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Review Article

The Antiviral Potential of Medicinal Plants in Treating Viral Infections

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Abstract

Due to growing concerns about the emergence of medication resistance and slow progress in the development of antiviral drugs, there have recently been notable advancements in the field of herbal antiviral therapy. Since medicinal plants have an extensive therapeutic range and few to no side effects, they have been utilized extensively throughout history in almost all nations for the treatment of illnesses and infections as traditional healing treatments. All available resources have been devoted to the search for novel medications and supplementary alternative treatments derived from various herbal formulations because synthetic antiviral pharmaceuticals are not currently accessible to treat the majority of viral agents. The utilization of medicinal plants and natural products for prophylaxis, therapies and other health-related purposes has a long history, but recent decades have seen a surge in scientific research and data supporting these claims. Various scientific investigations have been conducted, ranging from the determination of active ingredients to understanding the therapeutic mechanisms of antiviral herbs, their effective uses in the elimination of viral infections, and clinical trials. As a result, hundreds of herbs and plant metabolites have been screened, identified, and evaluated for their antiviral activities. Fortunately, some have exhibited significant therapeutic potential in the prevention or alleviation of various viral infections such as rabies, and influenza types A, B, C, hepatitis B, and C in both preclinical and clinical investigations.

Keywords: Influenza virus, Antiviral, Natural product, Medicinal plant

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Introduction

Globally, viral pathogens are mostly to blame for morbidity and mortality in both people and animals. One of the biggest risks to farm animals, humans, and the environment is viral infections. The four viral illnesses Ebola, AIDS (acquired immunodeficiency syndrome), influenza, and SARS-CoV2 (severe acute respiratory syndrome) are the most devastating diseases. For example, each year, influenza causes

around 3 million new incidences of serious illness and between 300,000 and 500,000 fatalities around the world. As blood transfusions, organ transplants, and the usage of hypodermic syringes rise, the number of patients suffering from viral infections is increasing every year worryingly or disturbingly.

For various purposes, viruses require the machinery of host cells. There are roughly 1,031 viruses on the earth, and since they are so widespread, they have taken over the marine ecology, where there are 5,000 viral genomes per 200 liters of water. Viruses are present everywhere and continue to move across environments. For instance, they can be found in deep oceans, polar ice, alkaline, hot and salt fluids, as well as at a depth of around 2,000 meters in terrestrial ecosystems (4-6).

Nearly 20 virus families have been identified, and many of them cause diseases in both humans and animals. Viral infections have also been linked to several difficult-to-treat conditions and complex syndromes, such as Alzheimer's disease, type 1 diabetes, and hepatocellular carcinoma (HCC). Only a small number of antiviral medications have clinical use approval, and numerous viruses continue to exist without appropriate immunity. Antivirals are antimicrobial substances produced by chemical synthesis or acquired from biological organisms that primarily prevent viral replication. Antivirals block one or more steps of the viral life cycle, including cell attachment, cell penetration, viral uncoating, viral genome (DNA/RNA) replication, assembly, and releasing virions (7-9).

Through a variety of processes, the antiviral medications that were created such as Moroxydine, Ganciclovir, Valganciclovir, and Valaciclovir, prevented the replication of viruses. However, difficulties in treating with medications have emerged because of their low efficiency, cytotoxicity, and the emergence of viral resistance (3). Almost 40% of currently accessible medications are either directly or indirectly derived from plants, making nature yet another reliable source of antiviral medicines. Many ethnobotanical studies have emphasized the use of medicinal plants in the healthcare delivery system by concentrating on the identification of potential therapeutic plants for even more efficient treatment of medical conditions. A large source of unique antiviral development medications is frequently found in herbal remedies and extracted natural materials. It is possible to target specific virus-host interactions by characterizing antiviral medications derived from such natural sources and learning how they interact with the viral replication cycle, which includes viral entrance, replication, assembly, and release (5, 6, 8, 10). The antiviral effects of numerous herbal medicines and natural items have been listed here against a variety of significant viral infections (Table 1).

Antiviral Potentials of Medicinal Plants

Antiviral Molecules of Plant Origin

Many plants have been traditionally utilized in medicine and are renowned for having potent healing properties. Several of these herbs have been used in conventional medicine to treat diseases that could have viral origins (Table 1) (2, 3, 11). Alkaloids, terpenes, flavonoids, different glycosides, and proteins were extracted in their crude form. Then, they were purified and several phytochemicals were separated. Many plants have substances that have antiviral properties. For instance, rutin, a flavonoid glycoside that exists in many plants is influential against the avian influenza virus as well as the HSV-1, HSV-2, and parainfluenza-3 viruses.

When exposed to quercetin, an aglycone of the rutin, many viruses may be less likely to replicate, such as the highly pathogenic influenza virus, the rhinovirus, the dengue virus type 2, the HSV-1, the poliovirus, the adenovirus, the Epstein-Barr virus, the Mayaro virus, the Japanese encephalitis virus, the respiratory syncytial virus, and the HCV. In a few instances, its antiviral action mode was studied. By restricting the activity of several heat shock proteins (HSPs) produced by cells in response to stress and are important in NS5A (nonstructural protein 5A)-mediated viral IRES (internal ribosome entry site) translation, it suppresses HCV in a well-known manner (5, 11). Another strategy involved blocking the HCV NS3 protease and HCV replication in a subgenomic HCV RNA replicon cell culture. Additionally, quercetin blocks the transcription of the viral genome, protein synthesis, and several other pathogenesis-related processes for rhinoviruses (11). In a different instance, it was demonstrated that quercetin operated in a more focused manner, slowing down the multiplication of dengue virus type 2 but not the viral attachment and entry processes (12). Furthermore,

Quercetin and three additional flavonoids, and 3,3′,4′,5,5′,7-hexahydroxyflavone (Myricetin), 3,3′,4′,5,6,7-hexahydroxyflavone (Quercetagetin),

Table 1. Antiviral properties of plant extracts.

Plant	Kind of extract	Virus	References
Achillea fragrantissima	Hydro-alcoholic extract	Poliomyelitis-1 virus (POLIO)	(1,3)
Aegle marmelos	Aqueous extract	Human coxsackieviruses B1-B6	(3,5,6)
Aloe vera	Glycerine extract	HSV-2	(3,4)
Artocarpus integrifolia	Aqueous extract	Human Rotaviruses	(4,5)
Balanites aegyptiaca	n-Hexane extract	VSV T2	(4,18)
Camellia sinensis	Aqueous extracts	HBV	(9)
Capparis spinosa	Methanolic extract	HSV-2, HIV-1	(1,3,12)
Cassine xylocarpa	Aqueous extract	HIV	(17)
Cistus incanus	Polyphenol-rich extract (CYSTUS052)	Avian and human influenza strains of different subtypes HIV-1 and HIV-2	(18,19)
Curcuma longa	Aqueous extract	HSV-1	(17,18)
Cyperus rotundus	Hydro-alcoholic extract	HSV-1, HBV	(17)
Daphne gnidium	Hydro-alcoholic extract	HIV	(5,6,8)
Diospyros kaki	Aqueous extract	Human Rotavirus	(5,6)
Dittrichia viscosa	Aqueous extract	VSV, HSV-1, Poliovirus type 1	(4,9)
Euphorbia hirta	Aqueous extracts, ethanol extracts	HIV-1, HIV-2, SIV mac 251	(6,8)
Euphorbia spinidens	Methanol extract	HSV-1	(1)
Ficus benjamina	Ethanol extract	HSV-1, HSV-2	(1,3,7)
Globularia arabica	Hydro-alcoholic extract	Poliomyelitis-1 virus (POLIO)	(3,5,8)
Glycyrrhiza glabra	Methanolic extract	NDV	(18,19)
Glycyrrhiza uralensis	Metabolic extract	Rotavirus diarrhea	(11,12)
Hyssopus officinalis	Methanolic extract	HSV-1	(6)
Leucojum vernum	Methanolic extract	HIV-1	(6,7)
Lilium candidum	Ethanol extract	HSV-1, HSV-2	(4,6,9)
Magnolia officinalis	Methanol extract	Dengue virus Type 2	(17,18,19)
Maytenus cuzcoina	Aqueous extract	HIV	(17,18)

Melissa officinalis	Aqueous extract	HSV-1, HSV-2, HIV	(35,36)
Mentha pulegium	Methanolic extract	HSV-1	(35,36)
Moringa peregrina	Hydro-alcoholic extract	HSV-1	(35,36)
Olea europaea	Hexanic extract	Influenza virus subtype H9N2	(14)
Panax notoginseng	Aqueous extract	Influenza A virus	(28)
Phyllanthus emblica	Aqueous extract	Influenza A virus strain H3N2	(28,29)
Prunella vulgaris	Aqueous extract	HIV-1, Ebola virus	(14,18)
Salacia reticulata	Aqueous extract	H1N1 influenza	(14,18)
Taraxacum officinale	MAqueous extract ethanol extract	HCV, Influenza virus type A, 1N1.	(17,15)
Viola diffusa	Ethanol extract	HBV	(1,4)
Vitis macrocarpon	Methanol extract	Human Rotaviruses	(1,3)
Zataria multiflora	Methanolic extract	HSV-1	(7,8)

5,6,7-trihydroxyflavone (Baicalein), all successfully hindered reverse transcriptases from the Rauscher murine leukemia virus (RLV) and HIV; Quercetin (13, 14). Myricetin, the aforementioned flavonoid, is widely present in vegetables, fruits, berries, nuts, and wild plants.

In vivo as well as in cell cultures, ellagic acid and myricetin (from the Aronia fruit) proved effective against various influenza virus subtypes, including an oseltamivir-resistant variant. With wide antiviral effects against enterovirus-71, foot and mouth disease virus, HCV, African swine fever virus (ASFV), and influenza A virus, apigenin (4′,5,7-trihydroxyflavone), an aglycone of the flavone class, is present in many plants (2, 12, 15, 16). Notably, many flavonoids with botanical origins have antiviral capabilities. For instance, six phytochemicals (Apigenin, Baicalein, Biochanin A, Kaempferol, Luteolin, and Naringenin) out of 22 distinct flavonoids were effective against the avian influenza H5N1 virus in human lung epithelial (A549) cells by preventing the formation of nucleoprotein.

Baicalin (the glucuronide of baicalein) proved effective against many viruses, including the enterovirus, dengue virus, respiratory syncytial virus, Newcastle disease virus, human immunodeficiency virus, and hepatitis B virus. Its antiviral actions have been explained by a number of different mechanisms. As demonstrated in a study on the avian influenza H5N1 virus, baicalin reduces the production of IL-6 and IL-8 without affecting IP-10 levels and hinders the production of HB, the templates for viral proteins and HBV-DNA synthesis. Oleanolic acid and ursolic acid, two triterpenoids found in numerous plant species, might be influential against HCV by decreasing HCV NS5B RdRp pathogenicity and by inhibiting the replication of Enterovirus 71 (Table 1). The final ingredient is Sambucus nigra L., which is a component of a standardized elderberry extract that is useful in treating fever, colds, and influenza types A, B, and C. (2, 9, 14, 17).

Plant Extracts and Natural Compounds

Azadirachta Indica A.Juss

At a dosage of 1000 micrograms/mL for 96 hours, the methanolic extract of neem (*Azadirachta indica A. Juss*) leaves prevented plaque formation in 6 antigenic types of Coxsackie virus B. The extract's flavonoids and triterpenoids glycosides demonstrated antiviral efficacy against Coxsackie B group viruses *in vitro* (18).

Cistus incanus

In vitro infections of the human immunodeficiency virus (HIV) were prevented by the methanolic extract of *Cistus incanus*. The initial attachment of the virus to the cell surface was prevented by antiviral activity,

which was also highly selective for virus particles. Viral envelope proteins were also prevented from attaching to heparin According to a bioassay-guided fractionation, the extract had a low propensity to create virus resistance because it included many antiviral chemicals. The fact that the extract was able to prevent infection by the pseudotyped virus particles carrying the Ebola and Marburg virus envelope proteins shows that the methanolic extract's antiviral action extends to newly developing viral diseases. As a result, the extract demonstrated a strong and widespread *in vitro* antiviral activity against viruses that lead to fatal illnesses in both humans and animals (1).

Coriandrum sativum

Due to its unique qualities, *Coriandrum sativum* is used in pharmaceutical formulations to treat viral infections such as severe acute respiratory syndrome (SARS-COV2), Middle East respiratory syndrome (MERS), human immunodeficiency virus (HIV), hepatitis A virus (HAV), and dengue fevers (DENG). In addition to the therapy of clinical aspects in viral infections, Coriander is advantageous as an immune booster to avoid infectious diseases (3).

Eugenia singampattiana Bedd.

Porcine reproductive and respiratory syndrome virus was resistant to the methanol and water extracts of *Eugenia singampattiana Bedd.* leaves (PRRSV). Different concentrations of the extracts' anti-PRRSV activity were assessed (14).

Glycyrrhiza glabra linn

The ethanolic extract of *Glycyrrhiza glabra linn* and its active ingredient, glycyrrhizin, demonstrated antiviral efficacy to a variety of viruses, including Hepatitis A, B, and C, Influenza A virus, Varicella zoster, HIV, HSV-1, SARS-related coronavirus, and CMV (7). The decreased transport to the membrane and sialylation of the hepatitis B virus surface antigen, the production of interferon-gamma in T cells, the inhibition of phosphorylating enzymes in the vesicular stomatitis virus infection (VSV), and the reduction of viral latency are some of the mechanisms underlying the antiviral activity of glycyrrhiza species. As a result, licorice may be useful in the prevention and treatment of influenza A virus pneumonia as well as adjuvant therapy for HIV patients who have become resistant to antiretroviral medications (7).

Gyrinops versteegii (Gilg.) Domke

The ethanolic extract of *Gyrinops versteegii* (Gilg.) Domke showed greater potential for antiviral activity against Dengue virus serotype 3 (DENV-3) on Reverse Transcription-Polymerase Chain Reaction (RT-PCR), with up to 99.59% virus suppression in comparison with positive control of viral infection in distributions over 125 g/mL. The presence of flavonoids, terpenoids, and phenolic chemicals is responsible for the antiviral activity (19).

Humulus lupulus var. lupuloides

It was noted that xanthohumol, a prenylchalcone flavonoid isolated from the ethanolic extract of the hop cones of *Humulus lupulus L.*, was efficient against HIV-1 and could be a fascinating lead molecule for a new chemotherapeutic treatment of HIV-1 infection (15, 20).

Hypericum perforatum

According to Pu *et al.*, the influenza A virus (IAV) (H1N1) was inhibited by *Hypericum perforatum* extract both in vitro and in vivo (8). The reference medicine Ribavirin and the extract of *H. perforatum* both have shown comparable effectiveness against IAV infections, and the plant extract was thought to be less hazardous. Additionally, the finding that the antiviral compound hypericin, which is present in *H. perforatum* and known as Saint John's Wort, has very high toxicity against some viruses, particularly the family of enveloped viruses including HIV which led to its discovery (21).

Hyssopus Officinalis

A methanolic extract of *Hyssopus officinalis* leaves was tested for *in vitro* and *in vivo* antiviral activity against Herpes simplex virus (HSV) The results revealed that both the wild and resistant strains of HSV were susceptible to the extract (13).

Nigella sativa linn

The ethanolic extract of *Nigella sativa* seeds and its component thymoquinone have been shown to have antiviral action against a variety of human, animal, bird, and plant cytopathogenic viruses, including murine cytomegalovirus (MCMV), Avian influenza (AIV) subtype H9N2 (23), Schistosoma mansoni infection (CMI), broad bean mosaic virus (BBMV), and HIV (22).

Opuntia streptacantha Lem.

At extract concentrations of 15-fold, above 50% viral inhibitory concentrations, an extract of the cactus plant Opuntia streptacantha LEM inhibited both DNA and RNA virus replication, including those of the herpes simplex, equine herpes, pseudorabies, influenza, respiratory syncytial, and HIV, while maintaining normal protein synthesis in uninfected cells. Oral administration of the extract to mice, horses, and human patients revealed that it was non-toxic. The non-toxicity of the intravenous injection of 70 mg to a mouse representative of at least fifty tissue cultures with 50% viral inhibitory doses suggests the use of this extract in clinical trials for human virus diseases (14). The relevant substance from the extract's activity was found to be a protein derivative coded as GFAHP, which directly inactivates HSV-1 and prevents HSV-1 from penetrating the Vero cell culture medium. GFAHP's molecular weight was determined by gel electrophoresis to be 29.5 KDa. The 11-amino acid peptide NH2-REQDNAPCGLNCOOH that made up the N-terminal sequence of GFAHP did not match any known amino acid sequences, suggesting that it is possibly a new antiviral protein (14).

Pelargonium sidoides

Local populations have been treating respiratory infections with pelargonium sidoides for millennia. Through modification of the viral binding proteins on human bronchial epithelial cells, the ethanolic extract of the radix of P. sidoides reduced Rhinovirus infection (23).

Sambucus nigra linearis

It has been demonstrated in vitro that *Sambucus nigra L*. fruit extract strongly inhibits HSV-1, even in strains that are resistant to a number of common antiviral drugs. A substantial antiviral impact against HIV in vitro has also been found. Sambucus nigra has the potential to be both a cheap and low-risk treatment for influenza and other viral and non-viral pathogens as well as a prophylactic for severe viral infections. However, more investigations on the possible preventative antiviral benefits of Sambucus nigra are required to confirm the findings of these encouraging preliminary studies in humans and to determine the effectiveness of S. nigra as a broad-spectrum antiviral, as the majority of studies concentrate on one or two particular viral diseases (24).

Zingiber officinale literatura

When evaluated in vitro utilizing the HCV-infected hepatocellular carcinoma HepG2 cell line, the lyophilized juice extract from Zingiber officinale L. was found to be most effective at a concentration of 100 g/mL. Other concentrations examined included 5, 25, 50, 75, 100, 150, and 200 g/ml (30). By preventing viral attachment and internalization, this extract also displays antiviral efficacy against the formation of plaque on the airway epithelium caused by the human respiratory syncytial virus (HRSV) (25).

The Impact of Antiviral Plant Extracts on Some Animal Viruses

Some traditional medicinal plants have been used in the past in the treatment of viral infections in both people and animals. Many of these herbs have been demonstrated to have strong antiviral effects. Ricinus communis, Brucea antidysenterica, Croton macrostachyus, and Cucumis ficolins were the medicinal plant species most frequently identified as being used to cure rabies in Ethiopia (Table 2) (1, 2, 8, 11).

The Impact of Antiviral Plant Extracts on Some Human Viruses

Hepatitis A, B, C, D, and E are five distinct viruses that can cause viral hepatitis, which is an infection of the liver. Type B and type C viruses are distinct in how they produce chronic disorders because all of these viruses cause acute infection (1, 31).

Hepatitis B Virus

In terms of lignans, flavonoids (such as termination), alkaloids (such as quercetin), and lignans (such as hypophyllanthine and andphyllanthine), Phyllanthus species are regarded as a crucial source of antiviral bioactive metabolites. They are able to stop the HBV endogenous DNA polymerase enzyme, which is necessary for the viral replication process, from working. Several bioactive metabolites isolated from Phyllanthus acidus were also investigated for their inhibitory potential using HBsAg-containing sera from chronic HBV patients (6, 10, 32). It has also been shown that P. niruri extract is efficient in treating HBV in mammals in 3–6 weeks in vivo. Following a 90-day Phyllanthus acidus extract treatment, the HBV antigen was successfully reduced to undetectable levels in two-thirds of HBV-positive people (6, 10, 18). The

Table 2: Antiviral effects from several plant extracts against viruses.

Viruses	Mode of action	Plant extracts	References
Picornaviridae, Foot-and-mouth disease (FMD)	combined effects of polyherbal drug phytochemicals against FMDV and individual plant extracts against FMDV	*Ashwagandha, Tulsi, Turmeric Morinda elliptica L.M. citrifolia L.*	(1)
Flaviviridae, Bovine viral diarrhoea virus (BVDV), Classical swine fever virus	Antiviral activity as on HCV. Antiviral effect partly due to enhancement of the IFN-associated JAK-STAT pathway. inhibitors of viral replication	*Phylantus orbicularis, Melia azedarach, Perseaamericana , Acanthospermum hispidum Guazuma ulmifolia Stryphnodendron adstringes*	(3,4)
Reoviridae, Rotaviruses, Bluetongue virus	Saikosaponin B2 inhibits viral attachment and penetration stages	*Black tea, Citrus aurantium, Marine sponges, Stevia rebaudiana Alpinia katsumadai (AK), Zingiberaceae*	(3)
Orthmyxoviridae, Influenza A.	Inhibits viral entry and release; inhibits viral hem-agglutination and NA activity. Inhibits viral NP RNA levels and polymerase activity	*H. erectum, T. chebula M. cochinchinensis*	(1,4)

identification of anti-HBV compounds from therapeutic herbs has also been the subject of numerous investigations over the past few years. Saikosaponins from Bupleurum species and the ethanol extract from Polygonum cuspidatum, for instance, have been reported to have antiviral activity against HBV in vitro (5). Moreover, curcumin demonstrated its ability to inhibit the HBV gene's replication and manifestation via regulating PGC-1, the co-activator of the HBV transcription. Other instances include the substantial anti-HBV effects of chlorogenic acid A, amide alkaloids, and dehydrocheilanthifoline from Corydalis saxicola, Piper longum, and Laggera data. By controlling viral protein-mediated gene expression and DNA replication through interactions with the NF-B nuclear factor pathway, the LPRP-Et-97,543, which was isolated from the roots of Liriope platyphylla, blocks the method by which HBV acts. Studies on the mechanisms by which bioactive components reduce HBV appear to be lacking, despite the fact that the majority of natural substances have been shown to do so. For instance, by reducing transaminase, Acanthus ilicifolius L. dramatically reduces liver damage caused by HBV (9). Gymnema Sylvestre phytoconstituents inhibit HBV DNA polymerase activity and HBsAg binding (1). In addition, after treatment with Phyllanthus extract, the expression of intracellular HBV DNA in HBV WT- or mutant transfected HepG2 cells decreased. Phyllanthus increased the expression of the genes for interferon-beta, cyclooxygenase-2, and interleukin-6 in HBV WT-transfected HepG2 cells. This was probably done via modifying the activity of c-jun N-terminal kinases and extracellular signal-regulated kinases, as well as by triggering the genes for retinoic acid-inducible gene-I, toll-like receptor 3, and myc (19, 20). Two novel important Cboivinopyranosyl flavones, chrysoberyl, and luteolin, were identified from Alternanthera philoxeroids and demonstrated significant anti-HBV action by lowering HBsAg secretion in HepG2.15 cells. Therefore, Sanguisorba officinalis ethanol extract and its important components (ziyuglycoside I and II) against HBV in HepG2.2.15 cells limit HBV replication and antigen secretion. identifying the plant's propensity to treat disorders associated with HBV as unique candidates (19, 25). Both in vitro and in vivo experiments were conducted to investigate the anti-HBV effect of Abrus cantonments. Treatment with A. cantonments significantly reduced the production of HBV DNA, HB Ag, and HBsAg in HepG2.2.15 cells and rAAV8-1.3HBV transfected mice, which establishes a foundation for its potential clinical application. (13) In HepG2.2.2.15 HBV-reporter cells, quercetin and myricetin-3-O-rhamnoside from Guiera senegalensis leave exhibited antiviral activity (HBsAg and HB Ag assay).

In comparison with myricetin-3-O-rhamnoside,

quercetin significantly reduced the synthesis of HBsAg and HB Ag by around 60 and 62%, respectively. Their capacity to bind with viral Pol/RT and core as well as host NTCP proteins predicted their likely anti-HBV mode of action (33, 34). Additionally, the IFN-dependent JAK/STAT signal pathway was stimulated by the polysaccharide from Radix satirist HBV inhibitory properties, and HBV-specific protein expression was also started (33, 34). Swertisin, a compound derived from Iris tectorum, has a significant inhibitory impact on HBV replication by lowering HBeAg, HBsAg, and HBV DNA (33, 34).

Hepatitis C virus (HCV)

The sterol regulatory element's ability to bind to protein-1 and its detrimental effects on Hepatitis C virus entry may be restricted by curcumin, which has been demonstrated to be a key inhibitor of HCV replication. Epigallocatechin-3-gallate, griffithsin, laden, and tellimagrandin I am just a few examples of natural compounds that prevent HCV entrance (1, 2, 20). Chebulagic acid and punicalagin hydrolyzable tannins were also discovered to be competitive inhibitors of Hepatitis C virus uptake. Both tannins render free virus particles inactive, prevent viral penetration and attachment to the host cell, and stop the post-infection spread of the Hepatitis C virus from cell to cell. Since there is no vaccine against the hepatitis C virus, finding new anti-HCV entry inhibitors could aid in creating a preventative hepatitis C therapy or drug. HCV is rendered inactive by collide, which is a derivative of Phyllanthus urinaria, and it prevents viral attachment, entrance, and fusion (7, 19). Using Huh7it cells, Ficus fistulosa leaves extract and fractions inhibited HCV JFH1a with an IC50 value of 20.43 4.51 g/ml (8, 14). The dichloromethane extract of Artocarpus heterophyllus demonstrated potent anti-HCV activity using Huh7it-1 cells and an inhibitory concentration (IC50) of (1.5 0.6) g/ml. A. vivirucidalssaults host cells and HCV RNA replication by directly targeting them. Heterophyllus prevented the viral entrance process. Treatment with a higher concentration significantly reduced the expression of the HCV protein. According to studies on the antiviral activities of methanol extracts of Ajuga bracteosa, Ajuga parviflora, Berberis lyceum, and Citrus lemon on HCV-infected HepG2 cells, Araeococcus parviflorus demonstrated the greatest degree of antiviral activity, followed by Agave bracteosa. These can be used to treat HCV infections instead of or along with other medications, according to the research. Two fractions, "N1" and "N8," produced from the acetone extract of Nymphaea alba decreased the expression of the Hepatitis C virus NS3 gene in transfected Huh-7 cells with EC50 values of 37 0.03 and 20 0.02 g/ml, respectively. Furthermore, the fractions and the conventional antiviral medication combined demonstrated stimulatory efficacy to reduce HCV replication. A promising source regimen against HCV may be provided by N. alba and its isolated compounds, either on their alone or in combination with other potential anti-HCVentities (2, 5, 34).

HIV/AIDS and Medicinal Plants

An extensive list of herbal remedies for HIV infection was looked at (6). As prospective HIV therapies; however, marine materials with anti-HIV activity have been reported (17, 24). A group of plant proteins referred to as "pokeweed antiviral protein" are found in large quantities in the plant phytolacca americana (PAP). Three isoforms, notably PAP-I from spring leaves, PAP-II from early summer leaves, and PAP-III from late summer leaves were discovered to belong to a group of RIPs that depurination the genomic RNA of HIV-1.

The anti-HIV proteins MAP30 and GAP31 found in Momordica charantia and Gelonium multiflorum are regarded as useful sources in a manner comparable to that of RIPs, which are well known for their anti-HIV effectiveness. The anti-HIV protein PAP29, which has a prophylactic anti-HIV potential, is also present in P. Americana leaves. The big rRNAs' normally conserved -sarcin loop is purified by the hazardous N-glycosidases known as RIPs. Depuration thus renders the ribosome inoperable and obstructs its continued participation in protein synthesis. Numerous investigations have demonstrated that the enzymatic activity of RIP includes not only site-specific activity on ribosomal rRNAs but also the purification and nucleic acid scission of other substrates (6).

It was demonstrated in an acute in vitro experiment that the RIP trichostatin, which is derived from the roots of Trichosanthes kirilowiiis, reduced the number of antigens in HIV-positive cells, but it was ineffective in chronic infections. By having a considerable contact with gp120, cyanovirin-N, which was generated from

sea algae, prevented the spread of HIV and its capacity to merge with other cells. Some sulfated polysaccharide groups derived from seaweeds have anti-HIV impacts because they can inhibit viral adsorption. By inhibiting HIV-induced cytopathogenic ty in human MT-4 cells, P. niruri alkaloid extracts have demonstrated a suppressive action on HIV. Furthermore, HIV was inhibited by Calophyllum species that contained coumarin. Likewise, potential anti-HIV effectiveness was seen in the crude extracts of Artemisia afra and A. annua (18, 25, 27). Regarding this, tricyclic coumarin found in the stem bark of Calophyllum brasiliense inhibited HIV replication in vitro models by suppressing the activation of nuclear factor-kappa B (NF-B). The root extract of Pelargonium sidoides demonstrated potent anti-HIV1 action by preventing peripheral blood mononuclear cells and macrophages from contracting various X4 and R5 tropic HIV-1 strains. It is recognized as a novel herbal medicine for anti-HIV-1 therapy because of its distinct action mechanisms and compatibility with currently available single-molecule drugs (14, 24, 34).

In vitro clinical HIV-1 and HIV-2 isolates were also inhibited by Cistus incanus, and no resistant viruses appeared during the length of 24 weeks of uninterrupted virus multiplication in the presence of C. watery incanus extract (16). Because of their high amounts of phenolics, terpenes, saponins, and flavonoid components, methanol extracts of Euphorbia spiders Bornm (Euphorbiaceae) exhibit significant antioxidant action. By inhibiting the virus from reproducing, they also have a significant antiviral impact on HSV-1 (14, 20, 26). Patentiflorin A, an isolated chemical from Justicia gendarussa, displays remarkable activity against a number of HIV strains with IC50 values ranging from 15 to 21 nM. (19, 20). A wide variety of other medicinal herbs, including Withania somnifera, Tinospora cordifolia, Moringa oleifera, Hypericum perforatum, Silybum marianum, Panax ginseng, Hypoxis hemerocallidea, Sutherlandia frutescens, Lobostemon trigonous, and Curcuma longa, have also been used to diagnose and treat AIDS (2, 6, 8, 20). In contrast, the anti-HIV1 activity of four novel lignans from Justicia procumbent aerial portions was investigated. A significant amount of anti-HIV1 activity was demonstrated by one of the novel secoisolariciresinol dimethyl ether acetates, with an in vitro IC50 of 5.27 M. Rapid advancements in the discovery of natural antivirals against HIV must result in new treatment regimens that would be central to the battle against the current immediateness of anti-HIV/AIDS therapies based on scientific developments to date (2, 10, 17).

Rabies and Medicinal Plants

The findings indicated that a total of 199 plant species from 47 families were employed for the control of rabies. The families Euphorbiaceae, Phytolaccaceae, Cucurbitaceae, Acanthaceae, Fabaceae, and Solanaceae were the most often used cases. Phytolacadodecandra, Justicaschimperiana, Recinuscommunis, Brucea antidysenterica, Croton macrostachyus, and Cucumis frivolous were the most often mentioned medicinal plant species used for the management of rabies. Roots and leaves were the two plant parts that were utilized for cure preparations, the most frequently with water being the most frequently stated solvent (Table 3). (1, 2, 8, 14, 18).

Influenza Virus and Medicinal Plants

The negative effects of many natural compounds on influenza have been investigated. Influenza restriction by the root extract of Pelargonium sides influenza-infected mice perform better, and viral hemagglutination and neuraminidase function are affected by the entrance of A. (26). Influenza is prevented by Taraxacum officinale aqueous extract. An infection decreases polymerase activity and nucleoprotein (NP) RNA levels (26). Moreover, it has been shown that several plant secondary metabolites, including homoisoflavonoids from Caesalpinia sappan, chalcones from Glycyrrhiza inflata, xanthones from Polygala magnesium, and spirooliganone B from the roots of Illicium oligandrum may act as NA influenza inhibitors. The IAV-induced pro-inflammatory response was prevented by lariciresinol4-O-D-glucopyranoside, which was isolated from the root of Isatis indigotica (1, 31). Pharmacological effects on the immune system, signal transduction, cell cycle, and metabolism are the source of the underlying coping mechanism against IAV infection (15). Substantial studies on the Sambucus nigras' anti-flu effects have been conducted (1, 8). Studies have demonstrated S. nigra's effectiveness against viral diseases, which may

Table 3: Plant species reported for the management of rabies

scientific name	Part(s) used	Method of preparation	Route of administration	Treatment for	References
Daturastramonium L.	Leafs	Crushed and homogenized leaves drunk with water	Oral	Human	[1,13,14]
Justitia schimperana (Hochst. ex Nees) T. anders	Buds, Roots, Leafs	Roots and leaves are pounded together and mixed with water and Salix mucronata leaf and given orally for human and animals in the morning before food	Oral	Human, Animals	[1,13,27]
Cucumisfcifolius	Roots	Powder of roots eaten with 'Teffkita/ Crushed fresh root with water fermented for 3 days is taken with honey early morning before breakfast orally until cure	Oral	Human, Animals	[1,18,27]
Dorsteniabarnimiana	Roots	Powder of roots taken with skimmed milk or noug orally in the morning for seven days	Oral	Human	[1,30,31]
Gnidiaglauca	Roots	Powder of roots mixed with skimmed milk and taken orally for seven days	Oral	Human	[1,30]
Phytolaccadodecandra	Roots, Leafs	Powder of roots or leaves mixed with water or domestic alcohol and given orally to humans and animals	Oral	Human, Animals	[1,16,18]
Salix subserrata	Leafs	Leaves from the tree given orally Leaves are pounded and dried, and then mixed with milk	Oral	Human	[1,19,34]
Croton macrostachyus Del.	Roots, Barks, Leafs	Pound the fresh root, add water and flter then administered orally for 3 days (dog) and 7 days (other animals) and apply topically; The Bark of Croton macrostachyus is dried, powdered and mixed with water one coffee cup is given for human and 1 bottle is given to castles and 6 bottles is given to camel once a day for 3	Oral	Human, Animals	[15,16,28]

Silenemacroselen	Roots	Root from herbs given orally	Oral	Human	[1,12]
Bruceaantidysentric a	Fruit, Leafs, Roots	Squeezed and baked with teff flour andgiven for 3 days [together with Croton macrostachyus and Rumexnervosus].	Oral	Human, Animals	[16,18,20]
Euphorbia abyssinica J. F. Gmel	Root, Latex, Leafs	One spoon root powder mixed with a cup of fresh milk. Give for dog or Powder of roots or leaves mixed with water and taken orally	Oral	Human, Animals	[1,17,24,3]
Ricinus- communis	Leaf, roots	Fresh leaves crushed and mixed with water and taken one cup of tea for 3 consecutive days	Oral	Human	[15,18-20]

result from immune system stimulation. S. nigra's polyphenols, flavonoids, and immune-modulating peptic polysaccharides are what prevent viruses from spreading. Numerous cultures have recorded the berries and blossoms of this shrub. Sambucus nigra fruit syrup (black elder) was administered, along with a placebo, either 1 tablespoon twice daily for children or 2 tablespoons twice daily for adults. The black elder group's symptoms were noticeably milder and lasted for a mean of 1.3 days less than in the placebo group. A comparable double-blind trial with 60 adult Norwegians with influenza A or B was carried out. Once more, black elders dramatically reduced the intensity of the symptoms compared to the placebo, and in this instance, black elders also sped up recovery by an average of 4 days. Comparing the black elder group to the placebo, we noticed that the utilization of rescue medication was also noticeably lower. In neither of these trials, there were any negative outcomes.

Discussion

Virus-based illnesses that keep resurfacing and evolving continue to be a concern to us. Over the past few decades, several viruses, including the Ebola virus, SARS and MERS coronaviruses, avian influenza viruses, enteroviruses, as well as vector-borne viruses like chikungunya, Zika, and dengue, to mention a few, have all produced extensive epidemics in various regions of the world posing a serious socioeconomic burden. There are no therapeutically effective antivirals or vaccines for many of these recently discovered and rediscovered viruses. Other strategies must be created as the treatment of emerging and reemerging infections has mostly been relegated to supportive therapies to find novel antiviral drugs against virus infections (2, 14, 31, 32). Traditional herbal therapy focuses on using herbal plants and plant extracts to treat a variety of diseases. Many contemporary medications were first derived from plant sources, even though they are now produced synthetically. Over 5700 traditional Chinese medicines have been listed in the Chinese Pharmacopoeia, the majority of which are derived from plants. In Ayurveda, approximately 2000 plant species are thought to have therapeutic uses. Many of the numerous plant species that are found all over the world are used medicinally because they contain active ingredients that have positive effects on humans directly. For instance, flavonoids have a variety of effects and numerous medical uses. Some flavonoids also have anti-inflammatory and antiviral properties, including quercetin, which blocks the growth of the herpes simplex virus type 1 and the poliovirus type 1, and baicalein as well as quercetagetin, which has been

proven to prevent chikungunya infection (10, 11, 19, 25, 27).

Numerous medicinal properties are shared by plant metabolites. They may have a synergistic impact, leading to better treatment results. The key elements that influence a molecule originating from plants' ability to be absorbed, distributed, metabolized, and eliminated are its pharmacokinetic ADME (absorption, distribution, metabolism, and elimination) parameters. We have outlined the 46 antiviral medicinal plants from 25 families that are cultivated and have origins around the world in this review. Medicinal plants are mainly tested for their ability to fight viruses in vitro and/or in vivo. Additionally, not all of these plants have profiles of their bioactive phytochemicals.

Seventy-nine different compounds with antiviral properties have been identified based on the information that is currently known about these plants. About 37 bioactive substances have substantial antiviral activity and a molecular explanation among them. These substances have shown possible inhibitory effects on the SARS-CoV-2, HIV, HBV, HCV, HSV, DENV, influenza, and other viruses. Multiple viruses were resistant to the effects of EGCG, oleanolic acid, hesperidin, quercetin, curcumin, kaempferol, and andrographolide (1, 2, 5, 10, 20).

Conclusion

In both people and animals, viral infections are significant factors in the development of certain diseases. Despite the extensive use of vaccinations and antiviral medications, viral escape mutants have led to the existence of numerous viruses lacking effective antiviral therapy. The primary strategies for assisting healthcare systems are natural goods and their bioactivity. It has also been demonstrated that a few volatile essential oils from common plants and herbal teas have strong antiviral activity against viral infections. Novel antiviral substances may be used to treat viral infections. Retroviridae and picornaviridae are next in line to experience inhibitory effects from plants, followed by herpesviral and Flaviviridae. Effective antiviral medications are created with the aid of bioactive ingredient exploration and characterization, research into antiviral mechanisms, analysis of inhibitory effects in vivo, and assessment of bioactive ingredient effects. Examining the possibility of using natural plants in combination therapy may help lower the danger of viral medication resistance. However, more in-depth research is still required to determine its safety and drug interaction potential. Even though medicinal plants are significant sources of antiviral medications for infections in both humans and animals, conducting further studies on the bioactive components of medicinal plants remains a top global goal. Many experiments have been carried out to increase the antiviral activity and water solubility of plant extracts. Studies on natural medicines paired with chemical antiviral therapeutics as a multitarget therapy for decreasing viral escape mutations are welcomed, as are investigations of the effectiveness of plant extracts in vivo. The design and execution of thorough trials are suggested to confirm the efficacy of these active plant species and bioactive secondary metabolites, either alone or in conjunction with currently available conventional medicines. The antiviral properties of plants have disrupted a variety of viral targets, including the attachment of the virus to the host cell and the suppression of enzymes (such as reverse transcriptase and protease) that release the virus from the cells. It is widely acknowledged that bioactive natural chemicals can be used as starting points for the synthesis of brand-new, more potent antiviral components. Natural substances originating from plants continue to be a source for the development of new pharmaceuticals, including antiviral drugs.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Khan T, Khan MA, Ullah N, Nadhman A. Therapeutic potential of medicinal plants against COVID-19: The role of antiviral medicinal metabolites. Biocatalysis and agricultural biotechnology. 2021;31:101890.

2. Hudson JB. The use of herbal extracts in the control of influenza.

J Med Plants Res. 2009;3(13):1189-95.
3. Ohashi H, Watashi K, Saso W, Shionoya K, Iwanami S, Hirokawa T, et al. Multidrug treatment with nelfinavir and cepharanthine against COVID-19. BioRxiv. 2020:2020.04. 14.039925.
4. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. nature. 2020;579(7798):270-3.
5. Rogosnitzky M, Danks R. Therapeutic potential of the biscoclaurine alkaloid, cepharanthine, for a range of clinical conditions. Pharmacological reports. 2011;63(2):337-47.
6. Ben-Shabat S, Yarmolinsky L, Porat D, Dahan A. Antiviral effect of phytochemicals from medicinal plants: Applications and drug delivery strategies. Drug delivery and translational research. 2020;10:354-67.
7. Kurokawa M, Shimizu T, Watanabe W, Shiraki K. Development of new antiviral agents from natural products. The Open Antimicrobial Agents Journal. 2010;2(1).
8. OKAMOTO M, ONO M, BABA M. Potent inhibition of HIV type 1 replication by an antiinflammatory alkaloid, cepharanthine, in chronically infected monocytic cells. AIDS research and human retroviruses. 1998;14(14):1239-45.
9. Boukhatem MN, Setzer WN. Aromatic herbs, medicinal plant-derived essential oils, and phytochemical extracts as potential therapies for coronaviruses: future perspectives. Plants. 2020;9(6):800.
10. Zhang C-h, Wang Y-f, Liu X-j, Lu J-H, Qian C-w, Wan Z-y, et al. Antiviral activity of cepharanthine against severe acute respiratory syndrome coronavirus in vitro. Chinese medical journal. 2005;118(06):493-6.
11. Aanouz I, Belhassan A, El-Khatabi K, Lakhlifi T, El-Ldrissi M, Bouachrine M. Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. Journal of Biomolecular Structure and Dynamics. 2021;39(8):2971-9.
12. Abu-Jafar A, Huleihel M. Antiviral activity of Eucalyptus camaldulensis leaves ethanolic extract on herpes viruses infection. Int J Clin Virol. 2017;1:1-9.
13. Akram M, Tahir IM, Shah SMA, Mahmood Z, Altaf A, Ahmad K, et al. Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: A systematic review. Phytotherapy Research. 2018;32(5):811-22.
14. Alfajaro MM, Rho M-C, Kim H-J, Park J-G, Kim D-S, Hosmillo M, et al. Anti-rotavirus effects by combination therapy of stevioside and Sophora flavescens extract. Research in veterinary science. 2014;96(3):567-75.
15. Andersson S. General polyhedra, virus structure and mutation. Zeitschrift für Kristallographie. 2010;225(8):309-12.
16. Black IV WC, Bennett KE, Gorrochótegui-Escalante N, Barillas-Mury CV, Fernández-Salas I, de Lourdes Muñoz Ma, et al. Flavivirus susceptibility in Aedes aegypti. Archives of medical research. 2002;33(4):379-88.
17. Ali SI, Sheikh WM, Rather MA, Venkatesalu V, Muzamil Bashir S, Nabi SU. Medicinal plants: Treasure for antiviral drug discovery. Phytotherapy Research. 2021;35(7):3447-83.
18. Bösl K, Ianevski A, Than TT, Andersen PI, Kuivanen S, Teppor M, et al. Common nodes of virus–host interaction revealed through an integrated network analysis. Frontiers in immunology. 2019;10:2186.
19. Chiu Y-H, Chan Y-L, Tsai L-W, Li T-L, Wu C-J. Prevention of human enterovirus 71 infection by kappa carrageenan. Antiviral research. 2012;95(2):128-34.
20. Wang X, Jia W, Zhao A, Wang X. Anti-influenza agents from plants and traditional Chinese medicine. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2006;20(5):335-41.
21. Rukachaisirikul V, Pailee P, Hiranrat A, Tuchinda P, Yoosook C, Kasisit J, et al. Anti-HIV-1 protostane triterpenes and digeranylbenzophenone from trunk bark and stems of Garcinia speciosa. Planta medica. 2003;69(12):1141-6.
22. Hussein G, Miyashiro H, Nakamura N, Hattori M, Kakiuchi N, Shimotohno K. Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2000;14(7):510-6.
23. Mao Y-M, Zeng M-D, Lu L-G, Wan M-B, Li C-Z, Chen C-W, et al. Capsule oxymatrine in treatment of hepatic fibrosis due to chronic viral hepatitis: a randomized, double blind, placebo-controlled, multicenter clinical study. World Journal of Gastroenterology: WJG. 2004;10(22):3269.
24. Dao TT, Dang TT, Nguyen PH, Kim E, Thuong PT, Oh WK. Xanthones from Polygala karensium inhibit neuraminidases from influenza A viruses. Bioorganic & medicinal chemistry letters. 2012;22(11):3688-92.
25. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clinical microbiology reviews. 2000;13(3):371-84.
26. Hardy ME, Hendricks JM, Paulson JM, Faunce NR. 18 β-glycyrrhetinic acid inhibits rotavirus replication in culture. Virology Journal. 2012;9(1):1-7.
27. Gandhi GR, Barreto PG, dos Santos Lima B, Quintans JdSS, de Souza Araujo AA, Narain N, et al. Medicinal plants and natural molecules with in vitro and in vivo activity against rotavirus: a systematic review. Phytomedicine. 2016;23(14):1830-42.
28. Henderson FW, Collier AM, Clyde Jr WA, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity: a prospective, longitudinal study in young children. New England Journal of Medicine. 1979;300(10):530-4.
29. Lu L-G, Zeng M-D, Mao Y-M, Fang J-Y, Song Y-L, Shen Z-H, et al. Inhibitory effect of oxymatrine on serum hepatitis B virus DNA in HBV transgenic mice. World Journal of Gastroenterology. 2004;10(8):1176.
30. Fuse T, Watanabe K, Kitazato K, Kobayashi N. Establishment of a new cell line inducibly expressing HIV-1 protease for performing safe and highly sensitive screening of HIV protease inhibitors. Microbes and infection. 2006;8(7):1783-9.
31. Van Rossum T, Vulto A, De Man R, Brouwer J, Schalm S. glycyrrhizin as a potential treatment for chronic hepatitis C. Alimentary pharmacology & therapeutics. 1998;12(3):199-205.
32. Patrick L. Hepatitis C: epidemiology and review of complementary/alternative medicine treatments. Alternative medicine review: a journal of clinical therapeutic. 1999;4(4):220-38.
33. Rajbhandari M, Wegner U, Jülich M, Schoepke T, Mentel R. Screening of Nepalese medicinal plants for antiviral activity. Journal

of ethnopharmacology. 2001;74(3):251-5.
34. Nagai T, Miyaichi Y, Tomimori T, Suzuki Y, Yamada H. In vivo anti-influenza virus activity of plant flavonoids possessing inhibitory activity for influenza virus sialidase. Antiviral research. 1992;19(3):207-17.
35. Vijayan P, Raghu C, Ashok G, Dhanaraj S, Suresh B. Antiviral activity of medicinal plants of Nilgiris. Indian Journal of medical research. 2004;120:24-9.