Review Article

Inhibitory Potential of Medicinal Plants Against Viral Pathogens and their Putative Modes of Action

Muhammad Akram[1], Anirban Mandal[2]*, Mehwish Iqbal[3], Arindam Mukherjee[4], Ritika Bandyopadhyay[5], Surendar Rangasamy[6], Rida Zainab[1], Muhammad Talha Khalil[1], Pragnesh Parmar[7] and Umme Laila[1]

[1]Department of Eastern Medicine and Surgery, Directorate of Medical Sciences, GC University Faisalabad, Pakistan; [2]Department of Microbiology, Mrinalini Datta Mahavidyapith, Kolkata, India; [3]Institute of Health Management, Dow University of Health Sciences, Karachi, Pakistan; [4]Department of Botany, Mrinalini Datta Mahavidyapith, Kolkata, India; [5]Department of Microbiology, Barrackpore Rastraguru Surendranath College, Kolkata, India; [6]Department of Community Medicine, Sri Venkateshwaraa Medical College Hospital and Research Centre, Puducherry, India; [7]Department Forensic Medicine and Toxicology, AIIMS, Bibinagar, Telangana, India.

Abstract | Plants are useful as food and drugs to human beings. People are becoming progressively conscious of complications with the abuse and over prescription of conventional antibiotics. Plant extracts can be good alternative in day-to-day illness instead of antibiotics misuse. Complementary and alternative medicines are good option for treatment of routine ailments. Complexes and constituents with antiviral activity exists in numerous plants, for instance, rutin, a flavonoid glycoside generally found in a range of botanicals, is efficient against herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), and influenza A virus. Ascorbic acid, beta carotene and lots of phenolics play active parts in decreasing inflammation, postponing aging, and averting certain kinds of carcinomas. There are some phenolic compounds such as tannins, flavonoids, vitamins and lignins derived from plants acts as antioxidants. In this review article, we discussed upon history of use of plants as medicine, role of plants in viral infections, and anti-viral effects of various plants.

Received | May 10, 2023; **Accepted** | December 20, 2023; **Published** | December 28, 2023
***Correspondence** | Anirban Mandal, Department of Microbiology, Mrinalini Datta Mahavidyapith, Kolkata, India; **Email:** anirbanmondal31@gmail.com
Citation | Akram, M., A. Mandal, M. Iqbal, A. Mukherjee, R. Bandyopadhyay, S. Rangasamy, R. Zainab, M.T. Khalil, P. Parmar and U. Laila. 2023. Inhibitory potential of medicinal plants against viral pathogens and their putative modes of action. *Hosts and Viruses*, 10: 58-71.
DOI | https://dx.doi.org/10.17582/journal.hv/2023/10.58.71
Keywords: Viral infections, Complementary and alternative medicines, Antiviral molecules, Medicinal plants, Herpes simplex virus, Influenza A virus

Introduction

Plants have assisted humans as a significant source of drugs and foods. Worldwide a large part of communities depends upon herbal medicines to meet their health necessities, either alone or in combination with other CAM (complementary and alternative medicines) (World Health Organization, 2013), (Jonas *et al*., 2013). In modern days, the study and use of plant products in medical science are increasing

day by day. For example, in 2017, the use of botanical products has increased rapidly 8.5 percent (in contrast with the last year) in United States, accomplishing an approximated amount of 8 billion Unites states dollar (Smith *et al*., 2018). With respect to pharmaceutical companies, frequent compounds acquired from sources of plant have extensively been identified to have pharmacological properties, and in history plants have produced numerous significant medicines for ingestion into human body, since morphine, used as the contemporary artemisinin and paclitaxel in early 19th century. In case of diabetes mellitus, research stated that the compounds of Amadori rearrangement acquired from the onion extract that is thermally-processed were capable of repress absorption of carbohydrate by means of reducing intestinal sucrose, thus inhibiting the postprandial rise in blood glucose (Kang *et al*., 2018). Conversely, one of the studies demonstrated that *in vitro* defensive property of gomisin N (acquired from the plant of *Schisandra chinensis*) conflicting to cannabinoid type-one receptor-prompted disablement of insulin signaling, in addition to *in vivo* influence of the composite on gluconeogenesis in high-fat-diet-prompted-obese mice (Nagappan *et al*., 2018). Moreover, procyanidin A2 and catechin were capable of restraining inflammation of nervous system in amyloid managed microglial cells of BV-2 cell line (Tang *et al*., 2018). A segment of glucan produced from the stem of *Pleurotus eryngii* restrained inflammation in a sulfated polysaccharide, named DSS-tempted mouse model of IBD. The section of glucan exhibited downregulation outcomes on levels of Interferon gamma and Macrophage Inflammatory Protein 2 (Vetvicka *et al*., 2018). In another research it was revealed that the flavonoids segregated from Chinese liquorice (*Glycyrrhiza glabra*) could encourage distinction of malignant melanoma B16-F10 cells or stimulate apoptosis (Zheng *et al*., 2018). Moreover, the pharmacokinetics of the liver protective triterpenic acids (TAs) acquired from the fruits of jujube by using an ultra-high performance liquid chromatography tandem mass spectrometry method to investigate the samples of plasma in normal and carbon tetrachloride-managed rats (Li *et al*., 2018).

A sequence of cinnamamide products have noteworthy anti-tubercular, anti-microbial, and anti-mycotic activities (Pospisilova *et al*., 2018). Discovering therapeutic strength of botanicals is a prehistoric concept. Individuals from all landmasses have extensively applied poultices and drank teas of hundreds or thousands, of aboriginal plants, antedate to early history. There is a proof that Neanderthals (an extinct species of archaic humans) existing 60,000 years ago presently Iraq utilized herbs for instance *Alcea rosea* (hollyhocks) (Stockwell, 1988; Thomson, 1978), these botanicals are still extensively utilized in ethnomedicine all over the world. After the beginning of antibiotics in the duration of 50s, the usage of plant derived products as anti-bacterial has been practically missing. After a decline in that speed in modern decades, the pace is yet once more advancing as researchers recognize that the efficient life expectancy of any antibiotic is bounded. Global expenditure on discovering novel anti-virulent mediators (counting vaccines) is supposed to escalate by sixty percent from the expenditure levels in 1993 (Cowan, 1999). Plant sources, are also being examined. Subsequently, the people are becoming progressively conscious of complications with the abuse and over prescription of conventional antibiotics. Additionally, numerous people are concerned in having extra autonomy in terms of their therapeutic care. A large number of plant compounds is easily accessible without doctor's prescription from suppliers of herbs and self-medication with these elements is usual. The use of plant-derived products, in addition to other substitutive forms of medicinal managements, is appreciating great admiration in the late 1990s. Previously in this decade, around 1/3rd of people examined in the US consumed no less than one "unusual" therapy in the last year (Eisenberg *et al*., 1993).

History

It is approximated that there are 50,200 to 500,000 species of botanicals on this planet (Borris, 1996). Comparatively minor percentages (1-10%) of plants are consumed in diet by both animal and humans. Hippocrates (the father of medicine) stated three hundred to four hundred healing plants (Thomson, 1978). Pedanius dioscorides (a Greek physician and botanist) inscribed De Materia Medica, a catalog of medicinal herb became the model for modern dispensary. The Bible proposes explanations of almost thirty medicinal plants. In fact, myrrh and frankincense possibly relished their position of great value because of their therapeutic properties. Stated to have germ-killing characteristics, they were also used as mouthwashes. The decline of prehistoric civilizations anticipated western developments in the interpretating of medicinal botanicals, with ample of the records of plant medicament being misplaced

or demolished (Stockwell, 1988). Throughout the middle ages, the Arab nation endured to unearth their particular older works and to construct upon them. Certainly, cultures of countries under Asia continent were also engaging in assembling their personal pharmacopoeia. In western regions, the era of Renaissance saw a restoration of prehistoric medicine, which constructed from the herbal medicines. History of North America's medicinal plant usage follows 2 strands one was to utilize native cultures (Native Americans), dating from ancient history (Weiner, 1980), and the another one was a substitutive motion among Americans of European origin, beginning in the 19th century. American utilization of indigenous medicinal plant has been evaluated broadly in a sequence of articles by Moerman (1996). He stated that after utilizing 1,625 species of plants by numerous aboriginal American groups as food, 2,564 species used as medicines (Cowan, 1999). Botanicals have nearly infinite capacity to produce aromatic constituents, like phenols or their derivatives (Geissman, 1963). Throughout the seventeenth and 18th centuries understanding of plant originated drugs developed speedily. Though, efforts to discover the dynamic molecule(s) were continuously ineffective. In 1817, a huge revolution was happened when Friedrich Sertürner, a German researcher extracted morphine from the seeds of *Papaver somniferum* (Schmitz, 1985) and it was becoming the 1st dynamic discovery of herbal medicine. Vigilant exploration of chemicals reported morphine to be the alkaloid. Quinine, a plant product of *Cinchona officinalis*, was the first efficient management of malaria; it continued to be the well-known medicine to manage this ailment well until into the 1940s and is still used in numerous progressing countries (Reyburn *et al*., 2009). The healing characteristics of *Cinchona officinalis*, were initially revealed by the Quechua Indians of Bolivia and Peru, consequently this information was brought to European regions by the Jesuits. The efficiency of bark of cinchona in managing malaria rapidly became the most appreciated raw materials transported from Peru to Europe. Quinine, was also secluded from both the cinchona bark and termed by Pierre Pelletier and Joseph Bienaime in 1820. Whereas a number of total combinations of quinine have been described (Woodward and Doering, 1945) additional important constituent from organic product used in biomedicine is salicin, extracted from willow bark and is recognized in 1838 by Johannes Buchner, the bark of which had initially been used as an analgesic by the early Greeks. It was then researched and used by the Bayer Company as aspirin. The segregation of other important herbal products shortly followed, hence the 1800's became a golden age for plant derived product research (Yun *et al*., 2012).

Viral diseases

Infections of viral origins continue to be a foremost reason of ill health and death globally. From all of them the most destructive virus-related diseases are severe acute respiratory syndrome Ebola, Influenza, and Acquired Immuno-Deficiency Syndrome. For example, Influenza is accountable for more than 3 million new patients of severe ailment, and approximately 0.5 million fatalities annually (Gasparini *et al*., 2012; Nováková *et al*., 2018). Distressingly, the quantity of patients identified with viral diseases is growing each year with increased transplantations of organ, blood transfusions, and the usage of infected subcutaneous syringes. Standard antiviral medicines for instance ribavirin and interferon are efficient in vitro against numerous viruses, however frequently they are not completely successful in humans. Currently 90 distinct anti-viral agents exist (Soltan and Zaki, 2009; Brijesh *et al*., 2009) and they can merely manage a range of viruses; these viruses include HIV, herpes simplex virus, influenza viruses, human alphaherpes virus 3, hCMV and hepatitis viruses. At present, appropriate therapy against a certain number of viruses, and vaccination is surrounded to mumps, hepatitis A and human alphaherpes virus 3 (Nováková *et al*., 2018). Additionally, these agents are unsuccessful and expensive most of the times because of viral resistance and can be the source of unwanted effects. Keeping that in notice, organically established pharmacotherapy can be an appropriate substitute for managing viral illnesses.

Antiviral properties of plant products

Plant product against herpes simplex virus (HSV): Herpes simplex viruses with double-stranded DNA as genetic material, a highly contagious viruses that cause frequent ulceration in both humans and animals of all age groups. Botanicals may be another significant option for HSV treatment as they are used in a variety of mechanisms and help in reducing the development of antiviral resistance. An extensive diverse plant from different geographical regions have been studied against herpes simplex viruses and showed varying degrees of antiviral activity. Aqueous leaf extract of *Melia azedarach* contains

antiviral molecule meliacine inhibited the lifecycle of herpes simplex virus type 1 (HSV-1). At non-toxic concentration, meliacine blocked HSV-1 infection through suppression of synthesis of some late infected-cell polypeptides (Villamil *et al*., 1995). The naked nucleic acids and capsids of HSV-1 could not be enveloped by a golgi-derived membrane in presence of meliacine (Alche *et al*., 2002). Geraniin and 1, 3, 4, 6-tetra-*O*-galloyl-beta D-glucose found in acetone extract of *Phyllanthus urinaria* suppress HSV-1 replication (Yang *et al*., 2007). In laboratory experiment, it was showed that aqueous root extract of *Carissa edulis* also has potent antiviral activity against both resistant and wild type strains of HSV (Tolo *et al*., 2006). According to a report, it was demonstrated that bioactive molecules, andrographolide and other derivatives such as neoandrographolide and 14-deoxy-11, 12-didehydroandrographolide from *Andrographis paniculata* have anti-HSV-1 activity (Wiart *et al*., 2005). A semi-synthetic compound of andrographolide (3, 19-isopropylidene andrographolide) showed inhibitory activity against HSV entry (Seubsasana *et al*., 2011). Mangiferin, an effective component of *Anemarrhena asphodeloides*, has antimicrobial properties along with effective antiviral property against this virus (Du *et al*., 2018). According to previous studies, aqueous extract of *Moringa oleifera* and methanol extract of *Salvia rosmarinus* leaves at a specific concentration can inhibit the growth of herpes simplex type 1 and type 2 (Anwar *et al*., 2007; Kriesel *et al*., 2005). These two plant extracts have antiviral properties because of the presence of flavonoid compound beta-amyrin and phenolic compound ferruginol which showed their antiviral properties by inhibiting lipid peroxidation, hindering replication of the viruses, destabilizing the lipid envelope of virus and hampering with adsorption and cell entry of virus (Jung, 2014). In some studies, it was also proved that there are some plants like *Actium lappa*, *Calendula officinalis* and *Geranium robertianum* may have different ways to inhibit the growth of HSV-1 (Corina *et al*., 1999). There are some plants like *Abbottina rivularis*, *Bergenia ciliata*, *Cassiope fastigiata* and *Tillandsia linearis* showed greater anti-HSV-1 activity, whereas extracts from *Cotoneaster integrifolius, Clinopodium umbrosum*, *Oxytropis williamsii*, *Rhododendron anthopogon* and *Rubus foliolosus* showed moderate to low anti-HSV-1 activity (Rajbhandari et al., 2007).

Plant product against corona virus: Since the outbreak of COVID-19, different indigenous herbal medicines have been used separately or with the conventional drugs in combination treatment to treat patients with SARS-CoV-2 (Mandal *et al*., 2022). Common spices with immunity bootstring properties present in our daily diet like garlic, turmeric, red pepper, and fenugreek have some antiviral property (Cardoso, 2022). There are almost eighteen antiviral compounds present in garlic oil, among them, leptin have the potentiality to prevent SARS-CoV-2 virus infection (Donma and Donma, 2020). Many antiviral compounds present in *Ferula asafetida* bind with the human ACE2 receptor and inhibit the viral entry within the host cell (Rajapaksa *et al*., 2020). There are some phytochemicals like quercetin and its derivatives can inhibit corona virus replication (Cardoso, 2022). Glycyrrhizin (GR) found in the root extract of *Glycyrrhiza glabra* has antitumor, antidiabetic, antioxidant, anti-inflammatory, hepatoprotective and antiviral properties. Glycyrrhizin is able to reduce the infection of SARS-CoV by inhibiting viral replication, penetration and adsorption (Baillya *et al*., 2020). Another antiviral molecule, glycyrrhizic acid isolated from the same plant is able to interact with spike glycoprotein of SARS-CoV and block the viral entry (Hoever *et al*., 2005). Four phyto compounds, including neoandrographolide, andrographolide, 14-deoxy andrographolide, and 14-deoxy 11, 12-didehydroandrographolide from *Andrographis paniculata* impeded coronaviruses life cycle by blocking the activity of non-structural proteins, papain-like protease and RNA dependent RNA polymerase. Among those phytocompounds, neoandrographolide have high affinity against SARS-CoV-2 infection (Murugan and Jeyakanthan, 2020). Molecular docking analysis showed that andrographolide can suppress Mpro of SARS-CoV-2 activity (Enmozhi *et al*., 2021). Similarly, withanolides isolated from *Withania somnifera* also able to inhibit the activity of Mpro of SARS-CoV-2 (Tripathi *et al*., 2021). Another important medicinal plant, *Curcuma longa* inhibits 3-CL protease which is one of the most important enzyme of coronavirus (Mandal *et al*., 2021). For all these beneficial activities, Ministry of Ayush, Govt. of India has approved Nilavembu Kudineer, a multiherbal formulation consisting of *A. paniculata*, *Z. officinale*, *S. album* in addition with other herbs act as a prophylactic add-on for COVID-19 (Khuntia *et al*., 2022). Phytocompounds like, isoflavone extracted from *Psorothamnus arborescens*, methyl rosmarinate from *Hyptis atrorubens*, myricitrin from *Myrica cerifera*, myricetin 3-O-beta-D-glucopyranoside

from *Camellia sinensis*, amaranthin from *Amaranthus tricolor* and licoleafol from *Glycyrrhiza uralensis* are effective against SARS-CoV-2 (Qamar *et al.*, 2020). Quinine extracted from the bark of *Cinchona* tree has potentiality to inhibit the growth this virus (Singh *et al.*, 2020). Phyto compounds present in the leaves of *Azadirachta indica*, like, nimbidin, nimocinol, nimbolide, nimbinene, isomeldenin, nimbandiol, meliacinanhydride, and zafaral showed antiviral activity against coronavirus (Baildya *et al.*, 2020). In *in silico* study, it was showed that luteolin-7-O-glucuronide and chlorogenic acid extracted from *Ocimum sanctum* likely binds to Cys145 of Mpro of SARS-CoV-2 and suppress the enzymes activity (Mohapatra *et al.*, 2020). Phytocompounds such as berberine, cardiofolioside B, tinosponone, tembetarine, xanosporic acid present in *Tinospora cordifolia*, also have antiviral properties. Among those compounds, tinosponone acts as a potent inhibitor of Mpro of SARS-CoV-2 (Krupanidhi *et al.*, 2020).

Plant product against human immunodeficiency virus: HIV has claimed ~40.4 million lives since the start of the epidemic (UNAIDS, 2022 fact sheet). There has been profound progress in the field of anti-HIV drug development that definitely restrained the progress of the disease and increased the life span of infected individuals. However, certain drawbacks still persist like emergence of drug resistant viral strains due to lifelong administration of HAART and absence of any vaccine so far (Shafer and Schapiro, 2008). There are number of plants that are used as herbal remedies against various viral infections, including HIV and are widely used as an essential part of traditional medicine (Mukhtar *et al.*, 2008; Kurapati *et al.*, 2016; Dhama *et al.*, 2018; Mandal *et al.*, 2020). For example, in laboratory experiment, it was proved that bioactive compounds extracted from *Phyllanthus amarus* (Notka *et al.*, 2004), water/alcohol extract from *Phyllanthus niruri* (Qian-Cutrone *et al.*, 1996), rosamultin from *Rose rugosa* (Park *et al.*, 2005), aqueous extract of dried rose flowers (Fu *et al.*, 2006), water and methanol extracts of *Rosa damascene* (Mahmood *et al.*, 1996) have anti-HIV activities by blocking HIV-1 attachment, integration, reverse transcription and protease activity of this virus. The n-butanol extracts of *Bridelia micrantha* (family *Euphorbiaceae*) in IC_{50} of 7.3µg/ml showed antiviral activity against the RDDP function of HIV-1 RT (Bessong *et al.*, 2006). The extracts of seed of *Areca cutechu,* and bark of *Saruca indica*, *Eugenia jambohnu, Terminalia arjuna*, Arecatannin B1, a procayanidin, extracted from *Areca catechu* (Kusumoto *et al.*, 1995) and peyssonol A and B, two sesquiterpene hydroquinones from the red sea algae *Peyssonelia* species (Loya *et al.*, 1995) showed inhibitory activity on HIV-1 PR. Calanolide-a plant derived compound acting as non-nucleoside analogues and suppressed human immunodeficiency virus replication (Xu *et al.*, 2000). Phytosterol, β-sitosterol-3-β-D-glucopyranoside isolated from the roots and bark parts of *Aleurites moluccana* capsule, a conventional Hawaiian medicine worked on herpes viral infections, also act on HIV-1 (Ashrafi *et al.*, 2022). Aqueous extract of the leaves of *Pluchea indica* has antiviral properties against HIV-1 (Locher *et al.*, 1996). Extracts from leaf part of *Scaevola tacadda* and root part of *Acorus calamus* showed antiviral activity against reverse transcriptase enzyme of HIV-1 (Silprasit et al., 2011). Betulinic acid and its derivatives derived from *Betula utilis* commonly known as Bhojpatra in India significantly inhibited HIV-1 entry and protease enzyme activity (Singh *et al.*, 2012; Lee, 2004). Cafeic acid, chlorogenic acid and 3,4-di-O-cafeoylquinic acid extracted from *Bidens pilosa* (known as xian feng cao) potentially inhibited HIV integrase (Xuan *et al.*, 2016). Secomet-V, isolated from *Trifollium* species showed effectivity against HIV and some other viruses including human papillomavirus, influenza, HBV and HCV (Kotwal *et al.*, 2005). Cyanovirin N, a 11-kDa protein isolated from the blue green algae, cyanobacterium *Nostoc ellipsosporum* inhibits HIV-1 infection by interacting with chemokine receptors, gp120 and inhibits entry of HIV (Clercq 2000). Shephagenins A and B, hippophaenin A and strictinin isolated from the leaf extract of *Shepherdia argentea* showed a remarkable antiviral activity against HIV-1 reverse transcriptase (Yoshida *et al.*, 1996). Baicalein, a flavonoid purified from *Scutellaria baicalensis* showed anti-HIV-1 activities by interfering with the envelope proteins with chemokine co-receptors and blocking viral entry into the target CD4 cells (Li *et al.*, 2000). Oligostilbene dibalanocarpol, purified from leaves extract of *Hopea malibato*, has antiviral activity against this virus (Dai *et al.*, 1998). Inophyllum, calanolide A and coumarins isolated from the terrestrial plants of *Calophyllum inophyllum*, *Calophyllum lanigerum*, *Calophyllum teysmannii* and *Calophyllum cerasiferum* act on HIV-1-RT (Currens *et al.*, 1996). *Malva sylvestris* also has the antiviral properties against reverse transcriptase enzyme of HIV (Benso *et al.*, 2021). Catechin, lauric acid, capric acid or myristic acid extracted from *Cocos*

nucifera, has antiviral properties by disrupting the viral membrane or by interfering with the virus maturation process (Mandal *et al*., 2011; Lima et al., 2015). α-Mangostine, a xanthone, polyphenolic compound found from *Garcinia mangostana* inhibits the activities of reverse transcriptase, protease of HIV-1 or by interfering with other replication processes (Bernal *et al*., 2015). *Mangifera indica* employed its antiviral activity because of the presence of xanthones and mangiferine which are interfering with the replication of the virus (Parvez, 2016). Fruit seeds extract of *Nephelium lappaceum* able to inhibit the HIV-1 reverse transcriptase activity. Two most important antiviral compounds, geraniin and hexadecanoic acid present in *Nephelium lappaceum,* blocks viral replication and inhibits HIV-1 infection to the host cell (Monrroy *et al*., 2020). Kaempferol, kaempferol 3-O-β-D-glucuronopyranosyl methyl ester, naringenin 7-O-β-D glucopyranoside, quercetin 3-O-β-D-glucuronopyranosyl methyl ester, resveratrol, caffeic acid, and scirpusins A and B found in *Vitis vinifera* are active against multiple RNA virus including HIV (Gaafar et al., 2019).

Plant product against viral hepatitis: Hepatitis viruses cause both severe to persistent liver illness, including liver misfunctioning, liver fibrosis and hepatocellular carcinoma etc., affect about several billions of the world's population and it has been reported that a number of plant products with diverse chemical classes have antiviral activities against this virus (Ganta *et al*., 2017) such as plants belonging to the genus *Phyllanthus* of the family *Euphorbiaceae* has antihepatitic activity. In a study, it showed that different species of *Phyllanthus*, i.e., *P. amarus*, *P. niruri* and *P. urinaria* have antihepatitic B properties (Wang *et al*., 1995). In the molecular biology, it was revealed that the antiviral properties of *P. amarus* act on HBV polymerase activity and mRNA transcription by interacting with HBV enhancer I and C/EBP alpha and beta transcription factors (Ott *et al*., 1997), the ethanolic extract of *P. nanus* showed its antiviral activity on expression of several genes specifically annexin 7 (Lam *et al*., 2006). Similarly, the methanolic extracts of *Acacia nilotica*, *Embelia schimperi*, *Valeriana wallichii*, *Boswellia carterii*, *Quercus infectoria*, *Trachyspermum ammi* and aqueous extracts of *Piper cubeba, Syzygium aromaticum*, and *Quercus infectoria* also have antihepatitic properties (Ganta *et al*., 2017; Hussein *et al*., 2000; Mandal and Hazra, 2023). Some plant derived molecules such as catechin, polysterols, glycyrrhizin, silymarin also showed antihepatitic C activity (Jassim and Naji, 2003).

Plant products with broad spectrum antiviral activity: Complexes and constituents with antiviral activity exists in numerous plants, for instance, rutin, a flavonoid glycoside present in a range of botanicals, effective against herpes simplex virus-1, herpes simplex virus-2 (Yarmolinsky *et al*., 2012), influenza A virus (Ibrahim *et al*., 2013), and parainfluenza type-3 virus (Orhan *et al*., 2010). Quercetin, is a plant chemical that is found in ample quantity in plants and may reduce the multiplication of numerous viruses: Rhinovirus (Ganesan *et al*., 2012), influenza virus (Wu *et al*., 2015), dengue type-2 virus (Zandi *et al*., 2011), herpes simplex type-1 virus, adenovirus (Chiang, 2003), poliovirus (Neznanov *et al*., 2008), RSV, EBV (Lee *et al*., 2015), MAYV (dos Santos *et al*., 2014), JEV (Johari *et al*., 2012) and HCV (Bachmetov *et al*., 2012; Gonzalez *et al*., 2009). Associates of *Phyllanthus* species are studied as most important sources of bioactive metabolites that have antiviral effects for instance lignans, alkaloids and flavonoids for instance quercetin. They are able to occlude endogenous deoxyribonucleic acid, a polymerase of HBV, play significant role in multiplication of virus (Venkateswaran *et al*., 1987). Additionally, a range of bioactive metabolites of *Phyllanthus niruri* have been assessed for their reducing utilization of sera comprising of HBV surface antigen, gathered from chronic HBV infected patients (Thyagarajan *et al*., 1982). Moreover, a ninety-day management with extracts of plant effectively reduced the antigen of hepatitis B virus to untraceable levels among 2/3rd of hepatitis B virus-positive patients (Wang *et al*., 1995). Alkaloid extract of *Phyllanthus niruri* has also been stated to have a hindering and repressive effect on human immunodeficiency virus. These effects on multiplication of human immunodeficiency virus was considered by observing the reduction of HIV-prompted pathogenic modifications in human MT-4 cells, which demonstrated that these plant extracts show antiviral activity against the effect of pathogenic alterations, encouraged by human immunodeficiency virus on human MT-4 cells (Naik and Juvekar, 2003). American pokeweed, a powerful source of pokeweed antiviral protein and 3 isoforms of this protein have been acknowledged, precisely from spring leaves Pokeweed antiviral protein isoforms-I, primary summer leaves Pokeweed antiviral protein isoforms-II and late summer leaves Pokeweed antiviral

protein isoforms-III which are similarly recognized as a category of RIPs and promotes depurination of genomic HIV-1 ribonucleic acid in a concentration-reliant way (Rajamohan *et al.*, 1999). Correspondingly, *Gelonium multiflorum* and *Momordica charantia* are similarly contemplated as beneficial sources of an anti-HIV protein GAP31 and MAP30, which are like RIPs that have been recognized for their anti-human immunodeficiency virus strength (Schreiber *et al.*, 1999). The plant of *Rheum palmatum* consists of organic aloe-emodin and anthraquinone used in Chinese medicine, active against influenza viruses, herpes simplex virus and cytomegalovirus (Sydiskis *et al.*, 1991). Gallotannins, one of most powerful antiviral constituents recognize to suppress and reduce Epstein–Barr virus, wild-variety of herpes simplex virus-2, acyclovir-phosphonoacetic acid resilient herpes simplex virus-1, as well as thymidine kinase-deficient herpes simplex virus-1 (Hussain *et al.*, 2017). Almost twenty percent of recognized botanicals have been utilized in pharmaceutical research projects, influencing the system of healthcare in constructive ways for instance managing cancer and injurious ailments (Naczk and Shahidi, 2006). Botanicals are capable of producing a huge amount of various bioactive constituents. High concentrations of plant-derived products, which may induce the damage of free radical, assembled in vegetables and fruits (Suffredini *et al.*, 2004). Botanicals that comprise of useful plant chemicals may act as organic antioxidants in human body (Boots *et al.*, 2008). Numerous research projects have discovered that lots of plants are affluent source of antioxidants. For example, phenolic compounds such as flavonoids, tannins, lignins, and vitamins A, C, E present in plants act as antioxidants (Suffredini *et al.*, 2004). The intake of vegetables and fruits has been associated with numerous health values, an outcome of high dietary values and therapeutic properties (Valko *et al.*, 2006). Ascorbic acid, beta carotene and lots of phenolics play active parts in decreasing inflammation, postponing aging, and averting certain kinds of carcinomas (Duthie *et al.*, 1996). Escalating the ingestion of vegetables and fruits has been endorsed by numerous health care systems and agencies all over the world (Vivekananthan *et al.*, 2003).

Conclusions and Recommendations

Among seven continents, in Asia, different types of flora is present which are the origin of several plant derived products with pharmacological importance, many of which contain antiviral substances. Identification of new plant-derived compounds with antiviral action is urgently needed and in high demand due to the prevalence of viral-related diseases as a worldwide health threat. Various chemicals presents in plants are useful against many viruses like rhinovirus, extremely contagious influenza virus, type-2 dengue virus, herpes simplex virus-1, adenovirus, poliovirus, RSV, EBV, JEV, and hepatitis C virus. Plant extracts and constituents are best choice in various viral infections instead of misuse of antibiotics. The intake of vegetables and fruits has been associated with numerous health values, an outcome of high dietary values and therapeutic properties. It would be more ideal if sophisticated pharmaceutical nanotechnologies and targeted methods are utilized that could help to utilize the natural herbal products for fighting against life-threatening viruses by evolving potent drugs which can act as adjuvant and protect the human-being from current and future pandemics.

Acknowledgments

AM would like to acknowledge the Principal, Mrinalini Datta Mahavidyapith, Birati, Kolkata 700051, India, for encouragement and necessary support.

Novelty Statement

In this review article we have tried to compile the available literature reporting antiviral plant products and herbal medicines active against different viral diseases. Traditional treatments for viral diseases not only constitute unique plant-based 'lead molecules' for discovering antiviral drugs, but also open up alternative strategies for management of viral infection. Each steps of viral life cycle is crucial for their sustenance, hence, could be considered as a prospective target for the development of antiviral therapeutics. Here we have selectively presented plant products / compounds in terms of these putative targets of antiviral mechanism of action, as described by the respective investigators.

Author's Contribution

AM designed and implemented the idea of this manuscript. MA, MI, AM, RB, RZ, MTK, SR, PP and UL collected the information and wrote the article. RB revised the text under the supervision of AM. All authors approved the final version of the manuscript.

Conflict of interest

The authors have declared no conflict of interest.

References

Alche, L.E., Barquero, A.A., Sanjuan, N.A. and Coto, C.E., 2002. An antiviral principal present in a purified fraction from *Melia azedarach* L. leaf aqueous extract restrains herpes simplex virus type 1 propagation. Phytother. Res., 16(4): 348–352. https://doi.org/10.1002/ptr.895

Anwar, F., Latif, S., Ashraf, M. and Gilani, A.H., 2007. *Moringa oleifera*: A food plant with multiple medicinal uses. Phytother. Res., 21(1): 17-25. https://doi.org/10.1002/ptr.2023

Ashrafi, S., Rahman, M., Ahmed, P., Alam, S. and Hossain, M.A., 2022. Prospective Asian plants with corroborated antiviral potentials: Position standing in recent years. Beni-Suef Univ. J. Basic Appl. Sci., 11(47): 1-26. https://doi.org/10.1186/s43088-022-00218-y

Bachmetov, L., Gal-Tanamy, M., Shapira, A., Vorobeychik, M., Giterman-Galam, T., Sathiyamoorthy, P., Golan-Goldhirsh, A., Benhar, I., Tur-Kaspa, R. and Zemel, R., 2012. Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity: Quercetin suppresses HCV through inhibition of NS3. J. Viral Hepat., 19(2): e81–e88. https://doi.org/10.1111/j.1365-2893.2011.01507.x

Baildya, N., Khan, A.A., Ghosh, N.N., Dutta, T. and Chattopadhyaya, A.P., 2020. Screening of potential drug from *Azadirachta Indica* (Neem) extracts for SARS-CoV-2: An insight from molecular docking and MD-simulation studies. J. Mol. Struct., 1227: 129390, pp. 1-9. https://doi.org/10.1016/j.molstruc.2020.129390

Baillya, C. and Vergotenb, G., 2020. Glycyrrhizin: An alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome? Pharmacol. Ther., 214(107618): 1-17. https://doi.org/10.1016/j.pharmthera.2020.107618

Benso, B., Rosalen, P.L., Pasetto, S., Marquezin, M.C.S., Freitas-Blanco, V. and Murata, R.M., 2021. Malva sylvestris derivatives as inhibitors of HIV-1 BaL infection. Nat. Prod. Res., 35(6): 1064-1069. https://doi.org/10.1080/14786419.2019.1619720

Bernal, F.A. and Coy-Barrera, E., 2015. Molecular docking and multivariate analysis of xanthones as antimicrobial and antiviral agents. Molecules, 20(7): 13165-13204. https://doi.org/10.3390/molecules200713165

Bessong, P.O., Rojas L.B., Obi C.L., Tshisikawe, P.M. and Igunbor, E.O., 2006. Further screening of Venda medicinal plants for activity against HIV type 1 reverse transcriptase and integrase. Afr. J. Biotechnol., 5(6): 526-528.

Boots, A.W., Haenen, G.R.M.M. and Bast, A., 2008. Health effects of quercetin: From antioxidant to nutraceutical. Eur. J. Pharmacol., 585(2–3): 325–337. https://doi.org/10.1016/j.ejphar.2008.03.008

Borris, R.P., 1996. Natural products research: Perspectives from a major pharmaceutical company. J. Ethnopharmacol., 51(1–3): 29–38. https://doi.org/10.1016/0378-8741(95)01347-4

Brijesh, S., Daswani, P., Tetali, P., Antia, N. and Birdi, T., 2009. Studies on the antidiarrhoeal activity of Aegle marmelos unripe fruit: Validating its traditional usage. BMC Complement. Altern. Med., 9: 47. https://doi.org/10.1186/1472-6882-9-47

Cardoso, B., 2022. Ntiviral properties of food plants could help to reduce contagion and severity in SARS-CoV-2 infection. Curr. Trad. Med., 8(1): 81-84. https://doi.org/10.2174/2215083807666210917144039

Chiang, L.C., 2003. *In vitro* antiviral activities of *Caesalpinia pulcherrima* and its related flavonoids. J. Antimicrob. Chemother., 52(2): 194–198. https://doi.org/10.1093/jac/dkg291

Clercq, E.D., 2000. Current lead natural products for the chemotherapy of human immunodeficiency virus (HIV) infection. Med. Res. Rev., 20(5): 323-349. https://doi.org/10.1002/1098-1128(200009)20:5<323::AID-MED1>3.0.CO;2-A

Corina, P., Dimitris, S., Emanuil, T. and Nora, R., 1999. Treatment with acyclovir combined with a new Romanian product from plants. Oftalmologia, 46(1): 55–57. https://doi.org/10.1093/nq/46-1-55

Cowan, M.M., 1999. Plant products as antimicrobial agents. Clin. Microbiol. Rev., 12(4): 564–582. https://doi.org/10.1128/CMR.12.4.564

Currens, M.J., Gulakowski, R.J., Mariner, J.M., Moran, R.A., Buckheit Jr, R.W., Gustafson, K.R., McMahon, J.B., Boyd, M.R. 1996. Antiviral

activity and mechanism of action of calanolide A against the human immunodeficiency virus type-1. J. Pharmacol. Exp. Ther., 279(2): 645-651.

Dai, J.R., Hallock, Y.F., Cardellina, J.H. and Boyd, M.R., 1998. HIV-Inhibitory and cytotoxic oligostilbenes from the leaves of *Hopea malibato*. J. Nat. Prod., 61(3): 351–353. https://doi.org/10.1021/np970519h

Dhama, K., Karthik, K., Khandia, R., Munjal, A., Tiwari, R., Rana, R., Khurana, S.K., Ullah, S., Khan, R.U., Alagawany, M., Farag, M.R., Dadar, M., Joshi, S.K., 2018. Medicinal and therapeutic potential of herbs and plant metabolites/ extracts countering viral pathogens. Current knowledge and future prospects. Curr. Drug Metab., 19(3): 236-263. https://doi.org/10.2174/1389200219666180129145252

Donma, M.M. and Donma, O., 2020. The effects of allium sativum on immunity within the scope of COVID-19 infection. Med. Hypotheses, 144(2020): 1-5. https://doi.org/10.1016/j.mehy.2020.109934

Dos Santos, A.E., Kuster, R.M., Yamamoto, K.A., Salles, T.S., Campos, R., de Meneses, M.D., Soares, M.R., and Ferreira, D., 2014. Quercetin and quercetin 3-O-glycosides from *Bauhinia longifolia* (Bong.) Steud. Show anti-Mayaro virus activity. Parasit. Vectors, 7(1): 130. https://doi.org/10.1186/1756-3305-7-130

Du, S., Liu, H., Lei, T., Xie, X., Wang, H., He, X., Tong, R. and Wang, Y., 2018. Mangiferin: An effective therapeutic agent against several disorders (Review). Mol. Med. Rep., 18(6): 4775-4786. https://doi.org/10.3892/mmr.2018.9529

Duthie, S.J., Ma, A., Ross, M.A. and Collins, A.R., 1996. Antioxidant supplementation decreases oxidative DNA damage in human lymphocytes. Cancer Res., 56(6): 1291–1295.

Eisenberg, D.M., Kessler, R.C., Foster, C., Norlock, F.E., Calkins, D.R. and Delbanco, T.L., 1993. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. New Eng. J. Med., 328(4): 246–252. https://doi.org/10.1056/NEJM199301283280406

Enmozhi, S.K., Raja, K., Sebastine, I. and Joseph, J., 2021. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: An *in silico* approach. J. Biomol. Struct. Dyn., 39(9): 3092-3098. https://doi.org/10.1080/07391102.2020.1760136

Fu, M., Ng, T.B., Jiang, Y., Pi, Z.F., Liu, Z.K., Li, L. and Liu, F., 2006. Compounds from rose (*Rosa rugosa*) flowers with human immunodeficiency virus type 1 reverse transcriptase inhibitory activity. J. Pharm. Pharmacol., 58: 1275–1280. https://doi.org/10.1211/jpp.58.9.0015

Gaafar, A. A., Asker, M. S., Ali M.A., Salama, Z. A., 2019. The effectiveness of the functional components of grape (Vitis vinifera) pomace as antioxidant, antimicrobial, and antiviral agents. Jordan J. Biol. Sci., 12(5): 625–635.

Ganta, K.K., Mandal, A., Debnath, S., Hazra, B. and Chaubey, B., 2017. Anti-HCV activity from semi-purified methanolic root extracts of *Valeriana wallichii*. Phytother. Res., 31(3): 433-440. https://doi.org/10.1002/ptr.5765

Ganesan, S., Faris, A.N., Comstock, A.T., Wang, Q., Nanua, S., Hershenson, M.B. and Sajjan, U.S., 2012. Quercetin inhibits rhinovirus replication *in vitro* and *in vivo*. Antiviral Res., 94(3): 258–271. https://doi.org/10.1016/j.antiviral.2012.03.005

Gasparini, R., Amicizia, D., Lai, P.L. and Panatto, D., 2012. Clinical and socioeconomic impact of seasonal and pandemic influenza in adults and the elderly. Hum. Vaccines Immunother., 8(1): 21–28. https://doi.org/10.4161/hv.8.1.17622

Geissman, T.A., 1963. Flavonoid compounds, tannins, lignins and, related compounds. In: Comprehensive Biochemistry. Elsevier. 9: 213–250. https://doi.org/10.1016/B978-1-4831-9718-0.50018-7

Gonzalez, O., Fontanes, V., Raychaudhuri, S., Loo, R., Loo, J., Arumugaswami, V., Sun, R., Dasgupta, A. and French, S.W., 2009. The heat shock protein inhibitor Quercetin attenuates hepatitis C virus production. Hepatology, 50(6): 1756–1764. https://doi.org/10.1002/hep.23232

Hoever, G., Baltina, L., Michaelis, M., Kondratenko, R., Baltina, L., Tolstikov, G.A., Doerr, H.W., Cinatl Jr., J., 2005. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. J. Med. Chem., 48(4): 1256-1259. https://doi.org/10.1021/jm0493008

Hussain, W., Haleem, K.S., Khan, I., Tauseef, I., Qayyum, S., Ahmed, B. and Riaz, M.N., 2017. Medicinal plants: A repository of antiviral metabolites. Future Virol., 12(6): 299–308. https://doi.org/10.2217/fvl-2016-0110

Hussein, G., Miyashiro, H., Nakamura, N.,

Hattori, M., Kakiuchi, N. and Shimotohno, K., 2000. Inhibitory effects of Sudanese medicinal plant extracts on hepatitis C virus (HCV) protease. Phytother. Res., 14(7): 510–516. https://doi.org/10.1002/1099-1573(200011)14:7<510::AID-PTR646>3.0.CO;2-B

Ibrahim, A.K., Youssef, A.I., Arafa, A.S. and Ahmed, S.A., 2013. Anti-H5N1 virus flavonoids from *Capparis sinaica* Veill. Natl. Prod. Res., 27(22): 2149–2153. https://doi.org/10.1080/14786419.2013.790027

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

Johari, J., Kianmehr, A., Mustafa, M., Abubakar, S. and Zandi, K., 2012. Antiviral activity of baicalein and quercetin against the japanese encephalitis virus. Int. J. Mol. Sci., 13(12): 16785–16795. https://doi.org/10.3390/ijms131216785

Jonas, W.B., Eisenberg, D., Hufford, D. and Crawford, C., 2013. The evolution of complementary and alternative medicine (CAM) in the USA over the last 20 years. Forschende Komplementarmedizin, (2006), 20(1): 65–72. https://doi.org/10.1159/000348284

Jung, I.L.L., 2014. Soluble extract from *Moringa oleifera* leaves with a new anticancer activity. PLoS One, 9(4): 1-10. https://doi.org/10.1371/journal.pone.0095492

Kang, Y.R., Choi, H.Y., Lee, J.Y., Jang, S.I., Kang, H., Oh, J.B., Jang, H.D. and Kwon, Y.I., 2018. Calorie restriction effect of heat-processed onion extract (ONI) using *in vitro* and *in vivo* animal models. Int. J. Mol. Sci., 19(3). https://doi.org/10.3390/ijms19030874

Khuntia, B.K., Sharma, V., Wadhawan, M., Chhabra, V., Kidambi, B., Rathore, S., Agrawal, A., Ram, A., Qazi, S., Ahmad, S., Raza, K., Sharma, G., 2022. Antiviral potential of Indian medicinal plants against influenza and SARS-CoV: A systematic review. Natl. Prod. Commun., 17(3): 1–10. https://doi.org/10.1177/1934578X221086988

Kotwal, G.J., Kaczmarek, J.N., Leivers, S., Ghebremariam, Y.T., Kulkarni, A.P., Bauer, G., De Beer, C., Preiser, W., Mohamed, A.R., 2005. Anti-HIV, anti-poxvirus, and anti-SARS activity of a nontoxic, acidic plant extract from the *Trifollium species* Secomet-V/anti-vac suggests that it contains a novel broad-spectrum antiviral. Ann. N. Y. Acad. Sci., 1056(1): 293-302. https://doi.org/10.1196/annals.1352.014

Kriesel, J.D., Spruance, S.L., Prichard, M., Parker, J.N. and Kern, E.R., 2005. Recurrent antiviral-resistant genital herpes in an immunocompetent patient. J. Infect. Dis., 192(1): 156-161. https://doi.org/10.1086/430612

Krupanidhi, S., Peele, K.A., Venkateswarulu, T.C., Ayyagari, V.S., Bobby, M.N., Babu, D.J., Narayana, A.V., Aishwarya, G., 2020. Screening of phytochemical compounds of *Tinospora cordifolia* for their inhibitory activity on SARS-CoV-2: An *in silico* study. J. Biomol. Struct. Dyn., 3: 1–5. https://doi.org/10.1080/07391102.2020.1787226

Kurapati, K.R.V., Atluri, V.S., Samikkannu, T., Garcia, G. and Nair, M.P.N., 2016. Natural products as Anti-HIV agents and role in HIV-associated neurocognitive disorders (HAND): A brief overview. Front. Microbiol., 12(6): 1-14. https://doi.org/10.3389/fmicb.2015.01444

Kusumoto, I.T., Nakabayashi, T., Kida, H., Miyashiro, H., Hattori, M., Namba, T. and Shimotohno, K., 1995. Screening of various plant extracts used in ayurvedic medicine for inhibitory effects on human immunodeficiency virus type 1 (HIV-1) Protease. Phytother. Res., 9: 180-184. https://doi.org/10.1002/ptr.2650090305

Lam, W.Y., Leung, K.T., Law, P.T., Lee, S.M., Chan, H.L., Fung, K.P., Ooi, V.E. and Waye, M.M., 2006. Antiviral effect of *Phyllanthus nanus* ethanolic extract against hepatitis B virus (HBV) by expression microarray analysis. J. Cell Biochem., 97(4): 795–812. https://doi.org/10.1002/jcb.20611

Lee, M., Son, M., Ryu, E., Shin, Y.S., Kim, J.G., Kang, B.W., Sung, G.H., Cho, H. and Kang, H., 2015. Quercetin-induced apoptosis prevents EBV infection. Oncotarget, 6(14): 12603–12624. https://doi.org/10.18632/oncotarget.3687

Lee, K.H., 2004. Current developments in the discovery and design of new drug candidates from plant natural product leads. J. Nat. Prod. 67(2): 273-283. https://doi.org/10.1021/np030373o.

Lima, V.D., Reuter, A., Harrigan, P.R., Lourenco, L., Chau, W., Hull, M., Mackenzie, L., Guillemi, S.,

Hogg, R.S., Barrios, R., and S.G. Montaner, J., 2015. Initiation of antiretroviral therapy at high CD4+ cell counts is associated with positive treatment outcomes. AIDS, 29(14): 1871-1882. doi:10.1097/QAD.0000000000000790.

Li, B.Q., Fu, T., Dongyan, Y., Mikovitsa, J.A., Ruscetti, F.W. and Wange, J.M., 2000. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem. Biophys. Res. Commun., 276(2): 534-538. https://doi.org/10.1006/bbrc.2000.3485

Li, Y., Guo, S., Ren, Q., Wei, D., Zhao, M., Su, S., Tang, Z. and Duan, J.A., 2018. Pharmacokinetic comparisons of multiple triterpenic acids from jujubae fructus extract following oral delivery in normal and acute liver injury rats. Int. J. Mol. Sci., 19(7): 2047. https://doi.org/10.3390/ijms19072047

Locher, C.P., Witvrouw, M., Béthune, M.P.D., Burch, M.T., Mower, H.F. and Davis, H., 1996. Antiviral activity of Hawaiian medicinal plants against human immunodeficiency virus type-1 (HIV-1). Phytomedicine, 2(3): 259-264. https://doi.org/10.1016/S0944-7113(96)80052-3

Loya, S., Bakhanashvili, M., Kashman, Y. and Hizi, A., 1995. Peyssonols A and B, two novel inhibitors of the reverse transcriptases of human immune deficiency virus types 1 and 2' Arch. Biochem. Biophys., 316: 789-796. https://doi.org/10.1006/abbi.1995.1105

Mahmood, N., Piacente, S. and Pizza, C., 1996. The anti-HIV activity and mechanisms of action of pure compounds isolated from *Rosa damascena*. Biochem. Biophys. Res. Commun., 229: 73–79. https://doi.org/10.1006/bbrc.1996.1759

Mandal, A., Biswas, D. and Hazra, B., 2020. Natural products from plants with prospective anti-HIV activity and relevant mechanisms of action. Chapter 9, Stud. Natl. Prod. Chem., 66: 225-271. https://doi.org/10.1016/B978-0-12-817907-9.00009-X

Mandal, A. and Hazra, B., 2023. Medicinal plant molecules against hepatitis C virus: Current status and future prospect. Phytother. Res., 37(10): 4353-4374. https://doi.org/10.1002/ptr.7936

Mandal, A., Hazra, B., Prajapati, V.K. and Moundipa, P.F., 2022. Editorial: Plant products for antiviral therapeutics. Front. Pharmacol., 13: 1039183. 1-4. https://doi.org/10.3389/fphar.2022.1039183

Mandal, A., Jha A.K. and Hazra, B., 2021. Plant products as inhibitors of coronavirus 3CL protease. Front. Pharmacol., 12: 1-16. https://doi.org/10.3389/fphar.2021.583387

Mandal, D.M. and Mandal, S., 2011. Coconut (*Cocos nucifera* L.: Arecaceae): In health promotion and disease prevention. Asian Pac. J. Trop. Med., 4(3): 241-247. https://doi.org/10.1016/S1995-7645(11)60078-3

Mukhtar, M., Arshad, M., Ahmad, M., Pomerantz, R.J., Wigdahl, B., Parveen, Z., 2008. Antiviral potentials of medicinal plants. Virus Res., 131(2): 111–120. https://doi.org/10.1016/j.virusres.2007.09.008

Moerman, D.E., 1996. An analysis of the food plants and drug plants of native North America. J. Ethnopharmacol., 52(1): 1–22. https://doi.org/10.1016/0378-8741(96)01393-1

Mohapatra, P.K., Chopdar, K.S., Dash, G.C. and Raval, M.K., 2020. In silico screening of phytochemicals of *Ocimum sanctum* against main protease of SARS-CoV-2. 1: 1-17. https://doi.org/10.26434/chemrxiv.12599915

Monrroy, M., Araúz, O. and García, J.R., 2020. Active compound identification in extracts of *N. lappaceum* peel and evaluation of antioxidant capacity. J. Chem., Article ID 4301891, pp. 1-14. https://doi.org/10.1155/2020/4301891

Murugan, N.A., Pandian, C.J. and Jeyakanthan, J., 2020. Computational investigation on *Andrographis paniculata* phytochemicals to evaluate their potency against SARS-CoV-2 in comparison to known antiviral compounds in drug trials. J. Biomol. Struct. Dyn., 39(12): 4415-4426. https://doi.org/10.1080/07391102.2020.1777901

Naczk, M. and Shahidi, F., 2006. Phenolics in cereals, fruits and vegetables: Occurrence, extraction and analysis. J. Pharma. Biomed. Anal., 41(5): 1523–1542. https://doi.org/10.1016/j.jpba.2006.04.002

Nagappan, A., Jung, D.Y., Kim, J.H. and Jung, M.H., 2018. Protective effects of Gomisin N against hepatic cannabinoid type 1 receptor-induced insulin resistance and gluconeogenesis. Int. J. Mol. Sci., 19(4). https://doi.org/10.3390/ijms19040968

Naik, A.D. and Juvekar, A.R., 2003. Effects of alkaloidal extract of *Phyllanthus niruri* on HIV replication. Indian J. Med. Sci., 57(9): 387–393.

Neznanov, N., Kondratova, A., Chumakov, K.M.,

Neznanova, L., Kondratov, R., Banerjee, A.K. and Gudkov, A.V., 2008. Quercetinase Pirin makes poliovirus replication resistant to flavonoid quercetin. DNA Cell Biol., 27(4): 191–198. https://doi.org/10.1089/dna.2007.0682

Notka, F., Meier, G.R. and Wagner, R., 2004. Concerted inhibitory activities of *Phyllanthus amarus* on HIV replication *in vitro* and *ex vivo*. Antiviral Res., 64: 93–102. https://doi.org/10.1016/S0166-3542(04)00129-9

Nováková, L., Pavlík, J., Chrenková, L., Martinec, O. and Červený, L., 2018. Current antiviral drugs and their analysis in biological materials. Part II: Antivirals against hepatitis and HIV viruses. J. Pharma. Biomed. Anal., 147: 378–399. https://doi.org/10.1016/j.jpba.2017.07.003

Orhan, D.D., Özçelik, B., Özgen, S. and Ergun, F., 2010. Antibacterial, antifungal, and antiviral activities of some flavonoids. Microbiol. Res., 165(6): 496–504. https://doi.org/10.1016/j.micres.2009.09.002

Ott, M., Thyagarajan, S.P. and Gupta, S., 1997. *Phyllanthus amarus* suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. Eur. J. Clin. Invest., 27(11): 908–915. https://doi.org/10.1046/j.1365-2362.1997.2020749.x

Park, J.C., Kim, S.C., Choi, M.R., Song, S.H., Yoo, E.J., Kim, S.H., Miyashiro, H., Hattori, M., 2005. Anti-HIV protease activity from rosa family plant extracts and rosamultin from *Rosa rugosa*. J. Med. Food, 8(1): 107–109. https://doi.org/10.1089/jmf.2005.8.107

Parvez, G.M.M., 2016. Pharmacological activities of mango (*Mangifera Indica*): A review. J. Pharmacogn. Phytochem., 5(3): 1-7.

Pospisilova, S., Kos, J., Michnova, H., Kapustikova, I., Strharsky, T., Oravec, M., Moricz, A. M., Bakonyi, J., Kauerova, T., Kollar, P., Cizek, A. and Jampilek, J., 2018. Synthesis and Spectrum of Biological Activities of Novel N-arylcinnamamides. Int. J. Mol. Sci., 19(8). https://doi.org/10.3390/ijms19082318

Qamar, M.T.U., Alqahtani, S.M., Alamri, M.A. and Chen, L.L., 2020. Structural basis of SARS- CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. J. Pharm. Anal., 10(4): 313-319. https://doi.org/10.1016/j.jpha.2020.03.009

Qian-Cutrone, J., Huang, S., Trimble, J., Li, H., Lin, P.F., Alam, M., Klohr, S.K., Kadow, K.F., 1996. Niruriside, a new HIV REV/RRE binding inhibitor from *Phyllanthus niruri*. J. Nat. Prod., 59: 196–199. https://doi.org/10.1021/np9600560

Rajamohan, F., Kurinov, I.V., Venkatachalam, T.K. and Uckun, F.M., 1999. Deguanylation of human immunodeficiency virus (HIV-1) RNA by recombinant pokeweed antiviral protein. Biochem. Biophys. Res. Commun., 263(2): 419–424. https://doi.org/10.1006/bbrc.1999.1335

Rajapaksa, R.M.H., Perera, B.T., Nisansala, M.J., Perera, W.P.R.T. and Dissanayake, K.G.C., 2020. Potential of inhibiting the receptor binding mechanism of sarscov-2 using phytochemical extracts of medicinal herb: Moleculer docking study. Glob. J. Eng. Sci. Res. Manage., 7(4): 51-61.

Rajbhandari, M., Mentel, R., Jha, P.K., Chaudhary, R.P., Bhattarai, S., Gewali, M.B., Karmacharya, N., Hipper, M., Lindequist, U., 2009. Antiviral activity of some plants used in Nepalese traditional medicine. Evid Based Complement Alternat Med.. 6(4): 517-522. https://doi.org/10.1093/ecam/nem156.

Reyburn, H., Mtove, G., Hendriksen, I. and Seidlein, L.V., 2009. Oral quinine for the treatment of uncomplicated malaria. Br. Med. J., 339: b2066–b2066. https://doi.org/10.1136/bmj.b2066

Schmitz, R., 1985. Friedrich wilhelm sertürner and the discovery of morphine. Pharma. History, 27(2): 61–74.

Schreiber, C.A., Wan, L., Sun, Y., Lu, L., Krey, L.C. and Lee-Huang, S., 1999. The antiviral agents, MAP30 and GAP31, are not toxic to human spermatozoa and may be useful in preventing the sexual transmission of human immunodeficiency virus type 1. Fertil. Steril., 72(4): 686–690. https://doi.org/10.1016/S0015-0282(99)00302-7

Seubsasana, S., Pientong, C., Ekalaksananan, T., Thongchai, S. and Aromdee, C., 2011. A potential andrographolide analogue against the replication of herpes simplex virus type 1 in vero cells. Med. Chem., 7(3): 237-244. https://doi.org/10.2174/157340611795564268

Shafer, R.W. and Schapiro, J.M., 2008. HIV-1 drug resistance mutations: An updated framework for the second decade of HAART. AIDS Rev.,

10(2): 67-84.

Silprasit, K., Seetaha, S., Pongsanarakul, P., Hannongbua, S. and Choowongkomon, K., 2011. Anti-HIV-1 reverse transcriptase activities of hexane extracts from some Asian medicinal plants. J. Med. Plants Res., 5(19): 4899-4906.

Singh, A.K., Singh, A., Shaikh, A., Singh, R. and Misra, A., 2020. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. Diabetes Metab. Synd. Clin. Res. Rev., 14(3): 241-246. https://doi.org/10.1016/j.dsx.2020.03.011

Singh, S., Yadav, S., Sharma, P. and Thapliyal, A., 2012. *Betula utilis*: A potential herbal medicine. Int.J.Pharma.Biol.Arch.,3(3):493-498.https://www.researchgate.net/publication/249967689.

Smith, T., Kawa, K., Eckl, V., Morton, C. and Stredney, R., 2018. Herbal supplement sales in US increased 8.5% in 2017, topping $8 Billion. In: *Herbal gram*. J. Am. Botan. Counc., pp. 62–71 http://cms.herbalgram.org/herbalgram/issue119/hg119-herbmk-trpt.html?ts=1551731923andsignature=a56d-285f95f81c6f6ce1e5b78b990ebeandts=1609945580andsignature=5c21dcf0eff1ab7bc99f-20855587d1cb

Soltan, M.M. and Zaki, A.K., 2009. Antiviral screening of forty-two Egyptian medicinal plants. J. Ethnopharmacol., 126(1): 102–107. https://doi.org/10.1016/j.jep.2009.08.001

Stockwell, C., 1988. Natures pharmacy: A history of plants and healing. Century.

Suffredini, I.B., Sader, H.S., Gonçalves, A.G., Reis, A.O., Gales, A.C., Varella, A.D. and Younes, R.N., 2004. Screening of antibacterial extracts from plants native to the Brazilian Amazon rain forest and atlantic forest. Braz. J. Med. Biol. Res. Rev. Brasil. Pesq. Med. Biol., 37(3): 379–384. https://doi.org/10.1590/S0100-879X2004000300015

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

Tang, Y., Xiong, R., Wu, A.G., Yu, C.L., Zhao, Y., Qiu, W.Q., Wang, X.L., Teng, J.F., Liu, J., Chen, H.X., Wu, J.M. and Qin, D.L., 2018. Polyphenols derived from lychee seed suppress Aβ (1-42)-induced neuroinflammation. Int. J. Mol. Sci., 19(7): 2109. https://doi.org/10.3390/ijms19072109

Thomson, W.A.R., 1978. Medicines from the earth: A guide to healing plants. McGraw-Hill.

Thyagarajan, S.P., Thiruneelakantan, K., Subramanian, S. and Sundaravelu, T., 1982. *In vitro* inactivation of HBsAg by Eclipta alba Hassk and Phyllanthus niruri Linn. Indian J. Med. Res., 76: 124–130.

Tolo, F.M., Rukunga, G.M., Muli, F.W., Njagi, E.N., Njue, W., Kumon, K., Mungai, G.M., Muthaura, C.N., Muli, J.M., Keter, L.K., Oishi, E., Kofi-Tsekpo, M.W., 2006. Anti-viral activity of the extracts of a Kenyan medicinal plant *Carissa edulis* against herpes simplex virus. J. Ethnopharmacol., 104(1/2): 92–99. https://doi.org/10.1016/j.jep.2005.08.053

Tripathi, M.K., Singh, P., Sharma, S., Singh, T.P., Ethayathulla, A.S. and Kaur, P., 2021. Identification of bioactive molecule from *Withania somnifera* (Ashwagandha) as SARS-CoV-2 main protease inhibitor. J. Biomol. Struct. Dyn., 39(15): 5668-5681. https://doi.org/10.1080/07391102.2020.1790425

United Nations Programme on HIV/AIDS (UNAIDS), 2022. Global HIV and AIDS statistics-fact sheet. pp. 1–376. Available at: https://www.unaids.org/en/resources/fact-sheet

Valko, M., Rhodes, C.J., Moncol, J., Izakovic, M. and Mazur, M., 2006. Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem. Biol. Interact., 160(1): 1–40. https://doi.org/10.1016/j.cbi.2005.12.009

Venkateswaran, P.S., Millman, I. and Blumberg, B.S., 1987. Effects of an extract from *Phyllanthus niruri* on hepatitis B and woodchuck hepatitis viruses: *In vitro* and *in vivo* studies. Proc. Nat. Acad. Sci. U.S.A., 84(1): 274–278. https://doi.org/10.1073/pnas.84.1.274

Vetvicka, V., Gover, O., Hayby, H., Danay, O., Ezov, N., Hadar, Y. and Schwartz, B., 2018. Spatial distribution of glucan type and content between caps and stalks in *Pleurotus eryngii*: Impact on the anti-inflammatory functionality. Int. J. Mol. Sci., 19(11): 3371. https://doi.org/10.3390/ijms19113371

Villamil, S.M., Alche, L.E. and Coto, C.E., 1995. Inhibition of herpes simplex virus type-1 multiplication by meliacine, a peptide of plant origin. Antiviral Chem. Chemother., 6(4): 239-244. https://doi.org/10.1177/095632029500600406

Vivekananthan, D.P., Penn, M.S., Sapp, S.K., Hsu, A. and Topol, E.J., 2003. Use of antioxidant vitamins for the prevention of cardiovascular disease: Meta-analysis of randomised trials. Lancet, 361(9374): 2017–2023. https://doi.org/10.1016/S0140-6736(03)13637-9

Wang, M., Cheng, H., Li, Y., Meng, L., Zhao, G. and Mai, K., 1995. Herbs of the genus *Phyllanthus* in the treatment of chronic hepatitis B: Observations with three preparations from different geographic sites. J. Lab. Clin. Med., 126(4): 350–352.

Weiner, M.A., 1980. Earth medicine earth food: Plant remedies, drugs, and natural foods of the North American Indians (1st Rev. and expanded ed). Macmillan Pub. Co. Collier Macmillan.

Wiart, C., Kumar, K., Yusof, M.Y., Hamimah, H., Fauzi, Z.M. and Sulaiman, M., 2005. Antiviral properties of ent-labdene diterpenes of *Andrographis paniculata* nees, inhibitors of herpes simplex virus type 1. Phytother. Res., 19(12): 1069-1070. https://doi.org/10.1002/ptr.1765

Woodward, R.B. and Doering, W.E., 1945. The total synthesis of quinine. J. Am. Chem. Soc., 67(5): 860–874. https://doi.org/10.1021/ja01221a051

World Health Organization, 2013. WHO traditional medicine strategy. 2014-2023. World Health Organization.

Wu, W., Li, R., Li, X., He, J., Jiang, S., Liu, S. and Yang, J., 2015. Quercetin as an antiviral agent inhibits influenza a virus (IAV) entry. Viruses, 8(1): 6. https://doi.org/10.3390/v8010006

Xu, Z.Q., Kern, E.R., Westbrook, A., Buckheit Jr, R.W., Tseng, C.K. and Jenta, T., 2000. Plant-derived and semi-synthetic calanolide compounds with *in vitro* activity against both human immunodeficiency virus type 1and human cytomegalovirus. Antiviral Chem. Chemother., 11: 23–29. https://doi.org/10.1177/095632020001100102

Xuan, T.D. and Khanh, T.D., 2016. Chemistry and pharmacology of *Bidens pilosa*: An overview. J. Pharma. Invest., 46: 91–132. https://doi.org/10.1007/s40005-016-0231-6

Yang, C.M., Cheng, H.Y., Lin, T.C., Chiang, L.C. and Lin, C.C., 2007. The *in vitro* activity of geraniin and 1, 3, 4, 6-tetra-O-galloyl-beta-d-glucose isolated from *Phyllanthus urinaria* against herpes simplex virus type 1 and type 2 infection. *J. Ethnopharmacol.*, 110(3): 555–558. https://doi.org/10.1016/j.jep.2006.09.039

Yarmolinsky, L., Huleihel, M., Zaccai, M. and Ben-Shabat, S., 2012. Potent antiviral flavone glycosides from Ficus benjamina leaves. Fitoterapia, 83(2): 362–367. https://doi.org/10.1016/j.fitote.2011.11.014

Yoshida, T., Ito, H., Hatano, T., Kurata, M., Nakanishi, T., Inada, A., Murata, H., Inatomi, Y., Matsuura, N., Ono, K., Nakane, H., Noda, M., Lang, F.A., Murata, J., 1996. New hydrolyzable tannins, shephagenins A and B, from *Shepherdia argentea* as HIV-1 reverse transcriptase inhibitors. Chem. Pharm. Bull. (Tokyo), 44(8): 1436-1439. https://doi.org/10.1248/cpb.44.1436

Yun, B.W., Yan, Z., Amir, R., Hong, S., Jin, Y.W., Lee, E.K. and Loake, G.J., 2012. Plant natural products: History, limitations and the potential of cambial meristematic cells. Biotechnol. Genet. Eng. Rev., 28(1): 47–60. https://doi.org/10.5661/bger-28-47

Zandi, K., Teoh, B.T., Sam, S.S., Wong, P.F., Mustafa, M. and AbuBakar, S., 2011. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol. J., 8(1): 560. https://doi.org/10.1186/1743-422X-8-560

Zheng, M.S. and Lu, Z.Y., 1990. Antiviral effect of mangiferin and isomangiferin on herpes simplex virus. Chin. Med. J. (Engl), 103(2): 160-165.

Zheng, Y., Wang, H., Yang, M., Peng, G., Dong, T.T.X., Xu, M.L. and Tsim, K.W.K., 2018. Prenylated Flavonoids from roots of *Glycyrrhiza uralensis* induce differentiation of B16-F10 melanoma cells. Int. J. Mol. Sci., 19(8): 2422. https://doi.org/10.3390/ijms19082422