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Effective antiviral medicinal plants and biological compounds against central nervous system infections: A mechanistic review

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Running title: Effective antiviral plants against CNS infections

Graphical Abstract

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Effective Antiviral Medicinal Plants and Biological Compounds Against Central Nervous System Infections: A Mechanistic Review

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Abstract

Background and objective

Infectious diseases are amongst the leading causes of death in the world and central nervous system infections produced by viruses may either be fatal or generate a wide range of symptoms that affect global human health. Most antiviral plants contain active phytoconstituents such as alkaloids, flavonoids, and polyphenols, some of which play an important antiviral role. Herein, we present a background to viral central nervous system (CNS) infections, followed by a review of medicinal plants and bioactive compounds that are effective against viral pathogens in CNS infections.

Method

A comprehensive literature search was conducted on scientific databases including: PubMed, Scopus, Google Scholar and Web of Science. The relevant key words used as search terms were: “myelitis”, “encephalitis”, “meningitis”, “meningoencephalitis”, “encephalomyelitis”, “central nervous system”, “brain”, “spinal cord”, “infection”, “virus”, “medicinal plants” and “biological compounds”.

Results

The most significant viruses involved in central nervous system infections are: *Herpes simplex* virus (HSV), Varicella zoster virus (VZV), West Nile virus (WNV), Enterovirus 71 (EV71), Japanese encephalitis virus (JEV) and Dengue virus (DENV). The inhibitory activity of medicinal plants against CNS viruses are mostly active through prevention of viral binding to cell membranes, blocking viral genome replication, prevention of viral protein expression, scavenging reactive oxygen species (ROS) and reduction of plaque formation.

Conclusion

Due to the increased resistance of microorganisms (bacteria, viruses and parasites) to antimicrobial therapies, alternative treatments, especially using plant sources and their bioactive constituents, appear to be more fruitful.

Keywords: CNS infection, Encephalitis, Meningitis, Myelitis, Virus, Medicinal plant, Bioactive compounds.

1. Introduction

Infectious diseases are amongst the leading causes of death in the world and are considered a permanent threat to the health of human populations [1]. Central nervous system (CNS) infections are inherently lethal diseases and a major source of mortality [2-4]. These central infections affect the brain and spinal cord and are instigated by a variety of pathogens [5, 6] including bacteria, viruses, fungi and parasites [1, 7]. Viruses can cause CNS infections in sporadic, endemic, epidemic, or pandemic patterns [8]. The distribution and disease severity generated by viruses are determined by the type of virus, the environment (certain environmental factors) and the host immunogenetics [9, 10].

Viral transmission may be accomplished by means of arthropod vectors (ectothermic or cold-blooded species and therefore, they are sensitive to climatic factors), animal bites, human-to-human contact, drug use, or consumption of raw meat [10]. There are two main routes for viruses to enter the central nervous system. Firstly, through the blood and secondly, by means of peripheral nerves (for example, rabies virus and poliovirus infect myocytes and mucosal epithelial cells, respectively). Nipah virus, influenza virus, rabies virus and herpes simplex virus-1 (HSV-1) enter the CNS through olfactory nerves, whilst others gain access via both routes [11].

Treatment of nervous system viral infections has always been a major challenge [10, 12]. The side effects of drugs used in the treatment of CNS infections, along with an increased resistance of microorganisms (bacteria, viruses or parasites) to antimicrobial therapies, have prompted researchers to pursue alternative treatments including those derived from plant sources [1]. Hence, many of the currently available drugs originate either directly or indirectly from plants [1, 13] and according to the World Health Organization, 80% of the world's population is dependent on herbal medicines for their primary health care [14]. Medicinal herbs are effective, inexpensive and relatively safe replacements for conventional drugs that are used to treat various types of central nervous system diseases [13] including viral infections [1].

Most antiviral plants contain active phytoconstituents such as alkaloids, flavonoids, polyphenols, glucosides, essential oils, tannins, fatty oils, saponins, steroids, mucilages, and gums, some of which play an important role against viruses [1]. The antiviral mechanisms of active phytochemicals and the bioactive compounds of medicinal plants are related to their antioxidant activity, ROS scavenging capability, inhibition of DNA plus RNA synthesis, and inhibition of viral entry or reproduction [15, 16]. Despite widespread reports of CNS infections arising from a viral origin along with an abundance of medicinal plants and bioactive compounds against these viruses, there is no comprehensive literature review on this topical issue. This article therefore aimed to provide a background to viral CNS infections, along with a subsequent review of

medicinal plants and bioactive compounds against centrally-active viral pathogens. Consequently, we summarized the antiviral activities of medicinal plants and natural products against important viral pathogens including Japanese encephalitis virus (JEV), dengue virus (DENV), enterovirus 71 (EV71), herpes simplex virus (HSV), human immunodeficiency virus (HIV), influenza virus, measles virus (MV), rabies virus, varicella-zoster virus (VZV) and West Nile virus (WNV).

2. Method

A comprehensive literature search was conducted on scientific databases including: PubMed, Scopus, Google Scholar and Web of Science. The relevant key words used as search terms were: “myelitis”, “encephalitis”, “meningitis”, “meningoencephalitis”, “encephalomyelitis”, “central nervous system”, “brain”, “spinal cord”, “infection”, “virus”, “medicinal plants” and “biological compounds”. Relevant full papers and abstracts were retrieved, then the reference lists of the key papers for further evaluation were searched and both *in vitro* and *in vivo* investigations were considered.

3. Results

3.1 Viral infections of the central nervous system

In general, CNS viral infections may be classified into four categories namely, congenital-, acute-, chronic- and slow- viral infections [10, 17].

1. Congenital viral infections: many viruses such as rubella, cytomegalovirus (CMV), Zika virus (ZIKV) and varicella-zoster virus (VZV) are associated with congenital viral infection. Some of the diseases that are caused by these viruses include: encephalitis, meningoencephalitis, calcification in the brain, cataract, microcephaly and sensory neural deafness [18].

2. Acute CNS infections: are caused by herpes simplex virus (HSV) [19], Japanese encephalitis virus (JEV), human immunodeficiency virus (HIV), CMV, VZV, ZIKV, Epstein Barr virus (EBV), enterovirus (EV), polio virus (PV), DENV, mumps and measles virus (MV). They cause sequelae such as meningitis, encephalitis, Guillain-Barre Syndrome (GBS), flaccid paralysis, aseptic meningitis and meningoencephalitis [10].

3. Chronic CNS infections: are caused by: human T-lymphotropic virus type 1 (HTLV1), Cytomegalovirus (CMV), Epstein Barr virus (EBV), John Cunningham virus (JCV), Human Immunodeficiency Virus (HIV) and Polio Virus (PV). These viral infections manifest diseases such as encephalitis, Progressive Multifocal Leukoencephalopathy (PML), Amyotrophic Lateral Sclerosis (ALS), Tropical Spastic Paraparesis (TSP) and PostPolio Syndrome (PPS) [10]. HTLV1 causes myelopathy and amyotrophic lateral sclerosis (ALS) [20] as well as being associated with neurological conditions like TSP [10, 20]. CMV and EBV can cause chronic encephalitis in immunosuppressed patients and EBV has also been recorded as an inducer of chronic

fatigue syndrome in the Northern hemisphere [21, 27]. JCV (a polyomavirus) is implicated in progressive multifocal leukoencephalopathy (PML), a fatal neurological demyelinating disease of the CNS related to the destruction of oligodendrocytes by lytic infection of myelin producing cells [22-26]. A capsid protein mutation of JCV is related to PML [27] and in addition, motor neuronal loss, muscle atrophy, denervation and interstitial inflammatory cells have been seen in patients with PPS [28].

4. Slow viral infections: examples of slow human viral infections include subacute sclerosing panencephalitis (SSPE) and PML which are caused by MV and JCV, respectively. There are also normally harmless prion proteins in the brain which are suspected to misfold and confer slow infectious properties responsible for transmissible spongiform encephalopathies exemplified by fatally neurodegenerative Creutzfeld-Jakob disease (CJD) [10].

The foremost types of neuroinvasive brain disease are meningitis, encephalitis, and acute flaccid paralysis/poliomyelitis [29] and of these, the two key CNS infections with viral origin are meningitis and encephalitis [5].

3.2 Encephalitis

Encephalitis is a prevalent CNS infection-related manifestation [30] entailing intense inflammation of the brain parenchyma accompanied by brain dysfunction [31]. Common symptoms of encephalitis are fever, headache, mental status changes, movement disorders including myoclonus, tremor, parkinsonism, ataxia, and weakness plus neurological dysfunction (seizures, cranial nerve palsies, dysarthria, abnormal reflexes and paralysis) [11, 29, 32-33]. Enteroviruses [poliovirus (PV) and enterovirus 71 (EV71)] as well as the alphaviruses [Eastern equine encephalitis virus (EEEV), Western equine encephalitis virus (WEEV), Venezuelan equine encephalitis virus (VEEV)], the Flaviviruses [JEV, St. Louis Encephalitis virus (SLEV) and West Nile virus (WNV)], HSV-1, HIV-1, VZV, Nipah virus and the Bunyavirus, La Crosse virus (LAC) are all capable of causing viral encephalitis [34-41].

MV can instigate SSPE in 6-13-year old children [42] and it has been reported that human herpesvirus 6A (HHV-6A) and 6B (HHV-6B) causes acute focal encephalitis in both immunocompetent children and adults [43-46]. The neuroinvasive properties of dengue virus have been evaluated [47] and a number of studies show that this virus also induces encephalitis [48-52] while infection with Chikungunya virus (CHIKV) results not only in encephalitis but also meningoencephalitis [53, 54].

3.3 Encephalomyelitis

Encephalomyelitis occurs during simultaneous inflammation of the brain and spinal cord usually due to acute viral infection [55]. In this context, Sindbis virus (SINV) can cause fatal encephalomyelitis by inducing apoptosis of immature neurons [56, 57].

3.4. Meningitis

Inflammation of the tissue lining and meningeal layers of the brain as well as the spinal cord constitute the condition, meningitis [14, 58]. Common symptoms include fever, headache, nausea and/or vomiting, tremors, myalgia, weakness, spotty rash and neck stiffness plus rigidity [5, 17, 29, 59]. Many viruses bring about meningitis and examples include: JEV [60], WNV [29, 61], SLEV [62], Bunyaviruses [63], mumps virus [11, 64], lymphocytic choriomeningitis virus (LCMV) [11], HSV-1 and 2 [65], HIV-1 [66], VZV [67], Toscana virus, Enteroviruses [(EV71, ECV and Coxsackie B viruses (CVB)] [29, 68, 69].

Combined viral infection of the brain, spinal cord and meninges is termed meningoencephalitis [9]. In this connection, Echovirus type 11 (ECV11) is a major cause of chronic meningoencephalitis in patients with impaired humoral immunity [70]. Similarly, Rabies virus, Herpes viruses and Arboviruses are also capable of instigating meningoencephalitis [17]. The neurological symptoms of this chronic condition are headache, seizures, hearing loss, lethargy/coma, weakness, ataxia and paresthesias in addition to non-neurological symptoms typified by dermatomyositis-like syndrome, peripheral “ligneous” edema, exanthema and hepatitis [70].

3.5. Mollaret’s meningitis or recurrent aseptic meningitis

Occurrence of this syndrome has been reported more commonly in women than men and HSV-2 is a major cause. Some signs of this disease are repeated self-limiting episodes of fever, meningeal inflammation and severe headache (usually of 2–5 days duration) [71, 72].

Most patients with meningitis and encephalitis ($\leq 90\%$ of cases) have abnormal cerebrospinal fluid (CSF) including: pleocytosis, elevated protein, and decreased glucose [6, 55].

3.6. Myelitis

Spinal cord inflammation caused by poliovirus is designated as poliomyelitis and as a result of myelitis generally, the spinal cord grey matter is damaged. VZV, HSV, CMV, EBV, enteroviruses (poliovirus, EV71, coxsackievirus, echovirus), rabies virus, HTLV1, WNV and HIV are the most prevalent viruses causing acute myelitis [11, 73]. In PV, EV71, WNV and JEV infections, viral antigens are present in the neuronal cell

bodies in the anterior horns of the spinal cord and this tends to be associated with severe perivascular inflammation and acute flaccid paralysis [11].

Rabies virus causes spinal cord disease (inflammation in the anterior spinal cord horns and loss of motor neuron function). Also, dorsal root ganglion neurons are infected by rabies virus. In fact, rabies virus initiates segmental demyelination in the spinal and peripheral nerves. Thus, several experiments have identified demyelination of peripheral nerves as the cause of rabies paralysis [11] and it has also been reported that the presence of rabies virus in the CSF brings about acute myelitis. It is notable that Flaviviruses such as DENV, JEV, and WNV elicit invasive encephalitis in addition to transverse or extensive myelitis [47] and CHIKV infection is associated with myelitis by neuronal necrosis in the spinal cord [74].

3.7. Acute flaccid paralysis

Acute flaccid paralysis (AFP) is one of two syndromes of acute viral myelitis that is attributable to cytolytic infection of anterior spinal cord horn cells. Enteroviruses (e.g. polioviruses 1, 2 and 3), non-polio enteroviruses (e.g. Coxsackie A and B virus, EV71), Herpes viruses (e.g. HSV, VZV, CMV, EBV), Flaviviruses (e.g. WNV, JEV) are all able to incite AFP [75, 76].

Polioviruses and enterovirus found in the CSF of patients with acute flaccid paralysis have been credited with causing this pathological condition [77] which has been associated with other viruses such as CHIKV [73, 78].

3.8. Diagnosis of CNS viral infections

Neuroimaging of the brain by computed tomography (CT) scanning or magnetic resonance imaging (MRI), lumbar puncture with CSF analysis or detection of viral nucleic acids by polymerase chain reaction (PCR) or reverse transcription PCR (RT-PCR), serology tests and brain biopsy are characteristically employed for the diagnosis of CNS viral infections [75].

3.9. Antiviral medicinal plants and biological compounds for CNS viral infections

Some of the data concerning the antiviral medicinal plants and their mechanisms against viral CNS infections are summarized in Table 2.

Polyphenols are natural compounds present in vegetables, fruits, grains, barks, roots, tea, and wine. They are the best sources of these phytochemicals [79]. In this group, the phytoconstituent flavonoids are a class of secondary metabolites of plant associated with the characteristic phenolic structure [80]. Both flavonoids and isoflavonoids possess antiviral properties by interfering with virus binding to host cell membranes,

impairing cellular entry and subsequent replication, disrupting intracellular viral protein translation and affecting viral envelope glycoprotein complex formation [81, 82]. Isoflavones have also been shown to perturb cell signaling, for instance, via gene transcription factors and cytokine secretion within the host cell [81].

A selection of examples of the major plant flavonoids are represented by anthocyanins (flavylium) e.g. cyanidin, flavonols (myricetin, quercetin), flavones (apigenin and luteolin), catechins (epicatechin, epigallocatechin gallate or EGCG ([[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl] 3,4,5-trihydroxybenzoate), and flavanones (hesperetin and naringenin) (table 1) [83- 89].

Table 1: Chemical structures of flavonoids.

Group of flavonoids	Structure backbones	Examples	
Anthocyanins	<p>flavylium</p>	<p>cyanidin</p>	
Flavonols	<p>flavonol</p>	<p>quercetin</p>	<p>myricetin</p>

<p>Flavones</p>	<p>flavone</p>	<p>apigenin</p>	<p>luteolin</p>
<p>Flavonones</p>	<p>flavonone</p>	<p>naringenin</p>	<p>3',5,7-Trihydroxy-4'-methoxyflavanone Hesperetin</p>
<p>Catechin</p>	<p>catechin</p>	<p>[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl] 3,4,5-trihydroxybenzoate</p>	<p>epicatechin</p>

The phenylpropanoid, Eugenol (4-allyl-1-hydroxy-2-methoxybenzene) present in oil of cloves and in the essential oils of cinnamon and basil, has inhibitory effects on lipid peroxidation and replication of either viral RNA or DNA [90, 91].

Quercetin (3,3',4',5,7-pentahydroxyflavone) is a notable flavonoid exemplar with antiviral activity [92, 93]. It is found in fruit, nuts as well as grains and additionally, as a plant pigment, it bestows bright colors to vegetables and fruit such as apples cherries and berries. Onion (*Allium cepa* L.), asparagus (*Asparagus officinalis* L.), and red leaf lettuce (*Lactuca sativa* L.) together with red wine and tea possess appreciable concentrations of Quercetin [92, 94]. This ubiquitous bioflavonoid is a therapeutic/nutraceutical agent that has been classed as a cognitive enhancer with a conceivable treatment potential for neurodegenerative disorders since it enhances neurogenesis, neuronal survival and synaptogenesis in the brain [93].

Quercetin also has antiviral activity against: human T-lymphotropic virus (HTLV-1) (by reducing cellular viral release) [95], JEV [96], dengue virus type 2 (by virtue of its anti-infective and anti-replicative effects) [97] and hepatitis C virus (through inhibition of NS3 protease activity) [98]. Moreover, it inhibits: encephalomyocarditis virus [99] and HSV-1 (by suppressing Toll like receptor 3 (TLR-3) expression leading to inhibition of the inflammatory transcriptional factors nuclear factor- κ B (NF- κ B) and interferon factor 3 (IRF3) [100], influenza virus A (IFA) [101] and porcine epidemic diarrhea virus (by an antioxidant-independent mechanism) [102].

Potent anti-IFA activities have been observed with extracts from *Sambucus nigra*, *Pelargonium sidoides*, *Taraxacum officinale*, *Illicium oligandrum* (spirooliganone B), *Glycyrrhiza inflata* (chalcones), *Polygala karensium* (xanthones), and *Caesalpinia sappan* (homoisoflavonoids) [103-109]. On a similar note, a hydroethanolic extract of *Phytolacca dodecandra* leaves (1000 mg/kg) displays anti-rabies activity which is thought to be due to the presence of the ribosomal inhibiting protein, dodecandrin. Likewise, methanolic extracts of the leaves and flowers of *Alamanda schottii* exhibit some activity against rabies virus [110].

The skin secretions of some amphibians such as the genus *Bufo* (*Rhinella*) contain a number of alkaloids which include bufotenine (N', N'-dimethyl 5-hydroxytryptamine). This biological compound is a tryptamine alkaloid that is also found in the *Leguminosae* (*Fabaceae*) family, a good example of which is provided by the seeds of *Anadenanthera colubrina*. At a concentration of 3.9 mg.mL⁻¹ bufotenine totally inhibits the rabies virus through an apparent competitive mechanism involving the nicotinic acetylcholine receptor [111].

Some of the polyphenols of green tea such as epigallocatechin gallate (EGCG) and gallic acid (GCG) have been shown to inhibit the replication of EV1 genomic RNA by modulating the cellular redox milieu. Also, EGCG precludes the formation of infectious progeny virions and diminishes EV1 induced oxidative stress along with prevention of neuronal death [112, 113]. Thus, the antiviral effect of EGCG has been largely attributed to its antioxidant properties [113].

Analogously, gallic acid found in the flowers of *Woodfordia fruticosa* blocks EV71 infection and replication [114].

Chen *et al.*, (2017) showed that a methanolic extract of *Melissa officinalis* and its bioactive compound rosmarinic acid prevents plaque formation, EV1 protein synthesis and replication thus counteracting the cytopathic effect of the virus. Moreover, this plant extract inhibits attachment of virion to host cells and removes reactive oxygen species as well [115]. *Salvia miltiorrhiza* (Danshen) with its magnesium lithospermate B and rosmarinic acid phytoconstituents, and *Ocimum basilicum* (sweet basil), both exhibit anti-EV71 activity [116-118]. Aqueous extract of *Schizonepeta tenuifolia* Briq has inhibitory activity against EV71 through reducing EV71 attachment, prevention of plaque formation and inhibition of viral genomic RNA replication [119].

The triterpenoids of *Glycyrrhiza uralensis* (Glycyrrhizic acid) and *Ganoderma lucidum* block adsorption of enteroviruses [120, 121].

Both aqueous and ethanolic extracts of *Ocimum basilicum* containing the bioactive constituents linalool (terpene alcohol), apigenin (flavone) and ursolic acid (triterpenoid) possess antiviral activity against CVB1 and inhibit its replication post-infection [116]. In fact, *Bupleurum kaoi* (containing flavonoid) and *Raoulia australis* (containing the terpene, raoulic acid) inhibit several CVB subtypes particularly infection with CVB1 [122, 123].

Three compounds including FGIN-1-27 (N, N-diethyl-2-(4-fluorophenyl) indole-3-acetamide), cilnidipine (1, 4-dihydropyridine-3, 5-dicarboxylic acid), and niclosamide (5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide) at concentrations of 10 and 20 μ M have inhibitory effects on JEV at the stage of viral replication (figure 1) [124-127]. Other studies have shown that indigo and indirubin-derived *Isatis indigotica* extract also have potent virucidal activities against JEV *in vitro* (blocking virus attachment, reducing virus yield in cell culture and inhibition of JEV replication) with low cytotoxicity [128].

Figure 1. Chemical structures of (N, N-dihexyl-2-(4-fluorophenyl) indole-3-acetamide) (FGIN-1-27), 1, 4-dihydropyridine-3, 5-dicarboxylic acid (cilnidipine) and 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (niclosamide).

The flavonoid Kaempferol (Kae) and isoflavonoid daidzin (Dai) have antiviral effects against JEV (figure 2) [82, 86]. Kae is found in tea, broccoli, delphinium, witch-hazel, grapefruit, Brussel sprouts, apples, and various other medicinal plants [82]. Also, this polyhydric flavonol has antiviral activity against influenza viruses (H1N1 and H9N2) by inhibiting neuraminidase activity. In addition, it is active against herpes simplex virus and hepatitis B virus under *in vitro* conditions [129, 130]. Individually, Kae and Dai prevent viral infection by inhibiting viral protein expression, cell growth, viral activity by binding to viral RNA within the cell cytosol, and viral genome replication [82]. It is notable however, that Kae is a more potent antiviral than Dai against JEV and this appears to stem from a greater proclivity to inactivate the virus by binding with the JEV frameshift site RNA (fsRNA) forming non-covalent complexes. Nevertheless, a combination of Kae and Dai is more effective against JEV infection indicating a conceivable antiviral synergy between isoflavonoids and flavonoids [82].

Figure 2. Chemical structures of Daidzein and Kaemferol

Interestingly, another plant-derived bioflavonoid, baicalein (5,6,7-trihydroxyflavone), originally isolated from *Scutellaria baicalensis* root, displays a potent antiviral effect against JEV replication in Vero cells. Furthermore, it not only possesses viral anti-adsorption activity, but also has a direct extracellular virucidal action on JEV as well (figure 3) [96, 131].

Figure 3. Chemical structure of 5, 6,7-trihydroxyflavone (Balcalein).

Furanonaphthoquinone derivatives, especially 2-methylnaphtho [2, 3-b]furan-4,9-dione (FNQ3) (figure 4), possess antiviral activity. Accordingly, JEV replication, protein synthesis, expression of viral proteins plus genomic RNA have all been reported to be inhibited by FNQ3 [132]. In this context, the FNQ derivatives in general exist in the inner bark of *Tecoma ipe* Mart, *Tabebuia impetiginosa*, *T. barbata* and *T. avellanedae* [132, 133].

2-methylnaphtho [2, 3-b]furan-4,9-dione

Figure 4. Chemical structure of 2-methylnaphtho [2,3-b] furan-4,9-dione (FNQ3).

Astragali radix extract has a protective effect against JEV during the early stage of infection and it has been proposed that this antiviral activity is due to a non-specific macrophage-based mechanism before transference to antibody production [134]. Some antioxidants such as minocycline, arctigenin (a plant lignin active against JEV), fenofibrate, and curcumin have antiviral properties [135]. Minocycline (synthetic tetracycline) decreases neuronal damage in JEV infection and prevents ROS production [135, 136]. Curcumin is a phenolic compound (non-flavonoid polyphenol) that occurs naturally in *Curcuma longa* L. rhizome [137-139]. This antiviral compound impedes the production of infectious JEV particles by blocking several intracellular signaling pathways including mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), and nuclear factor $\kappa\beta$ (NF- $\kappa\beta$) [140]. It also increases cell viability by decreasing ROS and preventing pro-apoptotic signals [141]. There are algae namely *Gracilaria* sp. and *Monostroma nitidum* that prevent JEV infection by their low-degree-polymerisation sulfated saccharides [142].

Medicinal plants and bioactive compounds have been reported to possess anti-HSV-1 activity. They include Houttuynoids A-E found in *Houttuynia cordata*, an aqueous extract from *Rhododendron ferrugineum*, blackberry extract, a proanthocyanidin-enriched extract from *Myrothamnus flabellifolia* Welw and glucoevatromonoside, a cardenolide from *Digitalis lanata* [143-147].

Not only do the phenolic plant components consisting of flavonoids, alkaloids, and terpenes have antiherpetic activity, [148] but so do high concentrations of the essential oils in *Eucalyptus caesia*, *Zataria multiflora*, *Artemisia kermanensis*, *Artemisia arborescens*, *Satureja hotensis*, and *Rosmarinus officinalis*. These essential oils have inhibitory effects on HSV-1 plaque formation and their major constituents include the phenol: thymol (*Z. multiflora*), the terpenes: α -pinene (*R. officinalis*), carvacrol (*S. hotensis*) and 1, 8-cineole (*E. caesia*) as well as the terpenoid: camphor (*A. kermanensis*) [91].

Studies have shown that the essential oil in *Thymus vulgaris* has a virucidal effect on HSV-2 in cell culture, the activity occurring prior to adsorption and probably involving the viral envelope [149]. Additionally, *Chamaecyparis obtuse* and *Tripterygium hypoglaucum* both have antiherpetic effects, but they are mediated by inhibition of HSV gene expression [150, 151]. *Melissa officinalis* on the other hand has antiviral activity not only against HSV-1, but also HSV-2 [152, 153].

Ent-epiafzelechin- (4a→8)-epiafzele chin, extracted from *Cassia javanica* and meliacine derived from *Melia azedarach* are both novel anti-HSV-2 agents [154-156]. Hippomanin A, geraniin, 1,3,4,6-tetra-O-galloyl-beta-D-glucose, and excoecarianin extracted from *Phyllanthus urinaria* represent a range of other plant derived compounds with the capability of inhibiting HSV infection [157-159].

Similarly, polysaccharides from red seaweeds, such as *Acanthophora spicifera*, *Schizymenia binderi*, *Gracilaria corticata* and *Caulerpa racemosa* have been shown to prevent HSV-1 and HSV-2 infections [160, 161].

Bioactive compounds such as the flavones baicalein and narasin have significant anti-DENV activity via inhibition of viral replication [162, 163]. Conversely, *Terminalia chebula* (containing chebulagic acid and punicalagin) prevents DENV attachment, fusion and entry during early infection [164]. Other polysaccharide examples such as *Meristiella gelidium* and *Callophyllis variegata* have a slightly broader antiviral spectrum against DENV-2, HSV-1, and HSV-2 infections [165, 166].

Herbal medicines with inhibitory effects against HIV include crude extracts of *Artemisia annua* and *Artemisia afra*, in addition to coumarin derived from the stem bark of *Calophyllum brasiliense* [167-169]. Also, bioflavonoid compounds found in *Rhus succedanea*, *Garcinia multiflora*, and *Cajanus cajan* possess antiviral activity against MV infection [170]. Furthermore, the roots and rhizomes of Liquorice (*Glycyrrhiza glabra*) and its bioactive compound Glycyrrhizin have a virucidal effect versus VZV [171].

Finally, Goodell et al., (2006) proved that pyrazolines have a noteworthy inhibitory effect against WNV by preventing RNA synthesis along with viral replication enzymes [172].

Table 2. Antiviral medicinal plants and biological compounds and their mechanisms against viral CNS infections.

Virus	Medicinal plants and biological compounds	Mechanism(s)	References
influenza virus A	<i>Sambucus nigra</i>	Inhibitory effect on the propagation of human pathogenic influenza viruses	[105]
	<i>Pelargonium sidoides</i>	Inhibits viral entry and release; inhibits viral hemagglutination and neuraminidase activity	[108]
	<i>Taraxacum officinale</i>	Inhibits viral nucleoprotein RNA levels and polymerase activity	[106]
	<i>Illicium oligandrum</i> , and <i>Glycyrrhiza inflata</i>	Inhibits viral nucleoprotein RNA levels and polymerase activity	[109] [104]
	<i>Polygala karensium</i>	IFA neuraminidase inhibition	[103]
	<i>Caesalpinia sappan</i>	IFA neuraminidase inhibition	[107]
	<i>Polygonum perfoliatum</i> (Quercetin)	IFA neuraminidase inhibition	[101]
Rabies virus	<i>Phytolacca dodecandra</i> , <i>Alamanda schottii</i>	Presence of ribosomal inhibiting protein (RIP) known as dodecandrin	[110]
	<i>Anadenanthera colubrina</i>	Competitive mechanism by the nicotinic acetylcholine receptor	[111]

Enterovirus 71	epigallocatechin gallate (EGCG) and gallic acid gallate (GCG)	Modulation of cellular redox milieu, prevention of infectious progeny virion formation	[112] [113]
	<i>Woodfordia fruticosa</i>	Blocking EV71 infection and replication	[114]
	<i>Melissa officinalis</i> , rosmarinic acid	Inhibit attachment of virion to host cells, removing ROS, inhibition plaque formation, protein synthesis and EV1 replication	[115]
	<i>Salvia miltiorrhiza</i>	Diminishing viral attachment and entry, ROS formation, plaque formation and RNA replication	[117, 118]
	<i>Ocimum basilicum</i> and <i>Schizonepeta tenuifolia</i>	Diminishing viral attachment and plaque formation	[116] [119]
	<i>Glycyrrhiza uralensis</i> (Glycyrrhizic acid),	Blocking adsorption of enteroviruses	[120]
	<i>Ganoderma lucidum</i>	Blocking adsorption of enteroviruses	[121]
Coxsackievirus	<i>Ocimum basilicum</i>	Inhibition of CVB1 replication post-infection	[116]
	<i>Bupleurum kaoi</i> ,	Induction of type I interferon response	[122]
	<i>Raoulia australis</i>	Induction of type I interferon response	[123]
Japanese Encephalitis	FGIN-1-27, cilnidipine, and niclosamide	Inhibition of viral replication	[124]

Virus

<i>Isatis indigotica</i>	Blocking virus attachment, reducing virus yield in cell culture and inhibition of JEV replication	[128]
kaempferol (Kae), daidzin (Dai)	Prevention of viral protein expression and cell growth	[82]
<i>Scutellaria baicalensis</i>	Inhibition of JEV replication	[96]
<i>Tecoma ipe</i> <i>Tabebuia impetiginosa</i> <i>T. barbata</i> , <i>T. avellaneda</i>	Inhibition of JEV replication, protein synthesis, and the expression of viral proteins	[132, 133]
<i>Astragali radix</i>	Anti-infective and anti-replicative effects	[134]
Minocycline	Decreasing neuronal damage, prevents ROS production	[135, 136]
Curcumin (<i>Curcuma longa</i>)	Blocking several intracellular signaling pathways including (MAPK), (PI3K/AKT), (pNF-K β)	[140]
<i>Gracilaria</i> sp.	Prevention of JEV infections by their low-degree-polymerisation sulfated saccharides	[142]
<i>Monostroma nitidum</i>	Prevention of JEV infections by their low-degree-polymerisation	[142]

		sulfated saccharides	
Herpes simplex virus	<i>Eucalyptus caesia</i>	Inhibition of plaque formation	[101]
	<i>Zataria multiflora</i>	Inhibition of plaque formation	
	<i>Artemisia kermanensis</i>	Inhibition of plaque formation	[152, 153]
	<i>Artemisia arborescens</i>	Inhibition of plaque formation	
	<i>Satureja hotensis</i>	Inhibition of plaque formation	
	<i>Rosmarinus officinalis</i>	Inhibition of plaque formation	
	<i>Melissa officinalis</i>		
	<i>Houttuynia cordata</i>		[147]
	<i>Rhododendron ferrugineum</i>	Inhibition of viral adsorption and penetration	[145]
	<i>Digitalis lanata</i>	Inhibition of viral protein synthesis	[143]
	<i>Myrothamnus flabellifolia</i>	Inhibition of viral adsorption and penetration	[144]
	<i>Thymus vulgaris</i>	Inhibition of the growth of virus in the cell culture	[149]
	<i>Cassia javanica</i>	Inhibition of viral replication	[154]
	<i>Melia azedarach</i>	Induces TNF- α and IFN- γ production	[155]
	<i>Phyllanthus urinaria</i>	Inactivation of virus particles	[157- 159]
	<i>Chamaecyparis obtuse</i>	Inhibition of HSV gene expression	[150, 151]
	<i>Tripterygium hypoglaucum</i>		
	<i>Acanthophora spicifera</i> , <i>Schizymenia binderi</i> , <i>Gracilaria corticata</i> and <i>Caulerpa racemose</i>	Interference with the initial adsorption of viruses to cells, inhibition of the initial virus attachment to the host cell	[160, 161]

	Quercetin	suppressing Toll like receptor 3 (TLR-3)	[100]
Dengue virus	Baicalein	Inhibition of viral replication post entry	[163]
	Narasin	Inhibition of viral protein synthesis	[162]
	<i>Terminalia chebula</i>	Preventing attachment and fusion during early viral entry	[164]
	<i>Meristiella gelidium</i>		[166]
	<i>Callophyllis variegata</i>		[165]
	Quercetin	Inhibition of viral replication	[97]
Human immunodeficiency virus	<i>Artemisia annua</i> <i>Artemisia afra</i>		[169]
	<i>Calophyllum brasiliense</i>	Inhibition of viral replication by suppressing NF-κB activation	[167, 168]
Measles Virus	<i>Rhus succedanea</i> <i>Garcinia multiflora</i> , and <i>Cajanus cajan</i>	Cytopathic effect inhibition	[170]
Varicella Zoster Virus	<i>Glycyrrhiza glabra</i>	Inhibition of the penetration, uncoating or release of virus particles	[171]
West Nile Virus	Pyrazolines	Prevention of RNA synthesis and viral replication enzymes	[172]

Conclusion

Nervous system infections are inherently lethal diseases that are caused by a variety of infectious agents such as viruses which can be very harmful pathogens for the CNS. Medicinal herbs are potentially effective, inexpensive and relatively safe replacements for synthetic chemical drugs in the treatment of CNS infections.

In this review, we described the major viral CNS infections and specified sequelae (encephalitis, meningitis and myelitis) as well as effective herbal plants and biological compounds against viruses causing these infections. The most important viruses involved in development of central nervous system infections include: herpes simplex virus (HSV), varicella zoster virus (VZV), West Nile virus (WNV), enterovirus 71 (EV71), Japanese encephalitis virus (JEV) and dengue virus (DENV).

Some bioactive compounds (alkaloids, flavonoids, and polyphenols), natural products and medicinal plants have inhibitory activity against different viruses. The phytochemicals, Quercetin, Kaempferol, Curcumin, Epigallocatechin gallate (EGCG) and Gallocatechin gallate (GCG) are the most notably active compounds in medicinal plants which are mentioned in the literature. Their antiviral mechanisms include: inhibition of virus binding to host cell membranes, blocking viral genome replication, preventing the expression of viral proteins, scavenging reactive oxygen species (ROS) and reducing plaque formation. These herbally-derived remedies are therefore promising sources for the development of antiviral drugs.

Conflict of interests

The authors declared no competing interests.

Author contributions

KM (Kh.Malekmohammad@gmail.com), MRK (rafieian@yahoo.com), SS (sardari.sa1992@gmail.com), RDES (sewell@cardiff.ac.uk) all contributed equally to the literature search, preparation and writing of the manuscript. All read and confirmed the final version for publication.

References

- [1] Ganjhu RK, Mudgal PP, Maity H, *et al.* Herbal plants and plant preparations as remedial approach for viral diseases. *Virusdisease* 2015; 26: 225-36.
- [2] Muzumdar D. Central nervous system infections and the neurosurgeon: A perspective. *Int. J. Surg* 2011; 9: 113-16.
- [3] Miranda HA, Castellar-Leones SM, Elzain MA, Moscote-Salazar LR. Brain abscess: current management. *J Neurosci Rural Pract* 2013; 4:S67.
- [4] Sahoo S. A review of some medicinal plants used for nervous disorders. *J Med Plant* 2018; 6: 220-24.
- [5] Whitley RJ, Gnann JW. Viral encephalitis: familiar infections and emerging pathogens. *Lancet* 2002; 359: 507-13.
- [6] Hsu CC. Epidemiological Features of Central Nervous System (CNS) Infections in Taiwan and Molecular Investigation of CNS Infections of Unknown Cause. PhD Thesis, University of Columbia, 2012.
- [7] Whitley RJ, Kimberlin DW. Viral encephalitis. *Pediatr Rev* 1999; 20:192-98.
- [8] Bookstaver PB, Mohorn PL, Shah A, *et al.* Management of viral central nervous system infections: a primer for clinicians. *J Cent Nerv Syst Dis* 2017; 9: 1179573517703342.
- [9] Steiner I, Budka H, Chaudhuri A, *et al.* Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *Eur. J. Neurol* 2010; 17: 999-e57.
- [10] Ramamurthy M, Sankara S, Arumugam I, Nandagopal B, Srikanth P, Gopalan S. Viral infections of the CNS: the unraveling of the mystery. *Sri Ramachandra J. Med* 2016; 9: 15-23.
- [11] Swanson II PA, McGavern DB. Viral diseases of the central nervous system. *Curr Opin Virol* 2015; 11: 44-54.
- [12] McGavern DB, Kang SS. Illuminating viral infections in the nervous system. *Nat. Rev. Immunol* 2011; 11: 318.
- [13] Shubhada VM, Dharammali, Dinesh RC. Herbal remedies for CNS disorders. *IJCAP* 2017; 2: 42-44.
- [14] Roy RN. Commentary: “Physicochemical Characterization and Antibacterial Activity of the Leaf oil of *Crotalaria pallida* Aiton. *Journal of Meningitis* 2016; 1:110.

- [15] Naithani R, Huma LC, Holland LE, *et al.* Antiviral activity of phytochemicals: a comprehensive review. *Mini-Rev. Med. Chem* 2008; 8: 1106-133.
- [16] Chattopadhyay D, Chawla-Sarkar M, Chatterjee T, *et al.* Recent advancements for the evaluation of anti-viral activities of natural products. *N Biotechnol* 2009; 25: 347-68.
- [17] Sarrazin JL, Bonneville F, Martin-Blondel G. Brain infections. *Diagn Interv Imaging* 2012; 93: 473-90.
- [18] Mendelson E, Aboudy Y, Smetana Z, Tepperberg M, Grossman Z. Laboratory assessment and diagnosis of congenital viral infections: Rubella, cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), parvovirus B19 and human immunodeficiency virus (HIV). *Reproductive Toxicol* 2006; 21: 350-82.
- [19] Smith G. Herpesvirus transport to the nervous system and back again. *Annu Rev Microbiol* 2012; 66: 153-76.
- [20] Gessain A, Mahieux R. Tropical spastic paraparesis and HTLV-1 associated myelopathy: clinical, epidemiological, virological and therapeutic aspects. *Rev Neurol* 2012; 168: 257-69.
- [21] Akkoc G, Kadayifci EK, Karaaslan A, Atici S, Yakut N, Ocal Demir S, *et al.* Epstein-Barr virus encephalitis in an immunocompetent child: a case report and management of Epstein-Barr virus encephalitis. *Case Rep Infect Dis* 2016; 2016.
- [22] Berger JR. Progressive multifocal leukoencephalopathy. *Handb Clin Neurol* 2007; 85: 169-83.
- [23] Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis* 2009 9: 625-36.
- [24] Focosi D, Marco T, Kast RE, Maggi F, Ceccherini-Nelli L, Petrini M. Progressive multifocal leukoencephalopathy: what's new? *Neuroscientist*, 2010; 16: 308-23.
- [25] Major EO. Progressive multifocal leukoencephalopathy in patients on immunomodulatory therapies. *Annu Rev Med* 2010; 61: 35-47.
- [26] Tan CS, Ellis LC, Wüthrich C, *et al.* JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. *J. Virol* 2010; 84: 9200-209.
- [27] Sunyaev SR, Lugovskoy A, Simon K, Gorelik L. Adaptive mutations in the JC virus protein capsid are associated with progressive multifocal leukoencephalopathy (PML). *PLoS Genet* 2009; 5: p.e1000368.
- [28] Gonzalez H, Olsson T, Borg K. Management of postpolio syndrome. *Lancet Neurol* 2010; 9: 634-42.
- [29] Tyler KL. Emerging viral infections of the central nervous system: part 1. *Arch Neurol* 2009; 66: 939-48.

- [30] Wasay M, Khatri IA, Abd-Allah F. Arbovirus infections of the nervous system: current trends and future threats. *Neurology* 2015; 84: 421-23.
- [31] Domingues RB. Treatment of viral encephalitis. *Cent Nerv Syst Agents Med Chem* 2009; 9: 56-62.
- [32] Romero JR, Newland JG. April. Viral meningitis and encephalitis: traditional and emerging viral agents. *Semin Pediatr Infect Dis* 2003; 14: 72-82.
- [33] Somand D, Meurer W. Central nervous system infections. *Emerg Med Clin North Am* 2009; 27: 89-100.
- [34] McJunkin JE, de los Reyes EC, Irazuzta JE, *et al.* La Crosse encephalitis in children. *N Engl J Med* 2001; 344: 801-07.
- [35] Häusler M, Schaade L, Kemeny S, Schweizer K, Schoenmackers C, Ramaekers VT. Encephalitis related to primary varicella-zoster virus infection in immunocompetent children. *J Neurol Sci* 2002; 195:111-16.
- [36] Chambers, Diamond MS. Pathogenesis of flavivirus encephalitis. *Adv Virus Res* 2003; 60: 273-342.
- [37] Olival KJ, Daszak P. The ecology of emerging neurotropic viruses. *J NEUROVIROL* 2005; 11: 441-46.
- [38] Solomon T. Control of Japanese encephalitis—within our grasp? *N Engl J Med* 2006; 355: 869-71.
- [39] Price RW, Spudich S. Antiretroviral therapy and central nervous system HIV type 1 infection. *J. Infect. Dis* 2008; 197: S294-S306.
- [40] Wong KT, Munisamy B, Ong KC, *et al.* The distribution of inflammation and virus in human enterovirus 71 encephalomyelitis suggests possible viral spread by neural pathways. *J. Neuropathol. Exp. Neurol* 2008; 67: 162-69.
- [41] Aylward B, Yamada T. The polio endgame. *N Engl J Med* 2011; 364: 2273-275.
- [42] Campbell H, Andrews N, Brown KE, Miller E. Review of the effect of measles vaccination on the epidemiology of SSPE. *Int J Epidemiol* 2007; 36: 1334-348.
- [43] McCullers JA, Lakeman FD, Whitley RJ. Human herpesvirus 6 is associated with focal encephalitis. *Clin. Infect. Dis* 1995; 21: 571-76.
- [44] Kleinschmidt-DeMasters BK, Gilden DH. The expanding spectrum of herpesvirus infections of the nervous system. *Brain Pathol* 2001; 11: 440-51.
- [45] Isaacson E, Glaser CA, Forghani B, *et al.* Evidence of human herpesvirus 6 infection in 4 immunocompetent patients with encephalitis. *Clin. Infect. Dis* 2005; 40: 890-93.

- [46] Yao K, Honarmand S, Espinosa A, Akhyani N, Glaser C, Jacobson S. Detection of human herpesvirus-6 in cerebrospinal fluid of patients with encephalitis. *Ann. Neurol* 2009; 65: 257-67.
- [47] Carod-Artal FJ, Wichmann O, Farrar J, Gascón J. Neurological complications of dengue virus infection. *Lancet Neurol* 2013; 12: 906-19.
- [48] Kankirawatana P, Chokeyhaibulkit K, Puthavathana P, Yoksan S, Apintanapong S, Pongthapisit V. Dengue infection presenting with central nervous system manifestation. *J. Child Neurol* 2000; 15: 544-47.
- [49] Chokeyhaibulkit K, Kankirawatana P, Apintanapong S, *et al.* Viral etiologies of encephalitis in Thai children. *Pediatr. Infect. Dis. J* 2001; 20: 216-18.
- [50] García-Rivera EJ, Vorndam V, Rigau-Pérez JG. Use of an enhanced surveillance system for encephalitis and aseptic meningitis for the detection of neurologic manifestations of dengue in Puerto Rico, 2003. *P R HEALTH SCI J* 2009; 28(2).
- [51] Qui PT, Hue NB, Bao LQ, *et al.* Viral etiology of encephalitis in children in southern Vietnam: results of a one-year prospective descriptive study. *PLoS Negl Trop Dis* 2010; 4: p.e854.
- [52] Soares CN, Cabral-Castro MJ, Peralta JM, de Freitas MR, Zalis M, Puccioni-Sohler M. Review of the etiologies of viral meningitis and encephalitis in a dengue endemic region. *J Neurol Sci* 2011; 303: 75-79.
- [53] Economopoulou A, Dominguez M, Helynck B, *et al.* 2009. Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Reunion. *Epidemiol Infect* 2009; 137:534-41.
- [54] Robin S, Ramful D, Le Seach F, Jaffar-Bandjee MC, Rigou G, Alessandri JL. Neurologic manifestations of pediatric chikungunya infection. *J. Child Neurol* 2008; 23: 1028-035.
- [55] DeBiasi RL, Tyler KL. Molecular methods for diagnosis of viral encephalitis. *Clin Microbiol Rev* 2004; 17: 903-25.
- [56] Griffin DE. Neuronal cell death in alphavirus encephalomyelitis. In *Role of Apoptosis in Infection* 2005; 289: 57-77.
- [57] Griffin DE, Metcalf T. Clearance of virus infection from the CNS. *Curr Opin Virol* 2011; 1: 216-21.
- [58] Zueter AM, Zaiter A. Infectious meningitis. *Clin Microbiol Newsl* 2015; 37: 43-51.
- [59] Liu SC, Lee PI, Lee CY, Wang JD, Chiang BL, Chou MC. Different cytokine levels in enterovirus meningitis and encephalitis. *Infect Dis Clin Pract (Baltim Md)* 2005; 13: 241-46.
- [60] Mackenzie JS, Gubler DJ, Petersen LR. Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. *Nat Med* 2004; 10: S98.

- [61] Nash D, Mostashari F, Fine A, *et al.* The outbreak of West Nile virus infection in the New York City area in 1999. *N Engl J Med* 2001; 344: 1807-814.
- [62] Tsai TF, Canfield MA, Reed CM, *et al.* Epidemiological aspects of a St. Louis encephalitis outbreak in Harris County, Texas, 1986. *J. Infect. Dis* 1988; 157: 351-56.
- [63] Balfour HH, Siem RA, Bauer H, Quie PG. California arbovirus (La Crosse) infections: I. Clinical and laboratory findings in 66 children with meningoencephalitis. *Pediatrics* 1973; 52: 680-91.
- [64] Shu M, Zhang YQ, Li Z, Liu GJ, Evertsen JM, Wan C. Chinese medicinal herbs for mumps. *Cochrane Database Syst Rev* 2010; 7: CD008578.
- [65] Tyler KL. Herpes simplex virus infections of the central nervous system: encephalitis and meningitis, including Mollaret's. *Herpes* 2004; 11: 57A-64A.
- [66] Hollander H, Stringari S. Human immunodeficiency virus-associated meningitis: clinical course and correlations. *Am J Med* 1987; 83: 813-16.
- [67] Koskiniemi M, Rantalaiho T, Piiparinen H, *et al.* Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. *J NEUROVIROL* 2001; 7: 400-08.
- [68] Rotbart HA. Viral meningitis. *SEMIN NEUROL* 2000; 20: 277-92.
- [69] Huang HI, Shih SR. Neurotropic enterovirus infections in the central nervous system. *Virus* 2015; 7: 6051-066.
- [70] McKinney Jr, RE, Katz SL, Wilfert CM. Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. *Reviews of Infectious Diseases* 1987; 9:334-56.
- [71] Chadwick DR. Viral meningitis. *Br. Med. Bull* 2005; 75: 1-14.
- [72] Ludlow M, Kortekaas J, Herden C, *et al.* Neurotropic virus infections as the cause of immediate and delayed neuropathology. *Acta Neuropathol* 2016; 131: 159-84.
- [73] Yokota H, Yamada K. Viral infection of the spinal cord and roots. *Neuroimaging Clin* 2015; 25: 247-58.
- [74] Arpino C, Curatolo P, Rezza G. Chikungunya and the nervous system: what we do and do not know. *Rev. Med. Virol* 2009; 19: 121-29.
- [75] Erasmus M. Viral infections of the central nervous system. *CME* 2011; 29: 190-93.
- [76] Messacar K, Schreiner TL, Van Haren K, *et al.* Acute flaccid myelitis: a clinical review of US cases 2012–2015. *Ann. Neurol* 2016; 80: 326-38.
- [77] Rhoades RE, Tabor-Godwin JM, Tsueng G, Feuer R. Enterovirus infections of the central nervous system. *Virology* 2011; 411: 288-305.
- [78] Singh SS, Manimunda SP, Sugunan AP, Vijayachari P. Four cases of acute flaccid paralysis associated with chikungunya virus infection. *Epidemiol Infect* 2008; 136: 1277-280.

- [79] S Panickar K, A Anderson R. Role of dietary polyphenols in attenuating brain edema and cell swelling in cerebral ischemia. *Recent Pat CNS Drug Discov* 2010; 5: 99-108.
- [80] Galochkina AV, Anikin VB, Babkin VA, Ostrouhova LA, ZarubaeV VV. Virus-inhibiting activity of dihydroquercetin, a flavonoid from *Larix sibirica*, against coxsackievirus B4 in a model of viral pancreatitis. *Arch. Virol.* 2016; 161: 929-38.
- [81] Andres A, Donovan SM, Kuhlenschmidt MS. Soy isoflavones and virus infections. *J. Nutr. Biochem* 2009; 20: 563-69.
- [82] Zhang T, Wu Z, Du J, *et al.* Anti-Japanese-encephalitis-viral effects of kaempferol and daidzin and their RNA-binding characteristics. *PLoS One* 2012; 7: p.e30259.
- [83] Hendrich AB. Flavonoid-membrane interactions: possible consequences for biological effects of some polyphenolic compounds 1. *Acta Pharmacol. Sin* 2006; 27: 27-40.
- [84] Han X, Shen T, Lou H. Dietary polyphenols and their biological significance. *Int J Mol Sci* 2007; 8: 950-88.
- [85] Hämäläinen M, Nieminen R, Vuorela P, Heinonen M, Moilanen E, Anti-inflammatory effects of flavonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF- κ B activations, whereas flavone, isorhamnetin, naringenin, and pelargonidin inhibit only NF- κ B activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediators Inflamm* 2007; 2007.
- [86] Kumar S, Pandey AK. Chemistry and biological activities of flavonoids: an overview. *Sci. World J* 2013; 2013.
- [87] Bedrood Z, Rameshrad M, Hosseinzadeh H. Toxicological effects of *Camellia sinensis* (green tea): A review. *Phytother Res* 2018; 32:1163-80.
- [88] Khoo HE, Azlan A, Tang ST, Lim SM. Anthocyanidins and anthocyanins: Colored pigments as food, pharmaceutical ingredients, and the potential health benefits. *Food Nutr. Res* 2017; 61:1361779.
- [89] Franklin SJ, Myrdal PB. Solid-state and solution characterization of myricetin. *AAPS PharmSciTech* 2015;16:1400-8.
- [90] Minami M, Kita M, Nakaya T, Yamamoto T, Kuriyama H, Imanishi J. The inhibitory effect of essential oils on herpes simplex virus type-1 replication in vitro. *Microbiol. Immunol* 2003; 47: 681-84.
- [91] Gavanji S, Sayedipour SS, Larki B, Bakhtari A. Antiviral activity of some plant oils against herpes simplex virus type 1 in Vero cell culture. *Acute Med* 2015; 5: 62-68.
- [92] Nishimuro H, Ohnishi H, Sato M. *et al.* Estimated daily intake and seasonal food sources of quercetin in Japan. *Nutrients* 2015; 7: 2345–358.

- [93] Suganthi N, Devi KP, Nabavi SF, Braidy N, Nabavi SM. Bioactive effects of quercetin in the central nervous system: Focusing on the mechanisms of actions. *Biomed. Pharmacother* 2016; 84: 892-908.
- [94] Hertog MG, Feskens EJ, Kromhout D, Hollman PCH, Katan MB. Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet* 1993; 342:1007-011.
- [95] Coelho-dos-Reis JGA, Ab Gomes O, Bortolini DE, *et al.* Evaluation of the effects of Quercetin and Kaempferol on the surface of MT-2 cells visualized by atomic force microscopy. *J Virol Methods* 2011; 174: 47-52.
- [96] Johari J, Kianmehr A, Mustafa MR, Abubakar S, Zandi K. Antiviral activity of baicalein and quercetin against the Japanese encephalitis virus. *Int J Mol Sci* 2012; 13: 16785-6795.
- [97] Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, AbuBakar S. Antiviral activity of four types of bioflavonoid against dengue virus type-2. *BMC Virol J* 2011; 8: 560.
- [98] Bachmetov L, Gal-Tanamy M, Shapira A, *et al.* Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity. *J Viral Hepat* 2012; 19: e81-8.
- [99] Veckenstedt A, Pusztai R. Mechanism of antiviral action of quercetin against cardiovirus infection in mice. *Antivir. Res* 1981; 1: 249-61.
- [100] Lee S, Lee HH, Shin YS, Kang H, Cho H. The anti-HSV-1 effect of quercetin is dependent on the suppression of TLR-3 in Raw 264.7 cells. *Arch Pharm Res.* 2017; 40: 623-30.
- [101] Fan D, Zhou X, Zhao C, Chen H, Zhao Y, Gong X. Antiviral and quantitative study of quercetin-3-O-b-D-glucuronide in *Polygonum perfoliatum* L. *Fitoterapia* 2011; 82: 805–10.
- [102] Song JH, Shim JK, Choi HJ. Quercetin 7-rhamnoside reduces porcine epidemic diarrhea virus replication via independent pathway of viral induced reactive oxygen species. *Virology* 2011; 8: 460.
- [103] Dao TT, Dang TT, Nguyen PH, Kim E, Thuong PT, Oh WK. Xanthones from *Polygala karensium* inhibit neuraminidases from influenza A viruses. *Bioorganic Med. Chem. Lett.* 2012; 22: 3688-692.
- [104] Dao TT, Nguyen PH, Lee HS, *et al.* Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from *Glycyrrhiza inflata*. *Bioorganic Med. Chem. Lett* 2011; 21: 294-98.
- [105] Krawitz C, Mraheil MA, Stein M, *et al.* Inhibitory activity of a standardized elderberry liquid extract against clinically-relevant human respiratory bacterial pathogens and influenza A and B viruses. *BMC Complement Altern Med* 2011; 11: 16.
- [106] He W, Han H, Wang W, Gao B. Anti-influenza virus effect of aqueous extracts from dandelion. *Virology* 2011; 8: 538.

- [107] Jeong HJ, Kim YM, Kim JH, *et al.* Homoisoflavonoids from *Caesalpinia sappan* displaying viral neuraminidases inhibition. *Biol. Pharm. Bull* 2012; 35: 786-90.
- [108] Theisen LL, Muller C.P. EPs® 7630 (Umckaloabo®), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity in vitro and in vivo. *Antivir. Res* 2012; 94: 147-56.
- [109] Ma SG, Gao RM, Li YH, *et al.* Antiviral Spirooliganones A and B with Unprecedented Skeletons from the Roots of *Illicium oligandrum*. *Org. Lett* 2013; 15: 4450-453.
- [110] Admasu P, Deressa A, Mengistu A, Gebrewold G, Feyera T. In vivo antirabies activity evaluation of hydroethanolic extract of roots and leaves of *Phytolacca dodecandra*. *Glob Vet* 2014; 12: 12-18.
- [111] Vigerelli H, Sciani JM, Jared C, *et al.* Bufotenine is able to block rabies virus infection in BHK-21 cells. *J Venom Anim Toxins Incl Trop Dis* 2014; 20: 45.
- [112] Koh SH, Kwon H, Kim KS, *et al.* Epigallocatechin gallate prevents oxidative-stress-induced death of mutant Cu/Zn-superoxide dismutase (G93A) motoneuron cells by alteration of cell survival and death signals. *Toxicology* 2004; 202: 213-25.
- [113] Ho HY, Cheng ML, Weng SF, Leu YL, Chiu DTY. Antiviral effect of epigallocatechin gallate on enterovirus 71. *J Agric Food Chem* 2009; 57: 6140-147.
- [114] Choi HJ, Song JH, Park KS, Baek SH. In vitro anti-enterovirus 71 activity of gallic acid from *Woodfordia fruticosa* flowers. *Lett Appl Microbiol* 2010; 50: 438-40.
- [115] Chen SG, Leu YL, Cheng ML, *et al.* Anti-enterovirus 71 activities of *Melissa officinalis* extract and its biologically active constituent rosmarinic acid. *Sci Rep* 2017; 7: 12264.
- [116] Chiang LC, Ng LT, Cheng PW, Chiang W, Lin C.C. Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*. *Clin. Exp. Pharmacol. Physiol.* 2005; 32: 811-16.
- [117] Wu BW, Pan TL, Leu YL, *et al.* Antiviral effects of *Salvia miltiorrhiza* (Danshen) against enterovirus 71. *Am J Chin Med* 2007; 35: 153- 68.
- [118] Chung YC, Hsieh C, Lin YJ, *et al.* Magnesium lithospermate B and rosmarinic acid, two compounds present in *Salvia miltiorrhiza*, have potent antiviral activity against enterovirus 71 infections. *Eur. J. Pharmacol* 2015; 755:127-33.
- [119] Chen SG, Cheng ML, Chen KH, *et al.* Antiviral activities of *Schizonepeta tenuifolia* Briq. against enterovirus 71 in vitro and in vivo. *Sci Rep* 2017; 7: 935.
- [120] Wang J, Chen X, Wang W, *et al.* Glycyrrhizic acid as the antiviral component of *Glycyrrhiza uralensis* Fisch. against coxsackievirus A16 and enterovirus 71 of hand foot and mouth disease. *J Ethnopharmacol* 2013; 147: 114-21.

- [121] Zhang, W., Tao, J., Yang, X., *et al.* Antiviral effects of two *Ganoderma lucidum* triterpenoids against enterovirus 71 infection. *Biochem. Biophys. Res. Commun* 2014; 449: 307-12.
- [122] Cheng PW, Chiang LC, Yen MH, Lin C.C. Bupleurum kaoi inhibits Coxsackie B virus type 1 infection of CCFS-1 cells by induction of type I interferons expression. *Food Chem. Toxicol.* 2007; 45: 24-31.
- [123] Choi HJ, Lim CH, Song JH, Baek SH, Kwon DH. Antiviral activity of raoulic acid from *Raoulia australis* against Picornaviruses. *Phytomedicine* 2009; 16: 35-39.
- [124] Fang JE, Sun L, Peng G. *et al.* Identification of three antiviral inhibitors against Japanese encephalitis virus from library of pharmacologically active compounds 1280. *PloS one* 2013; 8: p.e78425.
- [125] Rupareliya RH, Joshi HS. Stability Indicating Simultaneous Validation of Telmisartan and Cilnidipine with Forced Degradation Behavior Study by RP-HPLC in Tablet Dosage Form. *ISRN Chromatography* 2013; 2013.
- [126] Chang YW, Yeh TK, Lin KT, Chen WC, Yao HT. Pharmacokinetics of anti-SARS-CoV agent niclosamide and its analogs in rats. *J Food Drug Anal* 2006; 14.
- [127] caymanchem. <https://www.caymanchem.com/product/18461> (Accessed March 8, 2019).
- [128] Chang SJ, Chang YC, Lu KZ, Tsou Y, Lin CW. Antiviral activity of *Isatis indigotica* extract and its derived indirubin against Japanese encephalitis virus. *Evid Based Complement Alternat Med* 2012; 2012: 1-7.
- [129] Li J, Huang H, Feng M, Zhou W, Shi X, Zhou P. In vitro and in vivo anti-hepatitis B virus activities of a plant extract from *Geranium carolinianum* L. *Antivir. Res* 2008; 79: 114-20.
- [130] Jeong HJ, Ryu YB, Park SJ, *et al.* Neuraminidase inhibitory activities of flavonols isolated from *Rhodiola rosea* roots and their in vitro anti-influenza viral activities. *Bioorg Med Chem* 2009; 17: 6816-823.
- [131] Shin H, Bae MJ, Choi D, Shon DH. Skullcap (*Scutellaria baicalensis*) extract and its active compound, wogonin, inhibit ovalbumin-induced Th2-mediated response. *Molecules* 2014; 19: 2536-45.
- [132] Takegami T, Simamura E, Hirai KI, Koyama J. Inhibitory effect of furanonaphthoquinone derivatives on the replication of Japanese encephalitis virus. *Antivir. Res* 1998; 37: 37-45.
- [133] Fujimoto Y, Eguchi T, Murasaki C, *et al.* Studies on the structure and stereochemistry of cytotoxic furanonaphthoquinones from *Tabebuia impetiginosa*: 5-and 8-hydroxy-2-(1-hydroxyethyl) naphtho [2, 3-b] furan-4, 9-diones. *J. Chem. Soc., Perkin Trans. 1* 1991; 10: 2323-327.

- [134] Kajimura K, Takagi Y, Ueba N, *et al.* Protective effect of Astragali radix by oral administration against Japanese encephalitis virus infection in mice. *Biol. Pharm. Bull* 1996; 19: 1166-169.
- [135] Zhang Y, Wang Z, Chen H, Chen Z, Tian Y. Antioxidants: potential antiviral agents for Japanese encephalitis virus infection. *Int J Infect Dis* 2014; 24: 30-36.
- [136] Mishra MK, Ghosh D, Duseja R, Basu A. Antioxidant potential of Minocycline in Japanese Encephalitis Virus infection in murine neuroblastoma cells: correlation with membrane fluidity and cell death. *Neurochem Int* 2009; 54: 464-70.
- [137] Calabrese V, Bates TE, Mancuso C, *et al.* Curcumin and the cellular stress response in free radical-related diseases. *Mol. Nutr. Food Res* 2008; 52:1062-073.
- [138] Kavakli HS, Koca C, Alici O. Antioxidant effects of curcumin in spinal cord injury in rats. *Ulus Travma Acil Cerrahi Derg* 2011; 17: 14-18.
- [139] Ataie A, Shadifar M, Ataee R. Polyphenolic antioxidants and neuronal regeneration. *Basic Clin Neurosci* 2016; 7: 81.
- [140] Joe B, Vijaykumar M, Lokesh BR. Biological properties of curcumin-cellular and molecular mechanisms of action. *Crit. Rev. Food Sci. Nutr* 2004; 44: 97-111.
- [141] Dutta K, Ghosh D, Basu A. Curcumin protects neuronal cells from Japanese encephalitis virus-mediated cell death and also inhibits infective viral particle formation by dysregulation of ubiquitin–proteasome system. *J. Neuroimmune Pharmacol* 2009; 4: 328-37.
- [142] Kazłowski B, Chiu YH, Kazłowska K, Pan CL, Wu C.J. Prevention of Japanese encephalitis virus infections by low-degree-polymerisation sulfated saccharides from *Gracilaria* sp. and *Monostroma nitidum*. *Food Chem* 2012; 133: 866-74.
- [143] Bertol JW, Rigotto C, de Pádua RM, *et al.* Antiherpes activity of glucoevatromonoside, a cardenolide isolated from a Brazilian cultivar of *Digitalis lanata*. *Antivir. Res* 2011; 92: 73-80.
- [144] Danaher RJ, Wang C, Dai J, Mumper RJ, Miller CS. Antiviral effects of blackberry extract against herpes simplex virus type 1. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; 112: e31-e35.
- [145] Gescher K, Kühn J, Hafezi W, *et al.* Inhibition of viral adsorption and penetration by an aqueous extract from *Rhododendron ferrugineum* L. as antiviral principle against herpes simplex virus type-1. *Fitoterapia* 2011; 82: 408-13.
- [146] Gescher K, Kühn J, Lorentzen E. Proanthocyanidin-enriched extract from *Myrothamnus flabellifolia* Welw. exerts antiviral activity against herpes simplex virus type 1 by inhibition of viral adsorption and penetration. *J Ethnopharmacol* 2011; 134: 468-74.
- [147] Chen SD, Gao H, Zhu QC, *et al.* Houttuynoids A–E, anti-herpes simplex virus active flavonoids with novel skeletons from *Houttuynia cordata*. *ORG LETT* 2012; 14: 1772-775.

- [148] Xiang YF, Pei Y, Wang YF. Current status of natural products from plants as anti-herpes simplex virus 1 agents. *Virologica Sinica* 2008; 23: 305.
- [149] Koch C, Reichling J, Schöne J, Schnitzler P. Inhibitory effect of essential oils against herpes simplex virus type 2. *Phytomedicine* 2008; 15:71-78.
- [150] Hirabayashi K, Iwata S, Matsumoto H, *et al.* Antiviral activities of glycyrrhizin and its modified compounds against human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 1 (HSV-1) in vitro. *Chem. Pharm. Bull* 1991; 39: 112-15.
- [151] Ren Z, Zhang CH, Wang LJ, *et al.* In vitro anti-viral activity of the total alkaloids from *Tripterygium hypoglaucum* against herpes simplex virus type 1. *Virologica Sinica* 2010; 25: 107-14.
- [152] Schnitzler P, Schuhmacher A, Astani A, Reichling J. Melissa officinalis oil affects infectivity of enveloped herpesviruses. *Phytomedicine* 2008; 15: 734-40.
- [153] Astani A, Reichling J, Schnitzler P. Melissa officinalis extract inhibits attachment of herpes simplex virus in vitro. *Chemotherapy* 2012; 58: 70–77.
- [154] Cheng HY, Yang CM, Lin TC, Shieh DE, Lin CC. ent-Epiarznelechin (4 α - $\rightarrow$ 8)-arznelechin extracted from *Cassia javanica* inhibits herpes simplex virus type 2 replication. *J. Med. Microbiol* 2006; 55:201-06.
- [155] Petrera E, Coto CE. Therapeutic effect of meliacine, an antiviral derived from *Melia azedarach* L., in mice genital herpetic infection. *Phytother. Res* 2009; 23: 1771-777.
- [156] Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. *J Tradit Complement Med* 2014; 4: 24-35.
- [157] Yang CM, Cheng HY, Lin TC, Chiang LC, Lin CC. The in vitro activity of geraniin and 1, 3, 4, 6-tetra-O-galloyl- β -d-glucose isolated from *Phyllanthus urinaria* against herpes simplex virus type 1 and type 2 infection. *J Ethnopharmacol* 2007; 110: 555-58.
- [158] Yang CM, Cheng HY, Lin TC, Chiang LC, Lin CC. Hippomanin from acetone extract of *Phyllanthus urinaria* inhibited HSV-2 but not HSV-1 infection in vitro. *Phytother. Res* 2007; 21:1182-186.
- [159] Cheng HY, Yang CM, Lin TC, Lin LT, Chiang LC, Lin CC. Excoecarianin, isolated from *Phyllanthus urinaria* Linnaea, inhibits herpes simplex virus type 2 infection through inactivation of viral particles. *Evid Based Complement Alternat Med* 2011; 2011: 1-10.
- [160] Mazumder S, Ghosal PK, Pujol CA, Carlucci MJ, Damonte EB, Ray B. Isolation, chemical investigation and antiviral activity of polysaccharides from *Gracilaria corticata* (Gracilariaceae, Rhodophyta). *Int. J. Biol. Macromol* 2002; 31: 87-95.
- [161] Matsuhiro B, Conte AF, Damonte EB, *et al.* Structural analysis and antiviral activity of a sulfated galactan from the red seaweed *Schizymenia binderi* (Gigartinales, Rhodophyta). *Carbohydr. Res* 2005; 340: 2392-402.

- [162] Low JSY, Wu KX, Chen KC, Ng MM, Chu JJH. Narasin, a novel antiviral compound that blocks dengue virus protein expression. *Antiviral Therapy* 2011; 16: 1203-1218.
- [163] Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, AbuBakar S. Novel antiviral activity of baicalein against dengue virus. *BMC Complement Altern Med* 2012; 12: 214.
- [164] Lin LT, Chen TY, Lin SC, *et al.* Broad-spectrum antiviral activity of chebulagic acid and punicalagin against viruses that use glycosaminoglycans for entry. *BMC Microbiol* 2013; 13: 187.
- [165] Rodríguez MC, Merino ER, Pujol CA, Damonte EB, Cerezo AS, Matulewicz MC. Galactans from cystocarpic plants of the red seaweed *Callophyllis variegata* (Kallymeniaceae, Gigartinales). *Carbohydr. Res* 2005; 340: 2742-751.
- [166] de SF-Tischer PC, Talarico LB, Nosedá MD, Guimarães SMPB, Damonte EB, Duarte MER. Chemical structure and antiviral activity of carrageenans from *Meristiella gelidium* against herpes simplex and dengue virus. *CARBOHYD POLYM* 2006; 63: 459-65.
- [167] Huerta-Reyes M, del Carmen Basualdo M, Abe F, Jimenez-Estrada M, Soler C, Reyes-Chilpa R. HIV-1 inhibitory compounds from *Calophyllum brasiliense* leaves. *Biol. Pharm. Bull* 2004; 27: 1471-475.
- [168] César GZJ, Alfonso MGG, Marius MM, *et al.* Inhibition of HIV-1 reverse transcriptase, toxicological and chemical profile of *Calophyllum brasiliense* extracts from Chiapas, Mexico. *Fitoterapia* 2011; 82: 1027-034.
- [169] Lubbe A, Seibert I, Klimkait T, Van der Kooy F. Ethnopharmacology in overdrive: the remarkable anti-HIV activity of *Artemisia annua*. *J Ethnopharmacol* 2012; 141: 854-59.
- [170] Lin YM, Flavin MT, Schure R, *et al.* Antiviral activities of biflavonoids. *Planta Med* 1999; 65: 120-25.
- [171] Asl MN, Hosseinzadeh H. Review of pharmacological effects of *Glycyrrhiza* sp. and its bioactive compounds. *Phytother. Res* 2008; 22: 709-24.
- [172] Goodell, J.R., Puig-Basagoiti, F., Forshey, B.M., Shi, P.Y. and Ferguson, D.M., Identification of compounds with anti-West Nile virus activity. *J. Med. Chem* 2006; 49: 2127-137.