REVIEW ARTICLE

Medicinal Plants Cultivated in Egypt with Antiviral Potential: A Systematic Review

Abdallah M. Elkhouly, BM; Maram Y. Baldam, BM; Shaimaa Al-Touny, BM; Amany S. Almeanawy, BSc; Mohamed N. Abohalawa, BM; Mahmoud Hamed, MSc; Fotouh R. Mansour, PhD

ABSTRACT

Background • Viral diseases are a worldwide concern as some of them are associated with unexpectedly high mortality rates. Common viruses include e.g., Influenza virus, HIV, hepatitis viruses, and recently COVID-19. Many viral diseases are still incurable by conventional antiviral drugs. Moreover, the emergence of resistant viral strains has reinforced the search for other alternatives. In ancient times, herbal therapy was commonly used where medicinal formulations were created from various plants. In recent times, *in vitro*, *in vivo*, animal studies, and clinical trials have revealed the antiviral properties of these plants, sparking hope for the treatment of serious viral diseases. The present review aims to summarize studies that focus on medicinal plants available in Egypt with antiviral properties.

Methods • The articles published in English between 1988 and 2022 and available in PubMed and Scopus databases with the relevant keywords were included.

Results • Thirty-two plants in Egypt have met the criteria and possess *in vitro* or *in vivo* antiviral activity via different mechanisms. Only five of them; *Camellia sinensis, Marine algae, Zizyphus spina-christi L., Trachyspermum Ammi*, and *Aloe Vera* have been proven to be effective *in vivo*. For COVID-19, thirteen plants have shown efficacy against SARS-Cov-2 via different mechanisms including *Camellia sinensis, Cinnamomum Verum, Punica granatum, Glycyrrhiza glabra, Zingiber officinale, Curcuma longa, Marine algae, Phlomis aurea oil, Solanum nigrum, Trachyspermum Ammi, Arum palaestinum, Aloe Vera,* and *Cyperus rotundus*.

Conclusion • This review summarizes the current scientific evidence on 32 medicinal plant species cultivated in Egypt that have demonstrated antiviral properties against various DNA and RNA viruses through *in vitro* and *in vivo* studies, highlighting their potential as prospective sources for the development of novel antiviral therapies. Further clinical research is still warranted to validate the effectiveness and safety of these plants as complementary treatment options for viral infections. (*Altern Ther Health Med.* 2024;30(8):43-51).

Abdallah M. Elkhouly, BM; Maram Y. Baldam, BM; Mohamed N. Abohalawa, BM; Amany S. Almeanawy, BM; Tanta Students' Research Academy (TSRA), Faculty of Medicine, Tanta University, Tanta, Egypt. **Shimaa A. Al-Touny, MD,** Anesthesiology & Critical Care, Faculty of Medicine, Suez Canal University. **Mahmoud Hamed, MSc,** Pharmaceutical Chemistry Department, Faculty of Pharmacy, Misr International University, Cairo, Egypt. **Fotouh R. Mansour, PhD,** Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Tanta University, Tanta, Egypt.

Corresponding author: Fotouh R. Mansour, PhD
E-mail: fotouhrashed@pharm.tanta.edu.eg

BACKGROUND

Viral infections can vary from self-limited or mild infections to viral epidemics that can disrupt our lives and societies. New viral diseases continue to emerge e.g., SARS-CoV-2 virus, Ebola virus, Hantavirus, etc.[1] These existing, emerging, and re-emerging viral diseases are an ever-growing problem, especially in developing countries.[2] Unfortunately, viral diseases are a worldwide concern as they are associated with higher mortality rates. Antiviral drugs usually target major steps of the viral life cycle e.g., attachment, penetration, replication, and release, and they are continuously being developed for clinical applications.[3,4] Despite research and clinical trials, effective treatments for many viral diseases are not available.[5] Many viruses remain without successful immunization and only a few antiviral drugs have been approved for clinical use. Hence, the development of novel antiviral drugs is very significant, and natural products are excellent sources for such drug developments.[6]

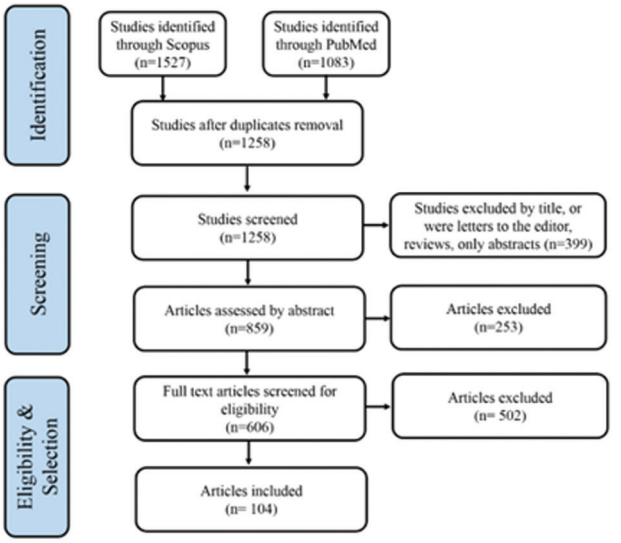
The plant kingdom offers many phytochemicals that have a vast number of medicinally active compounds. Many of them have been studied for their potential antiviral activity against different DNA and RNA viruses.[5] These herbal medicines and refined natural products are promising for the

development of novel antiviral drugs.[6] Historically, ancient Egyptians had a great knowledge of different medical fields and had a huge diversity of sources as plants, animals, and minerals for the treatment of different diseases.[7] This review aims to summarize the literature on Egyptian medicinal plants with antiviral bioactive compounds, their antiviral mechanisms, and effective extracts against each target virus.

METHODS

The literature review was conducted by six co-authors who independently searched two scholarly databases- Scopus and PubMed. The search process was limited to peer-reviewed articles in English. To ensure a comprehensive search, the authors used three keywords as search terms: "Plants", "Egypt", and "Antiviral" in combination with the "AND" operator in Scopus, while mesh search was employed in PubMed. The search was conducted within the article title, abstract, and keywords. The authors filtered the studies based on their titles and abstracts, removing papers that were abstract only, reviews, duplicated, not applicable in phytotherapy of cancer, or unrelated. Additionally, the authors manually searched the references of some research to identify relevant studies for further screening. Ultimately, 104 studies were included in the review. The PRISMA of the systematic review is presented in Figure 1.

Figure 1. A Flow Chart Showing the Selection Process of Studies Included in the Review, According to the PRISMA Guidelines

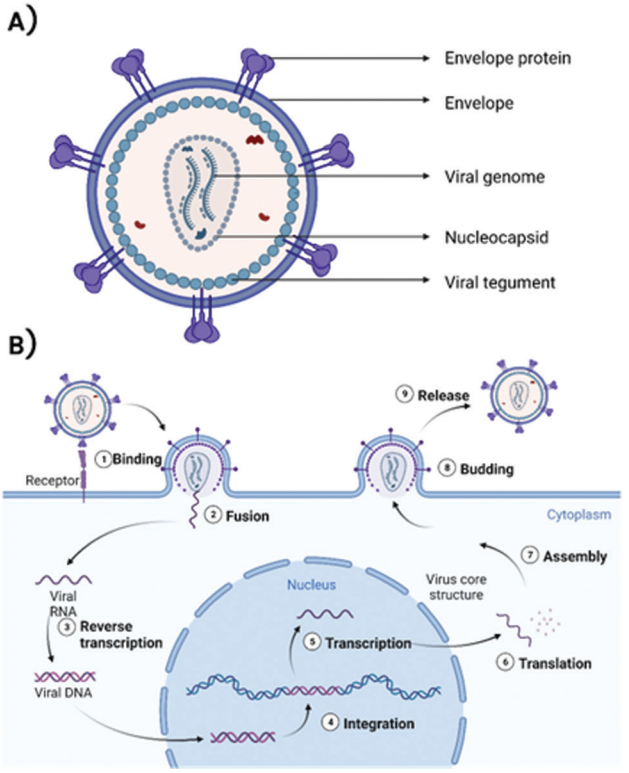


MECHANISMS OF POTENTIAL ANTIVIRAL ACTIVITIES OF HERBAL MEDICINE

The virus particle has nucleic acid genome either dsDNA, ssDNA, dsRNA, or ssRNA. To protect the nucleic acid, the virus surrounds its nucleic acid with a protein shell, called the capsid. Together, the nucleic acid and the capsid form the nucleocapsid of the virion. Most viruses also have an envelope surrounding the capsid which is a lipid membrane as illustrated in Figure 2A.[8] Viruses rely on the host cell's machinery to reproduce, amplify, and be released from the cell. [9]

Antiviral activities depend mainly on two different approaches: targeting the viruses themselves or the host cell factors. Antiviral agents that directly target the viruses include the inhibitors of virus attachment, inhibitors of virus entry, uncoating inhibitors, polymerase inhibitors, protease inhibitors, inhibitors of nucleoside and nucleotide reverse transcriptase, and inhibitors of integrase as illustrated in Figure 2B. Other antiviral agents can increase the cell's resistance to a virus, suppress the virus adsorption in the cell or its diffusion into the cell, and its deproteinization process in the cell along with anti-metabolites that cause the inhibition of nucleic acid synthesis.[9,10]

Figure 2. (A) Basic Structure of a Virus and (B) Antiviral Agents Targeting the Viruses During Different Phases of Viral Invasion



ssRNA VIRUSES

Positive strand ssRNA viruses

Coronaviridae. SARS-CoV-2, a member of the coronavirus family, is responsible for causing coronavirus disease 19 (COVID-19), a respiratory illness affecting both humans and animals. In infected humans, the resulting respiratory symptoms can range from mild to moderate,

Table 1. Egyptian Medicinal Plants with Antiviral Properties

Scientific Name	Important Compound	Mechanism	Virus name & culture	Target protein	References
Camellia sinensis	EGCG: Epigallo Catchin -3-Gallate, Theaflavin (TF1), theaflavin-3-monogallate (TF2A), theaflavin-3'-monogallate (TF2B), and theaflavin-3,3'-digallate (TF3)	- Inhibiting spike binding to ACE2 receptor. EGCG also reduced the replication of SARS-CoV-2 - Inhibition of the main protease (3CLpro) of HHV-3 virus - Inactivation of virions by forming complexes with viral glycoproteins B and D of HSV-2 virus - Decreasing the secretion of HBsAg and HBeAg and extracellular HBV DNA *in vitro*, and this may interfere with the replication cycle of HBV DNA	**SARS-CoV-2** (BALB/c mice *in vivo*, canine kidney cells *in vitro*, Cercopithecus aethiops derived epithelial kidney cells, and Vero or Green monkey kidney cells) **Influenza A virus (IAV), adenovirus Type 5,** and **HSV-2** (Vero or Green monkey kidney cells) **HSV-1 virus** (Green monkey kidney cell and human lung adenocarcinoma epithelial cells (A549)) **Hepatitis B virus** (HepG2 2.2.15 cell line)	The main protease (3CLpro) of SARS-CoV-2 Glycoproteins B and D of HSV-1 virus	11–15
Cinnamomum Verum	Procyanidin B1	- Directly inactivating free-virus particles and might interfere with virion envelope structures required for entry into host cells - Interaction with the CX3C chemokine motif on the CCD of RSV G protein and blocked attachment to cellular CX3CR1. These *in vitro* results were confirmed by *in vivo* analysis, that oral administration of maoto to mice infected with RSV showed antiviral and anti-inflammatory effects in lung - Through its anti-obstructive, diuretic, and tonic effects in SARS-CoV-2	**H1N1 virus** (MDCK cells) **HSV1 virus** (Vero cells) **Respiratory syncytial virus (RS8V)** (A549 cell line derived from human lung cancer) **SARS-CoV-2, HCV** (Human hepatocarcinoma Huh-7 cells)	CX3C chemokine motif on the CCD of RSV G protein Spro, hACE2, (SARS-CoV-2 M pro) HCV serine protease or RNA-dependent RNA polymerase.	16–19
Punica granatum	α-punicalagin, β-punicalagin, ellagic acid, and gallic acid.	- Interaction with the protease enzyme & interference with the capsid assembly of the HHV-3 - Inhibition of ADV replication in the post-adsorption phase - Interaction with the catalytic and substrate binding residues of NS3/4A protease and reducing the HCV replication - Inhibition of the interaction between Spike and ACE2 and reducing the activity of the viral 3CL protease of the SARS-CoV-2 virus - Inhibition of viral mRNA expression and viral RNA synthesis of Influenza virus	**HHV-3** **Mayaro virus (MAYV), HCV, Respiratory syncytial virus** (Vero cells in (DMEM) **Adenoviruses** (Hep-2 cells) **HCV** (Huh7 cell line) **SARS-CoV-2** (Human kidney-2 cells, HK-2) **Influenza vir**us (MDCK cell line)	Protease of HHV-3. HCV NS3/4A protease. Human angiotensin-converting enzyme 2 receptor, and 3CL protease of SARS-CoV-2	20–25
Glycyrrhiza glabra	Triterpene glycoside glycyrrhizic acid (glycyrrhizin), its aglycone 18-beta-glycyrrhetinic acid, dehydroglyasperin C, licochalcone D, liquiritin, and licorice	- Inhibition of SARS-CoV-2 viral adsorption and penetration - Directly inactivation of HSV-1 or anti-adhesive property of *G. glabra* aqueous extract - Blocking viral replication of enterovirus 71 and coxsackievirus A16 - Inhibition of viral penetration, uncoating, mRNA translation, protein synthesis, genome replication, virus assembly, and releasing of HRSV.	**SARS-CoV-2** **Herpes Simplex Virus (HSV-1), Enterovirus 71 (EV71)** and **Coxsackievirus A16 (CVA16)** (Vero cells) **Human respiratory syncytial virus (HRSV**) Human airway mucosal cell lines, HEp-2 cells, and A549 cells)	The main protease (Mpro), the spike protein (S protein), and the (ACE2) of SARS-CoV-2	26–30
Ocimum basilicum	Ursolic acid, apigenin, and linalol	- Inhibition of multiplication of both HSV types, three viral types of ADV (ADV-3, ADV-8, and ADV-11), two enteroviruses (EV71 and CVB1), and HBV.	**Herpes viruses (HSV), adenoviruses (ADV), hepatitis B virus, coxsackievirus B1 (CVB1),** and **enterovirus 71 (EV71)** (The human skin basal cell carcinoma cell line (BCC-1/KMC))	not reported	31
Zingiber officinale	6-gingerol, 3-decanone, and Xanthorrhizol (AgNPs)	- Inhibition of the viral replication inside the HCV-infected HepG2 cells - Interference with viral replication of CHIKV through various mechanisms, inactivating extracellular viral particles, or by penetrating virions and destroying the viral genome - CoV replication inhibitory mechanism	**HCV** (HepG2 cell line) **Chikungunya virus (CHIKV)** (Vero cell line and HepG2 cell line) **SARS-CoV-1, SARS-CoV-2** (Vero E6 cell line, Calu-3 cell line, HEK293 cell line, HEK293T cell line, MRC-5 cell line, and murine macrophage cell line RAW264.7)	Mpro, ADP ribose phosphatase, NSP14, NSP16, and PLpro of SARS-CoV-2 Viral RNA polymerase (Nsp12), RNA helicase (Nsp13), or the 3CL main protease (Nsp5) of SARS-CoV-1 and SARS-CoV-2	32–36
Curcuma longa	Curcumin, MTT, cycloheximide, and anti-β-actin.	- Mechanism against HIV-1 and HIV-2: 1) Inhibition of the HIV-1 LTR1 directed gene expression without any major effects on cell viability 2) Inhibition of HIV-1 and HIV-2 protease 3) Curcumin inhibited the acetylation of Tat protein of HIV associated with suppression of HIV-1 multiplication 4) The curcumin boron complexes exhibited noteworthy inhibition - Inhibition of SARS-CoV-2 binding to host receptors, impairment of envelope integrity, leading to the disruption of the viral particles and the release of RNA. - Binding to viral particles as well as host cell membrane to inhibit JEV - Inhibition of pathogenic H5N1 influenza virus replication. - Inhibition of enzymatic reaction of APE1 redox through blocking APE1-mediated redox function and thus inhibiting KSHV replication and virus-associated pathogenic properties	**HIV-1** and **HIV-2** (Chang liver cell line) **SARS-CoV2** (Vero E6 cell line) **Japanese encephalitis virus (JEV)** (BHK-21 cell line) **Avian influenza H5N1** (MDCK cell line) **Kaposi's sarcoma-associated herpesvirus (KSH**V) (BCBL-1 cell line)	p53 protein of HIV-1 and HIV-2 SARS-CoV-2 spike protein and the ACE2 receptor E protein ū of Japanese encephalitis virus	37–42
Capsicum annuum	Polyphenols, flavonoids, gallic acid, and Saponins	- Antiradical scavenging mechanism against HSV-1 and HSV-2 - Inhibition of urease enzyme of H. pylori	**HSV-1** and **HSV-2** (Vero cells) ***H. pylori*** **SARS-CoV-2** (HEK293T cells)	Ureases enzyme of *H. pylori*	43–45
Marine algae	Sulfated polysaccharides, polysaccharide derivatives, polyphenols, carotenoids, tannins, tetradecanoic, oleic acid, alkaloid (caulerpin), and griffithsin	- Inhibition of the viral entry, attachment, spike-ACE2 complex formation, and viral genome replication in the host cell of SARS-CoV-2 - Inhibition of the reverse transcriptase enzyme by interference with the viral RNA binding to HIV-1 RT of HIV-1 - Interference with the binding process of HPV to the cell surface - Inhibit viral infectivity and replication of Chikungunya virus - Inhibition of Influenza H1N1 virus by increasing anti-HA1 antibodies and cytokines - Inhibiting HSV attachment to cells by direct interaction of polysaccharides with viral particles - Inhibition of the cellular binding of Dengue-virus (DENV- 1) - Inhibition of viral entry into host cells of particles pseudo-typed with the MERS-CoV spike protein - Inhibition of HMPV replication	**SARS-CoV-2** (HEK293 cell line) **HIV-1** (PBMCs cell line) **HPV** (HeLa cells) **Chikungunya virus** (Vero cells) **Influenza H1N1 virus** (MDCK cell line) **Herpes viruses (HSV-1, HSV-2), HHV-6** (RC-37 cells, Vero cells, mosquito C6/36 cell lines, and human T-lymphoblasts) **Dengue virus (DENV- 1)** (BHK-21 cells, Vero cells, and mosquito C6/36 cell line) **MERS-CoV** (Huh-7, MRC-5, and Vero-81 cells) **Human metapneumovirus (HMPV**) (LLC-MK2 cells)	Spike protein and main protease (3CL) enzyme of SARS-CoV-2 Reverse transcriptase enzyme and p24 of HIV-1 Viral capsid proteins of HPV HA1 subunit of Influenza H1N1 virus Virion particles of Herpes viruses Envelope glycoprotein (EGP) of Dengue virus Spike proteins of MERS-CoV Viral particles of HMPV	46–71
Phlomis aurea oil	Phytoligands, germacrene D, trans-β-farnesene, α-pinene, and limonene	- Inhibition of SARS-CoV-2 entry into the host cell by Spike-angiotensin-converting enzyme 2 complex inhibition - Inhibition of HSV-1 viral replication	**SARS-CoV-2** **Herpes simplex-1 (HSV-1)** (Vero cells)	Spike-angiotensin-converting enzyme 2 complex of SARS-CoV-2 ATP-binding site residues of HSV-1	72,73
Thallasodendron ciliatum (Red Sea grass)	Diglyceride ester and asebotin	Reduction of H5N1 virus titer by inhibition of the growth of the virus	**Avian influenza H5N1 virus** (MDCK cells)	not reported	74
Zizyphus spina-christi L. *Zizyphus jujuba*	Betulinic acid (BeA)	Inhibition of the proliferation of influenza A/PR/8 virus	**H1N1 influenza virus** (A549 cells and C57BL/6 mice cells)	not reported	75
Adansonia digitata African Baobab	Not reported	- Inhibition of reverse transcriptase and protease of HIV-1 - Virucidal (direct inactivation of virus particles)	**HIV-1** **Herpes simplex virus (HSV)** (Vero cells)	Reverse transcriptase and protease of HIV-1 Viral particles of HSV	76,77
Arum palaestinum	B-Sitosterol, Androstan-3-one, Phenobarbital, Maltose, α-Tocopherol, vitexin, isovitexin, isoorientin, chrysoeriol 7-Oneohesperidoside and chrysoeriol 7-O-(β-apiosyl)-β-glucopyranoside	Targeting 3CLpro and Nsp15 of SARS-CoV-2	**SARS-CoV-2** H5N1 virus (MDCK cells)	3CLpro and Nsp15 of SARS-CoV-2	78,79
Astragalus spinosus	astragaloside II	Not reported	**HIV**	Not reported	80
Asphodelus microcarpus leaves	lyophilized plant materials (not reported)	- Affection of the Ebola virus VP35 inhibition of the viral RNA (vRNA) induced IFN response	**Ebola virus** (A549 cells)	VP35 protein	81

Table 1. (continued)

Scientific Name	Important Compound	Mechanism	Virus name & culture	Target protein	References
Solanum nigrum	Solanocapsine, Spirostan-3-ol, N-methylsolasodine, Diosgenin, Solasodine, Epicatechin, and Epigallocatechin	- Inhibition of the main protease of SARS-Cov - Inhibition of NS3 protease of HCV	**SARS-Cov-2** and **MERS-CoV** (Huh-7 cell line) **HCV**	SARS-CoV-2 MPro, NSP9, NSP16, and NSP10 NS3 of HCV	82,83
Zygophyllum album L. ssp. Album	Triterpene glycosides, flavonoid glycosides, and triterpenoid saponin	- Inhibition of the viral DNA synthesis or by membrane-mediated mechanisms	**HSV-1** (Vero, ATCC CCL-81 cell lines)	Not reported	84,85
Lotus arabicus L and Lotus glaber Mill.	Dodecanoic acid, Lucenin 2, Hexadecanoic acid, and n-Hexadecanoic acid (Palmitic acid)	- Reduction in the yield of the virus after application of the plant extract.	**Coxsackie B virus** and **HAV** (Vero cell line)	CoxB4 of Coxsackie B virus	86
Centaurea aegyptiaca	Phenolic acids and their derivatives, flavonols, and flavones	Not reported	**Hepatitis A virus** (Vero cells)	Not reported	87
Callistemon viminalis and Schinus molle	1,8-Cineol, α-pinene, α-terpineol in *Callistemon Viminalis* α-phellandrene and elemol in Schinus molle	- Direct interaction with free virus particles	**Herpes simplex virus type-1 (HSV-1)** (RC-37 cells)	Free particles of the virus	88
Trachyspermum Ammi	Thymol oil (p-cymene, γ-terpinene, and thymol) + non-thymol compound (Paracymene, Gamma-terpinene, Alpha-pinene, Betapinene, α-terpinene, and Styrene)	- Inhibition of growth of JEV - Delaying the COVID-19 progression from mild to moderate and moderate to severe - Inhibition of SARS-CoV-2 TMPRSS2	**Japanese encephalitis virus**, **SARS-CoV-2,** and **HCV** (Vero cells)	SARS-CoV-2 TMPRSS2 HCV protease	89–93
Aloe Vera	Emodin and its analogs, aloin B, chrysophanol, two anthraquinones, (aloesaponarin-I and aloesaponarin-II) glycosides aloesin and aloeresin D	- Suppression of the replication of Influenza A virus (PR8) and reduced cell injury, increased in the expressions of PPARα, PPARγ, and AMPK and upregulate the phosphorylation and enzymatic activity of AMPK, antagonize the inflammatory pathways - Suppression of HBeAg synthesis - Inhibition of replication and transcription of the virus through high-content protease inhibitor (Mpro inhibitor)	**Influenza A virus (**MDCK and HepG2 derivative cell lines) **HBV** (HepG2.2.15) **HSV-2** (Vero cells) **HIV, herpes simplex, varicella zoster, adenovirus,** and **SARS-CoV-2**	The peroxisome proliferator-activated receptor (PPAR) α/γ of the Influenza A virus HBV pre-Core protein "e" (HBeAg) The main protease of SARS-CoV-2 (Mpro and 3CLpro)	94–101
Achillea fragrantissima	Phenolic compounds and flavonoids	- Inhibition of the cytopathogenic effect of the virus	**POLIO** (Vero cells) **Adenovirus type 7, rotavirus Wa strain,** and **Coxsackievirus B4 (**Hep-2, MA104 and BGM cell lines)	Not reported	102,103
Jasonia montana, Globularia Arabica, and *Tanacetum sinaicum*	3-methoxyflavones and its synthetic derivatives of *Jasonia montana* Iridoid glucosides of *Globularia Arabica*	- Inhibition of the cytopathogenic effect of the virus	POLIO (Vero cells)	Not reported	102
Moringa peregrine and *Ephedra alata Decne.*	*Moringa peregrine* extract contains some fatty acids from olive oil	- Inhibition of the cytopathogenic effect of the virus	HSV-1 (Vero cells)	Not reported	102
Capparis sinaica Aerial parts	quercetin, isoquercetin, and rutin	- Virtucidal against HSV-1	**HSV-1** (Vero cells) **Avian influenza strain H5N1** (MDCK cell)	Not reported	102,104
Tamarix nilotica Aerial parts Stems&galls	Not reported	- Virucidal against HSV-1 - Selective inhibition of HIV-1 reverse transcriptase (RT)	**HSV-1** & **HIV-1** (Vero cells)	HIV-1 reverse transcriptase (RT)	102,105
Cyperus rotundus L. Tuber Rhizomes	Eudesmane-type sesquiterpenoid, Cyperol, 1β-hydroxy-α-cyperone, 10-epieudesm-11-ene-3β, 5α-diol, 3β-hydroxyilicic alcohol, cyperusol C, α-corymbolol, 3β, 4α-dihydroxy-7-epieudesm-11, -ene., β-amyrin and stigmasta-5,22-dien-3-ol Myrtenol, and Vitexin	- Virucidal against HSV-1 - Inhibition of the HBV DNA replication, inhibition of HBsAg expressions - Inhibition of Mpro of SARS-Cov-2, inhibition of 3CLpro and RdRp of SARS-CoV-2, and blocking its replication and transcription	**HSV-1** (Vero cells) **Hepatitis A virus, Herpes simplex virus type I,** and **Coxsackie B4 virus** **Hepatitis B virus** (HepG2.2.15 cell) **SARS-CoV-2**	HBe antigen of HBV SARS-CoV-2 Mpro 3-chymotrypsin-like protease (3CLpro) and RNA-dependent RNA polymerase (RdRp)	90,102,106–114

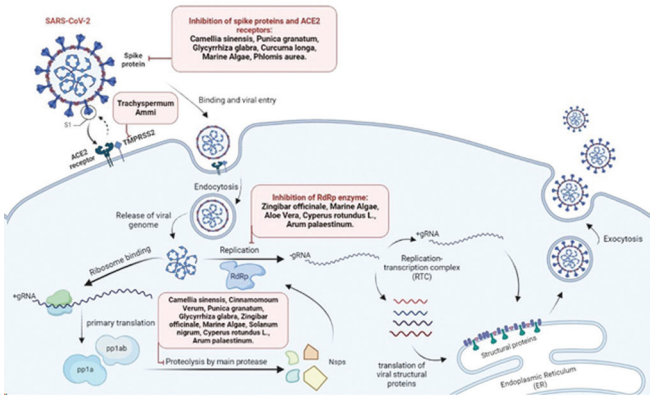
Abbreviations: ACE2: Angiotensin-converting enzyme 2; 3CLpro: 3-chymotrypsin-like protease; HHV: human herpes virus; HBV: Hepatitis B virus; HBeAg: HBV e antigen; HBsAg: HBV surface antigen; HSV: herpes simplex virus; H1N1: Influenza A virus subtype H1N1; MDCK: Madin-Darby canine kidney; CCD: central conserved domain; RSV: Respiratory Syncytial Virus; CX3CR1: CX3C motif chemokine receptor 1; HCV: hepatitis C virus; ADV: adenovirus; MAYV: Mayaro virus, IAV: Influenza A virus; DMEM: Dulbecco's Modified Eagle Medium; EV: Enterovirus; CV: Coxsackievirus; HRSV: Human respiratory syncytial virus; CHIKV: Chikungunya virus; LTR: long terminal repeats; JEV: Japanese encephalitis virus; H5N1: Avian influenza; KSHV: Kaposi's sarcoma-associated herpesvirus; PBMC: peripheral blood mononuclear cell; DENV: Dengue-virus; MERS-CoV: Middle East respiratory syndrome coronavirus; PPAR: proliferator-activated receptor; RT: reverse transcriptase; RdRp: RNA dependent RNA polymerase

often resolving without specific medical treatment.[115] However, some individuals experience a worsening of symptoms, leading to critical conditions that require medical intervention.[116] Our study identified 12 distinct plant extracts with antiviral properties against the SARS-CoV-2 virus, primarily achieved by inhibiting spike protein binding and protease enzyme, as detailed in Table 1 and Figure 3. Additionally, we conducted randomized controlled trials (RCTs) *in vivo* using extracts from Curcuma longa and *Trachyspermum Ammi*. For Curcuma longa, curcumin administered with piperine significantly improved symptoms, hastened recovery, reduced deterioration, shortened hospital stays for moderate to severe cases, and enhanced overall outcomes with reduced mortality rates.[41] Another RCT involving 116 patients utilized a herbo-mineral additive therapy, comprising extracts from *Zingiber officinale, Trachyspermum Ammi*, and other medicinal plants, in conjunction with standard therapy for hospitalized adults diagnosed with COVID-19. This additive therapy demonstrated safety and effectiveness in delaying disease progression from mild to moderate and moderate to severe.[90]

Moving to the Middle East respiratory syndrome (MERS), this viral respiratory illness is caused by MERS-CoV and was first identified in Saudi Arabia in 2012. Clinical manifestations of MERS-CoV infection encompass a wide spectrum, ranging from asymptomatic or mild respiratory symptoms to severe acute respiratory disease, often culminating in fatality, with WHO reporting a mortality rate of approximately 35% for MERS patients.[117] An *in vitro* study utilizing marine algae extract demonstrated inhibition of viral entry by targeting the spike protein.

Flaviridae. The Japanese encephalitis virus (JEV) which is classified as a Flaviridae is transmitted by Culex mosquitoes, and its clinical manifestations vary, with most cases being

Figure 3. Mechanism of Antiviral Activities Against SARS-CoV-2



asymptomatic or exhibiting mild symptoms. Less than 1% progress to neuroinvasive disease and may develop encephalitis symptoms.[118] This review highlights two medicinal plants with antiviral effects against JEV: *Curcuma longa*, which inhibits viral entry into host cells,[119] and *Trachyspermum Ammi*, which impedes virus growth.[120] Next, dengue virus, it encompasses four subtypes (DENV-1, DENV-2, DENV-3, and DENV-4) closely related to each other. Dengue infections can range from subclinical (asymptomatic) to severe flu-like diseases in infected individuals.[121] Our study reveals that marine algae possesses antiviral properties against this virus by inhibiting the cellular binding of Dengue-virus (DENV-1) to host cells. Hepatitis C virus (HCV), a single-stranded RNA virus and a member of the Hepacivirus genus in the Flaviviridae family, results in chronic hepatitis, progressing to cirrhosis and hepatocellular carcinoma.[122,123] This research highlights five plants (*Cinnamomum Verum, Punica granatum, Zingiber officinale, Solanum nigrum, Trachyspermum Ammi*) with antiviral actions against HCV [124–129] by reducing the HCV replication process, primarily demonstrated using Human hepatocarcinoma Huh-7 cells and HepG2 cell lines.

Togaviridae. The Mayaro virus (MAYV) is transmitted from infected non-human primates, such as monkeys, to humans through the bite of a female Hemagogus mosquito.[130] In our study, we illustrate that *Punica granatum*, a plant, exhibits *in vitro* antiviral activity against the Mayaro virus using Vero cell culture. Moving to chikungunya, it is a mosquito-borne viral infection characterized by symptoms like fever and severe arthralgia, often debilitating and varying in duration. Chikungunya is frequently misdiagnosed as dengue or Zika due to similar symptoms. Severe symptoms and fatalities are rare, typically occurring in individuals with coexisting chronic diseases.[131] Our research unveils that extracts of *Zingiber officinale* and *marine algae* exert antiviral effects by inhibiting viral replication.

Retroviridae. The human immunodeficiency virus (HIV) affects the immunity of humans leading to compromised body defense against many infections, including some types of cancer that healthy people can easily encounter. It is reported that in 2021, 650000 people had died from HIV infection and 1.5 million people were infected with HIV.[132] Our study involved 5 plants that showed antiviral activities against HIV mainly through two key mechanisms. The first mechanism involves the inhibition of protease enzyme while the second one involves the interference of viral RNA binding to HIV-1 RT resulting in the inhibition of reverse transcriptase enzyme. A preliminary trial involving the use of aloe vera gruel on ten patients who were not fit for antiretroviral therapy in Nigeria resulted in a slightly higher weight in comparison to patients on conventional antiretroviral therapy.[98]

Picornaviridae. In Picornaviridae, specific focus on Enterovirus and Coxsackievirus is vital. These viruses are categorized within the Picornaviridae family, which encompasses a spectrum of viruses such as enteroviruses, coxsackieviruses, rhinoviruses, polioviruses, and echoviruses. Enteroviruses are known culprits for a diverse array of diseases, including the common cold, poliomyelitis, and aseptic meningitis.[133,134] The study elucidated that extracts from *Glycyrrhiza glabra* and *Ocimum basilicum* showcased inhibitory effects on both viral replication and entry of Enterovirus 71. In the case of Coxsackievirus B, the multiplication is hindered by (*Ocimum basilicum, Lotus arabicus,* and *Lotus glaber*) while *Glycyrrhiza glabra* impedes the viral replication of Coxsackievirus A16. Delving deeper into this family, we encounter Poliovirus, a member of the enterovirus genus within the Picornaviridae family, notorious for causing Poliomyelitis—an epidemic infectious disease. Clinical manifestations of Poliovirus range from asymptomatic cases (the majority) to severe symptoms, notably paralytic poliomyelitis marked by back and lower limb pain.[135] Remarkably, our research identifies four medicinal plants—*Achillea fragrantissima, Jasonia montana, Globularia Arabica,* and *Tanacetum sinaicum*—with *in vitro* antiviral efficacy against poliovirus, achieved by inhibiting the cytopathogenic effect of the virus. Delving deeper into the Picornaviridae family, we encounter Hepatovirus, particularly Hepatitis A virus (HAV). HAV, a positive-sense RNA virus lacking an envelope presents itself as a significant public health concern, grouped within the Picornaviridae family and characterized by four genotypes.[136] Unlike its counterparts, HAV does not lead to chronic hepatitis; instead, its symptoms are usually self-limited.[134] Our study utilizing the Vero cell line, highlights three medicinal plants (*Lotus arabicus, Lotus glaber*, and *Centaurea aegyptiaca*) that exhibit antiviral effects against HAV, employing unknown mechanisms.

Negative strand ssRNA viruses

Filoviridae. In the domain of Filoviridae, a significant focus is placed on the Ebola virus (EBOV), a negative-sense, single-stranded RNA virus known for its severe impact on the human immune system. The main symptoms encompass an impaired immune response, lymphopenia, disseminated intravascular coagulation (DIC), and a systemic inflammatory reaction often leading to septic shock.[137] This study by Muñoz-Fontela and McElroy presented compelling evidence

that *Asphodelus microcarpus* possesses potent *in vitro* antiviral properties against Ebola VP35, achieved through the inhibition of viral RNA-induced interferon response.

Paramyxoviridae. Within the Paramyxoviridae family, the Human metapneumovirus (HMPV) stands as a significant player, responsible for acute respiratory infections. Initially identified in the Netherlands in 2001, HMPV manifests as common cold-like symptoms, typically lasting 2-5 days and resolving without specific interventions. Primarily affecting children aged 5 years or younger, only a small percentage (5-16%) of infected children progress to lower respiratory tract diseases.[138] Our research has unveiled the inhibitory effects of *Marine algae* extract on HMPV viral replication, presenting a potential avenue for antiviral intervention.

Orthomyxoviridae. Within the Orthomyxoviridae family, Influenza A and B are significant viral subtypes known to cause human infection. Symptoms of influenza infection vary in severity depending on factors such as age, immune response, and the presence of chronic diseases, typically encompassing fever, headache, sore throat, dry cough, and more.[139] Notably, Influenza B tends to affect children more prominently. Three medicinal plants (*Camellia sinensis*, *Punica granatum*, and *Aloe Vera*) have been examined for their antiviral potential against influenza viruses *in vitro*. These plants exhibited effectiveness against the influenza A virus by inhibiting viral mRNA expression and viral RNA synthesis.

Avian influenza (bird flu) is attributed to the influenza A virus, characterized by a single-stranded RNA genome that is negative-sense and segmented.[140] While these viruses primarily impact birds and not humans, sporadic infections may occur.[141] Our research identified seven plants (*Cinnamomum Verum, Curcuma longa, Marine algae, Thallasodendron ciliatum, Zizyphus jujube, Arum palaestinum,* and *Capparis sinaica*) that showcased antiviral effects against avian influenza using MDCK cells *in vitro*. Specifically, *Cinnamomum Verum, Marine algae*, and *Zizyphus jujube* displayed efficacy against the H1N1 virus, enhancing anti-HA1 antibodies and cytokines. On the other hand, *Curcuma longa, Thallasodendron ciliatum, Arum palaestinum,* and *Capparis sinaica* proved effective against the H5N1 virus by inhibiting viral growth.

The human respiratory syncytial virus (HRSV) represents a primary cause of acute lower respiratory tract infections (ALRTIs) in pediatrics under 2 years of age. Our study delved into three plants (*Cinnamomum Verum, Punica granatum*, and *Glycyrrhiza glabra*) which exhibited *in vitro* antiviral effects through distinct mechanisms. However, conducting randomized controlled trials for the medicinal extracts of these plants presents challenges, particularly due to the vulnerability of the target group, infants, who are highly susceptible to viral infections.[142]

dsRNA VIRUSES

dsRNA viruses are a noteworthy category, with the Reoviridae family being a prominent group within this classification. Specifically, within Reoviridae, Rotavirus holds significance as a major causative agent of gastroenteritis in children, resulting in distressing symptoms like vomiting and diarrhea that can lead to severe dehydration.[143] Remarkably, in Egypt, *Achillea fragrantissima* has emerged as a distinctive plant studied for its potential antiviral properties against rotavirus *in vitro*, presenting a glimmer of hope in countering this viral menace. However, it's important to acknowledge that despite these findings, there exist significant limitations, chiefly concerning our understanding of its exact mechanism of action.

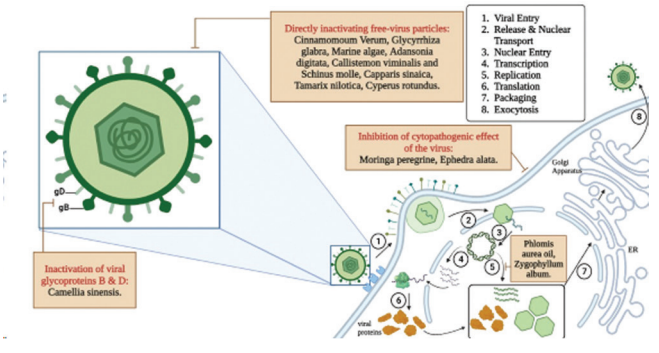
dsDNA VIRUSES

Herpesviridae

The Herpesviridae family stands prominent within the domain of dsDNA viruses, boasting nine distinct members, namely herpes simplex virus 1 (HSV-1), HSV-2, varicella zoster virus (VZV), human cytomegalovirus (HCMV), human herpesvirus 6A (HHV6A), HHV6B, Epstein–Barr virus (EBV), HHV7, and Kaposi's sarcoma herpesvirus (KSHV), all characterized by their enveloped, double-stranded DNA structure.[144] In our study, a notable revelation came to light regarding 11 medicinal plants demonstrating antiviral efficacy against HSV, including *Camellia sinensis, Cinnamomum Verum, Glycyrrhiza glabra, Ocimum basilicum, Capsicum annuum, Marine algae, Phlomis aurea oil, Adansonia digitate, Zygophyllum album, Callistemon viminalis, and Schinus molle,* along with *Aloe Vera*. Conversely, only three plants displayed antiviral effects against HHV, namely, *Punica granatum, Marine algae,* and *Aloe Vera*. The primary mechanism involves the direct inactivation of free-virus particles *in vitro*, with *Camellia sinensis* notably inactivating viral glycoproteins B and D, as depicted in Figure 4.

Shifting focus to Kaposi's sarcoma-associated herpes virus (KSHV), also known as human herpes virus 8 (HHV-8), it presents as a linear, double-stranded DNA virus.[145] Notably, the seroprevalence of KSHV aligns with KS prevalence and fulminant KS, both accompanied by an escalation in KSHV viral load in blood.[146] In Egypt, Curcuma longa has emerged as the sole plant studied for its *in vitro* antiviral effect against KSHV, achieved through the inhibition of replication and virus-associated pathogenic properties.

Figure 4. Mechanism of Antiviral Activities Against HSV



Papillomaviridae

A notable member is the Human papilloma virus (HPV), a non-enveloped DNA virus with a diverse range comprising over 150 types, some of which exhibit high carcinogenic potential.[147] The transmission of HPV primarily occurs through sexual routes, with the virus entering the skin and mucous membrane of specific areas such as the anus, penis, vagina, and mouth.[148] Interestingly, among the various medicinal plants studied, only marine algae have demonstrated significant antiviral activity against HPV. This effect is achieved by disrupting the binding process of HPV to the cell surface, showcasing the potential of marine algae in combating this viral threat.

Adenoviridae

Human adenoviruses are double-stranded DNA non-enveloped viruses, with over fifty subtypes and nine distinct species falling under this category. These adenoviruses manifest in a range of clinical presentations affecting diverse systems within the body, spanning the respiratory tract (exhibiting symptoms like fever, pharyngitis, tonsillitis, cough, and sore throat), urinary tract (displaying dysuria, hematuria, hemorrhagic cystitis, and renal allograft dysfunction), gastrointestinal tract (leading to diarrhea, vomiting, and abdominal pain), and ocular regions such as the cornea and conjunctiva (manifesting as Keratoconjunctivitis).[149] Delving into the specifics of antiviral effects, our review identified a limited set of five plants in Egypt showcasing *in vitro* antiviral activity against Adenovirus, namely, *Camellia sinensis, Punica granatum, Ocimum basilicum, Aloe Vera,* and *Achillea fragrantissima*. Notably, Punica granatum intervenes in ADV replication during the post-adsorption phase. In the case of *Ocimum basilicum*, it inhibits the multiplication of three viral types of ADV (ADV-3, ADV-8, and ADV-11), while *Camellia sinensis* and *Achillea fragrantissima* inhibit ADV-5 and ADV-7, respectively.

Hepadnaviridae

The Hepatitis B virus (HBV) takes center stage, characterized as a compact DNA virus with a predilection for hepatocytes. The infection can be acute or chronic and lifelong. This depends on the immune system and its ability to fight infection. Hepatic cancer and cirrhosis may occur due to immune-mediated hepatic cell damage as a result of chronic hepatitis.[150] HBV spreads through body fluids such as blood, seminal fluids, and others.[151] Our study illustrates four plants (*Camellia sinensis, Ocimum basilicum, Aloe Vera, Cyperus rotundus*) that have anti-HBV activity through different mechanisms such as suppression of HBeAg synthesis, inhibition of the HBV DNA replication, inhibition of HBsAg expressions, in addition to decreasing the secretion of HBsAg and HBeAg and extracellular HBV DNA *in vitro*.

CONCLUSION

Our study shows that 33 plants in Egypt have been identified with *in vitro* antiviral effects through different mechanisms, as demonstrated in Table 1. Only seven of them, namely, *Camellia sinensis*, *Marine algae*, *Zizyphus spina-christi L.*, *Achyspermum Ammi*, *Aloe Vera*, *Cyperus rotundus L.*, and *Tuber Rhizomes* showed proven *in vivo* antiviral effects via different mechanisms. The rest of the medicinal plants cultivated in Egypt need further testing before initiating clinical trials. Only two plants: *Curcuma longa and Cyperus rotundus L* were used in randomized clinical trials. Both were used as a part of adjunctive therapy in adult patients with mild to moderate COVID-19 and were found effective and safe in managing COVID-19 infections, delaying disease progression, and reducing morbidity and mortality. Further studies are needed to confirm the antiviral activities of the Egyptian medicinal plants on humans.

AUTHOR DISCLOSURE STATEMENT

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

AME, MYB, SA, ASA, and MNA participated in Conceptualization, Data Collection, Formal analysis, Investigation, Methodology, and Writing the original draft. MH participated in Data Collection and Manuscript Preparation. FRM participated in Conceptualization, Methodology, Project Administration, Supervision, Writing - review and editing.

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