ACS Pharmacology & Translational Science

pubs.acs.org/ptsci

Review

A Reappraisal of the Antiviral Properties of and Immune Regulation through Dietary Phytochemicals

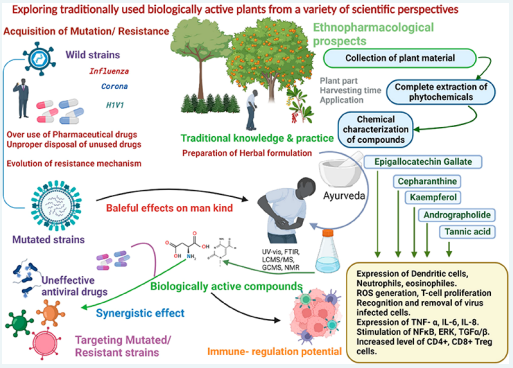
Mony Thakur, Mona Singh, Sandeep Kumar, Ved Prakash Dwivedi, Tikam Chand Dakal,* and Vinod Yadav*

Cite This: *ACS Pharmacol. Transl. Sci.* 2023, 6, 1600−1615

Read Online

ACCESS | Metrics & More | Article Recommendations

ABSTRACT: In the present era of the COVID-19 pandemic, viral infections remain a major cause of morbidity and mortality worldwide. In this day and age, viral infections are rampant and spreading rapidly. Among the most aggressive viral infections are ebola, AIDS (acquired immunodeficiency syndrome), influenza, and SARS (severe acute respiratory syndrome). Even though there are few treatment options for viral diseases, most of the antiviral therapies are ineffective owing to frequent mutations, the development of more aggressive strains, drug resistance, and possible side effects. Traditionally, herbal remedies have been used by healers, including for dietary and medicinal purposes. Many clinical and scientific studies have demonstrated the therapeutic potential of plant-derived natural compounds. Because of unsafe practices like blood transfusions and organ transplants from infected patients, medical supply contamination. Our antiviral therapies cannot achieve sterile immunity, and we have yet to find a cure for these pernicious infections. Herbs have been shown to improve therapeutic efficacy against a wide variety of viral diseases because of their high concentration of immunomodulatory phytochemicals (both immunoinhibitory and anti-inflammatory). Combined with biotechnology, this folk medicine system can lead to the development of novel antiviral drugs and therapies. In this Review, we will summarize some selected bioactive compounds with probable mechanisms of their antiviral actions, focusing on the immunological axis of these compounds.



KEYWORDS: *catechins, ethno-medicine, immunomodulatory phytochemicals, cepharanthine, kaempferol, licorice*

INTRODUCTION

The immune system of the host plays a central role in the maintenance of normal physiological and immunological status. Any perturbation in the functioning of the immune system may lead to numerous pathophysiological and inflammatory disorders, for instance, viral infections, respiratory syndromes, and others.[1] The immune system comprises a complex network of white blood cells (lymphocytes, monocytes, neutrophils, and macrophages) and specific immunomodulatory chemical mediators (antibodies, proteins, and cytokines) that systematically play a pivotal role in mounting an appropriate resistance against a variety of infections, including those caused by viruses. Subsequently, it performs various interconnecting actions such as microbial detection, inflammation, microbial clearance, cell or tissue damage, death, as well as healing of wounds. Host immunity serves as a defense system that restricts the insertion of various pathogens and allows timely negotiation of immune cells with these substances into the tissue of microbes or pathogens to maintain the balance.[2] Redox homeostasis in immune cells also provides protection against various diseases. Consequently, the failure in balance may lead to the development of immune-mediated diseases such as metabolic syndrome, infections, dermatitis, inflammatory bowel disease, and cancers. The ideal immune responses mainly have three core components which are recognition of the insertion of pathogens, phagocytosis reaction, and sparing the issues of the individual.[3] The human body has immune responses which are classified as innate immunity and adaptive immunity, which serve the specific responses against pathogens and microorganisms. Innate immunity, termed as the nonspecific immune system, is responsible for the primary defense system which works against numerous pathogens whereas the adaptive immunity, termed as acquired or specific immune system, is produced gradually and serves as the defensive action against the infections.[4] The occurrence of memory cells facilitates these responses, as they detect the invasion of similar antigens. The

Received: August 5, 2023
Published: October 10, 2023

ACS Publications

© 2023 American Chemical Society

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

lack of these long-term memory cells in innate immunity provides incomplete protection against foreign pathogens.[5] This innate immune system comprises complement, phagocytic cells, acute phase proteins, and specific types of receptors named toll-like receptors (TLRs). TLRs are the integral part of the recognized receptor hierarchy, found in plants as well as in vertebrate and invertebrate animals, which have the ability to detect the preserved molecular configuration associated with respective pathogens such as cell wall components (bacterial lipopeptides, β-glucans, and lipopolysaccharides) of fungus and bacteria.[6] TLRs as well as other recognized receptors permit intrinsic cells to differentiate their own cells from foreign cells, but in certain cases, they lack the ability to recognize between non-self molecules. For instance, the ability to respond against pathogenic and nonpathogenic bacteria is distinctive.[7] Often the affected cells generate interferons (IF) that further induce a number of cellular responses in order to cease the reproduction of the virus within the cells as well as also promote the cell destruction mode of cytotoxic T-lymphocytes and natural killer cells.[8,9] The acquired immune responses are powerful immune responses that comprise long-term memory cells (T-cells and B-cells) and other specific receptors. All pathogens are identified by the signature antigen present in the cells.[10] Moreover, these cells have the ability to remember particular antigens and serve as protection against various pathogens in the host.[11,12] Despite all of these vaccines and antiviral drugs, viruses take the lives of a large population every year. In addition to various side effects, the viruses also develop resistance to these drugs, limiting their usefulness. The situation, therefore, calls for breakthrough approaches to protect people from viral infections in a cost-effective manner without side effects.

Classical antiviral therapy employing interferon and ribavirin is effective against most viruses under *in vitro* settings; however, their potency and effectiveness have remained limited in patients. Approximately 90 different antiviral agents are available today,[13,14] and that are also for the treatment of selected viral diseases, for instance, HIV (human immunodeficiency virus), herpes virus, hCMV (human cytomegalovirus), VZV (varicella zoster virus), influenza virus, and the hepatitis virus. Currently, there is no approved remedy for many types of viruses, and vaccinations are available for only a handful of viruses such as SARS-COV-2, hepatitis A virus, mumps, and varicella.[15] In addition, these agents are often costly and ineffective due to viral resistance and can cause side effects. With that in mind, naturally based pharmacotherapy may be a proper alternative for treating viral diseases. Thus, it is necessary to further examine the topic of antiviral phytochemicals, highlighting drug delivery applications in overcoming the multiple biological barriers that exist for antiviral agents to successfully reach their intended site(s) of action. The present review focuses on the antiviral properties of herb extracts and bioactive constituent isolates from medicinal plants and the efforts to obtain their efficient delivery. Since there is no approved drug to combat viral infections, natural therapy based on bioactive plant molecules may be a better approach for the treatment of viral diseases. Some new antiviral compounds are currently undergoing either preclinical or clinical evaluation and perspectives for finding new interesting antiviral drugs are promising.[16] In this Review, we focus on the current knowledge of the antiviral properties of medicinal plants and their immunological perspectives.

PLANT-DERIVED ANTIMICROBIALS IN THE GLOBAL MARKET

The utilization of phytochemicals in technology is experiencing a notable upward trajectory. Phytochemicals encompass a diverse range of chemical compounds derived from plants, which find application in several domains such as food additives, cosmetic constituents, and medications. Natural alternatives are frequently employed as substitutes for synthetic chemicals due to their potential to cause less harm to both human health and the environment. Medicines from plants are used in various forms, such as capsules, tinctures (antiseptic), infusions (wherein medication is administered through a needle or catheter, usually intravenously), macerates, decoctions, and many others. Much of the population in developing countries relies on herbal therapeutics for primary health care. The effective use of phytochemicals as an alternative to modern medicine against various bacterial and viral diseases has created the second largest therapeutic market at the global level, as recognized by the WHO.[17,18] Currently, researchers are focusing on recognizing the specific groups of compounds isolated from plants, such as flavonoids, lactones, glycosides, alkaloids, etc., with their immunomodulatory effects.[19,20] Phytomedicines are more effective than their synthetic counterparts in terms of safety, cultural compatibility, and acceptability in the treatment of chronic diseases.[21]

Various traditional medicines from different ethnic medicinal plants, like *Arctostaphylos uva-ursi* and *Vaccinium macrocarpon*, are used to get rid of urinary tract infections, while the essential oils of some plants, such as *Melissa officinalis, Allium sativum,* and *Melaleuca alternifolia*, are used against a variety of pathogens infecting the respiratory tract, GI tract, urinary tract, and skin.[22] The therapeutic use of tea tree oil against acne and other skin infections is a common example of natural medicine.[23,24]

In 2001−2002, nearly one-quarter of the world's best-selling medicines were derived from ethnomedicinal plants:[25] artemotil, an antimalarial drug synthesized from artemisinin and isolated from *Artemisia annua* L.; galantamine, a natural drug for the treatment of Alzheimer's disease produced from the plant *Galanthus woronowii* Losinsk; orfadin, a modified form of mesotrione, a constituent of *Callistemon citrinus* Stapf.; and tiotropium, an anticholinergic bronchodilator isolated from *Atropa belladonna*, used for the treatment of chronic obstructive pulmonary disease (COPD). These four drugs represent the world economy related to ethnic medicines.[22,26−30]

Nearly 70−80% of the world's population essentially relies on traditional ethnic medicines to cure and treat various diseases.[31] The market for Ayurvedic medicines is growing at 20% annually in developing countries like India.[32] Growing populations and inadequate control of western medicine are the factors promoting the growth of traditional medicine in various developing countries such as Kenya, Malawi, etc. The population in developed countries such as Europe and North America tends to use herbal medicines, so the market is growing by 10−20% annually.[33] Some medicines are extracted directly from plants, while some natural compounds can also be modified by methods of structural transformation. Certainly, there are many more unidentified biochemical in plants and that their potential biological actions are still to be deciphered.[34]

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

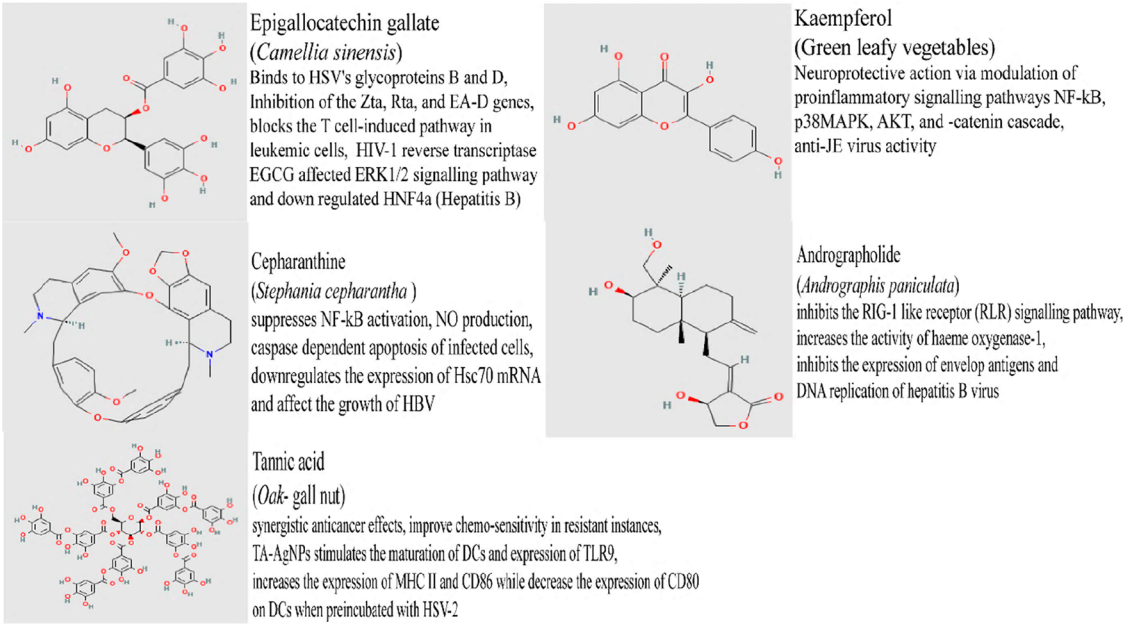


Figure 1. Structures of plant-derived bioactive compounds and their possible mechanism of action for the prevention and treatment of viral infections. The chemical structures were taken from Pubchem.

No other factor can outweigh the importance of medicinal plants in people's lives, as they contribute significantly to a healthy life. In 1997, a study showed that 11 of the 25 best-selling drugs were either extracted from medicinal plants or were a modified version of the extracted compound, which was worth US$ 17.5 billion.[35] Taxol, a drug isolated from *Taxus baccata*, had a market value of US$ 2.3 billion in 2000. In 1999, the net value of herbal medicines in the world market was US$ 19.4 billion, while in Europe it was US$ 6.7 billion, followed by Asia, North America, and Japan, with net market values of US$ 5.1 billion, US$ 4.0 billion, and US$ 2.2 billion, respectively.[36]

Although every single person on the planet takes advantage of medicinal plants, it is the populations of developing countries that are most closely associated with plants for their health and income. Previous work found that only 15% of synthetic medicines are consumed in developing countries, indicating their dependence on natural remedies. The sale of wild harvested material provides significant income to rural populations.[37] 50−100% of families in the northern region and 25−50% of families in the central region of central Nepal depend on income from medicinal plants.[38,39] A compound called rutin has antiviral properties against various influenza viruses.[40,41] Quercetin, a potent phytochemical, is effective against a number of viruses such as poliovirus, Epstein−Barr virus, HCV, HSV-1, rhinovirus, adenovirus, etc.[42] The utilization of phytochemicals in technology is experiencing a noticeable upward trajectory. Phytochemicals refer to a class of chemical compounds derived from plants, which find application in diverse sectors, such as food additives, cosmetics, and pharmaceuticals. Natural alternatives are frequently employed as substitutes for synthetic chemicals due to their potential to cause less harm to both human health and the environment.

MECHANISTIC BASIS OF ACTION OF THE PHYTOCHEMICALS USED FOR TREATING VIRAL DISEASES

Different phytochemicals such as flavonoids, phenolic acids and derivatives, alkaloids, and terpenoids are under study for their use in developing novel antiviral drugs. High-level, systematic clinical studies are still warranted to establish the safety and efficacy of using these natural products in human clinical trials in a wide range of patients. The structures of major phyto-compounds with immune modulation potential are shown in Figure 1.

Epigallocatechin Gallate (EGCG). Green tea catechins, derived from the leaves of the *Camellia sinensis* plant, have been studied extensively for their potential benefits. Epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCG) are the major components of these polyphenolic compounds. The most complex and important component of GTCs is EGCG, which accounts for about 59% of the phenolic content of GTCs. Previous research has shown that EGCG has important antioxidant, anticancer, antimicrobial, neuroprotective, and anti-infective properties and could be used to treat a number of human diseases.[43]

In addition to these properties, EGCG has antiviral activity against numerous viruses.[44] Viral adsorption is affected by the ability of EGCG to reduce endoplasmic and lysosomal acidification, which, in turn, alters the integrity of viral particles. Specifically, it binds to the conserved cavity domain of nucleic acids, which in turn inhibits nucleic acid activity and thus RNA synthesis in influenza A virus.[45] In addition, EGCG has been shown to bind to glycoproteins B and D of HSV and prevent their infectivity. EGCG blocks the entry of chikungunya virus (CHIKV) by competing for cellular coreceptors such as heparan sulfate or sialic acid. EGCG was also effective in inhibiting Zika virus by interacting with the lipid envelope and preventing the virus from entering cells.[46]

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

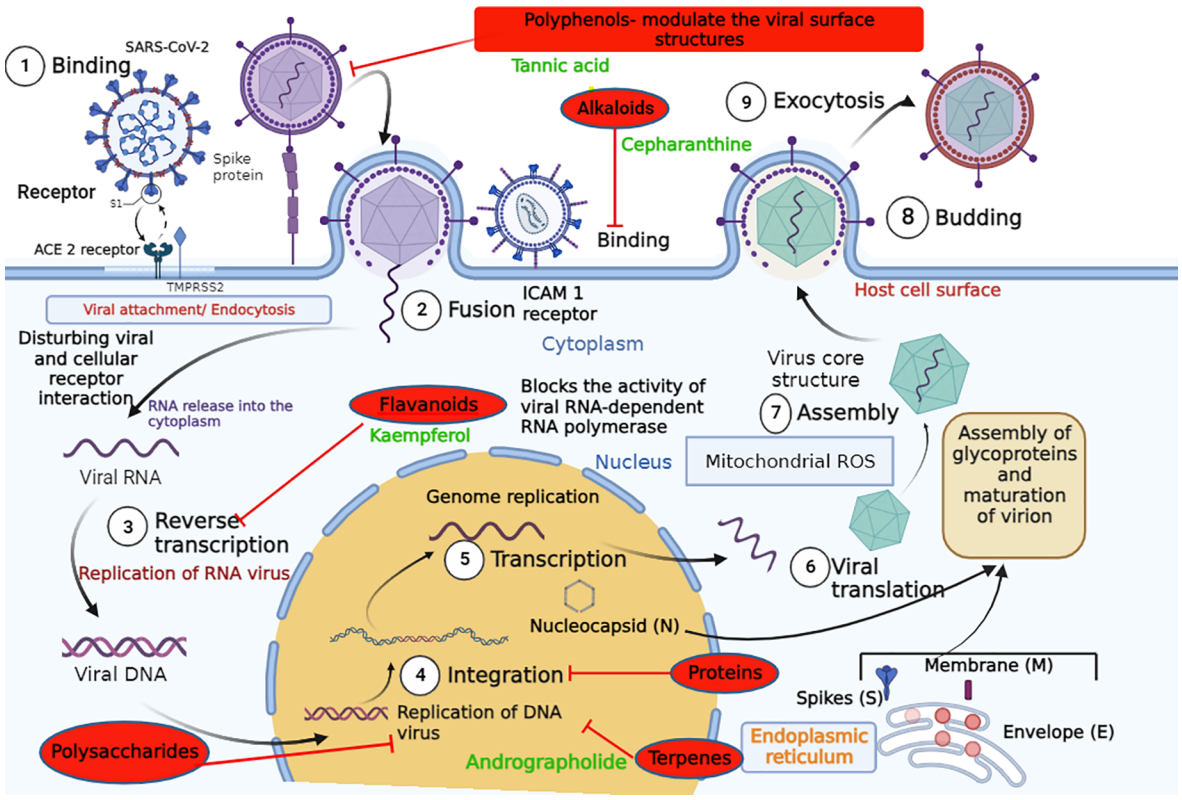


Figure 2. Schematic graphic of virus life cycle (Transmission and replication) and inhibitory effects of natural compounds on probable targets during viral infection. Virus enters the host cell by endocytosis and releases viral genome inside the cytoplasm. Polyphenols and alkaloids can disturb attachment of viral surface proteins (glycoproteins or capsid proteins) to the cellular receptors of host cells for viral entry. Flavonoids and terpenoids inhibit different phases of transcription, translation, and replication during viral infection. Abbreviations used TMPRSS2 (Transmembrane protease, serine 2), ACE-2 (angiotensin converting enzyme), and ICAM1 (Intercellular Adhesion Molecule).

Immune cells are equipped with a plethora of receptors that act as messengers between the outside world and the cell's own activation mechanisms. To control the adhesion and inflammatory processes of neutrophils, monocytes/macrophages, and mast cells, EGCG targets the retinoic-acid-inducible gene (RIG-I) and the 67 kDa laminin receptors (67LR). EGCG also blocks the T cell-induced pathway in leukemic cells to inhibit the activity of zeta chain-associated protein (ZAP-70).[47] In the case of HIV/AIDS, EGCG stops viral replication by blocking reverse transcriptase of HIV-1 and reduces the binding of HIV viral DNA-integrase in human peripheral blood cells by downregulating the expression of the CD4 receptor. It also inhibits the serine protease activity of hepatitis C virus.[44] To control hepatitis B virus infection, EGCG affected the ERK1/2 (extracellular signal-regulated kinase 1/2) pathway and downregulated HNF4α (hepatocyte nuclear factor 4α) in a dose-dependent manner. This inhibition prevented the EBV lytic cycle from completing its MEK/ERK1/2 and PI3−K/Akt signaling pathways. By impairing the production of precore mRNA and DNA replication intermediates, EGCG also prevented hepatitis B virus (HBV) replication.[46] Autophagy is an important means for healthy cells to remove waste and keep their metabolism going. EGCG can increase the acidity of lysosomes and prevent HBV from causing incomplete autophagy. This prevents HBV from making copies of its DNA.[48] The expression of genes responsible for antiviral responses is regulated by the cytoprotective transcription factor Nrf2. EGCG reduces viral entry and replication and act as an Nrf2 activator, resulting in increased expression of type 1 interferons.[49] Min et al. demonstrated that T-cell proliferation and the relative abundances of CD4 T cells, CD8 T cells, and B-cell subsets, including marginal zone B cells and T1 and T2 transitional B-cells, were significantly suppressed by EGCG, whereas the expression of $CD4^+$ $Foxp3^+$ regulatory T cells (Tregs) and indoleamine2,3-dioxygenase (IDO) by $CD11b^+$ dendritic cells (DC) was significantly increased by EGCG.[50] Yang et al. demonstrated that intraperitoneal injection of EGCG significantly increased the number of neutrophils and monocytes/macrophages in the peritoneal cavity and peripheral blood of mice. Remarkably, EGCG did not directly induce the migration of neutrophils and macrophages but induce the migration of phagocytes in the presence of macrophages, suggesting that EGCG-induced migration of phagocytes depends on its immune-regulatory effects on macrophages.[51]

Cepharanthine. Cepharanthine (CEP), an alkaloid isolated from *Stephania cepharantha* that occurs in many other *Stephania* species.[52] This compound has been used in Japanese medicine since 1951. It is an approved drug and is used to treat a variety of diseases, including malaria, alopecia, and snakebite. It has been shown to possess anti-inflammatory, antioxidant, immunomodulation, antiparasitic, and antiviral activity against HIV-1, HTLV, SARSCO, SARS-CoV-2, and hepatitis virus. CEP suppresses nuclear factor kappa B (NF-κB) activation, lipid peroxidation, nitric oxide production (NO), cytokine production, and cyclooxygenase expression; all of which are critical for viral replication and the inflammatory response.[53] In HIV-1, CEP causes inhibition of NF-κB to suppress the activity

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

of the long-terminal repeat gene. NF-κB plays an important role in the induction of HIV-1 gene expression. CEP indirectly inhibits the HIV-1 replication in infected monocytes and lymphocytes, and its attenuating effect is long-lasting because NF-κB is the most potent factor for HIV-1 replication.[54] This drug also has the potential to treat virus-infected central nervous system (CNS) cells by suppressing the production of inflammatory cytokines because it can easily cross the blood-brain barrier.[55] In addition, CEP decreases plasma membrane fluidity to impair HIV-1 entry in to the host cell.[56] Studies have shown that structural changes in CEP enhance antiviral activity against HIV-1;[57] this drug is also effective against hepatitis B in both forms, i.e., wild type and lamivudine-resistant forms.[58] Herpes zoster virus also cannot replicate in the presence of CEP. In 2005, Zhang et al. demonstrated the inhibitory effect of this drug against SARS-related coronaviruses.[59] Other studies demonstrated the binding of CEP drug to the target protein of Ebola virus through molecular docking.[60,61]

Along with HIV-1, CEP is also effective against human T-lymphotropic virus type 1 (HTLV-1) by inducing caspase-dependent apoptosis in infected cells. HTLV-1 is responsible for adult T-cell (ATL) leukemia, and NF-κB and activated protein-1 (AP-1) are highly expressed in ATL cells. In addition to the apoptosis effect, the inhibitory effect of CEP on NF-κB also helps control the deleterious effect of HTLV-1.[62−64] In addition, CEP makes cancer cells more sensitive to antitumor agents.[65,66] Hepatitis B virus (HBV) growth is also controlled by CEP. This drug inhibits viral DNA replication and antigen production (HBeAg) in a dose-dependent manner. CEP also downregulates the expression of Hsc70 mRNA synthesized by host cells, thereby impairing HBV growth.[58,67]

SARS-CoV (severe acute respiratory syndrome-coronavirus), as the name implies, severely affects the respiratory system of humans.[68] Researchers are continuously working to find a vaccine or drug to treat respiratory illness caused by SARS-CoV. CEP has proven to be a ray of hope, as it has shown positive preclinical effects against SARS. Researchers investigated the anti-SARS-CoV effect of CEP on VeroE6 cells under in vitro conditions. A concentration of 10 μg/mL CEP was sufficient to exhibit cytopathic effect against SARS-CoV.[59] However, Zhang et al. had no idea of the mechanism behind the cytopathic effect of CEP.

In another study, the researchers examined the effect of CEP on the MRC-5 lung cell lines infected with human coronavirus type OC43 (HCoV-OC43).[69,70] Here, MRC-5 cells were treated with CEP before viral infection, and no morphological changes or cytotoxic effects on the cells were observed. CEP inhibits RNA replication, viral protein expression, and proinflammatory molecules to prevent an enhanced cytokine response to viral infection. To investigate antiviral properties of CEP against SARS-CoV-2, VeroE6/TMPRSS2 cells were inoculated with the corresponding virus. CEP exhibits its antiviral effect mainly by interfering with the entry of the virus into the host cell by disrupting the binding of the virus to the target cell (Figure 2).[71] The antiviral effect of CEP is more potent in combination with nelfinavir because both drugs interfere with both entry and replication of SARS-CoV-2 into the host cell in a cooperative manner.[72]

Fan et al. investigated the effect of CEP against 2019-nCoV-related pangolin coronaviruses. The spike protein of 2019-nCoV is 92.2% similar to the spike proteins of SARS-CoV-2. Even at very low IC_{50} and CC_{50}, i.e., 0.73 and 39.30 μmol/L, CEP exhibits very dynamic and potent antiviral activity. Treatment of infected cells with CEP decreases viral RNA yield by 2.17- and 1.61-fold, respectively, in both the entry and post entry phases compared with the infected cells without treatment.[70] Another study showed that CEP is effective against SARS-CoV-2 because of its binding potential with NSP multiple subunit complex (nonstructural proteins).[73] This multisubunit complex of NSP is very much crucial for replication as well as transcription of SARS-CoV-2 (RNA virus).[74] Binding of CEP to the NSP machinery blocks the formation of the relevant proteins synthesized by SARS-CoV-2. The inhibitory effect of CEP against SARS-CoV-2 confirms its therapeutic potential to target COVID-19.[53] Uto et al. demonstrated that CEP inhibited antigen uptake by DCs as well as LPS-induced DC maturation. CEP also reduced interleukin-6 and tumor necrosis factor-alpha production in LPS-stimulated DCs. CEP-treated DCs were ineffective in stimulating allogeneic T-cell proliferation and interferon production.[75]

Kaempferol. Kaempferol (KPF) is a typical dietary flavonoid with anti-inflammatory and antioxidant properties and is found in a variety of fruits, vegetables, teas, soybeans, and medicinal herbs. Several studies have described how KPF intake reduces the risk of chronic diseases, especially cancer. However, the molecular and cell-based mechanisms underlying the action of KPF in the central nervous system are poorly understood. KPF has shown versatile neuroprotective effects by modulating several proinflammatory signaling pathways, including nuclear factor kappa B (NF-κB), p38 mitogen-activated protein kinases (p38MAPK), serine/threonine kinase (AKT), and the β-catenin cascade.[76] Because of its anti-inflammatory properties, KPF has been shown to be beneficial in the treatment of numerous acute and chronic inflammation related diseases, including intervertebral disc degeneration and colitis, as well as postmenopausal bone loss and acute lung injury.[77]

The antiviral activity of kaempferol has been demonstrated *in vitro* against influenza A viruses (H1N1 and H9N2) and human immunodeficiency virus type 1 (HIV 1), and *in vivo* against enterovirus type 71. Kaempferol has been reported to have anti-JE virus activity and to reduce both the production of the E protein of the virus and its mRNA genome.[78]

Treatment of infected MH-S cells with kaempferol inhibited the production of reactive oxygen species (ROS), malondialdehyde, tumor necrosis factor alpha (TNF-α), interleukin-6, and interleukin (IL)-1β expression by increasing the number of activated macrophages; suppression of TNF-α mediates the translocation of NF-κB p65 to the nucleus.[77] Kaempferol significantly reduced phosphorylation of IB-IκB-α and nuclear factor-κB (NF-κB) p65, DNA binding activity of NF-κB p65, and mitogen-activated protein kinases (MAPKs), and upregulation of Toll like receptor 4.[79]

Kaempferol attenuated viral infection by inducing far upstream element-binding proteins (FUBP) and hnRPs that bind to the highly conserved 5′-UTR region of the virus. A general alteration in the makeup of the trans-factors interfered with IRES activity. Inhibition of translation and replication resulted in reduced viral infection (Figure 2).[80] Protein 3a (U274), the largest accessory viral-channel-forming protein, plays a critical role in the release of coronaviral particles from the infected host cell. Kaempferol derivatives were found to be potent inhibitors of the 3a channel.[81]

On DCs, kaempferol has an immunosuppressive effect. Kaempferol inhibited DC maturation and decreased the level

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

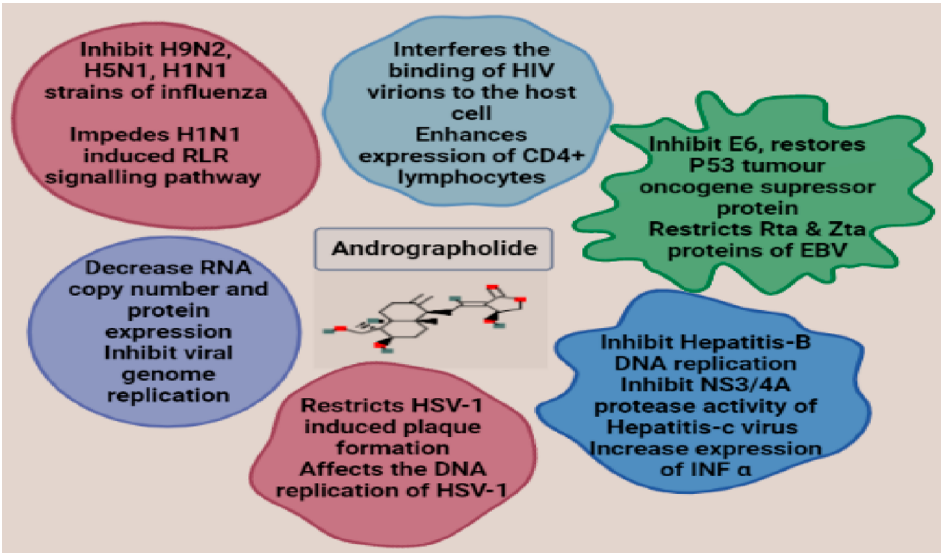


Figure 3. Major antiviral activities and immunological responses exhibited inside the host cell by phytocompound andrographolide to treat viral infections.

of production of cytokines and chemokines by LPS-stimulated DCs. In addition, kaempferol inhibited the ability of LPS-stimulated DCs to promote Ag-specific T-cell activation both *in vitro* and *in vivo*.[82]

Andrographolide. Andrographolide is a diterpenoid obtained from plants of the genus *Andrographis paniculata* that has long been utilized in Chinese and Indian medicine. It has been reported to have antibacterial, anti-inflammatory, and anticancer properties. Most research has shown that it has anti-inflammatory properties, and it has been used to treat inflammation-related disorders such as ulcerative colitis.[83] In addition to its anti-inflammatory effect, this compound also acts as immunomodulator via increasing the activity of cytotoxic T cells, NK cells, phagocytotic process, and ADCC. The immunomodulatory effect of andrographolide helps in restricting the replication and pathogenesis of the viruses. The increased proliferation of CTLs decrease the number of virus infected cells as they are killed by CTLs.[84] Andrographolide exhibits antiviral activity against a number of viruses such as influenza A virus, hepatitis B and C virus, EBV, HPV, HSV-1, HIV, CHIKV, etc.

Researchers demonstrated that andrographolide interact with viral proteins to inhibit their biological activity in many strains of influenza virus named as H9N2, H5N1, and H1N1 (Figure 3).[85]

Andrographolide inhibits the RIG-1 like receptor (RLR) signaling pathway induced by H1N1 virus in bronchial epithelial cell.[86] Infection with the hepatitis B virus activates B and T cells. Hepatitis B virus targets the DCs, NK cells, interferons, regulatory T cells.[87,88] Various chemical or natural compounds have been screened for the treatment of Hepatitis B virus.[89,90] Andrographolide exhibits activity against viruses by inhibiting the expression of envelope antigens and DNA replication (Figure 2).[86]

Hepatitis C virus mainly infects hepatocytes, B cells with CD81 molecules.[91] Host immune system produces IFNs against the virus to inhibit its propagation. However, hepatitis C virus has its own strategies to fight against the host defense system, i.e., NS4B protein of this virus suppress the production of IFNs by inhibiting the stimulator of IFN.[92] That is why antiviral drugs are required to limit the viral infection along with the stimulation of host immune system. Andrographolide increases the activity of heme oxygenase-1 (HO-1) which in turn enhances the production of biliverdin by the liver cells. Biliverdin inhibits the protease activity of NS3/4A protein along with the enhanced expression of IFNs to suppress the viral replication in the host cell. This diterpenoid also activates p38 MAPK phosphorylation which results in activation of Nrf2 mediated HO-1 expression to inhibit the viral infection.[93]

Infection caused by HSV affects the activity and maturation of DCs which reduces the function of $CD8^+$ T cells against HSV (Figure 3).[94] Various approved drugs are available against this virus, but mutations in the viral genome have developed resistance against these drugs. Studies demonstrated that andrographolide and its derivatives like neoandrographolides, 14-DDA inhibits the plaque formation by HSV-1 in Vero cells,[95] while DAD, IPAD, and another semisynthetic compound of this diterpenoid inhibits ≤50% entry of virus inside the host cell.[96] Further studies demonstrated that IPAD has no effect on the early stage of viral infection, while it shows 100% inhibition at post infection stage.

EBV directly weakens the immune system of the body as it infects B cells, T cells, NK cells, and epithelial cells of salivary gland along with smooth muscle cells. This virus is responsible for many types of cancer like Burkitt's lymphoma, gastric carcinoma, Hodgkin's lymphoma, as well as multiple sclerosis. EBV restrict the differentiation of dendritic cells from monocytes and also triggers apoptosis.[97,98] Rta and Zta are the two main transcription factors essential for the lytic cycle of EBV. It becomes necessary to restrict the expression of these transcription factors to control the viral infection. Studies demonstrated the effect of andrographolide against EBV and revealed the inhibition of BRLF1 and BZLF1 (genes encoding Rta and Zta, respectively) in Burkitt's lymphoma cell lines.[99]

HPV is also responsible for vaginal, cervical, penial, and oropharyngeal cancers and cancer many other regions of the body. To evade immune attack, the virus impedes the differentiation of immune cells. The infection of HPV weakens the cellular immune system and causes downregulation of dendritic cells maturation and activation.[100] Researchers

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

demonstrated that andrographolide exhibits anti-HPV activity via inhibiting the expression of E6 oncogene and restoring the activity of p53 protein in HPV16 pseudo virus infected cells. This diterpenoid and its derivatives also prevent the binding of virus to the host cells and prevents infection.

Infection caused by HIV is divided into three stages: In early stage, it is termed as M-tropic as it mainly attacks the macrophages along with DCs, monocytes, and microglial cells having CD4 and CCR5. In the middle phase, the virus affects the macrophages and T-cells and the infection is termed as dual tropic. The stage of infection is T-tropic, as the virus prefers to attack the T cells with CD4 and CXCR4. Chang et al. studied the antiviral activity of andrographolide in H9 and PBMCs of humans and revealed that succinyl derivative of andrographolide prevents the attachment of HIV virions to host cells along with disturbing the replication cycle of virus.[101] Another study described that andrographolide intrudes the dysregulation of signaling pathways triggered by the virus.

Chikungunya virus (CHIKV) enters in human body through the saliva of Aedes mosquitoes and initiates replication in epithelial, endothelial, macrophages, fibroblast, and other cells of the body.[102] Research study revealed that andrographolide reduces the copy number of RNA and as a result affects the protein expression in HepG2 and BHK-21 cells.[103] Andrographolide also affects the post entry step of virus along with genome replication. However, andrographolide is a cost-effective antiviral drug but further research is required to identify the target points in the virus to control the infections.[104] Lee et al. demonstrated that andrographolide treatment reduces hepatic neutrophil/macrophage infiltration, local inflammation, and liver damage in thioacetamide-induced mouse hepatic fibrosis.[105] Rajanna et al. has shown that standardized *A. paniculata* extract (SAPE) increased T cells and T helper cells and significantly increased IFN-γ, IL-4, and decreased IL-2 at day 30 in healthy adults.[106] It has also been reported that andrographolide can suppress humoral and cellular adaptive immune responses. *In vitro*, this molecule inhibited T cell proliferation and cytokine release in response to allogenic stimulation. Furthermore, it impaired DC maturation, antigen presentation ability, and thus inhibited T cell activation.[107]

Tannic Acid. Tannic acid is the most abundant gallo-tannin in gallnuts and other plant sources. Tannic acid has been shown to play an important role in tuning numerous oncological signaling pathways including JAK/STAT, RAS/RAF/mTOR, TGF-1/TGF-1R, VEGF/VEGFR, and CXCL12/CXCR4 axes. Tannic acid has been shown in the literature to have synergistic anticancer effects and to improve chemosensitivity in numerous resistant cases when combined with other conventional chemotherapeutic agents.[108]

Tannins and plant-derived polyphenols also possess anti-inflammatory and antiviral properties by interfering with the adsorption of viruses to the cell membrane.[109] Studies demonstrated that tannins interact with the glycoproteins of HSV-1 and obstruct the virus attachment, entry, and spread.[110] In addition to HSV-1, tannic acid is also effective against many other viruses, such as noroviruses, influenza A viruses, and papillomaviruses.[111,112] EGCG, punicalagin, and chebulagic acid are other forms of tannin with a wide range of antiviral properties against HIV, HSV-2, HCMV, HCV, DENV, MV, RSV, etc.[113,114] HSV-2 is one of the most common genital ulcerative diseases because it disintegrates the vaginal mucosa. The destroyed vaginal mucosa increases the risk of contracting other STDs, such as HIV-1.[115,116] Nucleoside analogues like ACV, FAM, and VCV target the DNA polymerase of HSV-2 and are therefore beneficial in the treatment of HSV-2 infections.[117,118] However, these nucleoside analogs are unable to treat latent infections caused by the virus. To date, there is no vaccine against this virus. The present situation demands the development of an effective antivirus to prevent its spread and infection. Along with that, the antiviral agent should not be toxic to the skin or epithelial tissue.

AgNPs are silver nanoparticles with a myriad of antimicrobial, anti-inflammatory, and immunomodulatory properties. AgNPs are used as ligands for numerous phytochemicals to reach the site of action and reduce the level of formation of contaminants. A number of researchers have used AgNPs against many viruses like HIV-1, HSV-1, hepatitis B, and influenza virus.[119,120] AgNPs synthesized with tannic acid (TA-AgNPs) block the attachment and entry of viruses into the cell and induce the production of antiviral cytokines and chemokines (Figure 2). Along with that, TA-AgNPs also stimulate the maturation of DCs and the expression of TLR9 *in vitro*. TA-AgNPs increase the expression of MHC II and CD86, whereas they decrease the expression of CD80 on DCs when preincubated with HSV-2.[121]

TA-AgNPs are more effective against viruses compared with tannic acid alone. The size of silver nanoparticles determines the antiviral properties of TA-AgNPs, with a size of 20−40 nm being the most effective without toxic or proinflammatory effects on cells.[122] TA-AgNPs help in the presentation of the viral antigen to the cytotoxic T cells and memory T cells in lymph nodes. Treatment with TA-AgNPs in the early stages of infection with HSV-2 induces the strong expression of chemokine CXCL17. Studies have shown that the CXCL17/CXCR8 chemokine pathway contributes to the enhancement of vaginal mucosa immunity by inducing the mobilization of CD^{8+} effector and memory T cells to the site of infection.[123] The nontoxic and protective TA-AgNPs strengthen the defense system by developing a virus-specific cellular and humoral response. Feduska et al. demonstrated that a subset of TA-based microcapsules can suppress DC responses, as evidenced by a significant decrease in the mRNA of the pro-inflammatory cytokines TNF-α and IL12, as well as the chemokine CXCL10 and a significant decrease in the secreted pro-inflammatory cytokine IL-12p70.[124] In contrast, Orlowski et al. have shown that silver and gold nanoparticles modified with tannic acid act as potential stimulators of dendritic cells because tannic acid nanoparticles help overcome virus-induced DC inhibition by upregulating the expression of MHC II and CD86 and downregulating the expression of CD80.[125] Tannic acid is a dopamine D2L receptor agonist, and treatment with TA decreased IFN-γ secretion and increased IL-10 secretion in CD3/CD28-stimulated splenocytes.[126]

MEDICINAL PLANTS USED THE MOST TRADITIONALLY IN INDIA AND CHINA DURING PANDEMIC SITUATION

Ginger. Ginger (*Zingiber officinale*), a well-known herbaceous plant, originated in India and is now widely cultivated in humid tropical areas. It has been used for centuries as a spice and as a medicinal plant. The plant is known for its antimicrobial, antifungal, antibacterial, antiviral, anti-inflammatory, and other effective properties. Various phytochemical compounds, such as polyphenols and flavonoids, are responsible for the medicinal properties of this plant;[127]

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

Ahkam et al. investigated the antiviral activity of bioactive constituents of ginger such as gingerenone A, geraniol-zingerone, shogaol, etc. against SARS-CoV-2. The study showed that gingerol, shogaol, zingerone, zingiberene, geraniol, and zingiberenol possess good antiviral properties and reduce the cytotoxic effect of SARS-CoV-2. Spike protein (S protein) and main protease (MPro) are the most vital components of SARS-CoV-2 to facilitate its entry into the host cell. The active components of ginger, such as geraniol, gingerol, shogaol, zingiberenol, zingerone, and zingiberene, inhibit the catalytic activity of MPro and thus indirectly affect the replication of virus. On the other hand, geraniol, shogaol, zingiberenol, zingerone, and zingiberene bind to the S Protein of virus to restrict the binding of the S Protein to the ACE2 receptor present on the host cell, indicating the antiviral potential of ginger.[128]

Camero et al. studied the antiviral effect of ginger essential oils (GEOs) against Caprine α-herpesvirus 1 (CpHV-1) *in vitro*.[129] The researchers observed nearly 100% inactivation of cell-free CpHV-1, indicating the virucidal activity of GEO. Basically, GEO causes the disintegration of the viral envelope along with other structures essential for the adsorption and entry of viruses inside the cell. However, GEO had not exhibited virucidal activity in the pre- and postinfected cells.[130] Chang et al. demonstrated the antiviral activity of fresh ginger on Hep2 and A549 cells infected with the human respiratory syncytial virus (HRSV). Fresh ginger (300 mg/mL) reduced nearly 70% of the infection caused by HRSV on both cell lines. Dried ginger exhibited only 20% protection against plaque formation by the virus in Hep-2 cells. Fresh ginger constrains the attachment and internalization of HRSV to the host cell.[131] Gingerols are the major active components of fresh ginger compared to dried ginger. Fresh ginger also encourages epithelial cells to secret IFN-β and inhibits the production of prostaglandins and inflammatory cytokines, which all help to prevent viral replication.[132] Kaushik et al. demonstrated the excellent antiviral effect of ginger against CHIKV.[133] Different extracts of ginger exhibit inhibitory effects against a number of viruses like H1NI influenza virus, rhino virus, HIV-1, rotavirus, etc.[134] *In vitro*, ginger volatile oil suppressed T lymphocyte proliferation and lowered total T lymphocytes and T helper cells in a concentration-dependent manner, but it increased the percentage of T suppressor cells to total T lymphocytes in mice. Its anti-inflammatory effects suggest that it could help with a variety of clinical disorders, including chronic inflammation and autoimmune diseases.[135] Tripathi et al. showed that ginger extract inhibits macrophage activation by downregulating the expression of B7.1, B7.2, and MHC class II molecules, as well as function by decreasing the production of IL-12, TNF-α, IL-1 (proinflammatory cytokines) and RANTES, MCP-1 (proinflammatory chemokines) in LPS-activated macrophages.[136]

Ginseng. Ginseng is an herb plant traditionally used in China to reduce tiredness and boost the immune system. Ginseng's antioxidative and anticancer benefits, as well as its impact on enhancing immunity, energy, and sexuality, and treating cardiovascular diseases, diabetes mellitus, and neurological diseases, have been explored in both basic and clinical studies during the last few decades.[137] Fatty acids, peptides, polysaccharides, polyacetylenic alcohols, and ginsenosides of this plant exhibit biological and medicinal properties.[138,139] A number of studies have provided evidence about the antiviral properties of ginseng. McElhaney et al. demonstrated the activity of CVT-E002 ginseng extract against influenza virus for the prevention of acute respiratory problems. Studies revealed that an aqueous extract of this plant improved resistance against influenza and RSV infections, suggesting the safe and effective role of ginseng.[140] Administration of ginseng polysaccharide prior to infection with influenza virus increases the chances of survival in experimental animals subjected to viral infection.[141−143] The production of IL-6 as well as the viral titer were low in the experimental animals treated with virus and ginseng polysaccharide at the same time.[143,144] Ginseng aqueous extract enhances the production of IFN-α, INF-γ, and macrophage activity to strengthen the defense mechanism against influenza virus.[145] In addition to influenza treatment, Rg1 and Rb1 ginsenosides of ginseng are effective against many other viruses like hepatitis A, murine norovirus, and feline calcivirus.[146] Rg1 enhances the proliferation of lymphocytes to fight against norovirus and feline calovirus (Figure 4).[147]

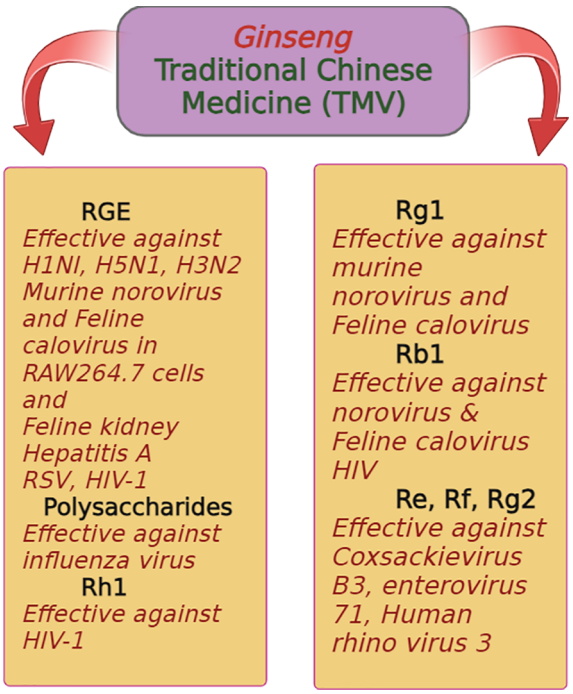


Figure 4. Impact on viral infections and immune-modulation mechanism shown by medicinal plant ginseng and its derivatives (Rg1, Rb1, Rh1, Re, Rf, and Rg2) in *in vitro* and *in vivo* experiments.

Red ginseng extract (RGE) works against the RSV infection to improve cell survival, as it partially inhibits the replication of the viral DNA and alters the production of cytokines along with increased migration of immune cells. RGE has been shown in studies to inhibit the production of RSV-induced TNF-α and viral replication in human epithelial cells. Intranasal administration of RGE prior to infection prevents to weight loss and enhances the level of IFN-γ in BAL cells of respiratory system upon infection of mice with RSV.[148] Another study described the oral administration of RGE and suggested that RGE reduces the viral load and activates dendritic cells to increase IFN-γ production in response to viral infection.[141]

The aqueous extract of ginseng improves NK cell activity as well as antibody-dependent cell cytotoxicity in AIDS patients to lyse HIV-infected cells in order to reduce the HIV

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

progression.[149] Study performed by Cho et al. on HIV infection demonstrated that ginseng enhances the production $CD4^+$ and $CD8^+$ T cells along with gain in body weight while it reduces $CD8^+$ solubilized antigens.[150] Rh1 and Rb1 ginsenosides proved beneficial in eliminating infected macrophages. In D3 transduced macrophages, Rh1 inhibits the phosphorylation of pyruvate dehydrogenase lipoamide kinase isozyme 1, whereas Rb1 inhibits the protein kinase B pathway.[151,152] Numerous studies have demonstrated that taking ginseng has varied effects on immune cells while controlling them simultaneously. Each type of immune cell, such as macrophages, natural killer cells, dendritic cells, T cells, and B cells, is controlled by ginseng.[153]

Licorice. Licorice, extracted from the roots of *Glycyrrhiza glabra* and often used in ancient Siddha medicine, is one of the most beneficial medicinal plants commonly used in industries associated with the food and pharmaceutical sectors.[154,155] Licorice is used in traditional medicine to treat coughs, arthritis, epilepsy, ulcers, inflammation, and digestive problems. Approximately 300 flavonoids and 20 triterpenoids are present in licorice. The two primary triterpenoids that prevent virus replication and gene expression are glycyrrhizin (GL) and 18-glycyrrhetinic acid, hence controlling the progression of viruses. These two compounds increase the proliferation of lymphocytes and suppress the apoptotic process in the host cell to fight against the virus. Both the compounds affect the adsorption and penetration of the virus into the host cells to control the infection.[156,157]

Sekizawa et al. demonstrated that GL treatment activates immune cells against virus in HSV-1-infected mice, while another study revealed that glycyrrhizic acid (GA) has the ability to terminate the infection caused by Kaposi sarcoma-associated herpes virus (KSHV) at the latent stage.[158,159] GA promotes apoptosis in virus-infected cells by decreasing the expression of the nuclear antigen in B lymphocytes, which is associated with the latent period of the virus. Cinatl et al. investigated the role of GL in the prevention of acute respiratory syndrome.[156] GL has the ability to inhibit the signaling pathways of protein kinase C, casein kinase II, activator protein 1, and NF-κB. GL and 18β-glycyrrhetinic acid induce the expression of nitric oxide synthase in macrophages to enhance the production of nitric oxide. Various studies also described the role of GL in treating HIV-1 patients as it enhances the production of chemokines.[160,161]

The Japanese have been using intravenous GL against the hepatitis C virus for more than 20 years. This compound reduces the concentration of serum aminotransferases and also significantly improves the histology of the liver, which has high therapeutic uses.[162] Intravenous administration of GL proved beneficial against autoimmune hepatitis.[163] Along with restricting the replication of the H5N1 influenza virus, the compound also controls the infection caused by porcine epidemic diarrhea virus (PEDV) by inhibiting the entry and replication of the virus in Vero cells.[164,165]

Along with HSV, GL also shows interesting inhibitory activity against SARS-CoV, the common enemy of the world, causing COVID-19. The amphiphilic nature and membrane crossing potential of GL promote the antiviral properties of this compound. The researchers studied the antiviral activity of GL against SARS-CoV and observed the inhibitory action of GL on the viral replication process, along with the adsorption and penetration in Vero cells. Dosing of GL during and after the adsorption period of the virus provides better results against the virus. For its antiviral properties, GL alters the casein kinase II and PKC signaling pathways as well as transcription factors such as NF-κB and AP-1. As mentioned earlier, the ACE2 receptor is highly essential for the entry of SARS-CoV-2 in the host cell, and thus, the binding of GL to ACE2 blocks the binding site of virus and controls the SARS-CoV-2 entry.[166]

Epithelial cells of esophagus, enterocytes of small intestine, and colon cells express the ACE2 receptor in abundance,[167,168] indicating a suitable entry point for SARS-CoV-2. On the basis of various studies, researchers proposed that GL and GA provide double protection to the enterocytes, first through oral ingestion and second through enterohepatic cycling. However, airborne transmission of SARS-CoV-2 is the primary route of infection. That is why the protection of respiratory cells from viral entry is the most preventive measure against infection. In the respiratory system, the ACE2 receptor is highly expressed by the nasal epithelial cells, facilitating the smooth entry of viruses.[169] The higher expression of ACE2 in nasal and oral epithelial cells suggests the topical utilization of GL against the SARS-CoV-2 infection. The saponin and amphiphilic nature of GL enhances its ability to modify virus lipid bilayer.[170,171] Clinical trials of GL should be conducted against SARS-CoV-2 to determine its efficacy and safety. Various studies demonstrated that GL also exhibits anti-HIV activity via inhibiting viral replication, interrupting the binding of the virus to the host cell, and inducing the expression of IFN.[172,173] In addition to anti-HIV activity, GL also affects infections caused by the Epstein−Barr virus, cytomegalovirus, hepatitis C virus (HCV), and HSV-1.[159]

Ashfaq et al. investigated the toxicological effect of GL in HCV-infected Huh-7 and CHO cell lines and discovered that GL affects HCV activity in a dose-dependent manner, i.e., at 13 μg concentration, it reduces HCV infection by 50%, while at 40 μg concentration, it inhibits HCV by nearly 85%.[174] GL basically inhibits the expression of HCV core genes via stimulation of the IFN pathway. The compound also reduces membrane fluidity along with the upregulation of the Cox2 pathway to exhibit an antiviral effect. Wolkerstorfer et al. reported the antiviral activity of GL against the Influenza A virus (IAV) infecting human lung cells and observed that this saponin compound directly affects the binding of virus to the host cell along with immune modulation. GL has virustatic but not virucidal activity against IVA, and higher concentration is required for the antiviral effect.[175] Guo et al. demonstrated that the two ingredients of licorice extract, isoliquiritigenin and naringenin, boosted Treg cell induction both *in vitro* and *in vivo*, as well as enhanced their immunological suppression.[176] In another study, licorice polysaccharides were found to improve mice immunological state by increasing blood leukocyte count, spleen weight, and T lymphocyte population in CT26 tumor-bearing mice.[177]

PHYTOCHEMICALS-MEDIATED SIGNALING PATHWAYS

Previous research has demonstrated that immunomodulators and antioxidant compounds possess the ability to regulate the signal transduction pathways that are essential for cellular responses, such as inflammation, survival, cellular proliferation, and cell death, all of which can be influenced by oxidative stress.[178,179] One illustration of this phenomenon involves the modulation of nuclear factor-erythroid-2-related factor-2 (Nrf2) by antioxidants. This modulation leads to the activation

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

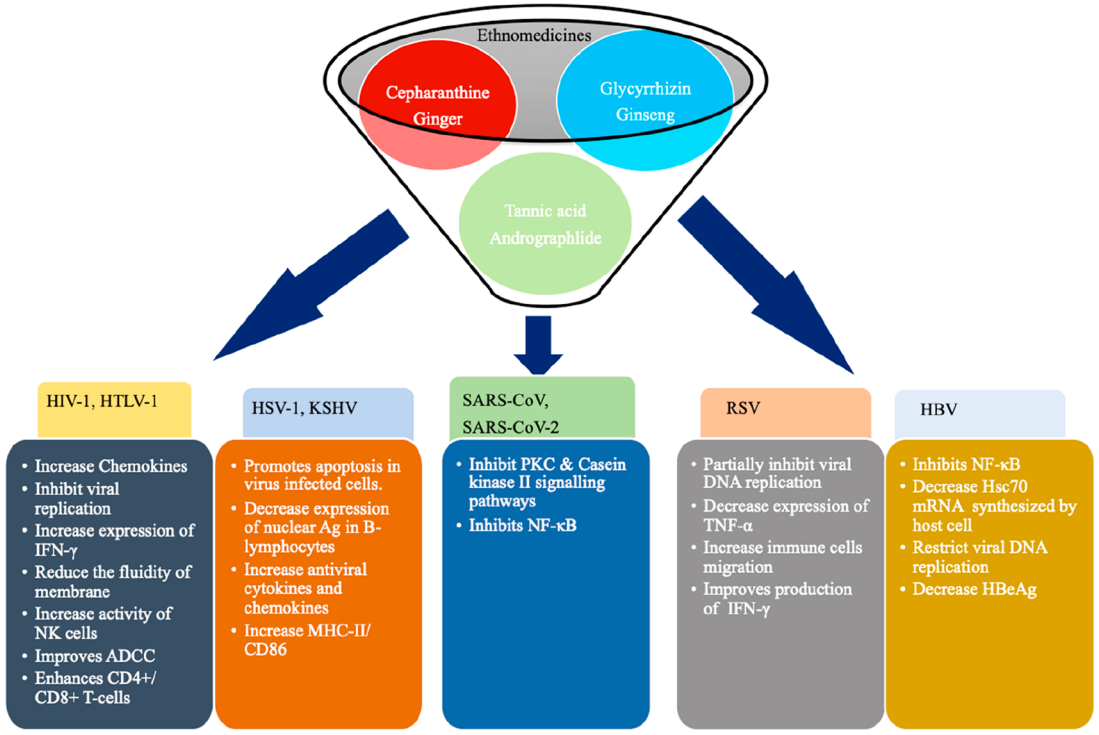


Figure 5. Conclusive multiple mechanisms of medicinal plants and derived compounds to treat different viral infections: interrupting viral host cell binding; inhibiting viral genome replication; stimulates the production of IFN-γ; increasing migration of immune cells; activating Th_1 and Th_2 response.

of several Nrf2 target gene candidates, such as Nrf2, SLC48A1, SLC7A11, p62, HO-1, and Bcl-2 genes. These genes play a crucial role in regulating antioxidant defense and autophagy.[180,181] Moreover, the promotion of the intracellular cyclic AMP (cAMP) second messenger pathway can occur through the inhibition of phosphodiesterases (PDE), which may be facilitated by antioxidant activity.[182] Hence, the activation of the cAMP response element-binding protein (CREB) leads to the targeting of specific genes and the AMP-activated protein kinase (AMPK) pathway. This system serves as a crucial regulator of autophagy and is also implicated in the control of the Nrf2 pathway.[183−185] In summary, the immune-enhancing properties of antioxidants derived from honey encompass more than just stimulating the multiplication and activation of lymphocytes and suppressing the synthesis of pro-inflammatory cytokines. Additionally, these antioxidants have the ability to initiate autophagy mechanisms. Therefore, the promotion of these three immune responses may potentially contribute to the mitigation of the effects of COVID-19.

CHALLENGES IN PHYTOCHEMICALS-BASED DRUG DELIVERY SYSTEMS

Introducing pharmaceutical nanotechnology into the field of natural medicine is useful and promising. New strategies for the delivery of poorly soluble phytochemicals and plant extracts allow improved pharmacokinetic and clinical outcomes.[186,187] Commonly used approached such as phytosomes, nanoparticles, hydrogels, microspheres, transferosomes and ethosomes, self-microemulsifying drug delivery systems (SMEDDS), and self-nanoemulsifying drug delivery systems (SNEDDS) have been applied for the delivery of antiviral plant agents GR.[188,189] These antiviral technologies may be preferred over older phytochemical drug formulations due to enhanced solubility and oral absorption, systemic bioavailability, safety, delayed metabolism, and better overall antiviral activity.[190]

However, there is a limited body of literature on the subject of antiviral herbal medication delivery. Therefore, our objective is to provide a number of successful endeavors aimed at enhancing the administration of phytodrugs that possess established antiviral properties.

CONCLUSION

Viruses have several strategies to invade. Each virus, in fact each strain, has its unique characteristics and biochemical configuration of surface molecules, which work on the principle of lock and key enabling viruses enter into hosts by accurately fitting the molecules on their surfaces of target cells.[191,192] Since viruses and hosts' cells make intimate connections during pathogenesis, blockage of such association could render an antiviral state. As already introduced in the "Introduction" section, antiviral therapies are limited in both number and efficacy with possible development of drug-resistance as well. Moreover, associated cytotoxicity and side-effects are enormous, and as such, it is an obvious need of the time to design and develop some novel, safe, and effective antiviral therapies that target and inhibit the viral enzymes or its replication without affecting the host cells.[193,194]

Further research on the mechanisms by which phytochemicals exhibit their antiviral effect will allow the development of successful target-specific drug delivery systems. At the moment, we cannot ensure that the plant phytochemicals directly reach viruses or the correct structures inside cells. Ideally, we would have smart pharmaceutical nanotechnologies and targeting strategies that can avoid cellular defenses, transport drugs to targeted intracellular sites, and release the drugs in response to specific molecular signals.

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

In this review, we summarized the selected compounds representing a different class of phytochemicals and the most commonly used medicinal plants in traditional systems of medicine. The review supports the notion that phytochemicals such as alkaloids, flavanols, phenols, and terpenoids have significant antiviral and immune modulatory roles and target key proteins and pathways to exert antiviral actions and attain immunity against viruses (Figure 5).

Indeed, it appears that there is an increasing inclination among clinicians and medical professionals to prefer or juxtapose to the conventional therapies preventive or curative adjuvant therapies based on bioactive nutraceuticals extracted from plants. It is probable that more research toward thorough identification and characterization will be undertaken in the coming decades; wherever possible, most of the diseases will be tackled more "naturally" through introduction of emerging concept of nutrition science and clinical nutrition alongside personalized treatments. Besides, development of new antiviral therapies and regimens, public health measures, and prophylactic vaccines are of great importance, by which society controls the spread of viral infections.

AUTHOR INFORMATION

Corresponding Authors

Vinod Yadav − *Department of Microbiology, Central University of Haryana, Mahendergarh, Haryana 123031, India*; Phone: +91-8199065338; Email: vinodyadav17@gmail.com, vinodyadav@cuh.ac.in

Tikam Chand Dakal − *Genome and Computational Biology Lab, Department of Biotechnology, Mohanlal Sukhadia University, Udaipur, Rajasthan 313001, India;* orcid.org/0000-0002-9248-7391; Email: tc.dakal@mlsu.ac.in, tikam26070@gmail.com

Authors

Mony Thakur − *Department of Microbiology, Central University of Haryana, Mahendergarh, Haryana 123031, India*

Mona Singh − *Department of Obstetrics and Gynaecology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, United States*

Sandeep Kumar − *Division of Cell Biology and Immunology, Council of Scientific and Industrial Research - Institute of Microbial Technology, Chandigarh 160036, India;* Present Address: Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, India

Ved Prakash Dwivedi − *International Centre for Genetic Engineering and Biotechnology, New Delhi 110067, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsptsci.3c00178

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors sincerely acknowledge the Central University of Haryana, Mahendergarh, for necessary facilities.

REFERENCES

(1) Menon, A. M.; Kumari, P.; Nagoda, C.; Tekriwal, S.; Kumar, A.; Purohit, S. D.; Dakal, T. C. Evaluation of Some Plant-Derived Natural Ingredients against SARS-CoV-2: An in-Silico Approach. *Int. J. Phytocosmet. Nat. Ingred.* **2021**, *8* (1), e5.

(2) Behl, T.; Kumar, K.; Brisc, C.; Rus, M.; Nistor-Cseppento, D. C.; Bustea, C.; Aron, R. A. C.; Pantis, C.; Zengin, G.; Sehgal, A.; et al. Exploring the Multifocal Role of Phytochemicals as Immunomodulators. *Biomed. Pharmacother.* **2021**, *133*, No. 110959.

(3) Stephens, L.; Ellson, C.; Hawkins, P. Roles of PI3Ks in Leukocyte Chemotaxis and Phagocytosis. *Curr. Opin. Cell Biol.* **2002**, *14* (2), 203−213.

(4) Greenberg, S.; Grinstein, S. Phagocytosis and Innate Immunity. *Curr. Opin. Immunol.* **2002**, *14* (1), 136−145.

(5) Netea, M. G.; Quintin, J.; Van Der Meer, J. W. M. Trained Immunity: A Memory for Innate Host Defense. *Cell Host Microbe* **2011**, *9* (5), 355−361.

(6) Kawai, T.; Akira, S. The Role of Pattern-Recognition Receptors in Innate Immunity: Update on Toll-like Receptors. *Nat. Immunol.* **2010**, *11* (5), 373−384.

(7) Ueta, M.; Kinoshita, S. Innate Immunity of the Ocular Surface. *Brain Res. Bull.* **2010**, *81* (2−3), 219−228.

(8) Chand Dakal, T.; Dhabhai, B.; Agarwal, D.; Gupta, R.; Nagda, G.; Meena, A. R.; Dhakar, R.; Menon, A.; Mathur, R.; Mona.; et al. Mechanistic Basis of Co-Stimulatory CD40-CD40L Ligation Mediated Regulation of Immune Responses in Cancer and Autoimmune Disorders. *Immunobiology* **2020**, *225* (2), No. 151899.

(9) Brindha, P. Role of Phytochemicals as Immunomodulatory Agents: A Review. *Int. J. Green Pharm.* **2016**, *10* (1). DOI: 118.

(10) Pancer, Z.; Cooper, M. D. The Evolution of Adaptive Immunity. *Annu. Rev. Immunol.* **2006**, *24*, 497−518.

(11) Mauri, C.; Bosma, A. Immune Regulatory Function of B Cells. *Annu. Rev. Immunol.* **2012**, *30*, 221−241.

(12) Ordovas-Montanes, J.; Beyaz, S.; Rakoff-Nahoum, S.; Shalek, A. K. Distribution and Storage of Inflammatory Memory in Barrier Tissues. *Nat. Rev. Immunol.* **2020**, *20* (5), 308−320.

(13) Brijesh, S.; Daswani, P.; Tetali, P.; Antia, N.; Birdi, T. Studies on the Antidiarrhoeal Activity of Aegle Marmelos Unripe Fruit: Validating Its Traditional Usage. *BMC Complement. Altern. Med.* **2009**, *9*, 1−12.

(14) Soltan, M. M.; Zaki, A. K. Antiviral Screening of Forty-Two Egyptian Medicinal Plants. *J. Ethnopharmacol.* **2009**, *126* (1), 102−107.

(15) Nováková, L.; Pavlík, J.; Chrenková, L.; Martinec, O.; Červený, L. Current Antiviral Drugs and Their Analysis in Biological Materials−Part II: Antivirals against Hepatitis and HIV Viruses. *J. Pharm. Biomed. Anal.* **2018**, *147*, 378−399.

(16) Chattopadhyay, D.; Chawla-Sarkar, M.; Chatterjee, T.; Sharma Dey, R.; Bag, P.; Chakraborti, S.; Khan, M. T. H. Recent Advancements for the Evaluation of Anti-Viral Activities of Natural Products. *N. Biotechnol.* **2009**, *25* (5), 347−368.

(17) Ernst, E.; Pittler, M. H. Herbal Medicine. *Med. Clin.* **2002**, *86* (1), 149−161.

(18) Pemmaraju, D. B.; Ghosh, A.; Gangasani, J. K.; Murthy, U. S. N.; Naidu, V. G. M.; Rengan, A. K. Herbal Biomolecules as Nutraceuticals. *Herbal Biomolecules in Healthcare Applications* **2022**, 525−549.

(19) Jantan, I.; Ahmad, W.; Bukhari, S. N. A. Plant-Derived Immunomodulators: An Insight on Their Preclinical Evaluation and Clinical Trials. *Front. Plant Sci.* **2015**, *6*, 655.

(20) Sultan, M. T.; Buttxs, M. S.; Qayyum, M. M. N.; Suleria, H. A. R. Immunity: Plants as Effective Mediators. *Crit. Rev. Food Sci. Nutr.* **2014**, *54* (10), 1298−1308.

(21) Dobrange, E.; Peshev, D.; Loedolff, B.; Van den Ende, W. Fructans as Immunomodulatory and Antiviral Agents: The Case of Echinacea. *Biomolecules* **2019**, *9* (10), 615.

(22) Heinrich, M.; Lee Teoh, H. Galanthamine from Snowdrop–the Development of a Modern Drug against Alzheimer's Disease from Local Caucasian Knowledge. *J. Ethnopharmacol.* **2004**, *92* (2−3), 147−162.

(23) Rios, J.-L.; Recio, M. C. Medicinal Plants and Antimicrobial Activity. *J. Ethnopharmacol.* **2005**, *100* (1−2), 80−84.

(24) Esmael, A.; Hassan, M. G.; Amer, M. M.; Abdelrahman, S.; Hamed, A. M.; Abd-Raboh, H. A.; Foda, M. F. Antimicrobial Activity

of Certain Natural-Based Plant Oils against the Antibiotic-Resistant Acne Bacteria. *Saudi J. Biol. Sci.* **2020**, *27* (1), 448−455.
(25) Butler, M. S. The Role of Natural Product Chemistry in Drug Discovery. *J. Nat. Prod.* **2004**, *67* (12), 2141−2153.
(26) Balunas, M. J.; Kinghorn, A. D. Drug Discovery from Medicinal Plants. *Life Sci.* **2005**, *78* (5), 431−441.
(27) Audah, K. A. Drug Discovery: A Biodiversity Perspective. *Nanotechnology: Applications in Energy, Drug and Food*; Springer, 2019; pp 249−265.
(28) Graul, A. I. The Year's New Drugs. *Drug News Perspect.* **2001**, *14*, 12−31.
(29) Hall, M. G.; Wilks, M. F.; Provan, W. M.; Eksborg, S.; Lumholtz, B. Pharmacokinetics and Pharmacodynamics of NTBC (2-(2-nitro-4-fluoromethylbenzoyl)-1, 3-cyclohexanedione) and Mesotrione, Inhibitors of 4-hydroxyphenyl Pyruvate Dioxygenase (HPPD) Following a Single Dose to Healthy Male Volunteers. *Br. J. Clin. Pharmacol.* **2001**, *52* (2), 169−177.
(30) Pirttilä, T.; Wilcock, G.; Truyen, L.; Damaraju, C. V. Long-term Efficacy and Safety of Galantamine in Patients with Mild-to-moderate Alzheimer's Disease: Multicenter Trial. *Eur. J. Neurol.* **2004**, *11* (11), 734−741.
(31) Sheng-Ji, P. Ethnobotanical Approaches of Traditional Medicine Studies: Some Experiences from Asia. *Pharm. Biol.* **2001**, *39* (sup1), 74−79.
(32) Ravi, S.; Bharadvaja, N. Market Analysis of Medicinal Plants in India. *Curr. Pharm. Biotechnol.* **2019**, *20* (14), 1172−1180.
(33) Isman, M. B. Botanical Insecticides in the Twenty-First Century—Fulfilling Their Promise? *Annu. Rev. Entomol* **2020**, *65*, 233−249.
(34) Mendelsohn, R.; Balick, M. J. The Value of Undiscovered Pharmaceuticals in Tropical Forests. *Econ. Bot.* **1995**, *49* (2), 223−228.
(35) Hussain, N.; Baqar, Z. Microbial Synthesized Antibiotics in Healthcare Management. In *Microbial Biomolecules*; Elsevier, 2023; pp 375−403.
(36) Calixto, J. B. The Role of Natural Products in Modern Drug Discovery. *An. Acad. Bras. Ciênc.* **2019**, *91*, e20190105.
(37) Mukherjee, P. K.; Banerjee, S.; Gupta, B. D.; Kar, A. Evidence-Based Validation of Herbal Medicine: Translational Approach. In *Evidence-Based Validation of Herbal Medicine*; Elsevier, 2022; pp 1−41.
(38) Hamilton, A. C. Medicinal Plants, Conservation and Livelihoods. *Biodivers. Conserv.* **2004**, *13* (8), 1477−1517.
(39) Ambu, G.; Chaudhary, R. P.; Mariotti, M.; Cornara, L. Traditional Uses of Medicinal Plants by Ethnic People in the Kavrepalanchok District, Central Nepal. *Plants* **2020**, *9* (6), 759.
(40) Chakraborty, S.; Basu, S.; Basak, S. Effect of β-Cyclodextrin on the Molecular Properties of Myricetin upon Nano-Encapsulation: Insight from Optical Spectroscopy and Quantum Chemical Studies. *Carbohydr. Polym.* **2014**, *99*, 116−125.
(41) Yarmolinsky, L.; Huleihel, M.; Zaccai, M.; Ben-Shabat, S. Potent Antiviral Flavone Glycosides from Ficus Benjamina Leaves. *Fitoterapia* **2012**, *83* (2), 362−367.
(42) Ben-Shabat, S.; Yarmolinsky, L.; Porat, D.; Dahan, A. Antiviral Effect of Phytochemicals from Medicinal Plants: Applications and Drug Delivery Strategies. *Drug Delivery Transl. Res.* **2020**, *10* (2), 354−367.
(43) Chakrawarti, L.; Agrawal, R.; Dang, S.; Gupta, S.; Gabrani, R. Therapeutic Effects of EGCG: A Patent Review. *Expert Opin. Ther. Pat.* **2016**, *26* (8), 907−916.
(44) Audah, K. A. Drug Discovery: A Biodiversity Perspective. In *Nanotechnology: Applications in Energy, Drug and Food*; Springer, 2019; pp 249−265.
(45) Zhao, Z.; Feng, M.; Wan, J.; Zheng, X.; Teng, C.; Xie, X.; Pan, W.; Hu, B.; Huang, J.; Liu, Z.; Wu, J.; Cai, S. Research Progress of Epigallocatechin-3-Gallate (EGCG) on Anti-Pathogenic Microbes and Immune Regulation Activities. *Food Funct.* **2021**, *12* (20), 9607−9619.
(46) Lalani, S.; Poh, C. L. Flavonoids as Antiviral Agents for Enterovirus A71 (EV-A71). *Viruses* **2020**, *12* (2), 184.
(47) Ding, S.; Jiang, H.; Fang, J. Review Article Regulation of Immune Function by Polyphenols. *J. Immunol. Res.* **2018**, *2018*, 1−8.
(48) Zhao, Z.; Feng, M.; Wan, J.; Zheng, X.; Teng, C.; Xie, X.; Pan, W.; Hu, B.; Huang, J.; Liu, Z.; et al. Research Progress of Epigallocatechin-3-Gallate (EGCG) on Anti-Pathogenic Microbes and Immune Regulation Activities. *Food Funct.* **2021**, *12* (20), 9607−9619.
(49) Zhang, Z.; Zhang, X.; Bi, K.; He, Y.; Yan, W.; Yang, C. S.; Zhang, J. Potential Protective Mechanisms of Green Tea Polyphenol EGCG against COVID-19. *Trends Food Sci. Technol.* **2021**, *114* (May), 11−24.
(50) Min, S.-Y.; Yan, M.; Kim, S. B.; Ravikumar, S.; Kwon, S.-R.; Vanarsa, K.; Kim, H.-Y.; Davis, L. S.; Mohan, C. Green Tea Epigallocatechin-3-Gallate Suppresses Autoimmune Arthritis through Indoleamine-2, 3-Dioxygenase Expressing Dendritic Cells and the Nuclear Factor, Erythroid 2-like 2 Antioxidant Pathway. *J. Inflamm.* **2015**, *12* (1), 1−15.
(51) Yang, Y.; Han, X.; Chen, Y.; Wu, J.; Li, M.; Yang, H.; Xu, W.; Wei, L. EGCG Induces Pro-Inflammatory Response in Macrophages to Prevent Bacterial Infection through the 67LR/P38/JNK Signaling Pathway. *J. Agric. Food Chem.* **2021**, *69* (20), 5638−5651.
(52) Hong, L.; Guo, Z.; Huang, K.; Wei, S.; Liu, B.; Meng, S.; Long, C. Ethnobotanical Study on Medicinal Plants Used by Maonan People in China. *J. Ethnobiol. Ethnomed.* **2015**, *11* (1), 1−35.
(53) Rogosnitzky, M.; Okediji, P.; Koman, I. Cepharanthine: A Review of the Antiviral Potential of a Japanese-Approved Alopecia Drug in COVID-19. *Pharmacological Rep.* **2020**, *72* (6), 1509−1516.
(54) Baba, M. Cellular Factors as Alternative Targets for Inhibition of HIV-1. *Antivir. Res.* **1997**, *33* (3), 141−152.
(55) OKAMOTO, M.; ONO, M.; BABA, M. Potent Inhibition of HIV Type 1 Replication by an Antiinflammatory Alkaloid, Cepharanthine, in Chronically Infected Monocytic Cells. *AIDS Res. Hum. Retroviruses* **1998**, *14* (14), 1239−1245.
(56) Matsuda, K.; Hattori, S.; Komizu, Y.; Kariya, R.; Ueoka, R.; Okada, S. Cepharanthine Inhibited HIV-1 Cell−Cell Transmission and Cell-Free Infection via Modification of Cell Membrane Fluidity. *Bioorg. Med. Chem. Lett.* **2014**, *24* (9), 2115−2117.
(57) Baba, M.; Okamoto, M.; Kashiwaba, N.; Ono, M. Anti-HIV-1 Activity and Structure-Activity Relationship of Cepharanoline Derivatives in Chronically Infected Cells. *Antivir. Chem. Chemother.* **2001**, *12* (5), 307−312.
(58) Zhou, Y.-B.; Wang, Y.-F.; Zhang, Y.; Zheng, L.-Y.; Yang, X.-A.; Wang, N.; Jiang, J.-H.; Ma, F.; Yin, D.-T.; Sun, C.-Y.; et al. In Vitro Activity of Cepharanthine Hydrochloride against Clinical Wild-Type and Lamivudine-Resistant Hepatitis B Virus Isolates. *Eur. J. Pharmacol.* **2012**, *683* (1−3), 10−15.
(59) Zhang, C.; Wang, Y.; Liu, X.; Lu, J.-H.; Qian, C.; Wan, Z.; Yan, X.; Zheng, H.; Zhang, M.; Xiong, S.; et al. Antiviral Activity of Cepharanthine against Severe Acute Respiratory Syndrome Coronavirus in Vitro. *Chin. Med. J.* **2005**, *118* (06), 493−496.
(60) Bailly, C. Cepharanthine: An Update of Its Mode of Action, Pharmacological Properties and Medical Applications. *Phytomedicine* **2019**, *62*, No. 152956.
(61) Abd El-Aziz, N. M.; Khalifa, I.; Darwish, A. M. G.; Badr, A. N.; Aljumayi, H.; Hafez, E.-S.; Shehata, M. G. Docking Analysis of Some Bioactive Compounds from Traditional Plants against SARS-CoV-2 Target Proteins. *Molecules* **2022**, *27* (9), 2662.
(62) Hall, W. W.; Fujii, M. Deregulation of Cell-Signaling Pathways in HTLV-1 Infection. *Oncogene* **2005**, *24* (39), 5965−5975.
(63) Sun, S.-C.; Yamaoka, S. Activation of NF-KB by HTLV-I and Implications for Cell Transformation. *Oncogene* **2005**, *24* (39), 5952−5964.
(64) Liang, D.; Li, Q.; Du, L.; Dou, G. Pharmacological Effects and Clinical Prospects of Cepharanthine. *Molecules* **2022**, *27* (24), 8933.
(65) Wang, Y.; Wang, T.; Wang, H.; Liu, W.; Li, X.; Wang, X.; Zhang, Y. A Mechanistic Updated Overview on Cepharanthine as Potential Anticancer Agent. *Biomed. Pharmacother.* **2023**, *165*, No. 115107.

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

(66) Ma, W.-H.; Lu, Y.; Huang, H.; Zhou, P.; Chen, D.-F. Schisanwilsonins A−G and Related Anti-HBV Lignans from the Fruits of Schisandra Wilsoniana. *Bioorg. Med. Chem. Lett.* **2009**, *19* (17), 4958−4962.
(67) Wu, Y.-H. Naturally Derived Anti-Hepatitis B Virus Agents and Their Mechanism of Action. *World J. Gastroenterol.* **2016**, *22* (1), 188.
(68) Petrosillo, N.; Viceconte, G.; Ergonul, O.; Ippolito, G.; Petersen, E. COVID-19, SARS and MERS: Are They Closely Related? *Clin. Microbiol. Infect.* **2020**, *26* (6), 729−734.
(69) Bhagya, N.; Chandrashekar, K. R. Tetrandrine−A Molecule of Wide Bioactivity. *Phytochemistry* **2016**, *125*, 5−13.
(70) Fan, H.-H.; Wang, L.-Q.; Liu, W.-L.; An, X.-P.; Liu, Z.-D.; He, X.-Q.; Song, L.-H.; Tong, Y.-G. Repurposing of Clinically Approved Drugs for Treatment of Coronavirus Disease 2019 in a 2019-Novel Coronavirus-Related Coronavirus Model. *Chin. Med. J.* **2020**, *133* (09), 1051−1056.
(71) Lan, J.; Ge, J.; Yu, J.; Shan, S.; Zhou, H.; Fan, S.; Zhang, Q.; Shi, X.; Wang, Q.; Zhang, L.; et al. Structure of the SARS-CoV-2 Spike Receptor-Binding Domain Bound to the ACE2 Receptor. *Nature* **2020**, *581* (7807), 215−220.
(72) Ohashi, H.; Watashi, K.; Saso, W.; Shionoya, K.; Iwanami, S.; Hirokawa, T.; Shirai, T.; Kanaya, S.; Ito, Y.; Kim, K. S. Multidrug Treatment with Nelfinavir and Cepharanthine against COVID-19. *bioRxiv (Microbiology)*, April 15, 2020, 2020.04.14.039925, DOI: 10.1101/2020.04.14.039925.
(73) Xia, B.; Zheng, L.; Li, Y.; Sun, W.; Liu, Y.; Li, L.; Pang, J.; Chen, J.; Li, J.; Cheng, H. The Brief Overview, Antivirus and Anti-SARS-CoV-2 Activity, Quantitative Methods, and Pharmacokinetics of Cepharanthine: A Potential Small-Molecule Drug against COVID-19. *Front. Pharmacol.* **2023**, *14*, No. 1098972, DOI: 10.3389/fphar.2023.1098972.
(74) Khan, A.; Khan, M.; Saleem, S.; Babar, Z.; Ali, A.; Khan, A. A.; Sardar, Z.; Hamayun, F.; Ali, S. S.; Wei, D.-Q. Phylogenetic Analysis and Structural Perspectives of RNA-Dependent RNA-Polymerase Inhibition from SARs-CoV-2 with Natural Products. *Interdiscip. Sci.* **2020**, *12*, 335−348.
(75) Uto, T.; Nishi, Y.; Toyama, M.; Yoshinaga, K.; Baba, M. Inhibitory Effect of Cepharanthine on Dendritic Cell Activation and Function. *Int. Immunopharmacol.* **2011**, *11* (11), 1932−1938.
(76) Silva dos Santos, J.; Gonçalves Cirino, J. P.; de Oliveira Carvalho, P.; Ortega, M. M. The Pharmacological Action of Kaempferol in Central Nervous System Diseases: A Review. *Front. Pharmacol.* **2021**, *11*, No. 565700.
(77) Ren, J. I. E.; Lu, Y.; Qian, Y.; Chen, B.; Wu, T. A. O.; Ji, G. Recent Progress Regarding Kaempferol for the Treatment of Various Diseases. *Exp. Ther. Med.* **2019**, *18* (4), 2759−2776.
(78) Care, C.; Sornjai, W.; Jaratsittisin, J.; Hitakarun, A.; Wikan, N.; Triwitayakorn, K.; Smith, D. R. Discordant Activity of Kaempferol towards Dengue Virus and Japanese Encephalitis Virus. *Molecules* **2020**, *25* (5), 1246.
(79) Zhang, R.; Ai, X.; Duan, Y.; Xue, M.; He, W.; Wang, C.; Xu, T.; Xu, M.; Liu, B.; Li, C.; et al. Kaempferol Ameliorates H9N2 Swine Influenza Virus-Induced Acute Lung Injury by Inactivation of TLR4/MyD88-Mediated NF-KB and MAPK Signaling Pathways. *Biomed. Pharmacother.* **2017**, *89*, 660−672.
(80) Tsai, F. J.; Lin, C. W.; Lai, C. C.; Lan, Y. C.; Lai, C. H.; Hung, C. H.; Hsueh, K. C.; Lin, T. H.; Chang, H. C.; Wan, L.; Sheu, J. J. C.; Lin, Y. J. Kaempferol Inhibits Enterovirus 71 Replication and Internal Ribosome Entry Site (IRES) Activity through FUBP and HNRP Proteins. *Food Chem.* **2011**, *128* (2), 312−322.
(81) Schwarz, S.; Sauter, D.; Wang, K.; Zhang, R.; Sun, B.; Karioti, A.; Bilia, A. R.; Efferth, T.; Schwarz, W. Kaempferol Derivatives as Antiviral Drugs against the 3a Channel Protein of Coronavirus. *Planta Med.* **2014**, *80*, 177−182.
(82) Sacks, D.; Baxter, B.; Campbell, B. C. V; Carpenter, J. S.; Cognard, C.; Dippel, D.; Eesa, M.; Fischer, U.; Hausegger, K.; et al. Multisociety Consensus Quality Improvement Revised Consensus Statement for Endovascular Therapy of Acute Ischemic Stroke. *Int. J. Stroke.* **2018**, *13* (6), 612−632.
(83) Vetvicka, V.; Vannucci, L. Biological Properties of Andrographolide, an Active Ingredient of Andrographis Paniculata: A Narrative Review. *J. Transl. Med.* **2021**, *9* (14), 1186.
(84) Sheeja, K.; Kuttan, G. Activation of Cytotoxic T Lymphocyte Responses and Attenuation of Tumor Growth in Vivo by Andrographis Paniculata Extract and Andrographolide. *Immunopharmacol. Immunotoxicol.* **2007**, *29* (1), 81−93.
(85) Chen, J.-X.; Xue, H.-J.; Ye, W.-C.; Fang, B.-H.; Liu, Y.-H.; Yuan, S.-H.; Yu, P.; Wang, Y.-Q. Activity of Andrographolide and Its Derivatives against Influenza Virus in Vivo and in Vitro. *Biol. Pharm. Bull.* **2009**, *32* (8), 1385−1391.
(86) Yu, B.; Dai, C.; Jiang, Z.; Li, E.; Chen, C.; Wu, X.; Chen, J.; Liu, Q.; Zhao, C.; He, J.; et al. Andrographolide as an Anti-H1N1 Drug and the Mechanism Related to Retinoic Acid-Inducible Gene-I-like Receptors Signaling Pathway. *Chin. J. Integr. Med.* **2014**, *20* (7), 540−545.
(87) Busca, A.; Kumar, A. Innate Immune Responses in Hepatitis B Virus (HBV) Infection. *Virol. J.* **2014**, *11* (1), 22.
(88) Stoop, J. N.; van der Molen, R. G.; Baan, C. C.; van der Laan, L. J. W.; Kuipers, E. J.; Kusters, J. G.; Janssen, H. L. A. Regulatory T Cells Contribute to the Impaired Immune Response in Patients with Chronic Hepatitis B Virus Infection. *Hepatology* **2005**, *41* (4), 771−778.
(89) Huang, Q.; Zhang, S.; Huang, R.; Wei, L.; Chen, Y.; Lv, S.; Liang, C.; Tan, S.; liang, S.; Zhuo, L.; et al. Isolation and Identification of an Anti-Hepatitis B Virus Compound from Hydrocotyle Sibthorpioides Lam. *J. Ethnopharmacol.* **2013**, *150* (2), 568−575.
(90) Chen, Y.; Zhu, J. Anti-HBV Effect of Individual Traditional C Hinese Herbal Medicine in Vitro and in Vivo: An Analytic Review. *J. Viral Hepat.* **2013**, *20* (7), 445−452.
(91) Ito, M.; Kusunoki, H.; Mizuochi, T. Peripheral B Cells as Reservoirs for Persistent HCV Infection. *Front. Microbiol.* **2011**, *2*, 177.
(92) Yi, G.; Wen, Y.; Shu, C.; Konan, K. V.; Han, Q.; Li, P.; Kao, C. C. Hepatitis C Virus NS4B Can Suppress STING Accumulation to Evade Innate Immune Responses. *J. Virol.* **2016**, *90* (1), 254−265.
(93) Chandramohan, V.; Kaphle, A.; Chekuri, M.; Gangarudraiah, S.; Bychapur Siddaiah, G. Evaluating Andrographolide as a Potent Inhibitor of NS3−4A Protease and Its Drug-Resistant Mutants Using in Silico Approaches. *Adv. Virol.* **2015**, *2015*, 1.
(94) Chentoufi, A. A.; Dervillez, X.; Dasgupta, G.; Nguyen, C.; Kabbara, K. W.; Jiang, X.; Nesburn, A. B.; Wechsler, S. L.; BenMohamed, L. The Herpes Simplex Virus Type 1 Latency-Associated Transcript Inhibits Phenotypic and Functional Maturation of Dendritic Cells. *Viral Immunol.* **2012**, *25* (3), 204−215.
(95) Wiart, C.; Kumar, K.; Yusof, M. Y.; Hamimah, H.; Fauzi, Z. M.; Sulaiman, M. Antiviral Properties of Ent-labdene Diterpenes of Andrographis Paniculata Nees, Inhibitors of Herpes Simplex Virus Type 1. *Phytother. Res.* **2005**, *19* (12), 1069−1070.
(96) Seubsasana, S.; Pientong, C.; Ekalaksananan, T.; Thongchai, S.; Aromdee, C. A Potential Andrographolide Analogue against the Replication of Herpes Simplex Virus Type 1 in Vero Cells. *Med. Chem.* **2011**, *7* (3), 237−244.
(97) Rancan, C.; Schirrmann, L.; Hüls, C.; Zeidler, R.; Moosmann, A. Latent Membrane Protein LMP2A Impairs Recognition of EBV-Infected Cells by CD8+ T Cells. *PLoS Pathog.* **2015**, *11* (6), No. e1004906.
(98) Wang, J.-J.; Li, Y.-F.; Jin, Y.-Y.; Wang, X.; Chen, T.-X. Effects of Epstein-Barr Virus on the Development of Dendritic Cells Derived from Cord Blood Monocytes: An Essential Role for Apoptosis. *Braz. J. Infect. Dis.* **2012**, *16*, 19−26.
(99) Lin, T.-P.; Chen, S.-Y.; Duh, P.-D.; Chang, L.-K.; Liu, Y.-N. Inhibition of the Epstein−Barr Virus Lytic Cycle by Andrographolide. *Biol. Pharm. Bull.* **2008**, *31* (11), 2018−2023.
(100) Song, D.; Li, H.; Li, H.; Dai, J. Effect of Human Papillomavirus Infection on the Immune System and Its Role in the Course of Cervical Cancer. *Oncol. Lett.* **2015**, *10* (2), 600−606.
(101) Chang, R. S.; Ding, L.; Gai-Qing, C.; Qi-Choa, P.; Ze-Lin, Z.; Smith, K. M. Dehydroandrographolide Succinic Acid Monoester as an

Inhibitor against the Human Immunodeficiency Virus. *Proc. Soc. Exp. Biol. Med.* **1991**, *197* (1), 59−66.
(102) Thon-Hon, V. G.; Denizot, M.; Li-Pat-Yuen, G.; Giry, C.; Jaffar-Bandjee, M.-C.; Gasque, P. Deciphering the Differential Response of Two Human Fibroblast Cell Lines Following Chikungunya Virus Infection. *Virol. J.* **2012**, *9* (1), 1−10.
(103) Wintachai, P.; Kaur, P.; Lee, R. C. H.; Ramphan, S.; Kuadkitkan, A.; Wikan, N.; Ubol, S.; Roytrakul, S.; Chu, J. J. H.; Smith, D. R. Activity of Andrographolide against Chikungunya Virus Infection. *Sci. Rep.* **2015**, *5* (1), 1−14.
(104) Gupta, S.; Mishra, K. P.; Ganju, L. Broad-Spectrum Antiviral Properties of Andrographolide. *Arch. Virol.* **2017**, *162* (3), 611−623.
(105) Lee, T.-Y.; Chang, H.-H.; Wen, C.-K.; Huang, T.-H.; Chang, Y.-S. Modulation of Thioacetamide-Induced Hepatic Inflammations, Angiogenesis and Fibrosis by Andrographolide in Mice. *J. Ethnopharmacol.* **2014**, *158*, 423−430.
(106) Rajanna, M.; Bharathi, B.; Shivakumar, B.R.; Deepak, M.; Prashanth, D.; Prabakaran, D.; Vijayabhaskar, T.; Arun, B. Immunomodulatory Effects of Andrographis Paniculata Extract in Healthy Adults−An Open-Label Study. *J. Ayurveda Integr. Med.* **2021**, *12* (3), 529−534.
(107) Lu, J.; Ma, Y.; Wu, J.; Huang, H.; Wang, X.; Chen, Z.; Chen, J.; He, H.; Huang, C. A Review for the Neuroprotective Effects of Andrographolide in the Central Nervous System. *Biomed. Pharmacother.* **2019**, *117*, No. 109078.
(108) A. Youness, R.; Kamel, R.; A. Elkasabgy, N.; Shao, P.; A. Farag, M. Recent Advances in Tannic Acid (Gallotannin) Anticancer Activities and Drug Delivery Systems for Efficacy Improvement; a Comprehensive Review. *Molecules* **2021**, *26* (5), 1486.
(109) Baldwin, A.; Booth, B. W. Biomedical Applications of Tannic Acid. *J. Biomater Appl.* **2022**, *36* (8), 1503−1523.
(110) Lin, L.-T.; Chen, T.-Y.; Chung, C.-Y.; Noyce, R. S.; Grindley, T. B.; McCormick, C.; Lin, T.-C.; Wang, G.-H.; Lin, C.-C.; Richardson, C. D. Hydrolyzable Tannins (Chebulagic Acid and Punicalagin) Target Viral Glycoprotein-Glycosaminoglycan Interactions to Inhibit Herpes Simplex Virus 1 Entry and Cell-to-Cell Spread. *J. Virol.* **2011**, *85* (9), 4386−4398.
(111) Theisen, L. L.; Erdelmeier, C. A. J.; Spoden, G. A.; Boukhallouk, F.; Sausy, A.; Florin, L.; Muller, C. P. Tannins from Hamamelis Virginiana Bark Extract: Characterization and Improvement of the Antiviral Efficacy against Influenza A Virus and Human Papillomavirus. *PloS One* **2014**, *9* (1), No. e88062.
(112) Zhang, X.-F.; Dai, Y.-C.; Zhong, W.; Tan, M.; Lv, Z.-P.; Zhou, Y.-C.; Jiang, X. Tannic Acid Inhibited Norovirus Binding to HBGA Receptors, a Study of 50 Chinese Medicinal Herbs. *Bioorg. Med. Chem.* **2012**, *20* (4), 1616−1623.
(113) Dwevedi, A.; Dwivedi, R.; Sharma, Y. K. Exploration of Phytochemicals Found in Terminalia Sp. and Their Antiretroviral Activities. *Pharmacogn. Rev.* **2016**, *10* (20), 73.
(114) Lin, L.-T.; Chen, T.-Y.; Lin, S.-C.; Chung, C.-Y.; Lin, T.-C.; Wang, G.-H.; Anderson, R.; Lin, C.-C.; Richardson, C. D. Broad-Spectrum Antiviral Activity of Chebulagic Acid and Punicalagin against Viruses That Use Glycosaminoglycans for Entry. *BMC Microbiol.* **2013**, *13* (1), 187.
(115) Rebbapragada, A.; Wachihi, C.; Pettengell, C.; Sunderji, S.; Huibner, S.; Jaoko, W.; Ball, B.; Fowke, K.; Mazzulli, T.; Plummer, F. A.; et al. Negative Mucosal Synergy between Herpes Simplex Type 2 and HIV in the Female Genital Tract. *AIDS* **2007**, *21* (5), 589−598.
(116) Zhu, X.-P.; Muhammad, Z. S.; Wang, J.-G.; Lin, W.; Guo, S.-K.; Zhang, W. HSV-2 Vaccine: Current Status and Insight into Factors for Developing an Efficient Vaccine. *Viruses* **2014**, *6* (2), 371−390.
(117) Roizman, B.; Whitley, R. J. An Inquiry into the Molecular Basis of HSV Latency and Reactivation. *Annu. Rev. Microbiol.* **2013**, *67*, 355−374.
(118) Whitley, R. New Approaches to the Therapy of HSV Infections. *Herpes* **2006**, *13* (2), 53−55.
(119) Lara, H. H.; Ayala-Nuñez, N. V.; Ixtepan-Turrent, L.; Rodriguez-Padilla, C. Mode of Antiviral Action of Silver Nanoparticles against HIV-1. *J. Nanobiotechnology* **2010**, *8* (1), 1−10.
(120) Lu, L.; Sun, R. W.-Y.; Chen, R.; Hui, C.-K.; Ho, C.-M.; Luk, J. M.; Lau, G. K. K.; Che, C.-M. Silver Nanoparticles Inhibit Hepatitis B Virus Replication. *Antivir. Ther.* **2008**, *13* (2), 253−262.
(121) Orłowski, P.; Kowalczyk, A.; Tomaszewska, E.; Ranoszek-Soliwoda, K.; Węgrzyn, A.; Grzesiak, J.; Celichowski, G.; Grobelny, J.; Eriksson, K.; Krzyzowska, M. Antiviral Activity of Tannic Acid Modified Silver Nanoparticles: Potential to Activate Immune Response in Herpes Genitalis. *Viruses* **2018**, *10* (10), 524.
(122) Orlowski, P.; Tomaszewska, E.; Gniadek, M.; Baska, P.; Nowakowska, J.; Sokolowska, J.; Nowak, Z.; Donten, M.; Celichowski, G.; Grobelny, J.; et al. Tannic Acid Modified Silver Nanoparticles Show Antiviral Activity in Herpes Simplex Virus Type 2 Infection. *PloS ONE* **2014**, *9* (8), No. e104113.
(123) Srivastava, R.; Hernández-Ruiz, M.; Khan, A. A.; Fouladi, M. A.; Kim, G. J.; Ly, V. T.; Yamada, T.; Lam, C.; Sarain, S. A. B.; Boldbaatar, U.; et al. CXCL17 Chemokine−Dependent Mobilization of CXCR8+ CD8+ Effector Memory and Tissue-Resident Memory T Cells in the Vaginal Mucosa Is Associated with Protection against Genital Herpes. *J. Immunol.* **2018**, *200* (8), 2915−2926.
(124) Feduska, J.; Tse, H. M. Immunomodulation of Dendritic Cells Using Tannic Acid-Based Capsules. *Diabetes* **2018**, *67*, 225-LB.
(125) Orlowski, P.; Tomaszewska, E.; Ranoszek-Soliwoda, K.; Gniadek, M.; Labedz, O.; Malewski, T.; Nowakowska, J.; Chodaczek, G.; Celichowski, G.; Grobelny, J.; et al. Tannic Acid-Modified Silver and Gold Nanoparticles as Novel Stimulators of Dendritic Cells Activation. *Front. Immunol.* **2018**, *9*, 1115.
(126) Kawano, M.; Saika, K.; Takagi, R.; Matsui, M.; Matsushita, S. Tannic Acid Acts as an Agonist of the Dopamine D2L Receptor, Regulates Immune Responses, and Ameliorates Experimentally Induced Colitis in Mice. *Brain Behav. Immun. Health.* **2020**, *5*, No. 100071.
(127) Mao, Q.-Q.; Xu, X.-Y.; Cao, S.-Y.; Gan, R.-Y.; Corke, H.; Beta, T.; Li, H.-B. Bioactive Compounds and Bioactivities of Ginger (Zingiber Officinale Roscoe). *Foods* **2019**, *8* (6), 185.
(128) Ahkam, A. H.; Hermanto, F. E.; Alamsyah, A.; Aliyyah, I. H.; Fatchiyah, F. Virtual Prediction of Antiviral Potential of Ginger (Zingiber Officinale) Bioactive Compounds against Spike and MPro of SARS-CoV2 Protein. *Berk. Penelit. Hayati* **2020**, *25* (2), 52−57.
(129) Camero, M.; Marinaro, M.; Losurdo, M.; Larocca, V.; Bodnar, L.; Patruno, G.; Buonavoglia, C.; Tempesta, M. Caprine Herpesvirus 1 (CpHV-1) Vaginal Infection of Goats: Clinical Efficacy of Fig Latex. *Nat. Prod. Res.* **2016**, *30* (5), 605−607.
(130) Camero, M.; Lanave, G.; Catella, C.; Capozza, P.; Gentile, A.; Fracchiolla, G.; Britti, D.; Martella, V.; Buonavoglia, C.; Tempesta, M. Virucidal Activity of Ginger Essential Oil against Caprine Alphaherpesvirus-1. *Vet. Microbiol.* **2019**, *230*, 150−155.
(131) Chang, J. S.; Wang, K. C.; Yeh, C. F.; Shieh, D. E.; Chiang, L. C. Fresh Ginger (Zingiber Officinale) Has Anti-Viral Activity against Human Respiratory Syncytial Virus in Human Respiratory Tract Cell Lines. *J. Ethnopharmacol.* **2013**, *145* (1), 146−151.
(132) Chrubasik, S.; Pittler, M. H.; Roufogalis, B. D. Zingiberis Rhizoma: A Comprehensive Review on the Ginger Effect and Efficacy Profiles. *Phytomedicine* **2005**, *12* (9), 684−701.
(133) Kaushik, S.; Jangra, G.; Kundu, V.; Yadav, J. P.; Kaushik, S. Anti-Viral Activity of Zingiber Officinale (Ginger) Ingredients against the Chikungunya Virus. *Virusdisease* **2020**, *31* (3), 270−276.
(134) Behl, T.; Rocchetti, G.; Chadha, S.; Zengin, G.; Bungau, S.; Kumar, A.; Mehta, V.; Uddin, M. S.; Khullar, G.; Setia, D.; et al. Phytochemicals from Plant Foods as Potential Source of Antiviral Agents: An Overview. *Pharmaceuticals* **2021**, *14* (4), 381.
(135) Zhou, H.; Deng, Y.; Xie, Q. The Modulatory Effects of the Volatile Oil of Ginger on the Cellular Immune Response in Vitro and in Vivo in Mice. *J. Ethnopharmacol.* **2006**, *105* (1−2), 301−305.
(136) Tripathi, S.; Bruch, D.; Kittur, D. S. Ginger Extract Inhibits LPS Induced Macrophage Activation and Function. *BMC Complement. Altern. Med.* **2008**, *8* (1), 1−7.

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615

(137) Ratan, Z. A.; Haidere, M. F.; Hong, Y. H.; Park, S. H.; Lee, J.-O.; Lee, J.; Cho, J. Y. Pharmacological Potential of Ginseng and Its Major Component Ginsenosides. *J. Ginseng Res.* **2021**, *45* (2), 199−210.
(138) Truong, V.-L.; Jeong, W.-S. Red Ginseng (Panax Ginseng Meyer) Oil: A Comprehensive Review of Extraction Technologies, Chemical Composition, Health Benefits, Molecular Mechanisms, and Safety. *J. Ginseng Res.* **2022**, *46* (2), 214−224.
(139) Ru, W.; Wang, D.; Xu, Y.; He, X.; Sun, Y.-E.; Qian, L.; Zhou, X.; Qin, Y. Chemical Constituents and Bioactivities of Panax Ginseng (C. A. Mey.). *Drug Discov. Ther.* **2015**, *9* (1), 23−32.
(140) Mcelhaney, J. E.; Gravenstein, S.; Cole, S. K.; Davidson, E.; O'neill, D.; Petitjean, S.; Rumble, B.; Shan, J. J. A Placebo-controlled Trial of a Proprietary Extract of North American Ginseng (CVT-E002) to Prevent Acute Respiratory Illness in Institutionalized Older Adults. *J. Am. Geriatr. Soc.* **2004**, *52* (1), 13−19.
(141) Lee, J. S.; Hwang, H. S.; Ko, E.-J.; Lee, Y.-N.; Kwon, Y.-M.; Kim, M.-C.; Kang, S.-M. Immunomodulatory Activity of Red Ginseng against Influenza A Virus Infection. *Nutrients* **2014**, *6* (2), 517−529.
(142) Park, E. H.; Yum, J.; Ku, K. B.; Kim, H. M.; Kang, Y. M.; Kim, J. C.; Kim, J. A.; Kang, Y. K.; Seo, S. H. Red Ginseng-Containing Diet Helps to Protect Mice and Ferrets from the Lethal Infection by Highly Pathogenic H5N1 Influenza Virus. *J. Ginseng Res.* **2014**, *38* (1), 40−46.
(143) Yoo, D.-G.; Kim, M.-C.; Park, M.-K.; Park, K.-M.; Quan, F.-S.; Song, J.-M.; Wee, J. J.; Wang, B.-Z.; Cho, Y.-K.; Compans, R. W.; et al. Protective Effect of Ginseng Polysaccharides on Influenza Viral Infection. *PLoS ONE* **2012**, *7* (3), No. e33678.
(144) Yoo, D.-G.; Kim, M.-C.; Park, M.-K.; Song, J.-M.; Quan, F.-S.; Park, K.-M.; Cho, Y.-K.; Kang, S.-M. Protective Effect of Korean Red Ginseng Extract on the Infections by H1N1 and H3N2 Influenza Viruses in Mice. *J. Med. Food* **2012**, *15* (10), 855−862.
(145) Song, Z.; Wu, H.; Mathee, K.; Høiby, N.; Kharazmi, A. Gerimax Ginseng Regulates Both Humoral and Cellular Immunity during Chronic Pseudomonas Aeruginosa Lung Infection. *J. Altern. Complement. Med.* **2002**, *8* (4), 459−466.
(146) Kachur, K.; Suntres, Z. E. The Antimicrobial Properties of Ginseng and Ginseng Extracts. *Expert Rev. Anti-Infect. Ther.* **2016**, *14* (1), 81−94.
(147) Rivera, E.; Pettersson, F. E.; Inganäs, M.; Paulie, S.; Grönvik, K.-O. The Rb1 Fraction of Ginseng Elicits a Balanced Th1 and Th2 Immune Response. *Vaccine* **2005**, *23* (46−47), 5411−5419.
(148) Lee, J. S.; Lee, Y.-N.; Lee, Y.-T.; Hwang, H. S.; Kim, K.-H.; Ko, E.-J.; Kim, M.-C.; Kang, S.-M. Ginseng Protects against Respiratory Syncytial Virus by Modulating Multiple Immune Cells and Inhibiting Viral Replication. *Nutrients* **2015**, *7* (2), 1021−1036.
(149) See, D. M.; Broumand, N.; Sahl, L.; Tilles, J. G. In Vitro Effects of Echinacea and Ginseng on Natural Killer and Antibody-Dependent Cell Cytotoxicity in Healthy Subjects and Chronic Fatigue Syndrome or Acquired Immunodeficiency Syndrome Patients. *Immunopharmacology* **1997**, *35* (3), 229−235.
(150) Cho, Y. K.; Sung, H.; Lee, H. J.; Hyun Joo, C.; Jae Cho, G. Long-Term Intake of Korean Red Ginseng in HIV-1-Infected Patients: Development of Resistance Mutation to Zidovudine Is Delayed. *Int. Immunopharmacol.* **2001**, *1* (7), 1295−1305.
(151) Jeong, J.-J.; Kim, B.; Kim, D.-H. Ginsenoside Rh1 Eliminates the Cytoprotective Phenotype of Human Immunodeficiency Virus Type 1-Transduced Human Macrophages by Inhibiting the Phosphorylation of Pyruvate Dehydrogenase Lipoamide Kinase Isozyme 1. *Biol. Pharm. Bull.* **2013**, *36* (7), 1088−1094.
(152) Jeong, J.-J.; Kim, B.; Kim, D.-H. Ginsenoside Rb1 Eliminates HIV-1 (D3)-Transduced Cytoprotective Human Macrophages by Inhibiting the AKT Pathway. *J. Med. Food* **2014**, *17* (8), 849−854.
(153) Kang, S.; Min, H. Ginseng, the'immunity Boost': The Effects of Panax Ginseng on Immune System. *J. Ginseng Res.* **2012**, *36* (4), 354.
(154) Hayashi, H.; Sudo, H. Economic Importance of Licorice. *Plant Biotechnol.* **2009**, *26* (1), 101−104.
(155) Herrera, M.; Herrera, A.; Ariño, A. Estimation of Dietary Intake of Ochratoxin A from Liquorice Confectionery. *Food Chem. Toxicol.* **2009**, *47* (8), 2002−2006.
(156) Cinatl, J.; Morgenstern, B.; Bauer, G.; Chandra, P.; Rabenau, H.; Doerr, H. Glycyrrhizin, an Active Component of Liquorice Roots, and Replication of SARS-Associated Coronavirus. *Lancet* **2003**, *361* (9374), 2045−2046.
(157) Soufy, H.; Yassein, S.; Ahmed, A. R.; Khodier, M. H.; Kutkat, M. A.; Nasr, S. M.; Okda, F. A. Antiviral and Immune Stimulant Activities of Glycyrrhizin against Duck Hepatitis Virus. *Afr. J. Tradit. Complement. Altern. Med.* **2012**, *9* (3), 389−395.
(158) Huan, C.; Xu, Y.; Zhang, W.; Guo, T.; Pan, H.; Gao, S. Research Progress on the Antiviral Activity of Glycyrrhizin and Its Derivatives in Liquorice. *Front. Pharmacol.* **2021**, *12*, No. 680674.
(159) Sekizawa, T.; Yanagi, K.; Itoyama, Y. Glycyrrhizin Increases Survival of Mice with Herpes Simplex Encephalitis. *Acta Virol.* **2001**, *45* (1), 51−54.
(160) Dutta, T.; Baildya, N.; Khan, A. A.; Ghosh, N. N. Inhibitory Effect of Anti-HIV Compounds Extracted from Indian Medicinal Plants to Retard the Replication and Transcription Process of SARS-CoV-2: An Insight from Molecular Docking and MD-Simulation Studies. *Netw. Model. Anal. Health Inform. Bioinform.* **2021**, *10* (1), 1−11.
(161) Sasaki, H.; Takei, M.; Kobayashi, M.; Pollard, R. B.; Suzuki, F. Effect of Glycyrrhizin, an Active Component of Licorice Roots, on HIV Replication in Cultures of Peripheral Blood Mononuclear Cells from HIV-Seropositive Patients. *Pathobiology* **2003**, *70* (4), 229−236.
(162) Ploeger, B.; Mensinga, T.; Sips, A.; Seinen, W.; Meulenbelt, J.; DeJongh, J. The Pharmacokinetics of Glycyrrhizic Acid Evaluated by Physiologically Based Pharmacokinetic Modeling. *Drug Metab. Rev.* **2001**, *33* (2), 125−147.
(163) Yasui, S.; Fujiwara, K.; Tawada, A.; Fukuda, Y.; Nakano, M.; Yokosuka, O. Efficacy of Intravenous Glycyrrhizin in the Early Stage of Acute Onset Autoimmune Hepatitis. *Dig. Dis. Sci.* **2011**, *56* (12), 3638−3647.
(164) Michaelis, M.; Geiler, J.; Naczk, P.; Sithisarn, P.; Leutz, A.; Doerr, H. W.; Cinatl, J., Jr Glycyrrhizin Exerts Antioxidative Effects in H5N1 Influenza A Virus-Infected Cells and Inhibits Virus Replication and pro-Inflammatory Gene Expression. *PloS One* **2011**, *6* (5), No. e19705.
(165) Pastorino, G.; Cornara, L.; Soares, S.; Rodrigues, F.; Oliveira, M. B. P. P. Liquorice (Glycyrrhiza Glabra): A Phytochemical and Pharmacological Review. *Phytother. Res.* **2018**, *32* (12), 2323−2339.
(166) Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L. A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature* **2020**, *579* (7798), 270−273.
(167) Chai, X.; Hu, L.; Zhang, Y.; Han, W.; Lu, Z.; Ke, A.; Zhou, J.; Shi, G.; Fang, N.; Fan, J. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage after 2019-NCoV Infection. *bioRxiv (Genomics)*, Feb. 4, 2020, 2020.02.03.931766. DOI: 10.1101/2020.02.03.931766.
(168) Zhang, H.; Kang, Z.; Gong, H.; Xu, D.; Wang, J.; Li, Z.; Cui, X.; Xiao, J.; Meng, T.; Zhou, W.The Digestive System Is a Potential Route of 2019-NCov Infection: A Bioinformatics Analysis Based on Single-Cell Transcriptomes. *bioRxiv (Microbiology)*, Jan. 31, 2020, 2020.01.30.927806. DOI: 10.1101/2020.01.30.927806.
(169) Sungnak, W.; Huang, N.; Bécavin, C.; Berg, M.; Queen, R.; Litvinukova, M.; Talavera-López, C.; Maatz, H.; Reichart, D.; Sampaziotis, F.; et al. SARS-CoV-2 Entry Factors Are Highly Expressed in Nasal Epithelial Cells Together with Innate Immune Genes. *Nat. Med.* **2020**, *26* (5), 681−687.
(170) Chrzanowski, J.; Chrzanowska, A.; Graboń, W. Glycyrrhizin: An Old Weapon against a Novel Coronavirus. *Phytother. Res.* **2021**, *35* (2), 629−636.
(171) Geller, C.; Varbanov, M.; Duval, R. E. Human Coronaviruses: Insights into Environmental Resistance and Its Influence on the Development of New Antiseptic Strategies. *Viruses* **2012**, *4* (11), 3044−3068.

(172) Mori, K.; Sakai, H.; Suzuki, S.; Akutsu, Y.; Ishikawa, M.; Imaizumi, M.; Tada, K.; Aihara, M.; Sawada, Y.; Yokoyama, M.; et al. Effects of Glycyrrhizin (SNMC: Stronger Neo-Minophagen C) in Hemophilia Patients with HIV-1 Infection. *Tohoku J. Exp. Med.* **1990**, *162* (2), 183−193.
(173) Thyagarajan, S. P.; Jayaram, S.; Gopalakrishnan, V.; Hari, R.; Jeyakumar, P.; Sripathi, M. S. Herbal Medicines for Liver Diseases in India. *J. Gastroenterol. Hepatol.* **2002**, *17*, S370−S376.
(174) Ashfaq, U. A.; Masoud, M. S.; Nawaz, Z.; Riazuddin, S. Glycyrrhizin as Antiviral Agent against Hepatitis C Virus. *J. Transl. Med.* **2011**, *9* (1), 1−7.
(175) Wolkerstorfer, A.; Kurz, H.; Bachhofner, N.; Szolar, O. H. J. Glycyrrhizin Inhibits Influenza A Virus Uptake into the Cell. *Antivir. Res.* **2009**, *83* (2), 171−178.
(176) Guo, A.; He, D.; Xu, H.-B.; Geng, C.-A.; Zhao, J. Promotion of Regulatory T Cell Induction by Immunomodulatory Herbal Medicine Licorice and Its Two Constituents. *Sci. Rep.* **2015**, *5* (1), 1−12.
(177) Ayeka, P. A.; Bian, Y.; Githaiga, P. M.; Zhao, Y. The Immunomodulatory Activities of Licorice Polysaccharides (Glycyrrhiza Uralensis Fisch.) in CT 26 Tumor-Bearing Mice. *BMC Complement. Altern. Med.* **2017**, *17* (1), 1−9.
(178) Singh, B.; Singh, J. P.; Kaur, A.; Singh, N. Bioactive Compounds in Banana and Their Associated Health Benefits−A Review. *Food Chem.* **2016**, *206*, 1−11.
(179) Maheshwari, S.; Kumar, V.; Bhadauria, G.; Mishra, A. Immunomodulatory Potential of Phytochemicals and Other Bioactive Compounds of Fruits: A Review. *Food Front.* **2022**, *3* (2), 221−238.
(180) Al-Hatamleh, M. A. I.; Boer, J. C.; Wilson, K. L.; Plebanski, M.; Mohamud, R.; Mustafa, M. Z. Antioxidant-Based Medicinal Properties of Stingless Bee Products: Recent Progress and Future Directions. *Biomolecules* **2020**, *10* (6), 923.
(181) Reinisalo, M.; Kårlund, A.; Koskela, A.; Kaarniranta, K.; Karjalainen, R. O. Polyphenol Stilbenes: Molecular Mechanisms of Defence against Oxidative Stress and Aging-Related Diseases. *Oxid. Med. Cell Longev.* **2015**, *2015*, No. 340520.
(182) Hamidie, R. D. R.; Shibaguchi, T.; Yamada, T.; Koma, R.; Ishizawa, R.; Saito, Y.; Hosoi, T.; Masuda, K. Curcumin Induces Mitochondrial Biogenesis by Increasing Cyclic AMP Levels via Phosphodiesterase 4A Inhibition in Skeletal Muscle. *Br. J. Nutr.* **2021**, *126* (11), 1642−1650.
(183) Xu, W.; Luo, Y.; Yin, J.; Huang, M.; Luo, F. Targeting AMPK Signaling by Polyphenols: A Novel Strategy for Tackling Aging. *Food Funct.* **2023**, *14*, 56−73.
(184) Wu, A.-G.; Yong, Y.-Y.; Pan, Y.-R.; Zhang, L.; Wu, J.-M.; Zhang, Y.; Tang, Y.; Wei, J.; Yu, L.; Law, B. Y.-K.; et al. Targeting Nrf2-Mediated Oxidative Stress Response in Traumatic Brain Injury: Therapeutic Perspectives of Phytochemicals. *Oxid. Med. Cell Longev.* **2022**, *2022*, No. 1015791.
(185) Ramu, M.; Vishal, S. S.; Gogia, N. Role of AMP-Activated Protein Kinase and Sirtuins as Antiaging Proteins. In *Anti-Aging Drug Discovery on the Basis of Hallmarks of Aging*; Elsevier, 2022; pp 241−278.
(186) Shoaib, A.; Azmi, L.; Pal, S.; Alqahtani, S. S.; Rahamathulla, M.; Hani, U.; Alshehri, S.; Ghoneim, M. M.; Shakeel, F. Integrating Nanotechnology with Naturally Occurring Phytochemicals in Neuropathy Induced by Diabetes. *J. Mol. Liq.* **2022**, *350*, No. 118189.
(187) Solanki, R.; Jodha, B.; Prabina, K. E.; Aggarwal, N.; Patel, S. Recent Advances in Phytochemical Based Nano-Drug Delivery Systems to Combat Breast Cancer: A Review. *J. Drug Delivery Sci. Technol.* **2022**, *77*, No. 103832.
(188) Zaccai, M.; Yarmolinsky, L.; Khalfin, B.; Budovsky, A.; Gorelick, J.; Dahan, A.; Ben-Shabat, S. Medicinal Properties of Lilium Candidum L. and Its Phytochemicals. *Plants* **2020**, *9* (8), 959.
(189) Jahangir, M. A.; Zafar, A.; Khan, S.; Kala, C.; Muheem, A.; Taleuzzaman, M. Phytonutrients and Technological Development in Formulations. *J. Pharm. Res. Sci. Technol.* **2022**, *6* (1), 38−66.
(190) Ahmed, S.; Parvez, M. K. Recent Advances in Herb-Synthesized Nanoparticles for Viral Diseases. *Nanotechnology in Herbal Medicine* **2023**, 279−292.
(191) Jassim, S. A. A.; Naji, M. A. Novel Antiviral Agents: A Medicinal Plant Perspective. *J. Appl. Microbiol.* **2003**, *95* (3), 412−427.
(192) Dakal, T. C. Antigenic Sites in SARS-CoV-2 Spike RBD Show Molecular Similarity with Pathogenic Antigenic Determinants and Harbors Peptides for Vaccine Development. *Immunobiology* **2021**, *226* (5), No. 152091.
(193) Marian, A. J. Current State of Vaccine Development and Targeted Therapies for COVID-19: Impact of Basic Science Discoveries. *Cardiovasc. Pathol.* **2021**, *50*, No. 107278.
(194) Pillaiyar, T.; Meenakshisundaram, S.; Manickam, M. Recent Discovery and Development of Inhibitors Targeting Coronaviruses. *Drug Discovery Today* **2020**, *25* (4), 668−688.

https://doi.org/10.1021/acsptsci.3c00178
ACS Pharmacol. Transl. Sci. 2023, 6, 1600−1615