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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

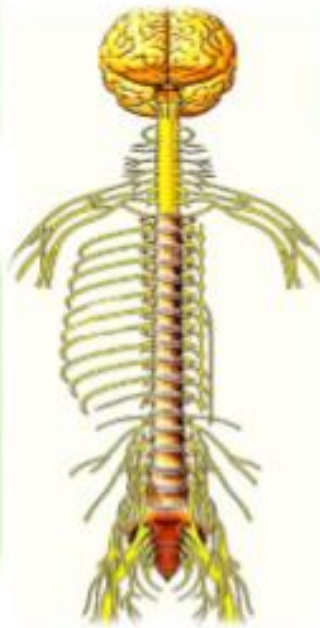
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Central Nervous System infections

The inhibitory activity of medicinal plants against CNS viruses infections

Reduction of plaque formation
Prevention of viral protein expression
Blocking viral genome replication
Scavenging reactive oxygen species



Most important viral pathogens

Dengue virus
Enterovirus 71
West Nile virus
Herpes simplex virus
varicella zoster virus
Japanese encephalitis virus

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

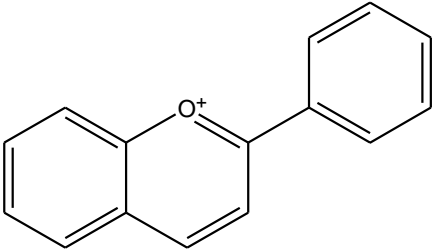
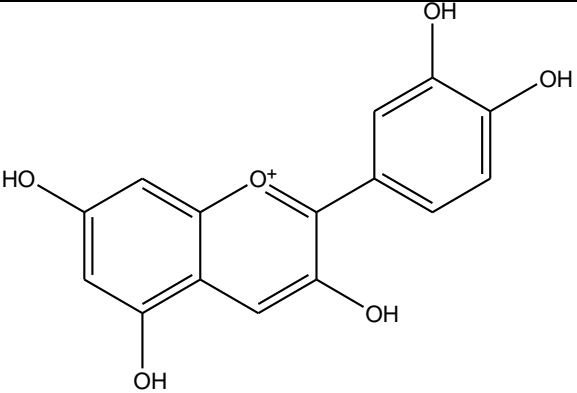
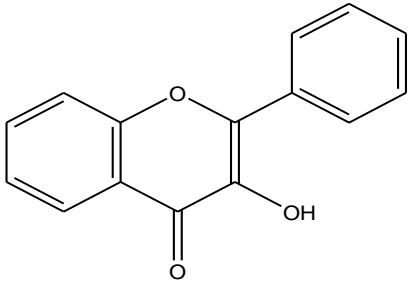
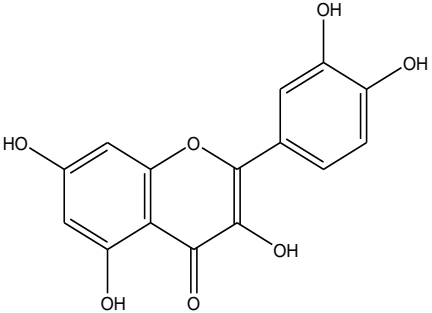
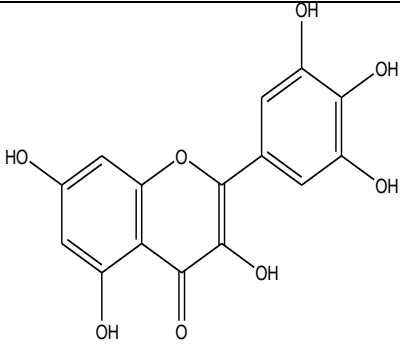
Some of the data concerning the antiviral medicinal plants and their mechanisms against viral CNS infections are summarized in Table 2.

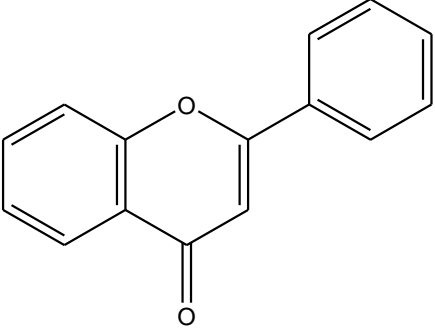
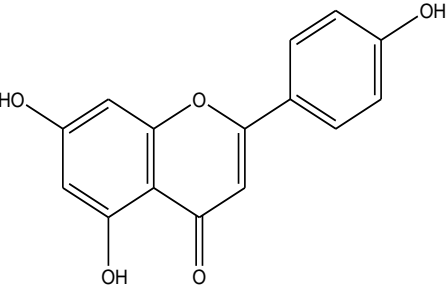
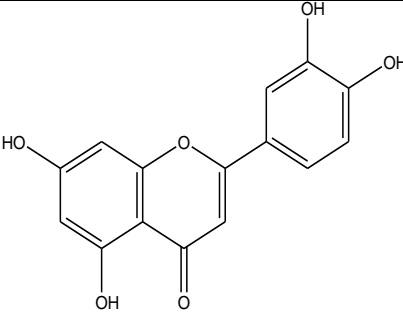
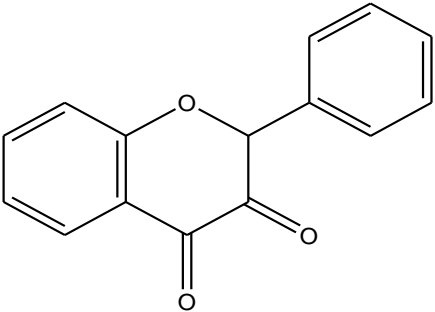
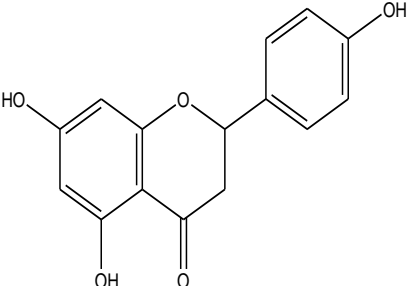
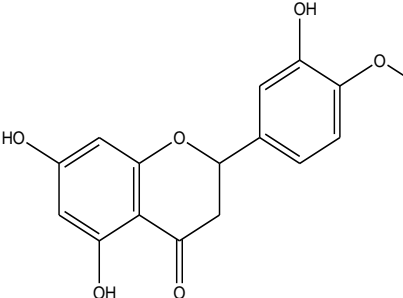
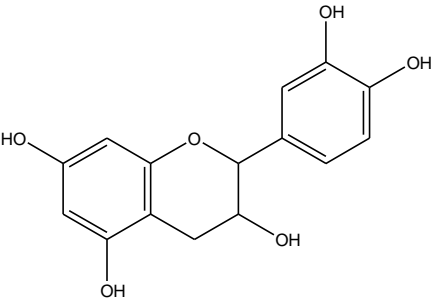
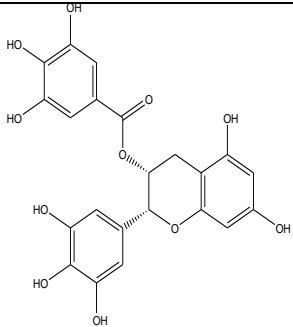
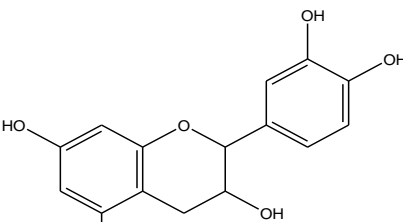
Polyphenols are natural compounds present in vegetables, fruits, grains, barks, roots, tea, and wine. They are the best sources of these phytochemicals [79]. In this group, the phytoconstituent flavonoids are a class of secondary metabolites of plant associated with the characteristic phenolic structure [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	
<p>Anthocyanins</p>	 <p>flavylium</p>	 <p>cyanidin</p>	
	 <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>flavanone</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* (xanthenes), 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-dihexyl-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].

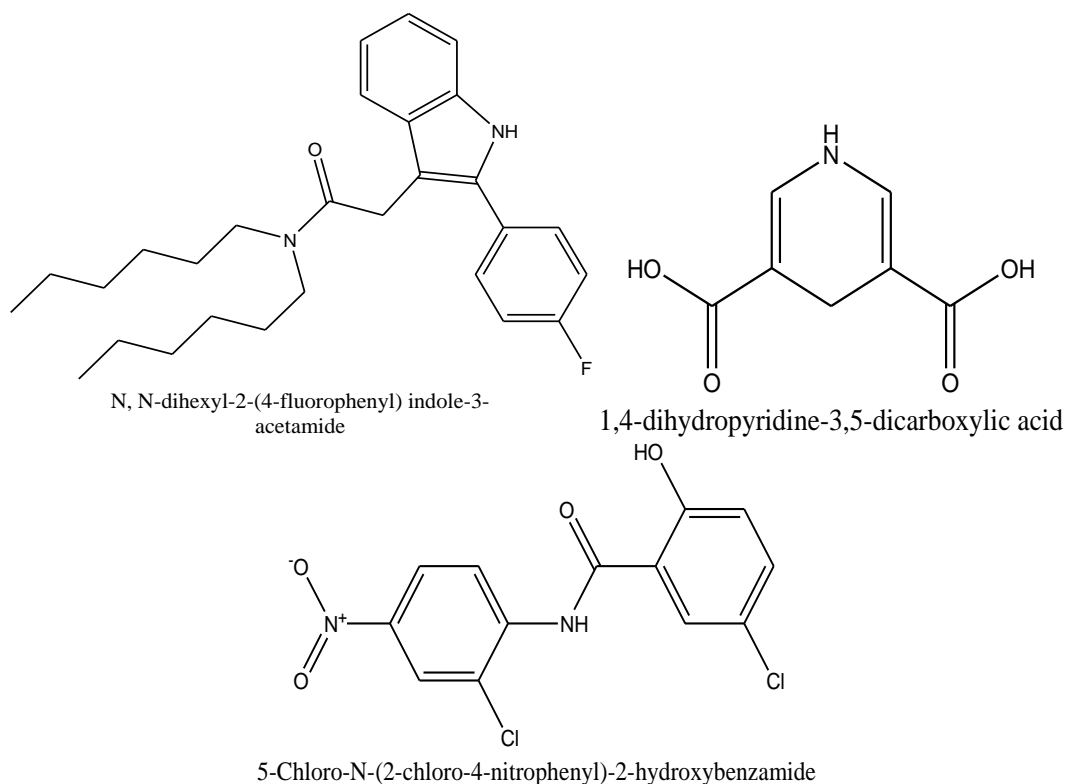


Figure 1. Chemical structures of (N, N-dihexyl-2-(4-fluorophenyl) indole-3-acetamide) (FGIN-1-27), 1, 4-dihydropyridine-3, 5-dicarboxylic acid (cilnidipine) and 5-Chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide (niclosamide).

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].

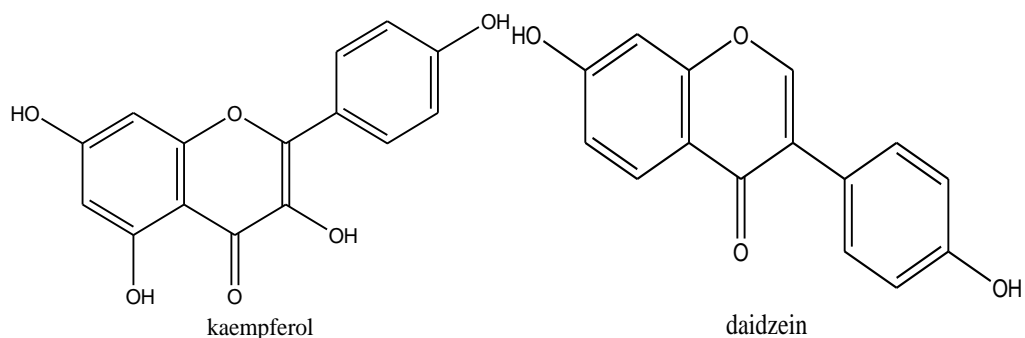


Figure 2. Chemical structures of Daidzein and Kaempferol

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].

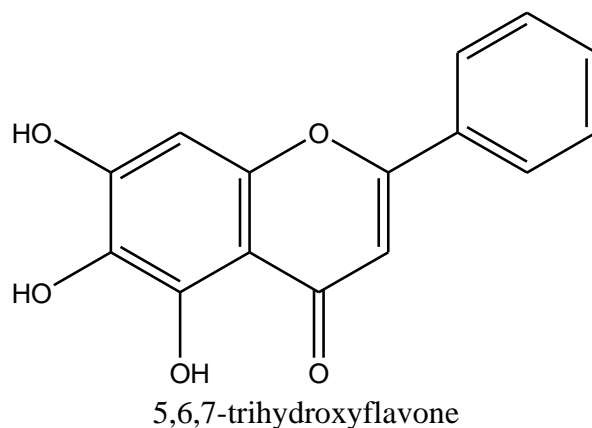
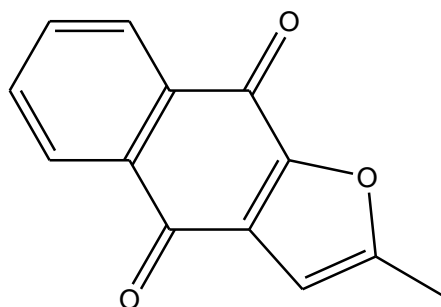


Figure 3. Chemical structure of 5, 6,7-trihydroxyflavone (Baicalein).

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. avellaneda* [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 racemose* 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 Licorice (*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> <i>Tripterygium hypoglaucum</i>	Inhibition of HSV gene expression	[150, 151]	
<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- κ B 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 Gallic acid (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.

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