

# Antiviral Drug Therapy- Exploiting Medicinal Plants

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## Abstract

Plants serve as rich sources of medicinal substances which can be used for a variety of therapeutic purposes. The increasing prevalence of microbial diseases calls for need to find new ways to cure these diseases. Among the many microbes, viruses exhibit themselves in the most severe forms resulting in high morbidity and mortality rates. HIV/AIDS, Hepatitis B and C viruses, Influenza virus and Dengue virus are some of the many viruses that have gained the attention of public health authorities in recent years. Though a number of prophylactic and therapeutic options are available yet the development of resistance to these agents results in failure to achieve the desired outcomes. Viral attachment and entry into the cell, its genome processing, assembly, release and immune stimulation are the main targets of these antiviral therapies. Most of the antivirals, currently licensed, are of synthetic origin or synthetic analogues of the natural products. These products possess chemical and therapeutic similarities with the products derived from plants. However, the isolation, analysis and regulatory approvals of these natural products are at a very early stage. The review discusses the similarity of therapeutic targets and mechanisms of actions of synthetic and natural products. Moreover, an outline is provided for incorporating the latest research techniques for plant-based antiviral drug discovery and development.

**Keywords:** Medicinal plants; Antiviral strategies; Drug isolation from plants

**Abbreviations:** CCR: Chemokine Co-receptor; CMV: Cytomegalovirus; CTL: Cytotoxic Lymphocytes; FIPV: Feline Infectious Peritonitis virus; HBV/HCV: Hepatitis B/C Virus; HIV/AIDS: Human Immunodeficiency Virus/ Acquired Immunodeficiency Syndrome; HSV: Herpes Simplex Virus; JEV: Japanese Encephalitis Virus; MS: Mass Spectrometry; NK: Natural Killer Cells; NMR: Nuclear Magnetic Resonance; NRTI: Nucleoside Reverse Transcriptase Inhibitors; NNRTI: Non-nucleoside Reverse Transcriptase Inhibitors; SARS-coV: Severe Acute Respiratory Syndrome coronavirus

## Introduction

Communicable diseases present a major challenge to health care practitioners and public health authorities. They account for one-third of all the deaths recorded annually and almost 63% of the mortality cases observed in children [1,2]. The emergence of newer, more pathogenic diseases in recent years, like hepatitis B and C, HIV/AIDS and dengue hemorrhagic fever, have resulted in millions of deaths worldwide. Among various types of microorganisms, viruses have managed to adjust themselves according to the new trends of human society. The population explosion, sex revolution, substance use and globalization have collectively caused an increase in the incidence and prevalence of viral diseases. Recent statistics show that HIV/AIDS is responsible for over 2 million deaths annually across the globe [3]. It is predicted that by year 2020, AIDS would become the deadliest of all the pandemics in human history. Similarly, influenza virus with its high rate of genetic reassortment has been associated with a number of outbreaks in recent years [4]. An estimated 500 million people are infected with hepatitis B or C virus worldwide [5]. These and many other human and zoonotic viral agents, therefore, pose a continuous threat to human health and economy.

Viruses have achieved efficient means to survive and propagate in a wide variety of hosts and cell types. They are the most diverse group of microorganisms with respect to their host distribution, genomic organization and clinical presentations. Birds, fish, insects, humans

and other mammals are the most prominent hosts in the animal kingdom. They may possess DNA or RNA genome and may follow diverse routes for replication, transcription and translation processes. Moreover, clinically, they may present themselves as self-resolving, localized infections or may attain severe forms to affect the whole body. Although belonging to various classes, viruses follow similar general pathway for causing pathogenesis in the host. On entering the body, it replicates at the initial site of infection to attain a higher viral titer [6]. Here the immune system may neutralize it or the virus may spread to other tissues of the body [7,8]. On reaching the target site, the virus interacts with cell surface receptors and ultimately enters into the host cell [9,10]. In the cell, the viral genome is released which gets integrated in the host genome [11,12]. Viral genes are translated with the help of host machinery [13]. Newly synthesized proteins assemble to form new viral particles [14]. These virions are released from the cell and are spread to neighboring cells, ultimately, affecting a wider population of cells [15,16]. Repetitive replication of viruses results in the appearance of clinical features.

Symptomatic treatment of viral diseases was the only therapeutic option available until the late 20<sup>th</sup> century due to the unavailability of efficient antivirals. However, advances in the field of molecular biology, infection biology and combinatorial chemistry lead to the discovery of dozens of antivirals. Currently licensed antiviral agents target specific proteins that are essential for survival of the virus. Most

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of these therapeutic strategies are targeted against HIV, Influenza virus, Hepatitis viruses and Herpes virus. Highly Active Anti-Retroviral Therapy (HAART) has been designed against the HIV viral infections [17]. It contains a combination of drugs which target the viral replication at various steps. Maraviroc, tenofovir, emtricitabine, darunavir and nevirapine are some of the drugs included in the regimen. Similarly, two classes of drugs targeting the viral assembly and release are used against the influenza virus infections [18,19]. The licensed anti-influenza virus drugs are amantadine, rimantadine, zanamivir and oseltamivir. For the treatment of Hepatitis C virus infections, a combination of interferon and an antiviral agent is used [20]. Interferon functions as a stimulant of immune system while intra-cellular viral replication is blocked by ribavirin or a protease inhibitor. Although, there has been an increase in the number of approved antiviral agents, yet these drugs cover a very narrow range of viruses. Moreover, an increased incidence of resistance to these antivirals, further decrease their therapeutic potential [21,22].

Drugs of natural origin have proved their effectiveness against a wide variety of viral diseases. The use of plant based antivirals is an integral part of many traditional systems of medicine. Extracts of Panax ginseng have proved to possess anti-retroviral activity and are used in the treatment of HIV infections. Various chemical substances of this extract have been found to act on the reverse transcriptase enzyme of HIV [23]. *Polysiphonia denudata*, a marine plant, has proved its activity against the HSV in *in vitro* studies [24]. Similarly, various phytochemicals of *Sambucus nigra* have established anti-influenza properties [25]. Patients suffering from Hepatitis B viral infections have shown positive clinical improvements on using preparations of *Phyllanthus amarus* [26]. Though these phytochemicals and crude extracts are effective against these diseases, yet they lag behind in the drug development process. Both allopathic and traditional systems of medicine are highly dependent upon the plants for extraction, derivatization, synthesis and manufacture of drugs against a wide variety of diseases. Research in the study of antiviral effects of plants needs to be done. Below we discuss the plant based antiviral agents and their mechanism of actions. Various steps of drug development process and the scope of plant based antivirals are also reviewed.

## Plant Derived Antiviral Agents

Plants form a fundamental part of many medicinal systems under practice today. Around 50% of prescribed drugs are either produced from plants or are derivatives of plant products [27]. Antivirals of natural origin have, like other plant based products, proved to possess adequate pharmacological and pharmaceutical activities. Combination therapy using medicinal plants have proved their effectiveness against a number of viruses including HSV and Influenza viruses [28,29]. Similarly, broad spectrum of antiviral activity is observed by many plant extracts. *Agrimonia pilosa* and *Ocimum basilicum*, for example, are efficient against a wide range of DNA and RNA viruses [30-32]. Many phytochemicals show dose-dependent viral inhibition [33,34]. Moreover, a major issue of drug resistance caused by synthetic drugs is solved [35,36]. Polycytone A, a plant derived product is active against the resistant forms of HIV [37]. Plant based products are cost effective and easily available in many parts of the world. In comparison to the synthetic drugs, natural products are less toxic and cheaper. At the same time, they have proved their therapeutic effectiveness for a wide variety of conditions. To the down side, the lack of research and appropriate clinical data prevent their use. These phytochemicals exhibit their

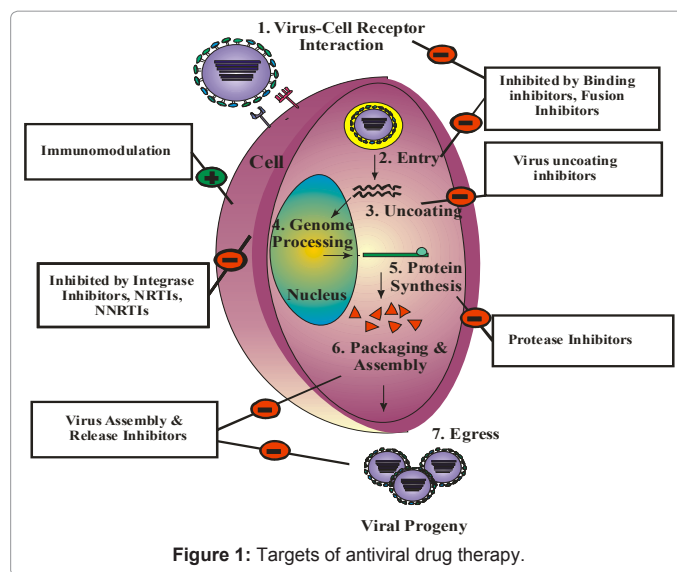


Figure 1: Targets of antiviral drug therapy.

antiviral effects through one of the ways described underneath. The main targets of plant based antiviral drugs are represented in figure 1.

## Immunomodulators

The induction of protective immune response is one of the primary targets of antiviral therapy. Many of the currently registered products adapt this mechanism against viral infections. Interferons, interleukins and colony stimulating factors are the most prominent immunostimulants. Interferons are the inducible polypeptides and glycoproteins that serve as mediators to induce the production of certain enzymes that inhibit viral replication in the cell [38,39]. Interleukins are involved in the stimulation, growth, differentiation, maturation and regulation of immune cells that can help in the neutralization of the virus [40]. Colony stimulating factors, similarly, regulate the proliferation and differentiation of progenitor cells in the white blood cells lineage [41]. Moreover, a few drugs, including ribavirin, potentiate the immune response too [42].

A number of natural products have been investigated for their immunomodulatory effects. Alkaloids, carbohydrates, lectins, polyphenols, stilbenoids and peptides are among the many classes of drugs that are used as immunomodulators. The  $\beta$ -sitosterol, obtained principally from the plants of genus *Nigella*, enhance the cellular immune response by enhancing the activity of natural killer (NK) cells, CTLs and by the increased secretion of cytokines [43,44]. Research studies have reported that extracts of certain plants like *Tinospora cordifolia* have the ability to cause lymphocytic activation [45]. The population of NK cells and T-cells has been reported to increase by 331% and 105% respectively, on using its extract [46]. Flowering tops of *Echinacea purpurea* have been used for its role in immune stimulation [47]. It is believed that the family Asteraceae is the largest plant family to be possessing immunomodulatory activity [48]. Proteins obtained from *Allium sativum* possess active mitogenic activity towards human lymphocytes, splenocytes and thymocytes [49]. These and many other plant products are used for enhancing immune responses against a number of viral pathogens. The use of immunomodulators, hence, prevents the replication in the body.

## Virus attachment and entry inhibitors

The attachment of virus to the host cell and its entry, thereafter, presents another target for the antiviral therapy. The virus enters the cell by interacting either with a single cell surface receptor or certain co-receptors may also be involved [50,51]. The fusions of viral envelop and host cell membrane takes place [52]. Once inside the cell, the virus is uncoated to release its genome [53]. A number of registered drugs target these steps of viral infection. Tromantadine, used in HSV infections, alters the glycoproteins on the surface of the host cells, thereby, preventing the adsorption, penetration and un-coating of the virus [54]. The entry of HIV into target cells is mediated by the interaction of the virus surface glycoproteins with a co-receptor CCR-5 [55]. Maraviroc and Vicriviroc, two of the approved drugs for antiretroviral therapy, target this co-receptor and prevent the interaction of the gp-120 of the virus with the CCR-5, preventing the virus from entering the macrophages and T-cells [56,57]. A number of licensed drugs, like Docosanol, Enfuvirtide and Fosfonet, collectively known as fusion or entry inhibitors prevent the cellular and viral membranes from joining and fusing with one another [58-60].

Research on various plant products have shown that they adapt similar mechanisms for stopping viral replication. Mannose specific plant lectins derived from genera *Galanthus* and *Hippeastrum* have been found to interrupt the HIV envelop glycoproteins, resulting in the inhibition of viral entry into the cell [61]. Other classes of plant products including N-acetylgalactosamine, glucose and galactose have been observed to possess antiviral activity against severe acute respiratory syndrome coronavirus (SARS-coV) and the feline infectious peritonitis virus (FIPV). These agents also tend to interrupt the viral attachment to the host cell [62]. Various derivatives of naturally occurring peptides, including azidoproline, have demonstrated anti-HIV affinity, by targeting the receptor and co-receptor binding sites of the virus [63]. Similarly, Glycyrrhizin derived from the roots of *Glycyrrhiza glabra* has been shown to possess exceptional affinity against the HIV surface proteins, thereby inhibiting the virus binding to the cell [64,65]. Geraniin, a tannin derived from genus *Phyllanthus*, also acts as an inhibitor of viral uptake by the cell [66]. A polyphenolic aldehyde derived from the cotton plant, Gossypol, has been described as an effective fusion inhibitor. It binds with the HIV surface gp41 glycoprotein and blocks the entry of the virus into the cell [67]. Dose dependent HIV-cell fusion inhibition has been shown by the extracts obtained from the bark of *Ailanthus altissima* [68]. A number of natural products are used against influenza virus receptor binding and fusion protein, haemagglutinin [69]. Inhibition of virus uncoating and release of genetic material into the cell has been observed by the extracts obtained from various sea weeds. Carrageenans, sea-weed derived heparin sulfate molecules, exert antiviral activity against dengue virus by preventing the un-coating of virus in host cells [70].

## Modifiers of viral genome and protein processing

Viral transcription and translation processes offer the next target for an antiviral strategy. The genome gets either directly integrated into the host genome (DNA viruses) or may be processed before it can utilize the cellular machinery to its benefit (RNA viruses). The replicon can then be transcribed and translated [71,72]. Hence, at this step reverse transcription, integration, replication, transcription and translation provide potential targets. Among the currently registered drugs, integrase inhibitors target the enzyme that helps

in the incorporation of the viral genetic material into the host cell DNA [73,74]. This class includes raltegravir and elvitegravir. Reverse transcription and replication is targeted by a number of drugs. Didanosine, emtricitabine, abacavir, stavudine and trifluridine are the principal drugs in this class that are currently being used in antiviral therapies against HIV, Hepatitis B and C and Herpes Simplex Virus [75]. Metisazone targets the viral mRNA and protein synthesis by either inhibiting the transcriptase enzyme or causing chain termination [76].

Among the significant plant-derived antivirals, one class of coumarins known as the calanolides stands apart [36]. Derived principally from *Calophyllum lanigerum*, they have been shown to target the reverse transcriptase enzyme by irreversibly binding to the active site of the enzyme. Large amounts of calanolides are isolated from the latex of related species of the plant [77]. Calanolide has now entered Phase II clinical studies for anti-retroviral therapy. It has a proven synergistic effect with currently licensed drugs [78]. Other chemical classes, including coumarins, flavonoids and pentacyclic triterpenoids, have shown to possess affinity against reverse transcriptase and other polymerases of the HIV. These compounds have been extracted from *Ferula sumbul*, *Tripterygium wilfordii* and *Calophyllum inophyllum* [79-81]. A novel target has been utilized by the compound Polycitone A. It inhibits the formation of RT-DNA complex in addition to inhibiting reverse transcriptase and DNA polymerase activity [81]. A number of species of *Trichosanthes* have been found to cause protein synthesis inhibition by inactivating the ribosomes [82].

## Virus assembly and release inhibitors

These drugs inhibit the arrangement of newly synthesized viral proteins into virions and their release from the cell. A number of licensed drugs target this stage of viral life cycle. Protease inhibitors prevent the cleavage of polyprotein [83]. These drugs are effectively being used against HIV, Hepatitis B and Hepatitis C virus. Saquinavir, ritonavir, indinavir, boceprevir and telaprevir are the most significant members of this group [84]. Neuraminidase inhibitors act by blocking the influenza virus release from the infected cells, resulting in prevention of cell-to-cell transmission [85]. Oseltamivir and zanamivir are the important members of this group.

There are currently more than 30 different protease inhibitors derived from plant sources with established antiviral activities. Compounds of various chemical sources and botanical origins have been investigated for the purpose [86]. Extracts from *Eclipta prostrata*, *Alpinia galanga*, *Zingiber zerumbet*, *Coccinia grandis*, *Boesenbergia pandurata*, *Cassia garretiana* and *Orostachys japonicus* have proved their antiretroviral efficacy utilizing their protease inhibiting property [87-90]. Bevirimat extracted from a Chinese herb, *Syzygium claviflorum*, has been shown to possess 'maturation inhibition' capability [91]. Similar to the protease inhibitors, this compound possesses the capability of suppressing the cleavage of gag polyprotein of HIV. Hence, both the structural and enzymatic proteins are not formed. Another Chinese preparation, *Ching-fang-pai-tu-san* (CFPTS) used as a traditional herbal decoction, contains chai-hu, quercetin and isoquercetin. These compounds inhibit influenza virus replication by obstructing the intracellular protein processing, transportation and budding properties [92]. Lycopyranocoumarin and Glycycoumarin, from *Glycyrrhiza glabra*, have been shown to inhibit the giant cell formation by HIV in in-vitro studies [93,94].

Mechanism of Action	Principal Ingredient	Botanical Source	Activity against
Immune stimulants	Polyphenol complex	<b>Geranium sanguineum</b>	Influenza viruses [98]
	β-sitosterol	<i>Nigella sativa</i> , <i>Serenoa repens</i>	Multiple viruses [99,100]
	Essential oils, extracts	Family Asteraceae	Respiratory viruses [101], HSV [102]
Entry inhibitors	Mannose-specific lectins	<b>Galanthus spp.</b> , <b>Narcissus spp.</b>	HIV [103], Influenza [104], CMV [105], FIPV [106]
	Elenoic acid	Olives spp.	Influenza [107], HSV [108]
	Galactofucan	<i>Achyrocline flaccida</i>	HSV [109]
	Polysaccharides	<b>Stevia rebaudiana</b>	Rotavirus [110]
Replication and Translation inhibitors	Glycyrrhizin	<b>Glycyrrhiza spp.</b>	HIV [111], SARS-coV [112], Hepatitis A [113],
	Phytolacca American Protein (PAP)	<i>Phytolacca americana</i> <i>Phytolacca farnosus</i>	HSV [114], HIV [115], HBV [116]
	Emetine	<i>Psychotria ipecacuanha</i>	Influenza [117], Dengue Virus [118], Animal viruses [119]
	Quercetin	Quercus spp.	Influenza [120], HCV [121], JEV [122]
	Fisetin	Acacia spp., Gleditsia spp.	Dengue [123], HCV [124]
Viral assembly and release inhibitors	Hesperidin	Citrus spp.	Influenza [125]
	Naringenin	Citrus spp.	HCV [126]

**Table 1:** Some plant-derived products possessing inhibitory effects on various viruses.

## Antiviral Drug Development from Plants

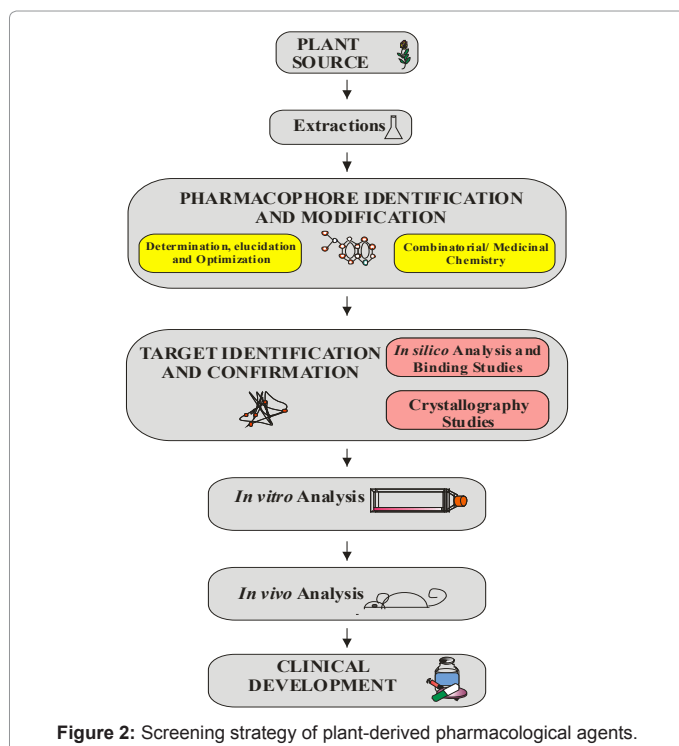
The drug discovery and development is an expensive and time consuming process. Billions of dollars are spent annually to find cure for diseases affecting the human population. Many of the currently approved drugs are being produced by synthetic processes. Natural products offer similar therapeutic benefits with lesser side effects in a cost-effective manner. Plant-derived antivirals hold great potential in augmenting and substituting the currently licensed products. A number of research groups have reported the antiviral potential of

many medicinal plants. Table 1 summarizes the antiviral drugs that have proved their efficacy in laboratory and clinical settings.

An ideal antiviral agent should affect the specific cellular responses without causing any additional damage to the cell [95]. Moreover, the viral resistance, as presented by most of the currently approved agents, should be abolished. *In-vivo- in-vitro* correlation (IVIVC) of the compounds isolated from natural sources helps in regulatory approvals in a shorter time. The compounds isolated from natural sources need to go through similar screening and testing procedures as the licensed drugs. With the advent of bio-informatics and modern analytical techniques, the identification of new drug molecules has become both cost and time effective [96,97]. Once the target has been identified, phytochemicals can be evaluated for their effectiveness. *In-vitro* studies are performed, followed by the safety and efficacy testing in suitable animal models. Formulations are developed and clinical trials are performed. Figure 2 represents a scheme for screening of plant-derived antivirals.

### Target identification

The first step in the development of a plant-derived antiviral is the determination of a target protein of the virus. As described earlier, structural or functional proteins may be targeted for an effective therapy. Once a target has been identified, High Throughput Screening (HTS) is performed. This process involves the collection of plants/ plant parts followed by the isolation and analysis of phytochemicals. In order to confirm the protein-ligand interaction, protein crystallography studies are performed. These studies help in determining the location and mode of ligand binding to the target [127]. Figure 3 represents the partial structure of Trichosanthin, a potent plant-derived anti-HIV agent, as obtained by x-ray diffraction studies [128]. Another similar method is the Fragment Based Lead Discovery. This strategy relies upon cleaving the isolated compounds and studying their affinity to the biological target [129]. NMR, MS or similar analytical techniques are employed to determine the chemical structure of the isolated compound. Figure 4 represents the chemical structures of some of the phytochemicals



**Figure 2:** Screening strategy of plant-derived pharmacological agents.



**Figure 3:** A protein-ligand complex of C-Terminal of acidic P2 protein with Trichosanthin [112]. Derived from *Trichosanthes kirilowii*, this phytochemical has proved its antiretroviral activity against HIV.

known to possess antiviral properties. Once the target and ligand structures are known, docking studies can be performed to determine the degree of interaction they may have. This approach, coupled with ligand fitting programs, has been used to isolate various compounds against the Hepatitis C virus [130]. The fragment-based approach has a higher success rate compared to conventional methods. It helps in the chemical derivatization process and, hence, the development of synthetic analogues [131,132]. Chemical derivatization can help in increasing the solubility, reactivity, receptor specificity and other pharmacological aspects of a drug molecule. The active derivatives are then processed for further studies.

### Viral replication studies

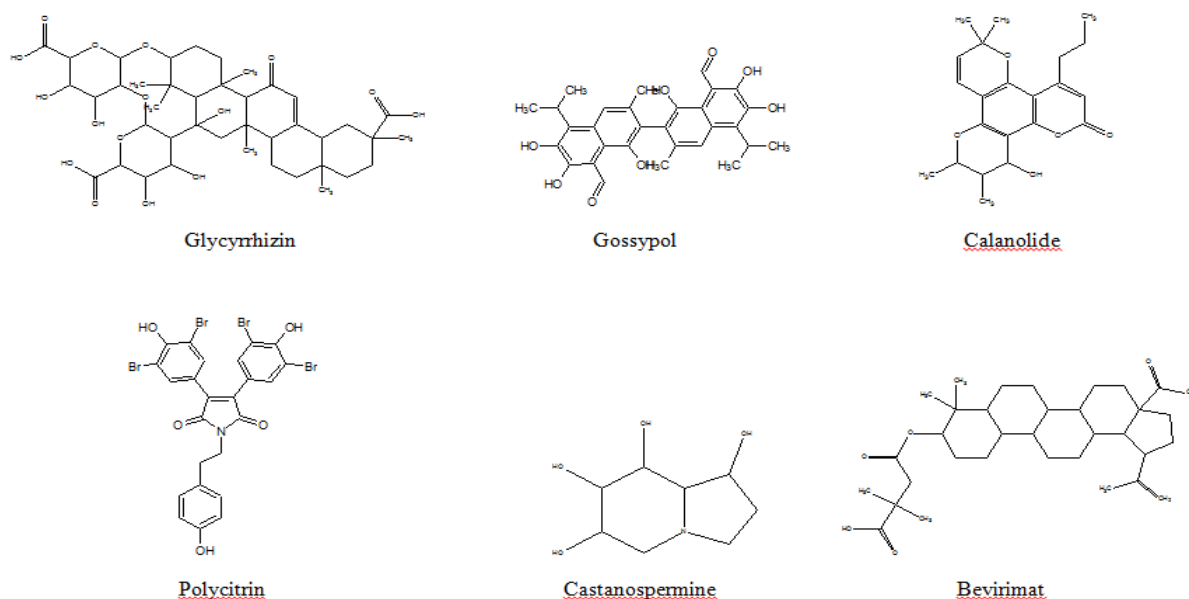
Following the structure elucidation and docking studies, the compound is tested for its *in-vitro* antiviral activity. The effect of a phytochemical on viral replication is analyzed. The assay is performed by culturing susceptible cells and then inoculating the cells with a particular virus. A potent antiviral agent tends to decrease/ eliminate the cytopathic effects caused by the virus [133]. Detection is done either

by direct microscopic evaluation or changes in the levels of structural or functional biomolecules. Moreover, cell-based immunoassays quantitatively identify the antiviral effects of a compound. These screening schemes, however, lack specificity and do not identify the exact mechanism by which the viral replication is inhibited. Alternatively, sub genomic replicon systems or virus-like particles are developed and employed for studying the inhibition of viral replication [134].

Cell culture assays are followed by *in-vitro-in-vivo* correlation studies. They help in identification of the effects of a phytochemical under physiological conditions. Animal models are developed to study the virus infections. The selected animal models and humans usually share similar pathogenesis and clinical presentations on being infected by a particular virus. Chimpanzee, *Pan troglodytes*, possesses over 95% genetic homology with humans and contributed to the discovery of Hepatitis C virus in 1978 [135]. Thereafter, they have been used for the study of hepatitis virus infections. HIV/AIDS shows its infection in humans and *Rhesus macaques*, making it a suitable model for HIV studies [136]. Similarly, rabbits, mice, pigs, monkeys, horses and other animals are used to study the novel therapeutic and prophylactic agents for viral diseases.

### Clinical trials

After proving their efficacy and safety in animal models, the plant-derived antivirals enter the clinical trials. The clinical trials are registered with a competent authority and a set of studies are performed. During various phases of clinical trials, the safety and efficacy of a product are determined. As is the case with currently licensed antivirals, clinical trials of these phytochemicals should be in accordance with the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). On getting successful clinical results, the drug product enters into the pharmaceutical market.



**Figure 4:** Chemical structures of some potent antiviral agents of natural origin.

Currently, recognizing the significance of viral diseases, there are over 9600 registered clinical trials with the U.S. National Institutes of Health that deal with viral diseases, as represented in the information on [clinicaltrials.gov](http://clinicaltrials.gov). These trials dealing with the prophylactic or therapeutic interventions are being conducted throughout the world. Maximum number of clinical trials is related to HIV/AIDS. However, none of them is directly related to the testing of any natural product or its derivative.

## Perspective of Plant-Derived Antivirals

Due to the high resistance rate of various viruses and newly emerging viral diseases, currently approved antivirals have failed to prove their effectiveness. Co-administration of two or more antivirals to increase the therapeutic outcomes is now a common prescribing practice. Today, a number of natural drug molecules have been identified. Safety, efficacy and cost-effectiveness are some of the advantages that plant-derived antivirals have over synthetic drugs. Time effective strategies to isolate lead products from plants are now available. However, drug isolation from natural sources has not gained due attention. As discussed in this review, the ease of bioinformatics studies and faster high throughput screening process can help in attaining appreciable results in drug and target identification. Cell culture techniques, animal models and regularization of clinical trials have helped in decreasing the time delay. The rich history of plant derived chemotherapeutic agents support the need to study natural products as the remedy for viral diseases.

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