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Plant Derived Antivirals: A Potential Source of Drug Development

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Abstract

Plants have been the traditional source of active substances for most therapies. Plant derived natural compounds have received increasing attention for their antiviral potential. Typical example is constituents of *Sarracenia purpurea* which is found active particularly against Herpes Simplex Virus (HSV). The plant extracts from *Phyllanthus spp.* showed inhibitory effect on Hepatitis B virus (HBV) by suppressing virus replication and translation of the viral proteins. Efficacy of this plant to be used as a therapeutic agent against HBV has been shown to be quite high in numerous studies. Calanolide A is another such antiviral plant compound which has been coveted as an antiviral agent against human immunodeficiency virus (HIV). The complexity in successful treatment and cure of HIV, using an effective drug is furthered by the problem of high rate of mutations. This fact is even more suggestive of the need to find alternatives to synthetic drugs, like calanolide A, that can inhibit the viral reverse transcriptase. Similarly, glycyrrhizin a compound found in *Glycyrrhiza glabra,* has antiviral activity against many viruses such as HBV, Hepatitis C virus (HCV), HIV and HSV infections. In this review, we have attempted to study some of the viral infections and the plants and their derivatives that have been identified to treat the diseases, which have undergone laboratory testing and clinical trials.

Keywords

Hepatitis C virus; Phytotherapeutics; Pathogens

Introduction

Medicinal plants became a new source of drug discovery with the advent of today's advanced analytical chemistry tools. Twenty five percent of the drugs in common use are of plant origin. The rich flora found in a variety of environments, offer an enormous source of potential plant derived compounds with anti-microbial and therapeutic uses. With the advancement of high performance and efficient tools and techniques it has now become possible to isolate highly pure plant compounds with ease and of good quality grade, which eventually become handy in treating existing and emerging diseases. Despite the fact that there are numerous plant based compounds exhibiting inhibitory effects against a broad spectrum of pathogens that have been reported, there are not many that reach to the stage of clinical trials [1]. It is rather inexpensive and quickly possible to screen the activity of plant compounds *in vitro* in the laboratory, whereas *in vivo* testing is lagging in such studies being expensive and time intensive. There is much to gain and learn about remedial qualities of plants from the pre-existing knowledge of traditional medicines of Chinese, Indian and other ethnicities that may be tested for various applications as potential drugs. Ethnopharmacology has contributed immensely in the development of phytotherapeautics and discovery of drugs [2]. It is thus convenient to find plants that can be researched upon, however, what is required is the traditional knowledge which must be translated into pharmaceutical application in formulating novel drugs, finally taking it from the lab bench to the bed side.

Plants have immense biosynthetic capacity and not only are they constantly evolving like most living organisms, but with that, the complexity of their bioactive components also seems to provide a rich source of natural compounds that may serve as potential phytotherapeutics [3]. Development of anti-microbial agents that are plant based have not progressed, particularly, in the case of antiviral chemotherapy as compared to antibacterial and antifungal due to the problem of selectivity [4]. Antimicrobial agents should be able to destroy pathogens or in the case of virus infection, eliminate target cells and yet not harm the healthy host cells. Antibacterial agents that are safe for human use are available in the market against a wide range of bacterial pathogens, in sharp contrast, to the fewer antiviral drugs. The reason can be attributed to the fact that there is elaborate understanding about bacterial systems, their molecular mechanisms of infection and pathogenesis. Whereas, the manner in which viruses infect the host cells is an enigma. Some viruses may multiply and cause lysis of the host cell to further infect and spread the infection, while others integrate into the host chromosome and remain latent for even upto years [5]. Viruses are constantly evolving and have been developing new ways to evade the immune system. All of these render the quest of antiviral therapy challenging since it is difficult to identify unique biochemical features of viruses that may be suitable for selective attack.

Viral infection control

Various aspects of viruses like their structure, strategies for multiplication by reverse transcription, replication followed by translation, etc. could serve as potential targets for antiviral therapy. While many viruses depend on the host polymerases, proteases and other vital enzymes for their survival and propagation, some are virally encoded, and their inhibition may provide key strategies to control the infection (Figure 1). Some enzymes like proteolytic viral enzymes, viral polymerase, integrase, reverse transcriptase, most of which are encoded by the virus are necessary for viral replication and assembly of the mature viral particle. The antiviral drug acycloguanosine, popularly known as acyclovir acts by altering the activity of some essential viral enzymes and has been found to curb the rate of Herpes virus infection [6]. This encourages more studies and research for devising strategies to develop specific inhibitors for each viral enzyme.

Today there is a huge repertoire of medicinal plants with broad-spectrum antiviral activity. The endeavour of discovering medicinal

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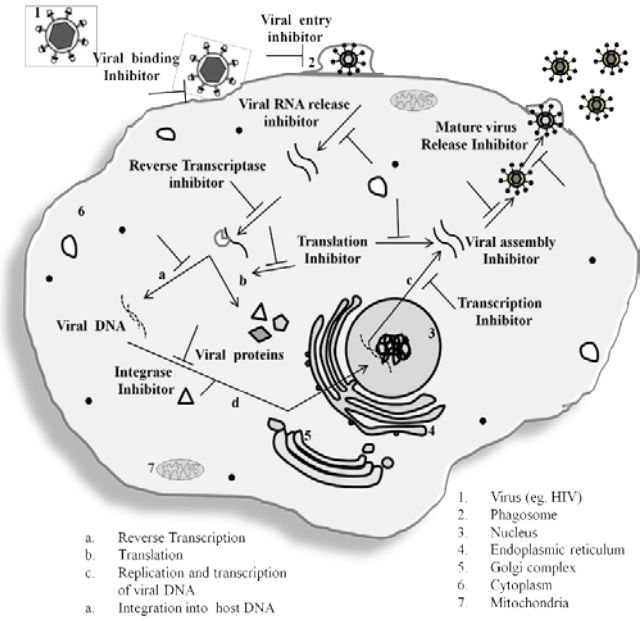

Figure 1: Potential inhibitors that can be used at various stages of virus infection.

plants with antiviral activity was limited in the past primarily due to two reasons, firstly, viruses are highly infectious and likely to cause deadly diseases and secondly, extraction and purification technologies existing in the past were not capable enough for efficient isolation of plant products of high purity and quality. Massive improvements in extraction and purification processes of plant extracts, their active compounds and also the use of vector based strategies for screening antiviral properties of medicinal plants can be tapped for the discovery of novel plant based drugs. In this review, an attempt has been made to study certain antiviral plants against various viruses, It provides an account of some of the mechanisms by which plants exert their antiviral effects, and those having antiviral activity against a wide spectrum of viruses have also been elucidated.

Herbal medicines and their antiviral effects

In the past, when researchers had pre-disposed viruses to be impossible to kill selectively and not susceptible to antibiotics, came about the discovery of 5-iodo-2'-desoxyuridine (idoxuridine, IDU) by Bill Prusoff, in 1959 [7]. It was a serendipitous finding of sorts, which emerged from the fact that IDU is a nucleoside analogue and was stumbled upon while looking for cytostatic drugs to treat neoplastic diseases. However, this drug was able to specifically inhibit DNA viruses such as HSV [8]. Proper laboratory tools, technical elements and systems are required to develop an antiviral molecule. Yet, at the same time, it is important to have *in vitro* cell systems, animal models and chronically infected patients to conduct research and test the effectiveness of the antiviral agents. It turned out that herpes was the only significant viral disease for which all the necessary paraphernalia became available.

The antiviral drug field came of age in 1960 with the first antiviral molecule, acyclovir, finding its way to the clinic. It was this scientific breakthrough by Gertrude B. Elion in the year 1959 which won her the Nobel prize in 1988 [9]. The subsequent emergence of AIDS in 1981, and various pandemics in the following years drastically changed the field of antiviral research. Anti-HCV protease and polymerase inhibitors are in various stages of clinical trials [10]. Crude drugs from a variety of plants have been formulated and used for centuries against several human ailments and diseases. Plants, indeed provide an enormous source of novel compounds that may have the potential to treat diseases [11]. Very few plants have reached upto clinical trials and shown positive results for the treatment of disease, so that they can be commercially exploited. Table 1 describes the plants and their products known to have antiviral activity against viral diseases. The diseases and the plants used for their cure are as follows.

Hepatitis Virus

Two diseases of major concern, Hepatitis B and Hepatitis C are caused by Hepatitis viruses.

Hepatitis B virus (HBV) causes an inflammatory liver disease called Hepatitis B in human beings, which is infectious. It is also known as "serum hepatitis" [12]. Blood or semen and vaginal fluids of the infected individual may cause the transmission of the virus. Infectious viral particles may also be present in the saliva, tears and urine, which may also causes transmission of the virus by chronic patients. Newborns are at a risk of acquiring the disease via prenatal transfer of HBV in endemic countries. Symptoms of HBV may span from commonly liver inflammation, vomiting and jaundice to infrequent death. Cirrhosis and liver cancer may eventually be caused in case of chronic hepatitis. Except few, current therapies show very poor response to the disease. But there is a good news that vaccine is available for this deadly disease [13].

Hepatitis B virus belongs to the *Hepadnaviridae* family- *hepa* from *hepatotropic* (tropism towards hepatocytes) and DNA since it comprises of circular genome containing partially double-stranded DNA [14]. The virus replicates through an RNA intermediate form by reverse transcription [15]. The propagation of the virus through replication cycles occurring in the liver, eventually reaches the blood which contains the HBV proteins and anti-HBV antibodies in diseased people. Infectivity of HBV is apparently of the order of 50 to 100 fold more than HIV [16].

Plants in clinical trials for treatment of hepatitis B

***Phyllanthus spp.*:** Plants belonging to the genus *Phyllanthus*, vernacularly known as "bhumyamalaki" of the Euphorbiaceae family have shown very promising results . The plants are generally found in tropical and subtropical countries. Traditional medicinal practices for treatment of diabetes, and proper functioning of the intestine, kidney, urinary bladder and also as a remedy against various microbial infections have been existent and practiced using this plant [17,18].

Phyllanthus is a rich source of the plant metabolites lignans (e.g., phyllanthine and hypophyllanthine), alkaloids, and flavonoids (e.g., quercetin). Endogenous DNA polymerase enzyme of HBV which is essential for viral replication is blocked by phyllanthus [19]. In a clinical trial 900-2,700 mg of *Phyllanthus* per day have been used for the treatment of Hepatitis B patients. For the first time, most promising results were reported by Thyagarajan et al. [20,21]. They treated chronic HBV patients with 200 mg of the plant *Phyllanthus amarus* three times a day for 30 days. It was found that 22 of 37 treated patients were not positive for Hepatitis B surface antigen when tested 15-20 days after the end of the treatment compared with only 1 of 23 placebo-treated controls. None of the cases showed reversal of

Table 1: Plants and their products known to have antiviral activity against selected diseases.

S.No.	Plant	Plant Family	Antiviral Plant Compounds	Antiviral Agent Against	Type of Study	Model Used	Major Findings	References
1.	*Phyllanthusniruri P.amarus*	Euphorbiaceae	Lignans, alkaloids & flavonoids	HBV	*in-vivo* & *in-vitro*	Human subjects Mice, Vero cell line	• Effective clearance of HbsAg by *P.urinaria, P.niruri*, & *P.amarus* • HBV elimination by *P.niruri*	[18-20,24] [20,23]
2.	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizin, SNMC	HCV	*in-vivo*	Rat Human subjects	• SNMC found to be effective for a short term • 66.7% efficacy of glycyrrhizin, in reducing symptoms	[35] [36]
3.	*Phyllanthusniruri*	Euphorbiaceae	Alkaloid extract	HIV	*in-vitro*	MT-4 cells	• *P.niruri* decreased cytopathogenicity caused by HIV infection	[39]
4.	*Aristolochia indica Cassia occidentalis, Phyllanthus niruri Withania somnifera Tinospora cordifolia*	Aristolochiaceae Leguminosae (Fabaceae) Euphorbiaceae Solanaceae Menispermaceae	Plant extracts	HIV	*in-vivo*	Human subjects	• Marked increase in $CD4^+$ T cell population in 7 out of 10 individuals observed	[40]
5.	*Camellia sinenis*	Theaceae	Epicatechin gallate epigallocatechin gallate	HIV	*in-vitro*	Radioactive Assay	• Inhibition of reverse transcriptase activity upto 90%	[41]
6.	*Calophyllum spp.*	Calophyllaceae	Inophyllum calanolide A coumarins	HIV	*in-vitro*	*Enzyme Assay*	• Inhibitory effects on HIV reverse transcriptase enzyme	[42-45]
7.	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizin	HIV	*in- vivo*	Human subjects	• Glycyrrhizin inhibits HIV-1 and reduces symptoms	[30,46]
8.	*Phytolacca americana*	Phytolaccaceae	Pokeweed antiviral protein (PAP I,II & III)	HIV	*in-vitro* & *in-vivo*	Biochemical Assay & human trial	• Antiviral property of PAP: Depurination of genomic HIV-1 RNA • HIV inactivation	[51-53]
9.	*Trichosanthes kirilowii*	Cucurbitaceae	Ribosome Inactivating proteins (RIPs) e.g. Trichobitacin	HIV	*in-vitro*	H9, C8166, H9/ HIV-1 III_B cell lines	• Depurination of rRNA, leading to inhibition of protein synthesis • Reduction in HIV-1 p24 antigen	[47-50]
10.	*Calophyllum lanigerum*	Calophyllaceae	Calanolide A	HIV	*in-vitro*, *in-vivo*	Human subjects	Calanolide A interacts with HIV reverse transcriptase and inhibits it	[56-59]
11.	*Sarracenia purpurea*	Sarraceniaceae	*S. purpurea* compounded in aloe based gel	HSV	Topical treatment	Human subjects	• *S. purpurea* aloe based gel serves as an effective HSV infection topical treatment	[63]
12.	*Glycyrrhiza glabra*	Fabaceae	Licorice roots	HSV	Topical treatment	Human subjects	• Licorice based cream resolves HSV infection symptoms	[64]
13.	*Rhus chinensis & Rhus javanica*	Anacardiaceae	Gallic acid, Moronic acid & Plant extract	HSV	*in-vitro* & *in-vivo*	U937 cell line, Mice & Guinea pigs	• Gallic acid induces apoptosis • Moronic acid exhibits anti-HSV activity • Suppresses HSV infection	[65-69]
14.	*Punica granatum*	Punicaceae	Aqueous extract	HSV	*in-vitro*	Vero cell line	• *P.granatum* showed anti-HSV activity	[85]
15.	*Phyllanthus emblica*	Phyllanthaceae	nor-sesquiterpenoid glycosides and ellagitannins	Coxsackie B virus	*in-vitro*	Cell lines	• Phyllaemblicin exhibits anti-Coxsackie B virus activity	[79,81]
16.	*Sophora spp.*	Fabaceae	Plant extract	Coxsackie B virus	*in-vivo*	Human subjects	• Relief from symptoms and antiviral activity	[82]

surface antigen. There was no toxic effects reported for *Phyllanthus amarus* [20]. The overall reliability on results obtained in this study are questionable owing to the placebo group which has been found to have large number of drop-outs. Tracking back and reproducing these studies have not been found to produce much benefits.

The effectiveness of *Phyllanthus* for HBV was more potent with *P. urinaria* and *P. niruri* as compared to the *P. amarus*. As evidenced from the clinical trials conducted at the Henan Institute of Medical Sciences, in China, the effect of *Phyllanthus* extracts were tested in 123 chronic Hepatitis B patients for serological parameters using three *Phyllanthus* extracts. Patients were treated with extracts of *Phyllanthus amarus,* 11 patients were given this extract obtained from S.P. Thyagarajan, Madras, India, *Phyllanthus niruri* (42 patients were given this extract obtained from Hainan Province in China) and *Phyllanthus urinaria* (35 patients were given this extract obtained from Henan Province). The control group comprised of 35 patients who received no herbal therapy. The patients receiving *P. urinaria* indicated undetectable Hbs antigen in their sera sample and also showed seroconversion status from negative to positive for the HB e-antibody. None of the patients treated with other two preparation of phyllanthus had any such changes [22].

Results of succeeding clinical trials evaluating the use of *Phyllanthus* species against HBV have not shown much coherence. Supposedly, because of inconsistencies in the process of extract standardization, the usage of different species, seasonal variations and the differences in the site of harvest, which may be responsible for the variations observed in the levels of the extract's active compounds. Crude extracts of *Phyllanthus amarus* alone seems to show contradictory results for antiviral activity against HBV in the literature. It is believed that some studies with *Phyllanthus amarus* may have accidentally missed the window period and skipped the doses and duration with antiviral activity of the plant. Perhaps, this makes the plant apparently not good enough to be used against HBV. This emphasizes the necessity of looking for concentration dependant significant decreases in viral load [23]. Certain studies show the possible inhibition of HBsAg levels found for the duration of 48 h *in vitro* using *P. amarus* at a concentration of 1 mg/ml. The mechanism has been found to involve suppression of HBV mRNA transcription. The plant interferes in the interactions between HBV enhancer I and C/EBP alpha and beta transcription factors. This may be exploited as a strategy for developing a therapeutic inhibitor against HBV [24]. *P. amarus* was found to disrupt the HBV polymerase activity, its replication and mRNA transcription processes. This suggests towards its use as an antiviral agent [24]. *Phyllanthus niruri* has also been evaluated for its inhibitory potential using HBsAg positive sera from chronic Hepatitis B patients [25]. HBsAg was inactivated, the effect being faster at 37°C than at 4^0C by the plant extract. *P. niruri* extract was found to be rather safe for use as evidenced from the toxicity studies. These studies to evaluate the extracts were carried out both *in vitro* and *in vivo*. Toxicity was observed neither in vero cells nor in mice [25]. The antiviral efficacy of *P. niruri* extract on HBsAg positive people was conducted in a clinical trial. The extract was given for 30 days on a daily basis, while some were placebo controls [26]. In fact, 90-days post-treatment, the plant extract course was found to effectively clear the HBV antigen among two-thirds of the treated positive individuals. Subsequent study elucidated the in vivo efficiency of *P. niruri* in eliminating Hepatitis B within 3-6 weeks, in mammals [22].

Glycyrrhiza glabra: *Glycyrrhiza glabra*, commonly known as licorice and sweetwood, is a native plant of the Mediterranean and certain areas of Asia [27]. Licorice is used in tobacco products, candies and drinks as a flavoring agent. It also has many medicinal uses, especially known as a cure for chronic hepatitis and is widely used in Japan. The licorice shrub requires fertile soil for its growth predominantly in the subtropical climates. It is a member of the pea family with oval leaflets, bearing white to purple colored flowers and pods with a flat shape. This plant has an extensive root system with the main taproot and numerous runners below ground. Its medicinal property is found in the main taproot which is soft and fibrous. It is colored bright yellow on the inside being rich in triterpenes, saponins, flavonoids, polysaccharides, pectins, simple sugars, amino acids, mineral salts and various other substances which have been isolated from licorice [28,29]. These compounds form the water-soluble and biologically active complex of licorice, accounting for almost half of its total dry weight. Licorice derives the yellow colour from the flavonoid content of the plant, which includes liquiritin, isoliquiritin (a chalcone) and other compounds [30].

Pompei et al. [31], have shown that glycyrrhizin, a component of licorice, has antiviral activity against *Herpes simplex* to the extent of being capable of irreversibly inactivating the virus. Glycyrrhizin and glycyrrhizic acid have also been shown to inhibit viral replication and infectivity of HIV [32,33], *Herpes zoster*, *Varicella zoster* [34].

Hepatitis C Virus

Hepatitis C virus is an enveloped, positive sense, single stranded RNA virus belonging to the family *Flaviviridae*. The genome ranges from 9.6 to 12.3 thousand nucleotides in length and encodes a polyprotein which gives rise to at least 11 proteins. HCV infection affects millions of people worldwide and has been found to cause liver cirrhosis, hepatic failure or hepatocellular carcinoma [35].

Glycyrrhizin

Glycyrrhizin is a free radical scavenger, with the potential to exert immunomodulatory effects (Figure 2). SNMC (Stronger neo minophagen C) is a solution made of 2 mg glycyrrhizin, 1 mg cysteine and 20 mg glycine per ml and is administered through the intravenous (IV) route [36]. IV infusions of SNMC were investigated in a clinical trial composed of a double-blind, randomized study including placebo-control groups. The efficacy of licorice with regard to ALT (alanine transaminase) levels was found to be satisfactory for

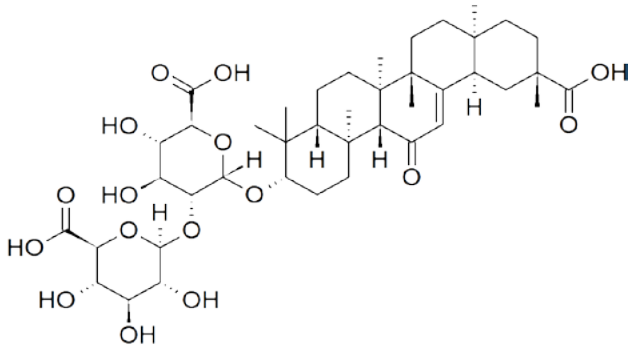

Figure 2: Structure of Glycyrrhizin.

a short-term. Rossum et al. [37] showed the requirement for SNMC to be administered on a daily basis through the IV route, although this has been found to be a rather impractical regimen for the patients. The study also threw light upon the fact that after completion and withdrawal of this therapy the ALT-decreasing effect of licorice disappeared. For prolonged effectiveness long-term administration is thus needed.

"Oral lichen planus" is a disease affecting the oral mucosa resulting in an inflammatory condition referred to as lymphocytic hyperkeratosis, that may occur in patients with Chronic Hepatitis C. There are hardly any treatments for this ailment and is therefore very difficult to cure. Nagao et al. [38], conducted an open clinical trial. In this trial 17 Hepatitis C-positive patients with oral lichen planus had enrolled, who were then given either routine dental care or 40 mL IV glycyrrhizin for a month on a daily basis. The distribution of results observed among the treated individuals were found to comprise improvement of clinical symptoms in six out of nine (66.7%) taking glycyrrhizin, such as decreased redness, fewer white papules and less erosion of the mucosa. Whereas, only one out of eight individuals (14.3%) was found to have improvement in the non-glycyrrhizin group.

Human Immunodeficiency Virus

Human immunodeficiency virus (HIV) is a *Lentivirus* belonging to the family *Retrovidae*, that causes an epidemic of severe immunodeficiency called Acquired Immuno Deficiency Syndrome (AIDS) [39]. It is an enveloped virus with a single-stranded, positive-sense, RNA genome. HIV specifically infects $CD4^+$ T cells which are important cells of the immune system that send signals and recruit other immune cells and help to eradicate the invading pathogen from the system, and also others like macrophages and dendritic cells [40], resulting in total failure of the immune systems and occurrence of life threatening opportunistic infections, ultimately leading to the death of the person. HIV is present both as a free virus particle and virus within infected immune cells in the body.

There is a huge decline in the number of $CD4^+$ T cells in an HIV positive patient, due to three way killing of $CD4^+$ T cells: First, direct viral killing of infected cells; second, increased rate of apoptosis in infected cells; and third, killing of infected $CD4^+$ T cells by CD8 cytotoxic lymphocytes that recognize infected cells. When $CD4^+$ T cell numbers decline below 200 cells per cubic mm, there is loss of cell-mediated immunity and the person is said to be suffering from full blown AIDS.

Plants in clinical trial for treatment of HIV

Phyllanthus niruri: Naik and Juvekar [41], conducted an intensive study to evaluate the effect of *P.niruri* on HIV [41]. The alkaloid extract of *Phyllanthus niruri* was found to have an inhibitory effect on HIV by them. The inhibitory effect of the extract on HIV-1 replication was assessed by observing the cytopathogenecity induced by HIV in MT-4 cells. The CC 50 for the extract (50% cytotoxic concentration) was found to be 279.85 µgmL. Whereas, the EC 50 (half maximal effective concentration) was found to be 20.98µgmL^{-1} for the extract. There was selective toxicity for the viral cells as indicated by Selectivity Index (SI) of 13.34, by the extract. In fact, the plant extract seemed to show inhibitory responses sensitive against both the strains of Human immunodeficiency virus which otherwise induced cytopathic effects in human MT-4 cells in the tested concentrations [41].

Calophyllum spp.: Around 180-200 species of *Calophyllum,* tropical evergreen trees belonging to the family *Calophyllacae*, are rich sources of anti HIV compounds namely inophyllum, calanolide A and coumarins. Calanolide A is part of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) group of medicines to treat HIV. This drug does not allow HIV to enter the nucleus of healthy T-cells, thereby, the cells fail to produce new viral particles and this leads to decreased viral titre in the body. This drug has been developed by Sarawak MediChem Pharmaceuticals (USA) on an experimental basis as of now. Moreover, it has not yet been evaluated for use by HIV infected people, by the U.S. Food and Drug Administration (FDA) [42,43]. It has been found that both inophyllum [44] and calanolide A [45] form a new subclass of NNRTIs and offer a novel and promising source of potential drug target against HIV.

Glycyrrhiza glabra: In one study glycyrrhizin obtained from *Glycyrrhiza glabra* was given intravenously, at 400-1600 mg doses, six times in one month duration, to three HIV patients suffering with hemophilia. A dose response study was planned to evaluate the treatment regime. After a month long treatment regime, it was found that p24 antigen levels seemed to have decreased significantly or become negative. With decreasing doses of glycyrrhizin an elevation in p24 antigen levels were observed almost immediately, suggesting that higher doses of glycyrrhizin was the reason for decreased antigen levels, perhaps through a mechanism that involved suppression of viral replication [32]. In another study carried out at the Osaka National Hospital, efficacy of oral doses of glycyrrhizin, ranging from 150 to 225 mg was tested in HIV infected patients. Ten asymptomatic, seropositive HIV patients, were given the drug daily. They did not show the symptoms over periods of one to two years, reiterating the effectiveness of glycyrrhizin. One out of the remaining ten people belonging to the untreated control group developed lymphadenopathy and two others were diagnosed with AIDS and subsequently died [46].

Certain plants have been found to contain intriguing antiviral proteins called ribosome-inactivating proteins (RIPs) that could alter ribosomal function of the cells infected with a virus and inhibit the viral protein synthesis [47]. These RIPs are basically N-glycosidases which function by depurinating large rRNAs at their highly conserved alpha-sarcin loop region. Interestingly, not only that, they have also been found to depurinate the nucleic acid scission of other targets [48,49]. This mechanism of depurination ensures that the ribosome gets inactivated and prevents its participation in protein synthesis. Trichobitacin is an RIP, obtained from the root of *Trichosanthes kirilowii.* It has been found to exhibit anti- HIV activity as evidenced from the reduction in the expression of the p24 HIV-1 antigen. It was also able to reduce the number of cells positive for the HIV antigen in acute and not in chronic HIV-1 *in vitro* [50].

Pokeweed antiviral protein (PAP) are a set of plant proteins found in the leaves of *Phytolacca Americana.* Three of its isoforms have been identified, namely, PAP-I from spring leaves, PAP-II from early summer leaves and PAP-III from late summer leaves. They are also a class of RIPs in that they cause the depurination of genomic HIV-1 RNA in a concentration dependent manner [51]. The activity of PAP

proteins can be estimated using quantitative high performance liquid chromatography which can be used to directly measure the amount of adenine released from the viral RNA.

PAP29 (molecular weight, 29 kDa), an anti-HIV, single chain RIP, obtained from leaves of *Phytolacca Americana* has particular clinical benefits to be used as a prophylactic anti-HIV agent. MAP30 (molecular weight: 30 kDa) and GAP31 (molecular weight: 31 kDa), obtained from *Momordica charantia* and *Gelonium multiflorum*, respectively are also RIPs that have been found to have anti-HIV activity [52]. These PAPs can inactivate infective viruses and virus-infected cells in semen with nonspermicidal intravaginal microbicide D'Cruz and Uckun [53]. A pharmacokinetic study using TXU (anti-CD7)-PAP immunoconjugate was found to have excellent anti-HIV-1 activity mediated by the PAP activity in HIV patients [54] in comparison to the activity of zidovudine. RIPs such as PAP thus lead the way towards discovering natural anti-HIV agents of plant origin, which can be highly effective as well.

Other plant derived compounds with anti- HIV activity: In another study conducted by Natarraj [55], extracts of *Aristolochia indica, Cassia occidentalis, Phyllanthus niruri*, *Withania somnifera* and *Tinospora cordifo* were administered to 10 HIV infected patients for a period of six months to one year. These patients were monitored regularly for their CD4 cell counts and clinical status. The results obtained were promising as there was a marked increase in CD4 count of seven patients resulting in improvement of their health, while in one patient CD4 count remained constant for one year, two of the patients amongst the ten were not benefitted so they progressed to full blown AIDS.

Many chemically synthesized antiretroviral compounds, specially active against HIV reverse transcriptase enzymes are available but they have many serious side effects like thrombocytopenia, anemia & leucopenia. Naturally occurring potent anti-HIV flavonoids such as betulinic acid, quercetin and myricetin which are not only active against reverse transcriptase but also against cellular DNA or RNA polymerase, are of utmost importance. Ono et al. [56] reported the mechanism of inhibition of reverse transcriptase, cellular DNA & RNA polymerase of HIV by epicatechin gallate and epigallocatechin gallate, the two components of *Camellia sinensis* (tea plant) . The degree of inhibition varied depending on the flavonoid.

Plant based drugs against HIV under clinical trials

Several plants, approximately 50 different species have been reported to contain anti-viral components such as terpenoids, coumarins, polyphenols, tannins, proteins, alkaloids, and biflavonoids which can inhibit HIV life cycle at different stages [57]. The number of plant based compounds that reached the clinical trials, however, are easily countable. (+)-Calanolide A, was first isolated from *Calophyllum lanigerum* found in the tropical Malaysian rain forest, is a non-nucleoside inhibitor of HIV-1 reverse transcriptase [58]. Its mode of action has been reported to be via a complex mechanism which involves possible binding at two sites. This is a rather unique property as it has not been found in any other NNRTI [57,58]. One of the (+)-calanolide A binding site is near both, the pyrophosphate binding site and the active site of the RT enzyme [59,60]. This natural compound had shown positive results in *in vitro* and animal studies. Creagh et al. [61] conducted Phase I clinical trials using (+)-calanolide A, in healthy, HIV negative persons, to test the safety and pharmacokinetics of single escalating doses of the drug. The toxicity of (+)-calanolide A was found to be minimal in 47 treated subjects and was found to be safe, exhibiting a favorable pharmacokinetic profile [61]. PA-457, a derivative of betulinic acid [62] and PA-334B, which is a khellactone coumarin [63] are the other two plant derived molecules other than calanolide A, that have been under clinical trials.

Herpes Simplex Virus

Herpes simplex virus 1 and 2 (HSV-1 and HSV-2) are enveloped DNA viruses, which belong to the Herpes virus family, *Herpesviridae*. HSV-1 mostly causes cold sores and HSV-2 causes genital herpes in human beings. These viruses are ubiquitously present and contagious. A mature HSV particle has a core containing viral DNA, an icosahedral capsid, an intermediate phase or 'tegument' that contains additional viral proteins and an outer membrane envelope studded with viral glycoprotein spikes [64].

Plants in clinical trial for treatment of Herpes simplex virus

***Sarracenia purpurea* (Pitcher plant):** *Sarracenia purpurea*, often referred to as the purple colored pitcher plant, is a carnivorous plant of the family *Sarraceniaceae*. It is mainly found in USA and Canada. It is the sole *Sarracenia spp.* member which can be found in cold temperate vegetations. S. *purpurea* primarily derives nutrients by consuming the prey it captures.

A clinical trial conducted by Brandie Gowey confirmed that topical use of *S. purpurea* when compounded in aloe based gel (manufactured by Professional Compounding Centers of America) on applying, gave patients immediate relief from pain caused by the virus, even lesions were resolved fully within 2-7 days [65]. In this double blind placebo controlled study, patients with recent (within 48 hours) outbreaks of HSV I and II lesions were given the compounded *S. purpurea* extract or placebo and applied either formulation directly to the lesions every 3-4 hours. On measuring the lesion number, size, and severity of pain, the outcomes were statistically significant, demonstrating possible effectiveness within 2 days of *S. purpurea* treatment against HSV I and II.

Glycyrrhiza glabra: Licorice roots have been used to prepare a two-percent topical acid cream which contains carbenoxolone sodium. In a study, this cream was used to treat 12 patients with acute oral herpetic (Herpes Simplex virus) infections. The disease symptoms such as pain and dysphagia were resolved on applying the cream for six times in a day within a short span of 24-48 hours of its use. Accompanying ulceration and lymphadenopathy were also found to gradually heal within 24-72 hours [66].

Rhus javanica: Chinese galls, obtained from the nutgall tree are rich in gallotannins. Gallotannins are a type of hydrolysable tannins. The nutgall tree, also known popularly as Chinese sumac belongs to the genus *Rhus*. *Rhus javanica or chinensis* are the plant species that have been known to have various healing properties ranging from treatment of cough, diarrhea, night sweat, dysentery and even to stop intestinal and uterine bleeding, in Chinese medicinal practices.

Rhus chinensis compounds possess strong antiviral, antibacterial, anticancer, hepatoprotective, antidiarrheal and antioxidant activities [67]. Gallic acid (3,4,5-trihydroxybenzoic acid) found in *Rhus chinensis*, has the ability to induce apoptosis in human monocytic lymphoma cell line U937. It may thus be considered to be a promising chemotherapeutic agent against lymphoma [68]. Inhibition of alpha-

glucosidase activity has been observed in the gall of *Rhus chinensis* [69]. Anti-HSV-2 activity has been found to be present in *Rhus javanica* [70]. Herbal extract of *Rhus javanica* contain a simple triterpenoid keto acid called Moronic acid [71]. This has been shown to be efficient in treating wild-type HSV- (type1 and type 2) oral infection in mice. Although the correct mechanism of action of this triterpenoid keto acid in HSV inhibition is still not known.

Other Plant derived compounds with anti- HSV activity

The phenolic extract *Geum japonicum* and *Syzygium aromaticum*, yield a compound called eugeniin (ellagitannin) which shows anti-HSV activity [70,72]. Eugeniin selectively blocks viral DNA synthesis inside the host cell [73,74]. This plant compound is one of the most potent antiviral compounds known to inhibit not just wild type HSV 2 virus and Epstein–Barr virus DNA polymerase but also the thymidine kinase-deficient HSV-1 virus, and even HSV-1 showing resistance to acyclovir-phosphonoacetic acid. *Rheum officinale*, *Aloe barbadensis* (Aloe vera), *Rhamnus frangula*, *Rhamnus purshianus* and *Cassia angustifolia* yielded different kinds of anthraquinones which were also found to be quite effective against HSV-1 [75]. In another study, *Punica granatum* aqueous extract has been shown to exhibit anti- HSV activity, showing selective index (SI) 14 and 12.5 [76]. In conclusion, the antiviral activity against a variety of viruses is attributable to the polyphenols, rosmarinic acid, and the low-molecular glycoside-forming compounds of chlorogenic acid and caffeic acid and their derivatives [77].

Coxsackie B virus

Coxsackie B virus belongs to a family of non enveloped, linear, positive-sense ssRNA viruses, *Picornaviridae* and the genus *Enterovirus*. These viruses mainly cause gastrointestinal diseases and sometimes may also lead to full-fledged, pericarditis and myocarditis [78]. The viral particles themselves are roughly 30 nm icosahedrons [79]. The virus is transmitted via the fecal-oral route, and infection commonly occurs after eating contaminated food. Coxsackie B viruses tend to infect the heart, pleura, pancreas, and liver, causing pleurodynia, myocarditis, pericarditis and hepatitis.

Plants in clinical trial for treatment of coxsackie B virus

Phyllanthus emblica: *Phyllanthus emblica*, popularly known as aamla or the Indian gooseberry belongs to the *Phyllanthaceae* family. These deciduous trees are known for their edible fruit of the same name. This fruit is widely used in India in a variety of preparations of pickles, dishes and indigenous medicinal concoctions, therefore its medicinal use is well known. However, the exact composition of its medicinal components are not known. They have been found to contain high amounts of ascorbic acid (vitamin C), 445 mg/100g [80], and the overall antioxidant strength of aamla may be attributed to its high density of ellagitannins (Dharmananda S. Emblic Myrobalans) such as emblicanin A (37%), emblicanin B (33%), punigluconin (12%) and pedunculagin (14%) [81]. It also contains punicafolin and phyllanemblinin A, B, C, D, E and F [82]. The fruit also contains other polyphenols: flavonoids, kaempferol, ellagic acid and gallic acid [83].

Qing Liu et al. [84] isolated three new nor sesquiterpenoid glycosides i.e., 4′-hydroxyphyllaemblicin B, phyllaemblicins E and F from the roots of *Phyllanthus emblica*, together with three known compounds, phyllaemblic acid, phyllaemblicin B, and phyllaemblicin C. Of these, phyllaemblicins F was a new norsesquiterpenoid dimer. They evaluated these phyllaemblicins along with phyllaemblic acid methyl ester and phyllaemblicin A which are known analogues with antiviral activity toward Coxsackie virus B3 (CVB3) using cytopathic effect (CPE) inhibitory assay *in vitro*. They found that Compounds phyllaemblicin B & phyllaemblic acid methyl ester exhibited strong anti-CVB3 activity [85].

Sophora spp.: *Sophora spp.* includes a large variety of small trees and shrubs which belong to the subfamily *Faboideae* of the pea family, *Fabaceae*. These plants can be found in the southern regions of Europe, Asia, Australasia and various islands in the Pacific Ocean, western regions of South America and the United States. Li et al., 1996 reported that the injection for of *Sophora* extract could be used to treat myocarditis, in humans [85]. 76 patients were treated with *Sophora* extract and it was claimed that Coxsackie B virus RNA clearance (evaluated by PCR test) was dose dependent and that all the patients treated had relief from arrhythmia. While the ejection fraction, stroke volume, cardiac output, and cardiac index showed improvement, the left ventricular mass and its index decreased significantly. The anti-Coxsackie antibodies returned to normal titer after five months of therapy [85]. *Sophora* may therefore be used for relieving symptoms relief and for its antiviral activity.

Future Prospects

Most antiviral drugs are expensive, and beyond the reach of the common man in most developing countries. There are many viral diseases that we continue to fight relentlessly yet they prove to be fatal and infectious. While some can be curbed by the use of antiviral drugs, some have become seemingly worse by developing resistance to these drugs over a period of time. Plant derived compounds such as ellagitannins have strong antiviral effects having the ability to inhibit even highly resistant strains of the HSV. Such plant derived compounds need to be commercialized and made available at low costs. These would prove to have minimum side effects in the long run and may also be used in combination with other known potent antiviral molecules and drugs to cure vicious infections such as HIV, which has a tendency to rapidly mutate into drug-resistant forms. Discovery of novel compounds of plant origin must continue with a lot of fervor, which could prove to be much better alternatives to chemically synthesized drugs available at sky rocketing prices in the market. Arguably, the development of safe, effective and inexpensive antiviral drugs active as RT inhibitors is among the top global priorities of drug development, as many viruses are not yet curable and mortality rates are high, for example with HIV and hepatitis. The advent of high-throughput technologies could be an useful tool for identifying the potential plant derived lead compounds against viral diseases for optimization and preclinical studies.

The lead compounds developed by high-throughput method could effectively mitigate the viral diseases, which will be developed at very low cost and can be afforded by developing countries as well.

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