VirusDis. (October–December 2015) 26(4):225–236
DOI 10.1007/s13337-015-0276-6

REVIEW ARTICLE

Herbal plants and plant preparations as remedial approach for viral diseases

Rajesh Kumar Ganjhu[1] · Piya Paul Mudgal[1] · Hindol Maity[1] · Deepu Dowarha[1] · Santhosha Devadiga[1] · Snehlata Nag[2] · Govindakarnavar Arunkumar[1]

Received: 27 April 2015 / Accepted: 18 August 2015 / Published online: 3 September 2015

Abstract Herbal plants, plant preparations and phytoconstituents have proved useful in attenuating infectious conditions and were the only remedies available, till the advent of antibiotics (many being of plant origin themselves). Among infectious diseases, viral diseases in particular, remain the leading cause of death in humans globally. A variety of phytoconstituents derived from medicinal herbs have been extensively studied for antiviral activity. Based on this rationale, an online search was performed, which helped to identify a large number of plant species harboring antiviral molecules. These herbal sources have been reported individually or in combinations across a large number of citations studied. Activities against rabies virus, Human immunodeficiency virus, Chandipura virus, Japanese Encephalitis Virus, Enterovirus, Influenza A/H1N1 and other influenza viruses were discovered during the literature search. This review includes all such plant species exhibiting antiviral properties. The review also encompasses composition and methodologies of preparing various antiviral formulations around the globe. An elaborate section on the formulations filed for patent registration, along with non-patented formulations, has also been included in this article. To conclude, herbal sources provide researchers enormous scope to explore and bring out viable alternatives against viral diseases, considering non-availability of suitable drug candidates and increasing resistance to existing drug molecules for many emerging and re-emerging viral diseases.

Keywords Ethnopharmacology · Antiviral · Herbal preparations · Patent information · Viral diseases

Introduction

Complementary and alternative medicine offers a wide variety of herbal plants, which may serve as key to unlock the many mysteries behind human pathologies. According to a World Health Organization (WHO) report, 80 % of the population in developing countries depends on traditional plants for health requirements [4, 65]. Natural products such as herbal plant extracts (used in Ayurveda as mentioned in Charaka Samhita and Susruta Samhita or other traditional medicine practices), plant derived compounds (also known as phytoconstituents), extracts of specific plant parts (roots, stem, bark, flowers, fruits and seeds), dietary supplements and nutraceuticals find wide application in treating ailments ranging from common to rare infectious and non-infectious diseases. According to reports, one quarter of the commonly used medicines contain compounds isolated from plants [80].

WHO quotes 'infectious diseases are the sixth leading cause of premature deaths in the world' (http://www.who.int/mediacentre/factsheets/fs310/en/). Emerging and re-emerging infectious diseases continue to impose a constant threat on human population. Among several infectious diseases, viral infections in particular, caused by a range of

Electronic supplementary material The online version of this article (doi:10.1007/s13337-015-0276-6) contains supplementary material, which is available to authorized users.

✉ Govindakarnavar Arunkumar
arun.kumar@manipal.edu

[1] Department of Virus Research (Manipal Centre for Virus Research), Manipal University, Manipal, Karnataka 576104, India

[2] Department of Zoology, Ranchi University, Ranchi, Jharkhand 834001, India

new and old infectious viruses, challenge survival of mankind on this planet [37]. With increasing resistance of microorganisms (bacteria, viruses and parasites) to standard antimicrobial therapy, alternative treatments especially from herbal sources are being re-explored at gaining speed. A number of medicinal plants have been explored and found potential against lethal viral infections. Ethnomedicinal literature documents several such herbal plants claiming broad-spectrum antiviral activity. In the light of the advancing technological tools at disposal, exploration of potential antiviral activity of numerous medicinal plants has acquired a phenomenal pace with the emergence and reemergence of highly infectious viruses. A classic example of a lead from herbal sources that got translated into potential anti-infective drug candidate is emetine (isoquinoline alkaloid obtained from the underground part of *Cephaelis ipecacuanha*, and related species), used both as an amoebicidal drug and for the treatment of abscesses due to *Escherichia histolytica* infections. Quinine is yet another important drug of plant origin derived from the bark of Cinchona tree with a long history of use. Also, drugs such as aspirin, morphine, and taxol have been developed from molecules, originally isolated from plant sources. Herbal sources have been investigated extensively for antiviral properties and through this review we have tried to consolidate information on such plants with antiviral potential. Objectives of this review are to gather and highlight the information on different plant formulations with antiviral properties in the backdrop of prior art patents, patent applications, non-patent art and commonly available traditional knowledge.

Methodology of search/rationale of selecting relevant art

The present search was limited to article having full text or at least abstract available in English. Databases used included Delphion, United States Patent & Trademark Office (USPTO) patent database, European Patent Office (EPO), World Intellectual Property Organization (WIPO), Japan Patent Office (JPO), AusPat, Scirus, Institute of Electrical and Electronics Engineers (IEEE) Xplore, Google Scholar, ScienceDirect, and Traditional Knowledge Digital Library (TKDL). Primary search words used were "antiviral", "herbs", "herbal medicine", "herbal formulations", "medicinal plants", "traditional medicine", etc. Searches were also done using the single name of the plant with known possible antiviral property. Bibliographies of included studies were also searched for additional references. Non patent prior art, i.e. journal publications, proceedings of conferences, etc. have been incorporated wherever possible to best extent of their availability and access.

Patent and non-patent literature search was performed. Relevant prior art and state of art are presented in this report, with their appropriate details. This search is limited to citations forming general state of art.

Literature findings

From literature survey we found substantial number of herbal plants and plant preparations with antiviral potential against different types of viruses. Majority of the antiviral herbs were found containing active components such as flavones, alkaloids and polyphenols, which play an important role against viruses. Based on the extensive search performed, the results are presented under three sections classified as antiviral plants, patent applications and non-patent art.

State of art search for plants being used for prevention/treatment of viral diseases

The aim of this search was to identify previously reported plants known for their role in prevention/treatment of viral diseases. Accordingly, patent databases, non- patent literature databases and TKDL (http://www.tkdl.res.in) were accessed for performance of this search. A plethora of antiviral plants with their mechanism of action and active constituents against different viruses are summarized in Supplementary Table 1.

Most relevant patent information

Chinese herbal medicine for treating rabies. Patent No. CN 200510003108; Filed June 17, 2005 [32]

The invention relates to a Chinese medicine for curing rabies. It is a Chinese medicine composition prepared by using the Chinese medicinal materials namely mylabris, wild buckwheat root and peppermint as raw material. This herbal medicine finds use in the treatment of sore and swollen wounds, bites (insects, snakes, rabid dog). Peppermint helps in detoxification. Consumption of this medicine stimulates urination, which helps in excreting the virus out of the body. The constituents of this herbal preparation may be processed into a tablet, pill or capsule. The pharmaceutical preparation usually involves boiling the constituent herbals in 50–100 ml of grain spirit for few minutes. This preparation is called Erwu, which is very safe and reliable for consumption and can be administered in any type of bite, be it by cats or dogs, with or without rabies. A 5 day course of 25 ml has to be followed for prevention of rabies. This invention is not safe for use in pregnant women and children.

Herbal medicine for treating and preventing rabies. Patent No. CN 200510032451; Filed November 23, 2005 [46]

The present invention provides a method of preventing and treating rabies and its clinical symptoms, with no side effects. This herbal medicine meant to cure hydrophobia, is prepared of the water from washed rice (85–90 %), endodermis of *Ulmus pumila* root (5–10 %), and endodermis of *Betula luminifera* Winkl root (4–6 %). This preparation is recommended for consumption up to three times a day for three consecutive days. The first day response post consumption of this herbal medicine are reduction in waist pain, swelling, revival of sanity, elimination of horror, fear of water, fear of the wind. The second day responses are absence of hematuria. Clarity in urine within 3 days indicate complete eradication of rabies virus and complete recovery of patient with no further recurrence. This medicinal preparation has shown efficacy in paralysis stage of rabies also and the recommended dosing regimen is three times a day for seven consecutive days. This herbal preparation is low in cost, simple to manufacture, contains no chemical drugs, moderate in property, and without toxicity and side effects on human physiology. Clinical practice shows that the herbal medicine has an efficacy up to 100 % exhibiting remarkable curative effect.

Chinese medicinal herb preparation for treating and preventing rabies. Patent No. CN 200810030881; Filed march 19, 2008 [86]

This Chinese herbal medicinal preparation claimed for curing and preventing hydrophobia, consists of the following ingredients by weight in parts: *Angelica sinensis* (6–20 parts), Chinese rhubarb (10–20 parts), bitter orange (10–25 parts), chrysanthemum flower (10–25 parts), Costustoot (10–25 parts), *Saposhnikovia divaricate* root (6–10 parts), goldthread root (3–15 parts) and root of Rehmannia (10–20 parts). Another protocol for preparation includes the following ingredients in their respective weight proportion: *Asarum sieboldi* (10–15 parts), Bupleurum (10–15 parts), honeysuckle flower (10–20 parts), wild chrysanthemum flower (10–15 parts), Chinese lobelia herb (10–20 parts), sweet wormwood herb (15–20 parts), Japanese climbing fern spore (15–20 parts), fineleaf schizonepeta herb (10–15 parts), *Nux vomica* (6–10 parts), slender dutchmanspipe root (15–30 parts), bitter orange (15–30 parts), Costustoot (15–20 parts), Chrysanthemum flower (15–20 parts), *Saposhnikovia divaricata* root (15–30 parts), tree-of-heaven ailanthus bark (15–30 parts) and peach seed (15–20 parts). This herbal medicine has the advantages of being stable at room temperature, non-injectable and without any serious side effect.

Chinese medicine for curing hydrophobia. Patent No. CN 200810054734, Filed April 03, 2008 [45]

The invention relates to a Chinese herbal medicine used for curing rabies, which is made of dried ginger and bitter almond (1:1) as raw materials and is processed into a formulation through parching, grinding and mixing process. This is a hereditary secret formula, claims to cure hundreds of people affected by rabies every year. As the active ingredients of this herbal medicine can directly stop and kill rabies viruses in a short period, the cure rate can reach 100 %. Compared with the strong-toxic ingredients like cantharis etc., which are contained in well-known herbs for curing rabies, dried ginger and bitter almond are less toxic, therefore render the herbal preparation non-toxic, with no side effect. This preparation can be taken orally as well as may be applied topically. On oral administration, symptoms such as pain, itching, warmness in lung and throat is reduced, nerves soothed and the virus load is quickly reduced, thus preventing in-depth invasion. Faster therapeutic effect is observed with this herbal preparation as fear of water and other typical rabies symptoms [breathing and swallowing difficulties] are counteracted. Topically, this herbal medicine may be applied over a large area of the bite, facilitating quick counteraction of the rabies virus.

Dioscorea Extracts. Patent No. US 20090041803; Filed September 02, 2008 [106]

This extract is an immunogenic composition that contains an antigen agent and an adjuvant agent, wherein the adjuvant agent contains an extract that is prepared from a tuber of a Dioscorea plant. This extract is prepared from the tuber of any of these Dioscorea species namely *D. batatas, D. ecne, D. alata* L., *D. pseudojaponica, or D. alata* L. *var. purpurea*. The antigen agent can be a polypeptide, such as a viral protein or a tumor antigen protein or a nucleic acid encoding the polypeptide. The invention is useful in but not limited to treating viral diseases such as infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus [e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)], a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV). This herbal

preparation also can be used as a dietary supplement, health food, or health drink for prevention of immune system impairment. It also finds use in treating a range of bacterial, fungal and neoplastic diseases.

Antiviral Composition. Patent No. EP19850109500; Filed August 19, 1987 [6]

The present invention describes methods and compositions of herbal preparations for inhibiting the infectious activity of viruses by the use of lectins. In particular, it includes lectins obtained from *Sambucus nigra, Sambucus racemosa* and *Sambucus ebulus* for inhibiting the activity of enveloped viruses. Pharmaceutical compositions comprising non-toxic lectins, for example *Sambucus nigra* agglutinin-I are of use in combating viral infections in animals and humans. Lectins are reported to act by (a) binding to the virions and agglutinating virus particles, thus preventing their penetration to cells; (b) binding to the cell surface thereby blocking virus receptor sites on the cell wall; (c) modifying the cell wall surface, preventing the release of viral replicates; and (d) interfering with the intracellular replication of viruses. Lectins may be administered either orally or parenterally in liquid composition. Formulations containing 0.2 to 20 mg/ml lectin may be employed. Administrable dosage to a patient is 0.02 to l g daily. This formulation has been proved effective against influenza virus in in vitro and in vivo models.

Antiviral astragalus extract. Patent No. GB 0612025.7; Filed June 16, 2006 [57]

This invention describes a novel antiviral product for the treatment of hepatitis C, and its process of manufacture. More particularly it relates to a characterized product exhibiting antiviral activity against Hepatitis C virus (HCV). The product exhibits activity when screened through a replicon test and a polymerase test (NS5B), which in particular is suggestive of probable activity against different *Flaviviridae* viruses. In one embodiment there is provided a single herb *Astragalus* extract, or an active fraction thereof, for use as an antiviral in the treatment of hepatitis C. The product is composed of four herbal extracts, which includes Milk Thistle Fruit dry extract, Chinese Sage Root dry extract, *Schisandra* Fruit dry extract and *Astralagus* Root dry extract. On further investigation of this product it was found that the plant *Astragalus membranaceus* was actually responsible for the anti-HCV activity, demonstrating both good activity and no detectable cell cytotoxicity. Characterization of the active fraction and sub-fractions of the Astragalus extract revealed the presence of marker compounds such as Astragaloside I, Formononetin-7-O-β-D-glucoside and 3′-hydroxyl-formononetin-7-O-β-D-glucoside, which in isolation or in combination may be responsible for the anti-HCV activity and polymerase inhibition.

Herbal formulation. Patent No. US 20090208598; Filed January 31, 2006 [72]

This invention describes a method for preparing herbal extract from Rosa sp. and/or *Urtica dioica* and/or *Tanacetum vulgare*, preferably by pulsed electromagnetic field of high frequency. In the preparation of the herbal extracts, 3–4 times radiation of electromagnetic pulses of high frequency is used for 2–5 min each. The electrical power (e.g. effective power) of the pulses is about 20–100 Watt, and the best effect is obtained at 45 Watt. The medicament, optionally comprising selenium and/or urea, is useful in the treatment of conditions associated with impaired immune system, e.g. in HIV infection and AIDS. Clinical studies of the herbal extract conducted in HIV positive patients revealed a statistically significant difference ($p < 0.01$) in the levels of CD4, CD8 and CD95 in patients during the treatment regime (comparison between observations on first day and 80 days after treatment with the herbal extract).

Compositions of matter useful in the treatment of viral infections derived from plant extracts. Patent No. US 5989556; Filed July 9, 1997 [92]

The present invention entails description on (i) compositions of matter (i.e., herbal blends and isolated chemical entities); (ii) methods for the treatment of HBV and HCV carriers; (iii) prevention and treatment of hepatitis B and hepatitis C; (iv) treatment of HIV carriers; and (v) prevention and treatment of AIDS through the administration of the compositions according to the invention.

The four herb mixtures mentioned in this invention have been prepared using various Chinese medicinal plants namely *Aeginetiae herba, Blechni rhizoma, Lespedezae herba, Polygoni cuspidati rhizoma, Forsythiae fructus,* and *Ligustri fructus,* or contain the herbal ingredients namely *Aeginetiae herba, Lonicerae flos, Prunellae spica,* and *Lespedezae herba* in varying proportion of weights. These mixtures are obtained through specific techniques and exhibit exceptional efficacy for treating human Hepatitis B virus carriers and Hepatitis C patients. The dosage regimen for these composition herbal mixtures varies from 0.4 to 120 g per day customized according to the subject under study. The frequency of administration is at least three (3) times per day, preferably as bolus administration, owing to its highest efficacy. The herb mixtures also exhibited in vitro antiviral activities against murine leukemia virus (MULV) and HIV.

Compositions for the treatment of acquired immunodeficiency disease. Patent No. US 7008650; Filed November 2, 2001 [52]

This invention relates to composition for the treatment of acquired immunodeficiency diseases, especially human immunodeficiency virus (HIV), and its simian and feline counterparts [simian immunodeficiency virus (SIV) and feline immunodeficiency virus (FIV)] and to methods for their use. In detail, the invention concerns compositions comprising the five herbs namely Radix *Gentianae Longdancao*, Fructus *Xanthii Sibirici*, Radix *Bupleuri*, Radix *Astragali*, and *Chrysanthemum Morifolium*, or an extract of the said herbs. The herbal compositions may additionally contain *Flos Magnoliae* as an optional ingredient. Another important point considered in this invention was designing the pharmaceutical formulation containing the extracts of the above herbs. The formulation ought to be compatible for administration through all possible routes such as parenteral, intramuscular, subcutaneous, oral, sublingual, intravenous, intravaginal, intraural, intraocular, nasal, bronchial, transdermal or topical.

Anti-SIV and anti-HIV activity were determined for the formulation, HIV Herbal^{TM}, using a focal infectivity assay. According to the results, SIV replication was inhibited by 50 % at 10,000-fold dilution and by 90 % at 1000-fold dilution. Inhibition of HIV replication by 50 % was achieved with dilutions of 20,000–100,000-fold of HIV Herbal^{TM}. This indicated greater sensitivity of HIV for the aforementioned formulation compared to either FIV or SIV.

Methods and compositions for treatment of viral infections. Patent No. US 20080124303; Filed July 12, 2007 [47]

This invention provides methods for therapeutically or prophylactically treating viral infections and/or viral indications in a subject. In particular, the present invention relates to compositions and methods for inhibition of viral infections and the diseases associated with such viral infections. The invention highlights naturally occurring and man-made compositions comprising of a substance exhibiting Tubercin and/or SSM activity or a functional derivative thereof. The preferred doses for administration ranges between 10 ng and 10 mg per ml or mg of the formulation. This invention targets viral diseases caused by DNA viruses, RNA viruses and retroviruses.

Antiviral substances from plant cuticular and epicuticular material. Patent No. US 20030206974; Filed March 28, 2003 [43]

The present invention discusses agents with antiviral therapeutic properties. These agents can be removed from the cuticular and epicuticular material present in plants, with minimal disruption of the plant tissue internal to the epidermis of the plant. The plant cuticular and epicuticular materials consist of mainly waxes, plant wax components, cutins, terpenoids, triterpenoids, phenolics, primary alcohols, secondary alcohols, hydrocarbons, diketones, fatty acids and flavonoids, to name a few, which may have antiviral properties. Parts used in the present invention are the fruits, leaves and stems of the plants Malus, Pyrus, Vita, Citrus, Lycopersicon, Brassica, Cucumis, Prunus, Persea, Vaccinium, Arctostaphylos, Olea, Nicotianum, Quercus, Eucalyptus, Rhododendron, Ilex, Eriobotrya, Salix, Copernicia, Euphorbia, Pedilanthus, Syagrus, Cocos, Attalea, Stipa, Glyceria, Saccharum, Myrica, Rhus, Sapium, Ceroxylon, Linum, Agave, Cannabis, Raphia, Coccus, Ligustrum, Fraxinus, Benincasa, Ricinus, Buxus, Mesembryanthemum, Rubus and Melaleuca. Samples from Cuticular and Epicuticular Layers of Selected Plant Species have been evaluated against HSV-1, HIV-1 and HCMV.

The study indicated several samples (numbers 56 (pear), 60 (apple), 62 (grape), 64 (apple) and 68 (tomato)) exhibiting 50 % inhibition of the HF strain of HSV-1, at sample concentrations between 44 mg/ml and 316 mg/ml. In the HIV-1 assay, the samples from willow leaf, wax palm and plum had Therapeutic Index (TI) >1.1. Wax palm had the highest TI, that being >20; indicating that it was very effective even at the 10 μg/ml concentration tested. The results against the HSV-1 virus also proved some compounds active towards this virus. The wax palm sample showed significant anti-herpes activity in these assays, the sample from plum showed activity at the higher concentration only, but again since little toxicity was observed even higher concentrations may be tested to gain additional antiviral effect. Pharmaceutical and nutraceutical formulations comprising the antiviral substances are also disclosed, as are methods of using such formulations to treat viral diseases.

Most relevant non-patent information

Immunopotentiation by orally-administered Quillaja saponins: effects in mice vaccinated intraperitoneally against rabies [7]

Orally fed *Quillaja* saponins amplified the immunopotentiating ability of an intraperitoneally (i.p.) administered inactivated rabies vaccine in mice. The number of animals surviving rabies infection was markedly higher (90–100 %) in groups of animals receiving a combined treatment of oral saponin (SAP) and i.p. vaccine, compared to groups receiving vaccine alone (25 %), or to unimmunized mice (0 %). Antibody production was significantly higher in animals fed SAP, 2 weeks after primary or secondary sensitization with an i.p.-injected vaccine. In mice given 2 i.p. doses of vaccine, 1 week apart, simultaneous

feeding of SAP resulted in an enhanced production of rabies-specific (whole Ig) antibodies. On the other hand, animals preconditioned with SAP, 3 days prior to administration of the vaccine, exhibited considerably increased IgG antibody levels. Moreover, SAP-preconditioned mice vaccinated with a very low dosage produced significantly higher levels of antibodies.

An insight into the ethnozoology of Panch Pargana area of Jharkhand, India [50]

Mylabris pustulata Thunb. Coleoptera (Cantharidae), Local Name: Kutma Poka Stage: Adult Habitat: On flowers of cucurbits and a pest of malvaceous plants. Locality: Used by Vaidyas of Baghadih and Kanchi. Disease: Dog bite, Hydrophobia.

Method of use: The insect is dried and preserved. Only one dose is prescribed. The dose comprises of one insect with paste of some fresh plants like Puru Ghas (*Ageratum conyzoides* L., Asteraceae) and Chirchitti (*Achyranthes aspera* L., Amaranthaceae), taken in empty stomach. The medicine is in use since generations.

An ethnobotanical survey of Rajshahi district in Rajshahi division, Bangladesh [71]

Kushtia district on the south, Natore district on the east and Nawabganj district on the west. Bangladesh has 64 districts; the predominantly rural populations of these districts rely on traditional medicinal practitioners for treatment of various ailments. These practitioners are experts in the knowledge of medicinal plants and their properties. Each has his own formulations and dosages based on the practitioner's individual experience, and this information is passed from generation to generation and not usually shared with other practitioners. Interviews were conducted with a number of traditional medicinal practitioners in Rajshahi district using a semi-structured questionnaire. Detailed information was collected pertaining to plants, plant parts or combination of plants used, formulation of medicines, dosages as well as ailments for which the plants are used. Plant specimens as pointed out by the traditional medicinal practitioners were collected and brought to Bangladesh National Herbarium for complete identification. Detailed information was obtained on 32 plant species belonging to 24 families.

Probable mechanisms of antiviral action elucidated

Considering the diversity and vastness of the plant kingdom, the area of antiviral plants explored so far is a mere trailer, leaving researchers with a huge scope to screen extensively and exhaustively several other plant species hailing from the same/different genus and families studied till date. Our attempt has been to enlist as many plants as possible with reported antiviral activity and their mechanisms elucidated thereof. We have also tried to retrieve information about the active molecule/s responsible for the said antiviral action after in-depth and exhaustive literature search.

From Supplementary Table 1, it is quite evident that maximum plant crude extracts obtained by various extraction methods display wide spectrum of antiviral activity, especially against herpes simplex viruses. The most important reason could be the presence of a plethora of chemical compounds such as polysaccharides [24, 101], triterpenes [68], phenolic acids, alkaloids, proteins & peptides, proanthocyanidins, anthraquinones, etc. [33] with established anti-herpes simplex virus activity. Second reason for such an observation could be the ease of propagation and adaptability of this particular virus in cell lines, which renders antiviral research quite conducive using this virus model.

Elaborating on the diverse classes of phytochemicals with proven anti-HSV activity first, we shall discuss about the phenolic acids. Phenolic acids represent a wide group of chemical compounds comprising of flavonoids, tannins, triterpenes, saponins, lignins, etc., which have reported anti-HSV properties. To quote a few are flavonoids such as quercetin 3-*O*-rutinoside, kaempferol 3-*O*-rutinoside and kaempferol 3-*O*-robinobioside derived from the ethanolic extract of *Ficus benjamina* leaves exhibiting potent inhibitory action against HSV infection [107], ellagitannins (Hippomanine A against HSV-2 [103] and Geraniin against HSV-1 and 2 [104]), isolated from *Phyllanthus urinaria* and saponins such as oleanane type triterpenoid saponins extracted from leaves of *Maesa lanceolate* against HSV-1. Structure–activity relationships have revealed that anti-HSV activity elicited by plant phenolic compounds is directly proportional to the number of hydroxyl groups present in their chemical structure. Reducing the number of hydroxyl groups reduces activity against HSV-1 [42].

Moving on to proteins, Stellarmedin A, a glycoprotein isolated from *Stellaria media* has shown potent inhibitory effect on HSV-2 replication in Vero cells with IC_{50} of 13.18 μg/ml [85] and Trichosanthin, a type 1 ribosome-inactivating protein isolated from Chinese plant *Trichosanthes kirilowii*, has been observed to down-regulate p38 mitogen-activated protein kinases (MAPK) and Bcl-2 in HSV-1 infected Vero cells [39], thereby inhibiting viral replication. Trichosanthin also protects brain injury in HSV-1 infected mice [8]. Plant alkaloid, berberine isolated from Chinese herbal plant *Coptidis rhizome*, has shown to prevent HSV penetration into the cell with an IC_{50} of 24.4 μM for HSV-1,

and IC_{50} of 26.8 μM for HSV-2 [18]. Most elucidated mechanisms of action exhibited by these plant extracts and their active moieties against herpes simplex virus include (i) inactivation of virus particles [11, 12, 14], (ii) inhibition of viral adsorption and penetration [29, 30], (iii) inhibition of viral replication [15] and (iv) inhibition of viral protein synthesis [5].

Discussing the unconventional mechanism of actions of anti-HSV activity, there are a few interesting findings pertaining to specific plant-derived chemical moieties. To elaborate, Curcumin, a phenolic compound isolated from the spice turmeric, has been found to inhibit viral gene expression and suppress histone acetyltransferase activity of the transcriptional coactivator proteins, namely p300 and CREB-binding protein (CBP) [recruited by the viral transactivator protein VP16 to gene promoter regions of HSV-1], thus ultimately interfering with virus replication [51]. Another mechanism explored for anti-HSV activity is by employing cell surface molecule competitors. For example, Chebulagic acid and Punicalagin isolated from *Terminalia chebulata* act by competing with the HSV-1 for binding with cell surface glycosaminoglycans, thereby inhibiting viral binding and fusion. This way these molecules are able to inhibit both viral entry as well as post infection cell to cell spread [59].

Chebulagic acid and Punicalagin have also shown activity against dengue virus (DENV-2) and the mechanism proposed is by inactivating free virus particles and by inhibiting early steps of virus entry, with no direct effect on inter cell virus transmission [60]. Moving on to dengue virus, flavonoid molecules such as baicalein and quercetin, have been found exhibiting activity against DENV-2 through different mechanisms. To elaborate, Baicalein acts by inducing virucidal response against extracellular viruses mediated through type I interferon induction and also by impeding virus adsorption onto host cell [112]. Quercetin, on the other hand has been found to act by inhibiting viral replication, however, has no effect on viral attachment and entry processes [111].

Elaborating on anti-influenza plants and their mechanism of antiviral action, most among the studied ones, function either by inhibiting viral hemagglutinin or neuraminidase activity. *Pelargonium sidoides* root extract have been observed exhibiting anti-Influenza A activity through the above mentioned mechanism. Aqueous extract of *Taraxacum officinale* also exhibits activity against Influenza A, however the mechanism proposed is different. In this case, inhibition of viral nucleoprotein RNA levels and polymerase activity are key to antiviral action [34]. Among single molecules exhibiting anti-Influenza A action, there are reports on specific groups of chemical compounds such as chalcones [22], xanthones [21], homoisoflavonoids [44] extracted from individual plants namely *Glycyrrhiza inflate*, *Polygala karensium* and *Caesalpinia sappan* respectively, with influenza A neuraminidase inhibiting properties.

Next for discussion are the phytomolecules active against respiratory syncytial viruses (RSVs). In this category also, Chebulagic acid and Punicalagin tannin compounds from *Terminalia chebulata* have been found exhibiting anti-viral activity possibly mediated through inhibition of early virus entry and inactivation of free virus particles [60]. However, these molecules do not affect cell-to-cell virus transmission. Another mechanism of anti-RSV activity reported along with the inhibition of viral attachment and internalization process is by stimulation of interferon-β (IFN-β). This is a possible modality of anti-RSV activity exhibited by Cimicifugin, a resinoid isolated from roots and rhizomes of *Cimicifuga foetida* [96]. The aspect of immunomodulation and its association with antiviral activity has been discussed separately later in this section. There are yet few molecules which have been found exhibiting anti-RSV activity but their precise molecular targets remains to be elucidated. To quote a few are uncinoside A & B (chromone glycosides) from *Selaginella uncinata* [64], bioflavonoids namely genkwanol B & C and stelleranol from *Radix Wikstroemiae* [40] and flavones from the leaves of *Lophatherum gracile* [97].

Apart from the plants mentioned under anti-hepatitis category in Supplementary Table 1, there are certain phytoconstituents also with potent anti-hepatitis B activity. Saikosaponin C from Bupleurum species is one such molecule with a potential to inhibit HBeAg expression and HBV DNA replication [17]. Several other phytoconstituents have also shown activity against hepatitis B virus, however their mechanism of action is not yet clear. For Hepatitis C, mostly studied and reported are individual phyto-molecules such as Curcumin, Epigallocatechin-3-gallate, Ladanein and Tellimagrandin I all from different plant species, exhibiting almost similar mechanism of action. All these molecules work by preventing viral entry, which may be mediated by altering the fluidity of the HCV envelope or by inactivating free virus particles [61].

Moving our focus to measles virus, most of the plant extracts and isolated active molecules studied, have been found to elicit antiviral action by neutralizing the virus particles, rendering them inactive and incapable of penetrating into a new cell. This way they prevent post infection cell-to-cell transmission [61]. Coming to Coxsackieviruses (CVs), these viruses hail from a family of nonenveloped, linear, positive-sense ssRNA viruses and are among the leading causes of pleurodynia, aseptic meningitis, meningoencephalitis, and myocarditis [90]. Plant extracts active against these viruses have been found to function probably by inducing type-I interferon response as seen with *Bupleurum kaoi* extract and Chinese herbal prescription Xiao-

Chai-Hu-Tang, both eliciting anti-CVB activity [61]. Ursolic acid, a *pentacyclic triterpenoid* isolated from *Ocimum basilicum*, however, exhibits anti CVB activity possibly by interfering with viral infection and replication [16].

Also, if we glance through the different plant preparations reported in this review, we will notice that most of them represent extracts made of more than one plant species. That draws our attention to the uniqueness of each plant species and their constituents, which together with other plants make a formulation effective in treating a plethora of viral infections. An in-depth analysis of such formulations along with a bio-activity guided isolation of active components shall definitely give a better idea about the active principles responsible for a varied antiviral action. Research in this direction is in progress as collated from different papers.

There are ample reports revealing immunomodulatory properties of many plant extracts mediated through induction and release of pro-inflammatory cytokines, IL-6 and IL-12. IL-12, produced by activated monocytes/macrophages and dendritic cells, stimulate cell-mediated immunity to release IFN-γ, promote Th-1 responses, and enhance CD8 + cytotoxic T cell activity, thereby playing a pivotal role in controlling viral replication [91]. There also exist evidence on IL-6 production by macrophages in response to virus infections [26], in addition to reports justifying its role in clearing viral infection from the physiological system [75]. Therefore, those plant extracts or phytoconstituents, which exhibit potential immune-stimulating effects may be useful in phagocytic enhancement, necessary for attenuating viral load and preventing infection spread. Type I interferons (IFN-α & IFN-β) are cytokines eliciting antiviral, antiproliferative, and immunomodulatory effects [10]. Also, as an early response to viral infections, these cytokines are expressed and are believed staging a central role in the innate immune antiviral response. Virus infected cells trigger production of interferons, which further induce a number of genes, called IFN stimulated genes (ISGs), thereby conferring an antiviral state [10, 89]. There are reports supporting antiviral potential of IFN-β against a plethora of viruses as has been discussed in the earlier sections with examples. IFN-β has been demonstrated exhibiting protective role against Coxsackie virus B3 infection, validated through in vitro [35] as well as in vivo models [66]. The IFN system has also been established as a contributing factor in inhibiting poliovirus replication [23, 41]. In this context, combined uses of interferons and phytoconstituents have been reported facilitating potential antiviral therapy. For example, interferon-beta (IFN-β) and glycyrrhizin have been shown eliciting significant antiviral activity against SARS coronavirus [19, 20]. Therefore, induction of IFN-α/β expression is very important in counteracting viral infection as well as imparting resistance to host cells against viruses. This very well justifies the need for further exploration of the pathways of immunomodulation signaled by various phytoconstituents *per se* or through a combined system in the form of plant extracts or herbal formulations, in a virus-induced pathology. The concept of immunomodulation by plants has been exploited in vaccine adjuvant technology also, with reports highlighting the immunopotentiating ability of plant extracts in conjunction with vaccines against viruses [7].

Continuing the discussion, yet another category of plants exhibiting antiviral activity against multiple viruses exist, clearly pointing at the multi-targeted action of these phytoconstituents molecules. In this context, it would be quite appropriate to highlight certain repurposing herbal extracts and phytomolecules, which initially had been implicated for a different pathological condition altogether, but eventually did display certain antiviral properties also. A few such plant derived molecules are artemisinin-type sesquiterpene lactones, from *Artemisia annua*, with antimalarial potential, found inhibiting a range of viruses including CMV, HSV, EBV, HBV and HCV and bovine viral diarrhea virus [63]. Another classical example is resveratrol, a good antioxidant, which is a stilbenoid, a type of natural phenol, and a phytoalexin, present mostly in skin of grapes, blueberries, raspberries, and mulberries. Resveratrol has been found attenuating RSV-induced inflammation, probably mediated via down-regulation of IFN-γ levels [113]. Phytoconstituents are quite varied in their chemistry, yet work in coordination to establish back the homeostasis lost during a pathological condition, thus directing our attention to the holistic nature of healing rendered by herbal sources.

Nature has always provided mankind with everything it needs and so has it inspired scientists to develop herbal plant-based compounds. However, owing to the challenges associated with designing antiviral molecules from natural plant sources, the pace and progress of antiviral research from this source has always been hindered. The trend seems to change though, as seen from the increasing number of reports on preparation methods for extracts suitable to specific needs, including antiviral research. Other hurdles confronted by researchers are batch to batch variation between herbal plants and constant availability of plant material in larger quantities. However, through proper designing of method validation protocols, plant extracts may be standardized with respect to their chemical composition, involving not too much of deviation from accepted limits. Also, with proper planning large scale cultivation of exquisite plants may be initiated to ensure unobstructed supply of herbal material. A few antiviral natural products those have made it to clinical trials especially against HIV and HCV are namely Calanolides A

and B [3], DCK(PA-334B), 3,5-DiO-caffeoylquinic acid, MX-3253, 4-Methylumbelliferone, Bevirimat, Sho-shaiko-to H09, and *Sutherlandia frutescens*, which is a clear indication of the changing trend and perspective among researchers. Also, an increasing need is felt towards encouraging large pharmaceutical companies to reboot their natural product drug discovery wing and motivating the academic world to create dedicated structures for conducting research on herbal sources. There is no cure for most of the viral diseases e.g. SARS-CoV, Dengue, Hepatitis B, and among the ones which have a therapy, there are some viral conditions which demand a life-long therapy, with whopping cost of treatment regimen. Considering the side effects and economic non-viability associated with antiviral chemotherapy, antiviral molecules or extracts from herbal sources could be considered as a viable alternative, thus presenting immense scope for exploration and research.

Concluding remarks

A substantial number of plant extracts and phytochemicals have been explored for antiviral property. Herbal preparations owing to their holistic approach strengthen the body's immune system, which in turn may help the body fight against invading infectious viruses. Herbal antiviral compounds, which are accessible and do not require laborious pharmaceutical synthesis are emerging as interesting alternatives in today's world of growing resistance to antiviral drug therapy. Many promising herbal treatments exist for viral diseases with proof of their efficacy and safety in advanced clinical trials. However, a lot of work still remains to be done to determine optimal treatments, doses, and formulae for those herbal preparations. Although, herbal plant preparations are widely used in several parts of the world, individually or in combination, data about the interactions of these medicinal plants in living system is non-existent. Therefore, the traditional medicine practice should be clubbed with scientific research facilitating modern drug discovery from phytochemicals. Scientific data pertaining to detailed pharmacokinetic and pharmacodynamics of medicinal plants and their preparations should be made available to researchers and policy makers so that larger randomized multicenter clinical trials may be designed and conducted. By adopting such approaches, the idea of incorporating and implementing a particular herbal formulation in routine therapy may be transformed into reality.

Acknowledgments We are thankful to Dr. TMA Pai Endowment Chair in Translational Virology Manipal University, Manipal for providing the necessary infrastructural support to carry out the background research towards drafting this review.

References

1. Abdallah RM, Ghazy NM, El-Sebakhy NA, Pirillo A, Verotta L. Astragalosides from Egyptian *Astragalus spinosus* Vahl. Pharmazie. 1993;48(6):452–4.
2. Alvarez AL, Habtemariam S, Juan-Badaturuge M, Jackson C, Parra F. In vitro anti HSV-1 and HSV-2 activity of *Tanacetum vulgare* extracts and isolated compounds: an approach to their mechanisms of action. Phytother Res. 2011;25(2):296–301. doi:10.1002/ptr.3382.
3. Babar M, Najam-us-Sahar SZ, Ashraf M, Kazi AG. Antiviral drug therapy- exploiting medicinal plants. J Antivir Antiretrovir. 2013;5:28–36. doi:10.4172/jaa.1000060.
4. Bennerman R, Burton J, Chen WC, eds. Medicinal plants and primary health care: an agenda for action. Traditional medicine and health care coverage; Geneva, Switzerland: World Health Organization; 1983
5. Bertol JW, Rigotto C, de Padua RM, Kreis W, Barardi CR, Braga FC, et al. Antiherpes activity of glucoevatromonoside, a cardenolide isolated from a Brazilian cultivar of Digitalis lanata. Antiviral Res. 2011;92(1):73–80. doi:10.1016/j.antiviral.2011.06.015.
6. Bliah MAM. Anti viral composition. Google Patents; 1987.
7. Chavali SR, Barton LD, Campbell JB. Immunopotentiation by orally-administered Quillaja saponins: effects in mice vaccinated intraperitoneally against rabies. Clin Exp Immunol. 1988;74(3):339–43.
8. Chen GF, Huang WG, Chen FY, Shan JL. Protective effects of trichosanthin in Herpes simplex virus-1 encephalitis in mice. Zhongguo Dang Dai Er Ke Za Zhi. 2006;8(3):239–41.
9. Chen Z-H, Hong-yuan LI, XIE Z-P. Antiviral active compound (RG3-1) from radix gentianae and its anti-RSV activity in vitro. J Harbin Med Univ 2007;4:19.
10. Cheng PW, Chiang LC, Yen MH, Lin CC. 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(1):24–31. doi:10.1016/j.fct.2006.06.007.
11. Cheng HY, Huang HH, Yang CM, Lin LT, Lin CC. The in vitro anti-herpes simplex virus type-1 and type-2 activity of Long Dan Xie Gan Tan, a prescription of traditional Chinese medicine. Chemotherapy. 2008;54(2):77–83. doi:10.1159/000119705.
12. Cheng HY, Lin LT, Huang HH, Yang CM, Lin CC. Yin Chen Hao Tang, a Chinese prescription, inhibits both herpes simplex virus type-1 and type-2 infections in vitro. Antiviral Res. 2008;77(1):14–9. doi:10.1016/j.antiviral.2007.08.012.
13. Cheng H-Y, Lin T-C, Yang C-M, Shieh D-E, Lin C-C. In vitro anti-HSV-2 activity and mechanism of action of proanthocyanidin A-1 from Vaccinium vitis-idaea. J Sci Food Agric. 2005;85(1):10–5. doi:10.1002/jsfa.1958.
14. Cheng HY, Yang CM, Lin TC, Lin LT, Chiang LC, Lin CC. Excoecarianin, Isolated from Phyllanthus urinaria Linnea, Inhibits Herpes Simplex Virus Type 2 Infection through Inactivation of Viral Particles. Evid Based Complement Alternat Med. 2011;2011:259103. doi:10.1093/ecam/nep157.
15. Cheng HY, Yang CM, Lin TC, Shieh DE, Lin CC. ent-Epiafzelechin-(4alpha– > 8)-epiafzelechin extracted from *Cassia javanica* inhibits herpes simplex virus type 2 replication. J Med Microbiol. 2006;55(Pt 2):201–6. doi:10.1099/jmm.0.46110-0.
16. Chiang LC, Ng LT, Cheng PW, Chiang W, Lin CC. Antiviral activities of extracts and selected pure constituents of *Ocimum basilicum*. Clin Exp Pharmacol Physiol. 2005;32(10):811–6. doi:10.1111/j.1440-1681.2005.04270.x.
17. Chiang LC, Ng LT, Liu LT, Shieh DE, Lin CC. Cytotoxicity and anti-hepatitis B virus activities of saikosaponins from Bupleurum species. Planta Med. 2003;69(8):705–9. doi:10.1055/s-2003-42797.

18. Chin LW, Cheng YW, Lin SS, Lai YY, Lin LY, Chou MY, et al. Anti-herpes simplex virus effects of berberine from Coptidis rhizoma, a major component of a Chinese herbal medicine, Ching-Wei-San. Arch Virol. 2010;155(12):1933–41. doi:10.1007/s00705-010-0779-9.
19. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. Lancet. 2003;362(9380):293–4.
20. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 2003;361(9374):2045–6.
21. Dao TT, Dang TT, Nguyen PH, Kim E, Thuong PT, Oh WK. Xanthones from *Polygala karensium* inhibit neuraminidases from influenza A viruses. Bioorg Med Chem Lett. 2012;22(11):3688–92. doi:10.1016/j.bmcl.2012.04.028.
22. Dao TT, Nguyen PH, Lee HS, Kim E, Park J, Lim SI, et al. Chalcones as novel influenza A (H1N1) neuraminidase inhibitors from Glycyrrhiza inflata. Bioorg Med Chem Lett. 2011;21(1):294–8. doi:10.1016/j.bmcl.2010.11.016.
23. Deonarain R, Cerullo D, Fuse K, Liu PP, Fish EN. Protective role for interferon-beta in coxsackievirus B3 infection. Circulation. 2004;110(23):3540–3. doi:10.1161/01.CIR.0000136824.73458.20.
24. Dong CX, Hayashi K, Mizukoshi Y, Lee JB, Hayashi T. Structures and anti-HSV-2 activities of neutral polysaccharides from an edible plant, Basella rubra L. Int J Biol Macromol. 2012;50(1):245–9. doi:10.1016/j.ijbiomac.2011.10.022.
25. Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJ, Marschall M. The antiviral activities of artemisinin and artesunate. Clin Infect Dis. 2008;47(6):804–11. doi:10.1086/591195.
26. Ellermann-Eriksen S. Autocrine secretion of interferon-alpha/beta and tumour necrosis factor-alpha synergistically activates mouse macrophages after infection with herpes simplex virus type 2. J Gen Virol. 1993;74(Pt 10):2191–9.
27. Fiore C, Eisenhut M, Krausse R, Ragazzi E, Pellati D, Armanini D, et al. Antiviral effects of Glycyrrhiza species. Phytother Res. 2008;22(2):141–8. doi:10.1002/ptr.2295.
28. Gebre-Mariam T, Neubert R, Schmidt PC, Wutzler P, Schmidtke M. Antiviral activities of some Ethiopian medicinal plants used for the treatment of dermatological disorders. J Ethnopharmacol. 2006;104(1–2):182–7. doi:10.1016/j.jep.2005.08.071.
29. Gescher K, Kuhn J, Hafezi W, Louis A, Derksen A, Deters A, 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(3):408–13. doi:10.1016/j.fitote.2010.11.022.
30. Gescher K, Kuhn J, Lorentzen E, Hafezi W, Derksen A, Deters A, et al. 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(2):468–74. doi:10.1016/j.jep.2010.12.038.
31. Getie M, Gebre-Mariam T, Rietz R, Hohne C, Huschka C, Schmidtke M, et al. Evaluation of the anti-microbial and anti-inflammatory activities of the medicinal plants *Dodonaea viscosa, Rumex nervosus* and *Rumex abyssinicus*. Fitoterapia. 2003;74(1–2):139–43.
32. Guolun C, Inventor Chinese herbal medicine for treating rabies, 2005.
33. Hassan ST, Masarcikova R, Berchova K. Bioactive natural products with anti-herpes simplex virus properties. J Pharm Pharmacol. 2015;. doi:10.1111/jphp.12436.
34. He W, Han H, Wang W, Gao B. Anti-influenza virus effect of aqueous extracts from dandelion. Virol J. 2011;8:538. doi:10.1186/1743-422X-8-538.
35. Heim A, Canu A, Kirschner P, Simon T, Mall G, Hofschneider PH, et al. Synergistic interaction of interferon-beta and interferon-gamma in coxsackievirus B3-infected carrier cultures of human myocardial fibroblasts. J Infect Dis. 1992;166(5):958–65.
36. Herrmann F, Romero MR, Blazquez AG, Kaufmann D, Ashour ML, Kahl S, et al. Diversity of pharmacological properties in chinese and european medicinal plants: cytotoxicity, antiviral and antitrypanosomal screening of 82 herbal drugs. Diversity. 2011;3(4):547–80.
37. Howard CR, Fletcher NF. Emerging virus diseases: can we ever expect the unexpected? Emerging Microbes Infect. 2012;1:1–11.
38. Hsiang CY, Hsieh CL, Wu SL, Lai IL, Ho TY. Inhibitory effect of anti-pyretic and anti-inflammatory herbs on herpes simplex virus replication. Am J Chin Med. 2001;29(3–4):459–67. doi:10.1142/S0192415X01000472.
39. Huang H, Chan H, Wang YY, Ouyang DY, Zheng YT, Tam SC. Trichosanthin suppresses the elevation of p38 MAPK, and Bcl-2 induced by HSV-1 infection in Vero cells. Life Sci. 2006;79(13):1287–92. doi:10.1016/j.lfs.2006.03.047.
40. Huang W, Zhang X, Wang Y, Ye W, Ooi VE, Chung HY, et al. Antiviral biflavonoids from Radix Wikstroemiae (Liaogewanggen). Chin Med. 2010;5:23. doi:10.1186/1749-8546-5-23.
41. Ida-Hosonuma M, Iwasaki T, Yoshikawa T, Nagata N, Sato Y, Sata T, et al. The alpha/beta interferon response controls tissue tropism and pathogenicity of poliovirus. J Virol. 2005;79(7):4460–9. doi:10.1128/JVI.79.7.4460-4469.2005.
42. Ikeda K, Tsujimoto K, Uozaki M, Nishide M, Suzuki Y, Koyama AH, et al. Inhibition of multiplication of herpes simplex virus by caffeic acid. Int J Mol Med. 2011;28(4):595–8. doi:10.3892/ijmm.2011.739.
43. Ilic N, Raskin I. Antiviral substances from plant cuticular and epicuticular material. Google Patents; 2003.
44. Jeong HJ, Kim YM, Kim JH, Kim JY, Park JY, Park SJ, et al. Homoisoflavonoids from *Caesalpinia sappan* displaying viral neuraminidases inhibition. Biol Pharm Bull. 2012;35(5):786–90.
45. Jinsuo S, Inventor Chinese medicine for curing hydrophobia, 2008.
46. Junhai J, inventor Herbal medicine for treating and preventing rabies, 2005.
47. King C. Exhibits tubercin activity; immune enhancers such as glycyrrhizin (GR), glycyrrhetic acid, and Chinese herbal extracts. Google Patents; 2008.
48. Krawitz C, Mraheil MA, Stein M, Imirzalioglu C, Domann E, Pleschka S, 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. doi:10.1186/1472-6882-11-16.
49. Kudo E, Taura M, Matsuda K, Shimamoto M, Kariya R, Goto H, et al. Inhibition of HIV-1 replication by a tricyclic coumarin GUT-70 in acutely and chronically infected cells. Bioorg Med Chem Lett. 2013;23(3):606–9. doi:10.1016/j.bmcl.2012.12.034.
50. Kumari B, Kumar S. An insight into the ethnozoology of Panch Pargana area of Jharkand, India. J Threat Taxa. 2009;1(8):441–3.
51. Kutluay SB, Doroghazi J, Roemer ME, Triezenberg SJ. Curcumin inhibits herpes simplex virus immediate-early gene expression by a mechanism independent of p300/CBP histone acetyltransferase activity. Virology. 2008;373(2):239–47. doi:10.1016/j.virol.2007.11.028.
52. Lam PYS. Compositions for the treatment of acquired immunodeficiency disease. Google Patents; 2006.

53. Lee JH, Kwon SM, Seo SH, Park YS, Kim YB, Kim SK, et al. Screening of a natural feed additive having anti-viral activity against influenza A/H5N1. Korean J Food Sci Technol. 2008;28:512–6.
54. Li BQ, Fu T, Dongyan Y, Mikovits JA, Ruscetti FW, Wang JM. Flavonoid baicalin inhibits HIV-1 infection at the level of viral entry. Biochem Biophys Res Commun. 2000;276(2):534–8. doi:10.1006/bbrc.2000.3485.
55. Li Y, Ooi LS, Wang H, But PP, Ooi VE. Antiviral activities of medicinal herbs traditionally used in southern mainland China. Phytother Res. 2004;18(9):718–22. doi:10.1002/ptr.1518.
56. Li T, Peng T. Traditional Chinese herbal medicine as a source of molecules with antiviral activity. Antiviral Res. 2013;97(1):1–9. doi:10.1016/j.antiviral.2012.10.006.
57. Limited P, inventor Antiviral Astragalus Extract, 2006.
58. Lin JC. Mechanism of action of glycyrrhizic acid in inhibition of Epstein-Barr virus replication in vitro. Antiviral Res. 2003; 59(1):41–7.
59. Lin LT, Chen TY, Chung CY, Noyce RS, Grindley TB, McCormick C, et al. Hydrolyzable tannins (chebulagic acid and punicalagin) target viral glycoprotein-glycosaminoglycan interactions to inhibit herpes simplex virus 1 entry and cell-to-cell spread. J Virol. 2011;85(9):4386–98. doi:10.1128/JVI.01492-10.
60. Lin LT, Chen TY, Lin SC, Chung CY, Lin TC, Wang GH, et al. Broad-spectrum antiviral activity of chebulagic acid and punicalagin against viruses that use glycosaminoglycans for entry. BMC Microbiol. 2013;13:187. doi:10.1186/1471-2180-13-187.
61. Lin LT, Hsu WC, Lin CC. Antiviral natural products and herbal medicines. J Tradit Complement Med. 2014;4(1):24–35. doi:10.4103/2225-4110.124335.
62. Locher CP, Burch MT, Mower HF, Berestecky J, Davis H, Van Poel B, et al. Anti-microbial activity and anti-complement activity of extracts obtained from selected Hawaiian medicinal plants. J Ethnopharmacol. 1995;49(1):23–32.
63. 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(3):854–9. doi:10.1016/j.jep.2012.03.024.
64. Ma LY, Ma SC, Wei F, Lin RC, But PP, Lee SH, et al. Uncinoside A and B, two new antiviral chromone glycosides from *Selaginella uncinata*. Chem Pharm Bull (Tokyo). 2003;51(11): 1264–7.
65. Mahady GB. Global harmonization of herbal health claims. J Nutr. 2001;131(3):1120S–3S.
66. Matsumori A, Tomioka N, Kawai C. Protective effect of recombinant alpha interferon on coxsackievirus B3 myocarditis in mice. Am Heart J. 1988;115(6):1229–32.
67. Mouhajir F, Hudson JB, Rejdali M, Towers GHN. Multiple antiviral activities of endemic medicinal plants used by berber peoples of morocco. Pharm Biol. 2001;39(5):364–74. doi:10.1076/phbi.39.5.364.5892.
68. Mukherjee H, Ojha D, Bag P, Chandel HS, Bhattacharyya S, Chatterjee TK, et al. Anti-herpes virus activities of Achyranthes aspera: an indian ethnomedicine, and its triterpene acid. Microbiol Res. 2013;168(4):238–44. doi:10.1016/j.micres.2012.11.002.
69. Nagai T, Suzuki Y, Tomimori T, Yamada H. Antiviral activity of plant flavonoid, 5,7,4′-trihydroxy-8-methoxyflavone, from the roots of *Scutellaria baicalensis* against influenza A (H3N2) and B viruses. Biol Pharm Bull. 1995;18(2):295–9.
70. Nakanishi T, Inada A, Murata H, Iinuma M, Tanaka T, Yamamoto H, et al. Antiviral and Antitumour Activities of Some Western North American Plants with Surface Exudates (1): Inhibitory Effects on HIV-1 Reverse Transcriptase. Jpn J Pharmacogn. 1993;47(3):295–300.
71. Nawaz AHMM, Hossain M, Karim M, Khan M, Jahan R, Rahmatullah M. An ethnobotanical survey of Rajshahi district in Rajshahi division, Bangladesh. American-Eur J Sustain Agric. 2009;3(2):143.
72. Novitsky YA, Madani H, Gharibdoust F, Farhadi M, Farzamfar B, Mohraz M. Use of a combination of ethanolic rosa sp., urtica dioica and tanacetum vulgare extracts, further compromising selenium and urea and having been exposed to a pulsed electromagnetic field, for the preparation of a medicament for immunostimulation and/or treatment of hiv infections. Google Patents; 2009.
73. Numazaki K, Nagata N, Sato T, Chiba S. Effect of glycyrrhizin, cyclosporin A, and tumor necrosis factor alpha on infection of U-937 and MRC-5 cells by human cytomegalovirus. J Leukoc Biol. 1994;55(1):24–8.
74. Obi RK, Iroagba II, Ojiako OA. Virucidal potential of some edible Nigerian vegetables. Afr J Biotechnol. 2006;5(19):1785–8.
75. Paludan SR. Requirements for the induction of interleukin-6 by herpes simplex virus-infected leukocytes. J Virol. 2001;75(17):8008–15.
76. Peng T, Yang Y, Riesemann H, Kandolf R. The inhibitory effect of astragalus membranaceus on coxsackie B-3 virus RNA replication. Chinese medical sciences journal=Chung-kuo i hsueh k'o hsueh tsa chih/Chinese Academy of Medical Sciences. 1995;10(3):146–50.
77. Petrera E, Coto CE. Therapeutic effect of meliacine, an antiviral derived from *Melia azedarach* L., in mice genital herpetic infection. Phytother Res. 2009;23(12):1771–7. doi:10.1002/ptr.2850.
78. Pleschka S, Stein M, Schoop R, Hudson JB. Anti-viral properties and mode of action of standardized *Echinacea purpurea* extract against highly pathogenic avian influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV). Virol J. 2009;6:197. doi:10.1186/1743-422X-6-197.
79. Polyak SJ, Morishima C, Lohmann V, Pal S, Lee DY, Liu Y, et al. Identification of hepatoprotective flavonolignans from silymarin. Proc Natl Acad Sci USA. 2010;107(13):5995–9. doi:10.1073/pnas.0914009107.
80. Rates SM. Plants as source of drugs. Toxicon. 2001;39(5): 603–13.
81. Rees LP, Minney SF, Plummer NT, Slater JH, Skyrme DA. A quantitative assessment of the antimicrobial activity of garlic (Allium sativum). World J Microbiol Biotechnol. 1993;9(3):303–7. doi:10.1007/BF00383068.
82. Roner MR, Sprayberry J, Spinks M, Dhanji S. Antiviral activity obtained from aqueous extracts of the *Chilean soapbark* tree (Quillaja saponaria Molina). J Gen Virol. 2007;88(Pt 1):275–85. doi:10.1099/vir.0.82321-0.
83. Saoo K, Miki H, Ohmori M, Winters WD. Antiviral activity of aloe extracts against cytomegalovirus. Phytother Res. 1996;10(4):348–50. doi:10.1002/(SICI)1099-1573(199606)10:4<348:AID-PTR836>3.0.CO;2-2.
84. Sassi AB, Harzallah-Skhiri F, Bourgougnon N, Aouni M. Antiviral activity of some Tunisian medicinal plants against Herpes simplex virus type 1. Nat Prod Res. 2008;22(1):53–65. doi:10.1080/14786410701589790.
85. Shan Y, Zheng Y, Guan F, Zhou J, Zhao H, Xia B, et al. Purification and characterization of a novel anti-HSV-2 protein with antiproliferative and peroxidase activities from Stellaria media. Acta Biochim Biophys Sin (Shanghai). 2013;45(8):649–55. doi:10.1093/abbs/gmt060.
86. Shulong L, Inventor Chinese medicinal herb preparation for treating and preventing rabies, 2008.
87. Singh S, Shenoy S, Nehete PN, Yang P, Nehete B, Fontenot D, et al. Nerium oleander derived cardiac glycoside oleandrin is a

novel inhibitor of HIV infectivity. Fitoterapia. 2013;84:32–9. doi:10.1016/j.fitote.2012.10.017.
88. Soltan MM, Zaki AK. Antiviral screening of forty-two Egyptian medicinal plants. J Ethnopharmacol. 2009;126(1):102–7. doi:10.1016/j.jep.2009.08.001.
89. Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD. How cells respond to interferons. Annu Rev Biochem. 1998;67:227–64. doi:10.1146/annurev.biochem.67.1.227.
90. Toniolo A, Onodera T, Jordan G, Yoon JW, Notkins AL. Virus-induced diabetes mellitus. Glucose abnormalities produced in mice by the six members of the Coxsackie B virus group. Diabetes. 1982; 31 (6 Pt 1):496-9.
91. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol. 2003;3(2):133–46. doi:10.1038/nri1001.
92. Tsai HH, Hwang SM. Compositions of matter useful in the treatment of viral infections derived from plant extracts. Google Patents; 1999.
93. Uncini Manganelli RE. Zaccaro L, Tomei PE. Antiviral activity in vitro of *Urtica dioica* L., *Parietaria diffus*a M. et K. and *Sambucus nigra* L. J Ethnopharmacol. 2005;98(3):323–7. doi:10.1016/j.jep.2005.01.021.
94. Verma H, Patil PR, Kolhapure RM, Gopalkrishna V. Antiviral activity of the Indian medicinal plant extract *Swertia chirata* against herpes simplex viruses: a study by in vitro and molecular approach. Indian J Med Microbiol. 2008;26(4):322–6.
95. Vijayan P, Raghu C, Ashok G, Dhanaraj SA, Suresh B. Antiviral activity of medicinal plants of Nilgiris. Ind J Med Res. 2004;120(1):24–9.
96. Wang KC, Chang JS, Lin LT, Chiang LC, Lin CC. Antiviral effect of cimicifugin from *Cimicifuga foetida* against human respiratory syncytial virus. Am J Chin Med. 2012;40(5):1033–45. doi:10.1142/S0192415X12500760.
97. Wang Y, Chen M, Zhang J, Zhang XL, Huang XJ, Wu X, et al. Flavone C-glycosides from the leaves of *Lophatherum gracile* and their in vitro antiviral activity. Planta Med. 2012;78(1):46–51. doi:10.1055/s-0031-1280128.
98. Wang X, Jia W, Zhao A, Wang X. Anti-influenza agents from plants and traditional Chinese medicine. Phytother Res. 2006;20(5):335–41. doi:10.1002/ptr.1892.
99. Wannang NN, Kwanashie HO, Ede SO. Antiviral Activity of the Fruit Extract of Cucumis metuliferus *E. Meye* (Curcubitaceae) in Chicks. Afr J Basic Appl Sci. 2010; 2(3–4):89–93.
100. Xiong H-R, Luo J, Hou W, Xiao H, Yang Z-Q. The effect of emodin, an anthraquinone derivative extracted from the roots of *Rheum tanguticum*, against herpes simplex virus in vitro and in vivo. J Ethnopharmacol. 2011;133(2):718–23. doi:10.1016/j.jep.2010.10.059.
101. Xu HX, Lee SH, Lee SF, White RL, Blay J. Isolation and characterization of an anti-HSV polysaccharide from *Prunella vulgaris*. Antiviral Res. 1999;44(1):43–54.
102. Yamasaki K, Nakano M, Kawahata T, Mori H, Otake T, Ueba N, et al. Anti-HIV-1 activity of herbs in Labiatae. Biol Pharm Bull. 1998;21(8):829–33.
103. Yang CM, Cheng HY, Lin TC, Chiang LC, Lin CC. Hippomanin A from acetone extract of *Phyllanthus urinaria* inhibited HSV-2 but not HSV-1 infection in vitro. Phytother Res. 2007;21(12):1182–6. doi:10.1002/ptr.2232.
104. Yang CM, Cheng HY, Lin TC, Chiang LC, Lin CC. The in vitro activity of geraniin and 1,3,4,6-tetra-O-galloyl-beta-D-glucose isolated from *Phyllanthus urinaria* against herpes simplex virus type 1 and type 2 infection. J Ethnopharmacol. 2007;110(3):555–8. doi:10.1016/j.jep.2006.09.039.
105. Yang T, Jia M, Zhou S, Pan F, Mei Q. Antivirus and immune enhancement activities of sulfated polysaccharide from Angelica sinensis. Int J Biol Macromol. 2012;50(3):768–72. doi:10.1016/j.ijbiomac.2011.11.027.
106. Yang NS, Wang JH, Wei WC. Dioscorea Extracts. Google Patents; 2009.
107. Yarmolinsky L, Zaccai M, Ben-Shabat S, Mills D, Huleihel M. Antiviral activity of ethanol extracts of *Ficus binjamina* and *Lilium candidum* in vitro. N Biotechnol. 2009;26(6):307–13. doi:10.1016/j.nbt.2009.08.005.
108. Yarnell E, Abascal K. Herbs for treating herpes zoster infections. Alternat Complement Ther. 2005;11(3):131–4.
109. Yarnell E, Abascal K. Herbal medicine for viral hepatitis. Alternat Complement Ther. 2010;16(3):151–7.
110. Yoosook C, Bunyapraphatsara N, Boonyakiat Y, Kantasuk C. Anti-herpes simplex virus activities of crude water extracts of Thai medicinal plants. Phytomedicine. 2000;6(6):411–9. doi:10.1016/S0944-7113(00)80068-9.
111. Zandi K, Teoh BT, Sam SS, Wong PF, Mustafa MR, Abubakar S. Antiviral activity of four types of bioflavonoid against dengue virus type-2. Virol J. 2011;8:560. doi:10.1186/1743-422X-8-560.
112. 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. doi:10.1186/1472-6882-12-214.
113. Zang N, Xie X, Deng Y, Wu S, Wang L, Peng C, et al. Resveratrol-mediated gamma interferon reduction prevents airway inflammation and airway hyper responsiveness in respiratory syncytial virus-infected immunocompromised mice. J Virol. 2011;85(24):13061–8. doi:10.1128/JVI.05869-11.
114. Zhang GG, Song SJ, Ren J, Xu SX. A new compound from *Forsythia suspensa* (Thunb.) Vahl with antiviral effect on RSV. J Herb Pharmacother. 2002;2(3):35–40.