24-(28)-trien-7-one | Penicillium sp. | HIV-1, HCV, and Influenza | Li et al. (2019) |
| Physcion, Neocholinin D, and Dihydroauroglaucin | Eurotium chevaleri                         | Influenza A virus                                   | Bovi et al. (2019) |

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 ant kraquinones against arenaviruses, respiratory syncytial virus, and HSV type 1 (Boustie and Grube, 2005; Stocker-Wörgötter, 2008; Zambare and Christopher, 2012; Lai et al., 2013).

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). Xinnycin A, a distinguished compound extracted from Bruguiera gymnorrhiz hus mango plant, demonstrated selective anti-HIV activity (Christina et al., 2013).
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. 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. 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.
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 Wahle, 2006).

Table 5
Antiviral compounds from bacteria.

| Name of the compound | Organisms | Active against | References |
|----------------------|-----------|----------------|------------|
| Sulfamethoxine C, soraphen F, epothilone D, and spiranigren B, and Kulpelen B | Sorangium cellulosum | HIV | Zander et al. (2012) |
| Rhizopodin | Myxococcus stipitalis | 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 ox-phenone | Sorangium cellulosum | HIV | Gerth et al. (1995) |
| Myxochelins A-F | Angiococcus disciformis | Human | Miyayaga et al. (2009) |
| Nannochelin A-C | Nannocystis exedens | Human | Kunze et al. (1992) |
| Hylacheline A-C | Hylangium minutum | Human | Nadmid et al. (2014) |
| Chondramide A-D | genus Chondromyces | EVD | Reichenbach (1988) |
| Norimucenol A-C | Sorangium cellulosum | EVD | Kunze et al. (1991) |
| Labindole A and B, 3-chloro-9H-carbazole, 4-hydroxymethyl-quinoline, and Soraphen A | Labiliithrix laterula | HCV | Mulwa et al. (2018) |
| Lanyamycin | Streptomyces sp. | HCV | Gentzsch et al. (2011) |
| Surfactin | Bacillus amyloliquefaciens | Antiviral activity | Komousiti et al. (2004) |
| Bacitracin | Bacillus licheniformis | Antiviral activity | Konz et al. (1997) |
| Lichenysin | Bacillus licheniformis | Antiviral activity | Veith et al. (2004) |
| Locitamycin | Bacillus subtilis | Antiviral activity | Lui et al. (2015) |
| Macroactin A | Pedicoccus, Leuconostoc, Lactobacillus | Human | Gustafson et al. (1989) |
| Exopolysaccharides (EPSs) | | Human adenovirus | Liubov et al. (2019) |

| Name of the compound | Organism | Active against | References |
|----------------------|-----------|----------------|------------|
| 4862F | Streptomyces parvus | Furan-2-yl acetate (C6H6O3) | Streptomyces sp. | Streptomyces sp. CPCC 202050 | Streptomyces aureofaciens | Dengue virus | Teixeira et al. (2014) |
| 4862F | Streptomyces sp. CPCC 202050 | Streptomyces aureofaciens | Dengue virus | Teixeira et al. (2014) |

Table 6
Antibacterial metabolites against viral pathogens.

| Name of the compound | Organism | Active against | References |
|----------------------|-----------|----------------|------------|
| 9-Methyl streptimidone | Streptomyces sp. S-885 | Poliovirus | Swallow et al. (1975) |
| Rifampin | Streptomyces mediterranei | Vaccinia and pox viruses | De Clercq (1973) |
| Novobiocin | Streptomyces etaphoroides (Actinomycetales) | Antiviral activity | Murray et al. (1982) |
| Guanine-7-N-oxide | Streptomyces sp. | Rhabdovirus and infectious | Nakagawa et al. (1985) |
| Antimycin A1a | Streptomyces kaviengensis | Western equine | Raveh et al. (2013) |
| Xiamycins C-E | Streptomyces sp. #HR18 | Porcine epidemic diarrhea | Kim et al. 2016; Xu et al. (2014) |
| Pentapeptide 4862F-N.N.N-[(trimethylated)-Tyr-L-Leu-L-Val-L-Leu-(dehydrated)-His | Streptomyces sp. | Poliovirus | Liu et al. (2012) |
| 4-amino-3-hydroxy-5-(4-methoxyphenyl) pentanoic acid | Streptomyces albomentos R33A-04862 | HIV-1 | Chen et al. (2018) |
| Daptomycin and Nanchangmycin | Streptomyces spp. CPC 202950 | HSV-1 | Barrows et al. (2016); Pascoalino et al. (2016); Rauch et al. (2017) |
| Chartreusins | Streptomyces roseosporas | ZIKV | Miyahara et al. (1958) |
| Mannose specific pradimicin-A (PRMA) | Streptomyces roseosporas | Influenza A | Tanabe-Tochikura et al. (1990) |
| Actinothoin | Streptomyces chartreusis | HIV | Chiba et al. (2004); Takahashi et al. (2005) |
| Benzastatin C, a 3-chloro-tetrahydroquinolone alkaid | Streptomyces sp. | HSV-1, HSV-2, and | Lee et al. (2007) |
| JBR-68 | Streptomyces sp. R18 | vesicular stomatitis virus | |
| Methylbactopin | Streptomyces sp. RT62K1 spg. | Influenza virus | Takagi et al. (2010) |
| Furaz-2-y acetate (C6H6O3) | Streptomyces parvus | Newcastle disease virus | Lee et al. (2011) |
| Di-n-octyl phthalate and bis (2-methylethyl) phthalate | Streptomyces microflavus | Fish nodavirus | Suthindhuran et al. (2011) |
| Fattiviracin A1 | Streptomyces griseoviridis | HCV | Elshab et al. (2016) |
| Musacin A | Actinomadura hibisca | Antiviral activity | Yokomizo et al. (1998) |
| MMG61356 | Actinomadura pradimicin-A (PRMA) | Antiviral activity | Schneider et al. (1996) |
| FK 506 | Actinomadura hibisca | Antiviral activity | Admon et al. (1990) |
| Benzastatin C | Streptomyces nitrosporeus | Antiviral activity | Reis et al. (2006) |
| (45)-4-hydroxy-10-methyl-11-oxo-dodec-2-en-1,4-olide | Streptomyces sp. Smu03 | Influenza A virus | Lee et al. (2010) |
| Ahmpatinini Bu | Streptomyces sp. CPCC 202050 | HCV-1 | Lee et al. (2011) |
| 4862F | Streptomyces aureofaciens | HCV-1 | Lee et al. (2011) |
| Narasin | Streptomyces aureofaciens | HCV-1 | Lee et al. (2011) |
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. Xiaoqionglong 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 (Wujie, 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, baicalin, and 5,7,8,4′-tetrahydroxyflavone. These extracts showed antiviral properties that inhibited the neuraminidase activity of Sendai virus and Influenza A H5N1 (Hou and Lu, 2009). *Houttuynia cordata* Thunb is a traditional Chinese medicine used for treating pneumonia and lung-related ailments. It is also found active against SARS-CoV (Lau et al., 2018).

5.3. Other traditional medicines

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

Korean Red Ginseng is used as traditional medicine in East Asian countries as it has enhanced pharmacological properties as compared with fresh ginseng (the root of *Panax ginseng*) because of the steaming process of ginseng (the root of *Panax ginseng*). Due to steaming, the root of *Panax ginseng* contains a variety of active ingredients, including saponins, ginsenosides, and flavonoids. These active ingredients have various medicinal properties, including immune-stimulating, anti-inflammatory, and anti-cancer effects.

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...
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

| Coroana Virus | Influenza Virus | Hepatitis B Virus | Respiratory Syntitial Virus | Dengue Virus |
|---------------|----------------|------------------|---------------------------|-------------|
| Bupleurum spp. (Chái Hú) | elderberry (Jié Gǔ Mǔ; Sambucus nigra) | Piper longum (Jiā Jú) | Lophatherum gracile (Dān Zhù Yè) | Terminalia chebula (Hē Zī) |
| Scrophularia scorodonia (Xuán Shēn) | dandelion (Pú Gōng Yíng; Taraxacum officinale) | Xiao-Chai-Hu Tang (Xiāo Chái Hú Tang), Bupleurum species (Chái Hú), Polygonum cuspidatum sieb. et zucc (Hū Zāng) | Sheng-Ma-Ge-Gen-Tang (Shèng Mǎ Gé Gèn Táng), Its major component herb Cimicifuga foetida L. (Shèng Mǎ), |
| Lycoris radiata (Shì Suàn) | homoisoflavanoids from Caesalpinia sappan (Sǔ Mǔ) | | |
| Artemisia annua (Huáng Huā Hǎo), Pyrosis lingua (Shí Wěi) | | | |
| Lindera aggregata (Wú Yào) | Other medications | | | |
| Isatis indigotica (Bān Lǎn Gèn) | Ocimum basilicum (Luò Lè) | Woodfordia fruticosa flowers (Xià Zǐ Hú) | | |
| Torreya nucifera (Fēi) | | Fructus arctii (Niú Bāng Zǐ) | | |
| Houttuynia cordata (Yú Xīng Cǎo) | | Uncaria tomentosa (Gōu Tēng) | | |

| Measles Virus | Human Immunodeficiency Virus | Sheng-Ma-Ge-Gen-Tang (SMGGT) is a Chinese formula, consisting of four herbal medicines: Rhizoma Cimicifuga-gae (Sheng Ma), P. lobata (Ge Gen), Glycyrrhiza uralensis (Gan Cao), and Raonemia lactiflora (Shào Yao) | Pu Di Lan is prepared as oral tablets or a liquid, and mainly consists of Taraxacum mongolicum (Pu Gong Ying), S. baicalensis (Huang Qin), Corydalis bungeana Turcz. (Ku Di Dīng), and Baphicacanthus cusiae Rhizoma et Radix (Bān Lān Gèn) |
|---------------|-----------------|-----------------|------------------|
| Rhus succedanea (Yè Qì) | Artemisia annua (Huáng Huā Hǎo) | | |
| Garcinia multiflora | | | |
| Olinia rochitiana (Olkireinj) | | | |
| Warburgia ugandensis (Osokoi) | | | |

| Ayurvedha | Unani | Decotions used in Unani |
|-----------|--------|-------------------------|
| Azadirachta indica A. Juss | Svetiachirata 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. | Borge 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 arbor-tractis | | Papaver somniferum |
| Carica papaya | | Myrtus communis |
| Holarrhena antidysenterica | | Lactuca sativa |
| Phyllanthus urinaria Linn. | | Rosa damascene |
| Euphorbia jolkindi Biss | | |

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.
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.

Acknowledgements

The authors acknowledge the support they received from Loyola College and King Saud University for the preparation of this manuscript.

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