



INHIBITORY EFFECT OF SIDDHA HERBS ON RNA TYPES OF VIRUS - A REVIEW

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ABSTRACT

Siddha System of Medicine (SSM) is the one of the famous medical system in southern regions of Asia, especially in India. The practitioners of SSM are using herbs and herbo-mineral formulations for treating the various kind of acute and chronic illness. Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host-specific interactions. And the medical system plays a vital role in various endemic outbreaks in southern regions like Chikungunya, Dengue, and H1N1. These outbreaks are mainly due to that of RNA type of viruses. In this brief review, explore the scientific evidence of Siddha Herbal of *Andrographis paniculate*, *Allium sativum*, *Azadirachta indica*, *Terminalia chebula*, *Curcuma longa*, *Glycyrrhiza glabra*, *Melia azadirach*, *Vitex negundo*, *Alpinia officinarum*, *Ocimum sanctum* are having significant antiviral activity against RNA type of viruses including Corona virus (CoV), dengue virus (DENV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, influenza virus, measles virus (MV), and respiratory syncytial virus (RSV).

KEYWORDS : Siddha herbs, Anti-viral activity, RNA virus, SARS CoV-2

INTRODUCTION

Viral infections play an important role in human diseases, and recent outbreaks in the advent of globalization and ease of travel have underscored their prevention as a critical issue in safeguarding public health^[1]. Viral infections have high mortality and morbidity rates worldwide and increasing resistance to antiviral agents causes serious medical problems. The lack of effective therapies and/or vaccines for several viral infections and drug intolerance support the need for new antiviral drug development^[2]. Moreover, due to increased global travel and rapid urbanization, epidemic outbreaks caused by emerging and re-emerging viruses represent a critical threat to public health, particularly when preventive vaccines and antiviral therapies are unavailable. Examples include the recent emergence of dengue virus, influenza virus, measles virus, SARS virus, West Nile virus outbreaks^[3,4] and SARS CoV-2. Siddha medicine is one of the ancient systems of medicines, treats the infections with herbs (*Mooligai*), Inorganic substances (*Thathu*) and animal products (*Jeevam*). Many of the Siddha formulations possess the herbs which have antimicrobial activity helps to treat acute and chronic infections^[5]. SSM in India has demonstrated path with record of 10000 years and forms part of the Health Service, existing beside conventional medicine. The published national Siddha formulary of India lists more than 500 well Siddha formulations in *Gunavagadam* (Siddha pharmacology)^[6]. In this review, an attempt has been set to underline the work on herbs in SSM having anti-viral activity, used in the treatment of viral infections during outbreak period. The selection of these herbs was based on their reputation in the treatment of viral illnesses. So, Siddha herbs having antiviral property against RNA type of viruses are listed.

METHODOLOGY:

RNA viruses, also known as retroviruses, have RNA as their genetic material. Some examples of retroviruses are hepatitis viruses and HIV. When these viruses enter a host cell, they must first convert their RNA into DNA. This process, called reverse transcription, enables the virus

to inject its genetic material into the host cell and use the host's biochemical machinery, like a DNA virus. Vaccines are available for many of the more common DNA viruses. These vaccines work by injecting the patient with an inactive form of the virus, usually the protein coat without the DNA. In the absence of the DNA, there is not any genetic material to copy, and the virus cannot replicate. However, exposing patients to viral proteins makes it more likely that their immune systems will recognize the virus as foreign and destroy it before it has a chance to infect host cells^[7]. Retroviruses, which use the host's biochemical system to reproduce, are more difficult to treat. Treatment for these viruses typically involves treatment with a drug that inhibits the activity of reverse transcriptase, the enzyme that converts retroviral RNA into DNA. Often, patients with retroviral infections such as HIV take a cocktail of many different types of drugs, each of which targets a different step in the viral life cycle^[8]. The recent pandemic, SAR-CoV2 is also a positive sense RNA virus and non-segmented that is included in the sarbeco virus, ortho corona viridae subfamily which is broadly distributed in humans and other mammals. SARS-CoV2 is a novel β -corona virus, after the previously identified SARS-CoV and MERS-CoV which led to pulmonary failure and potentially fatal respiratory tract infection and caused outbreaks mainly in Guangdong, China and Saudi Arabia^[9].

Herbal medicines and purified natural products provide a rich resource for novel antiviral drug development. Identification of the antiviral mechanisms from these natural agents has shed light on where they interact with the viral life cycle, such as viral entry, replication, assembly, and release, as well as on the targeting of virus–host-specific interactions. In this brief review, collection of Siddha Herbal Medicines having significant antiviral activity against RNA type of viruses including Corona virus (CoV), dengue virus (DENV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus, human immunodeficiency virus (HIV), influenza virus, measles virus (MV), and respiratory syncytial virus (RSV).

Table-1: Pharmacological studies, activities, and indications of Siddha Herbs

| S. No | Botanical name | Family | Name in Siddha medicine | Part Used ^[7] | Actions ^[10] | Indication as per the literature ^[10] | Pharmacological studies carried out |
|-------|--------------------------------|-------------|-------------------------|--------------------------|---|---|---|
| i. | <i>Andrographis paniculata</i> | Acanthaceae | Nilavembu | Whole part | Tonic, Stomachic, Alterative, Stimulant | All Types of Fever, Sinusitis, Syncope, Fever With Joint Pain | <ul style="list-style-type: none"> The methanolic extract of A. paniculata showed the highest antiviral inhibitory effect on DENV-1 by antiviral assay based on cytopathic effects^[11]. The antiviral activity of andrographolide showed significant activity against influenza A viruses including the H5N1 avian influenza virus. Significant inhibition of viral adsorption onto red blood cells with minimum inhibitory concentrations suggested that it was capable of directly interfering with viral hemagglutinin to block binding to cellular receptors^[12]. NVK provides protection against CHIKV and DENV-2 during active infection and helps to prevent virus infection in the cells which mainly depends on the cellular availability of drugs for maximum protection against both the infections^[13]. |

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|-------|----------------------------|----------------|---------------|---------|---|---|---|
| ii. | <i>Allium sativum</i> | Amaryllidaceae | Vellai poondu | Bulb | Carminative, Tonic, Stomachic, Alterative, Stimulant, Expectorant, Anthelmintic | Cough, Wheezing, Worm Infestation, Headache, Sinusitis, Dyspepsia, Abscess | <ul style="list-style-type: none"> Garlic extract have an effect on the Infective Bronchitis virus, a type of corona virus in replication phase. With the results of two strain of IBV, it was concluded that garlic extract has a significant effect on a sub-acute strain ^[14]. |
| iii. | <i>Azadirachta indica</i> | Meliaceae | Vembu | Leaves | Stimulant Anthelmintic Discutient | Dyspepsia, Fever, Scabies, Itching, Pox Infection | <ul style="list-style-type: none"> The aqueous extract of neem leaves completely inhibited 100–10,000 tissue culture infective dose (TCID) 50 of DENV virus type 2 indicated by the absence of cytopathic effects at its maximum non-toxic concentration and it inhibited the replication ^[15]. The aqueous extract preparation from the barks of neem plant <i>Azadirachta indica</i> acted as a potent entry inhibitor against HSV-1 infection into natural target cells ^[16]. |
| iv. | <i>Terminalia chebula</i> | Combretaceae | Kadukkai | Seed | Laxative, Digestive, Tonic, | Cough, Anemia, Jaundice, Peptic Ulcer, Liver Diseases, Hiccough, Stomach Pain, Piles, Vomiting, Vitiligo, Fistula | <ul style="list-style-type: none"> Chebulinic Acid and Chebulagic Acid derived from <i>Terminalia chebula</i> showed a significant effect on Novel Influenza Virus by inhibiting the Neuraminidase protein ^[17]. Chebulagic acid and punicalagin isolated from <i>Terminalia chebula</i> against DENV-2. Inactivated free virus particles and inhibit early viral entry including attachment and penetration phases ^[18]. |
| v. | <i>Curcuma longa</i> | Zingiberaceae | Manjal | Rhizome | Aromatic Carminative Stimulant Hepatic Tonic | Peptic Ulcer, Itching, Skin Diseases, Non-Healing Ulcer, Headache, Chickenpox, Rhinitis, Swelling. | <ul style="list-style-type: none"> The <i>C.longa</i> extracts in vivo, it was found that remarkable reduced of viral load after 24 hours. <i>C. longa</i> could potentially be used as antiviral against DENV with low cytotoxicity and effective inhibition ^[19]. Curcumin had a direct effect on viral particle infectivity that was reflected by the inhibition of haemagglutination; This effect was observed in H1N1 as well as in H6N1 subtype viruses ^[20]. Curcumin treatment induced the leakage of SRB from these liposomes and the addition of the influenza virus reduced the leakage, indicated that curcumin disrupts the integrity of the membranes of viral envelopes and of liposomes. Antiviral mechanisms of curcumin and its potential can be used as an antiviral agent for enveloped viruses ^[21]. |
| vi. | <i>Glycyrrhiza glabra</i> | Fabaceae | Athimathuram | Root | Emollient, Demulcent, Laxative, Tonic, Mild Expectorant | Dysuria, Jaundice, Vitiligo, Hiccough, Thirst, | <ul style="list-style-type: none"> Animal studies revealed the efficacy of Glycyrrhizic acid against the influenza A virus by stopping the virus replication. Glycyrrhizic acid presented in athimathuram inhibited virus growth and inactivated virus particles ^[22]. Expression of viral antigens was much lower in cultures treated with 1000 mg/L of glycyrrhizin than in any other culture. The high concentrations of glycyrrhizin (4000 mg/L) completely blocked replication of SARS -CORONA virus ^[23]. It was suggested that Glycyrrhizin protect mice exposed to a lethal amount of influenza virus through the stimulation of IFN-gamma production by T cells ^[24]. |
| vii. | <i>Melia azadirach</i> | Meliaceae | Malaivembu | Leaves | Anthelmintic, Diuretic, Emmenagogue, Cathartic, Antilithic | Worm Infestation, Dysmenorrhea, Skin Diseases, Infertility | <ul style="list-style-type: none"> 3-<i>α</i>-tigloyl-melianol and melianone derived from <i>Melia azadirach</i> showed a potent antiviral activity against three important human pathogens, belonging to <i>Flaviviridae</i> family, West Nile virus, Dengue virus and Yellow Fever virus ^[25] |
| viii. | <i>Vitex negundo</i> | Lamiaceae | Nochi | Leaves | Alterative Vermifuge | Intermittent Fever, Fever with Joint Pain, Fever with Rigor, Cough Wheezing | <ul style="list-style-type: none"> Methanol extract of <i>V. negundo</i> showed antiviral activities against RSV, whereas the essential oil of the plant showed antiviral activity against RSV and HSV-1 ^[26]. |
| ix. | <i>Alpinia officinarum</i> | Zingiberaceae | Chitrarathi | Rhizome | Expectorant, Febrifuge, Stomachic | Eczema, Cold, Cough, Fever, Vomiting, | <ul style="list-style-type: none"> Diarylheptanoids derived from <i>Alpinia officinarum</i> exhibited anti-influenza virus activity against all viruses used, including the oseltamivir-resistant strain in vitro. The compound had effect on dose-dependently suppressed the expression of viral messenger RNA and antigens ^[27]. Antiviral activities of nine diarylheptanoids isolated from <i>A.officinarum</i> against respiratory syncytial virus (RSV), poliovirus, measles virus, and herpes simplex virus type 1 (HSV-1) using a plaque reduction assay. Diarylheptanoids were suggested to have a broad spectrum of antiviral activity ^[28]. |

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| x. | <i>Ocimum sanctum</i> | Lamiaceae | Thulasi | Leaves | Stimulant, Expectorant, Diaphoretic | All Types of Fever, Cold, Cough, Allergic Rhinitis | <ul style="list-style-type: none"> The methanolic extract of <i>O. sanctum</i> showed a slight inhibitory effect on DENV-1 based on cytopathic effects^[29]. The antiviral activity of ethanolic extract of <i>Ocimum sanctum</i> against H1N1 virus assessed in MDCK cells through different virus inhibition assays. The treatment modalities indicated that post treatment mode was more effective than pretreatment and simultaneous treatment, thus inhibited viral replication and protein synthesis^[30] |
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DISCUSSION

Infections of RNA types of viruses develop into an emerging problem across the humanity. And infections and management of illness due to RNA type of virus are demanding to the developing countries like India. Chikungunya and Dengue like mosquito borne RNA type viral infections are the epidemic during seasonal and weather change periods in countries like India. They are big trouble to healthcare providers due to lack of novel antiviral drug and proper vaccines. People affected from Chikungunya are suffering a lot with symptoms like joint pain and swelling, after exposure to the alpha virus. And another one infectious disease most common in India is swine flu, which is caused by RNA type of virus. It is complicated to manage H1N1 infection because of the resistant to the antiviral drug oseltamivir. Adverse events of the antiviral drugs like ribavirin, oseltamivir restrict the usage of the drugs. SARS and MERS viral infections are also more challenging to the developed countries like China, America. No availability of appropriate anti-viral drugs to the various RNA types of viruses, leads in look for the anti-viral herbs to manage the condition. The pandemic situation due to SARS CoV-2 or COVID-19 virus, a type of RNA virus is very tough to medical professionals, healthcare providers and to the govt and it becomes a global burden nowadays.

Saint Agasthiyar, who is the father of SSM, explained 4448 diseases and treatment aspects to the conditions. A manuscript, *Gunavagadam* written by him speaks the usage of herbs, metals, minerals, and herbomineral formulations to the various ailments. *Vatham, Pitham, kapam* are the three humors and the basic of SSM. Siddha promotes the concept that if one's immune system (3 humors) is strong and normal then even if the body is exposed to any microorganism, one will not be affected^[31]. The people are south India are familiar to the various herbal formulations of SSM like Nilavembu Kudineer and Kapa Sura Kudineer because of the usage of the medicines on the various epidemic conditions like Chikungunya, Dengue, and ILLI. No major toxic effects were found while consuming the herbal concoction. The herbs in SSM, has various pharmacological activities without any toxicity. Most of the herbs studied for their antiviral and immunomodulatory activities by most of the researchers in India and other countries too. And they have potent antiviral activity with immune-stimulatory functions. These herbs can be utilized on this pandemic crisis along with the other trial drugs to prove its efficacy. It will save the affected people from the side effects of antiviral drugs and from other trial drugs.

Various phytochemical constituents like alkaloids, flavonoids, and tannins are responsible for the various pharmacological activities of the mentioned herbs in Table-1. Because of the constituents, they not only have antiviral and immunostimulatory activities and have anti-inflammatory, anti-pyretic, anti-tussive, hepatoprotective, Analgesic, anti-bacterial, anti-diabetic, antioxidant properties etc.

CONCLUSION

Siddha System of Medicine is one of the old medical system with full of pride which has a greater number of medicinal plants used for many specific diseases. This article supports the inclusion of herb for various RNA viral pandemic situations to save the society from the fearful, deadliest diseases. To best of our knowledge this review is first of its kind that highlights the herbs in Siddha System of Medicine having the inhibitory effect of RNA types of viruses. It will be more helpful to the health care providers and researchers to go further research on these herbs without any hesitation.

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