

Antiviral Phytochemicals: An Overview

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Abstract

The pandemic of viral diseases during recent years has forced the scientific community to investigate less toxic antiviral phytomolecules instead of using nucleic acid analogues, protease inhibitors or other toxic synthetic molecules as antiviral therapeutics. Plants and many of their secondary metabolites because of the healing properties have been in traditional use throughout the world since ancient times. They provide us diverse bioactive phytochemicals which play synergetic role in maintaining human health. The development of clinical products from phyto-pharmaceuticals is a trending approach to look for ecofriendly therapeutic molecules. More than 50% of drugs used in Western nations are derived from plants or their constituents. Many plants have significant antiviral properties too. Very little information is available about plants of antiviral significance. This article briefly reviews various phytochemicals/bioactive molecules which have been isolated from plants and possess antiviral constituents, their mode of action and potential applications in treating/preventing viral diseases.

Keywords: Viral diseases; Antiviral phytochemicals; Isolation; Mode of action

Introduction

Several infectious viral diseases have been reported till date and newer ones are occurring frequently. Among emerging diseases, most of the diseases involve viruses such as HIV, Influenza, Herpes simplex virus (HSV), Dengue, Chikungunya, Zika, Hepatitis A (HSV), Hepatitis B (HSB), Hepatitis C (HCV), etc. [1-3]. Viral diseases pose great risk to human health as viral infections are tough to control due to mutative nature of the viral genomes [4]. There is constant emergence of new resistant viral strains which demands novel antiviral agents with fewer side effects and cell toxicity [5]. In the past, deadly viruses caused pandemics in the world there by increasing the risk of spreading viral diseases between continents. Very few drugs have been developed till date to effectively treat viral diseases [6]. Majority of the approved antiviral drugs possess adverse drug reactions and have also developed viral resistance in long-term therapy [7]. Plants offer us a variety of therapeutic metabolites which have potential to inhibit viral replication by regulating viral adsorption, binding to cell receptors, inhibition of virus penetration into the host cell and by competing for pathways of activation of intracellular signals [8-10] (Figure 1).

Antiviral molecules of plant origin

Natural medicine is a valuable field of research to explore, extract and establish curative properties. However, a very little percentage of phytochemicals has been systematically investigated for their therapeutic potential [11,12]. Natural products provide an unusual approach for the discovery of antiviral agents with remarkable pharmacological effects [13,14]. At present, approximately 25% of the drugs prescribed are of plants origin [15]. Many anticancer and anti-infective drugs are derived from plant products [16]. Herbal practitioners use traditional plants since ancient times to heal several human and animal diseases especially in Asia [17]. People still rely on traditional plants and their products for their health, living and primary health care in many parts of the world [18]. Approximately 2500 medicinal plant species have been recorded globally [19,20] to treat a myriad of afflictions and diseases. Polyphenols, alkaloids, flavonoids, saponins, quinones, terpenes, proanthocyanidins, lignins, tannins, polysaccharides, steroids, thiosulfonates and coumarins are prominent bioactive phytochemicals, which have been observed to combat viral infections [21-40] (Table 1).

Plants have naturally evolved over the years in diverse climate conditions on earth and have been endowed with rich complex of secondary metabolites/phytochemicals with wide pharmacokinetic spectrum. Very few of the phytochemicals have been purified and studies for their structure and therapeutic properties. Most of the crude plant products have been marketed as pharmaceutical products without certified quality and efficacy. Many traditional medicinal plants and herbs have been reported to have strong antiviral activity against HCV, HBV and H1N1, etc. These phytochemicals must be subjected to animal and human studies to determine their effectiveness in whole-organism systems including reactogenicity and toxicity studies (Figure 2).

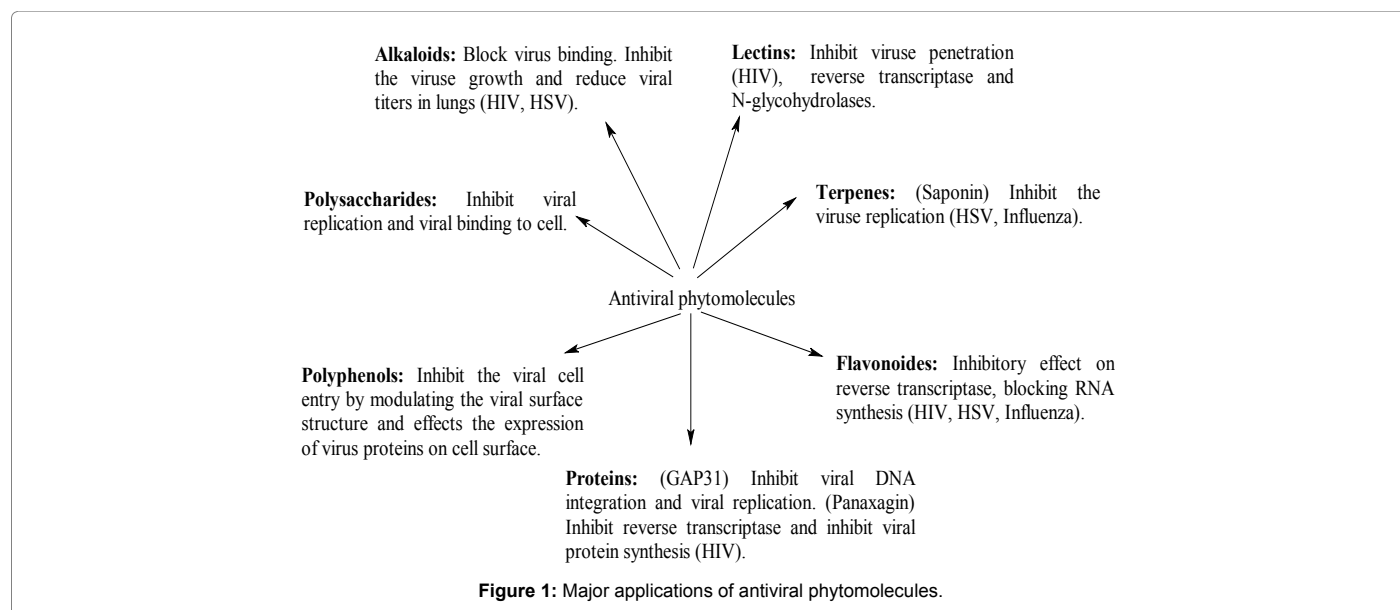
Gathering traditional information from local or indigenous people or using ethnomedicinally important plant(s) to extract bioactive molecules/phytochemicals for curing various diseases are quite challenging approaches. Many factors such as different solvents (polar, nonpolar) employed for the extraction of bioactive constituent(s), choice of plant part/tissue for extraction bioactive constituent(s) often play important roles in extracting the biologically active phytochemicals/natural constituents from plants efficiently. To appraise the antiviral activity of plants systematic approach to isolate and characterize the bioactive molecules/phytochemicals and virus replication inhibition assays in animals or mammalian cell system are indeed needed before such phytomolecules could actually be employed to treat viral infection [41]. Different methods for isolation, purification of bioactive molecules/phytochemicals from the extracts of plant to carry out biological activity such as their antibacterial, antifungal and antiviral properties are requires to be established. A variety of biological assay such as antiviral properties such as cytopathic effect screen, neutralization assays, yield reduction assays and haemagglutination inhibition test have been successfully used to study the. Extraction of bioactive principle is an important first step in the analysis of plants to

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Received May 17, 2017; Accepted June 19, 2017; Published June 27, 2017

Citation: Kapoor R, Sharma B, Kanwar SS (2017) Antiviral Phytochemicals: An Overview. Biochem Physiol 6: 220. doi: [10.4172/2168-9652.1000220](https://doi.org/10.4172/2168-9652.1000220)

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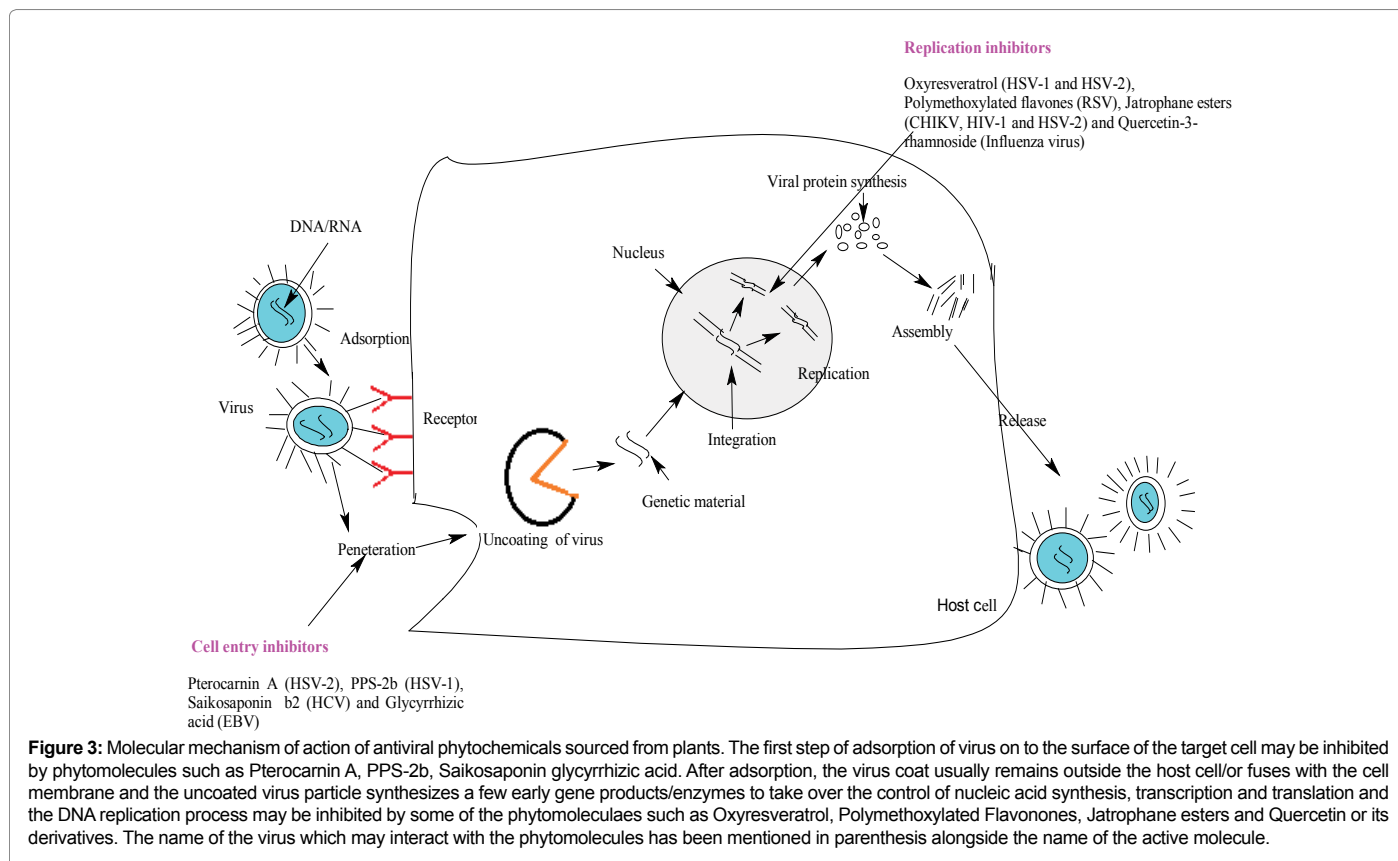
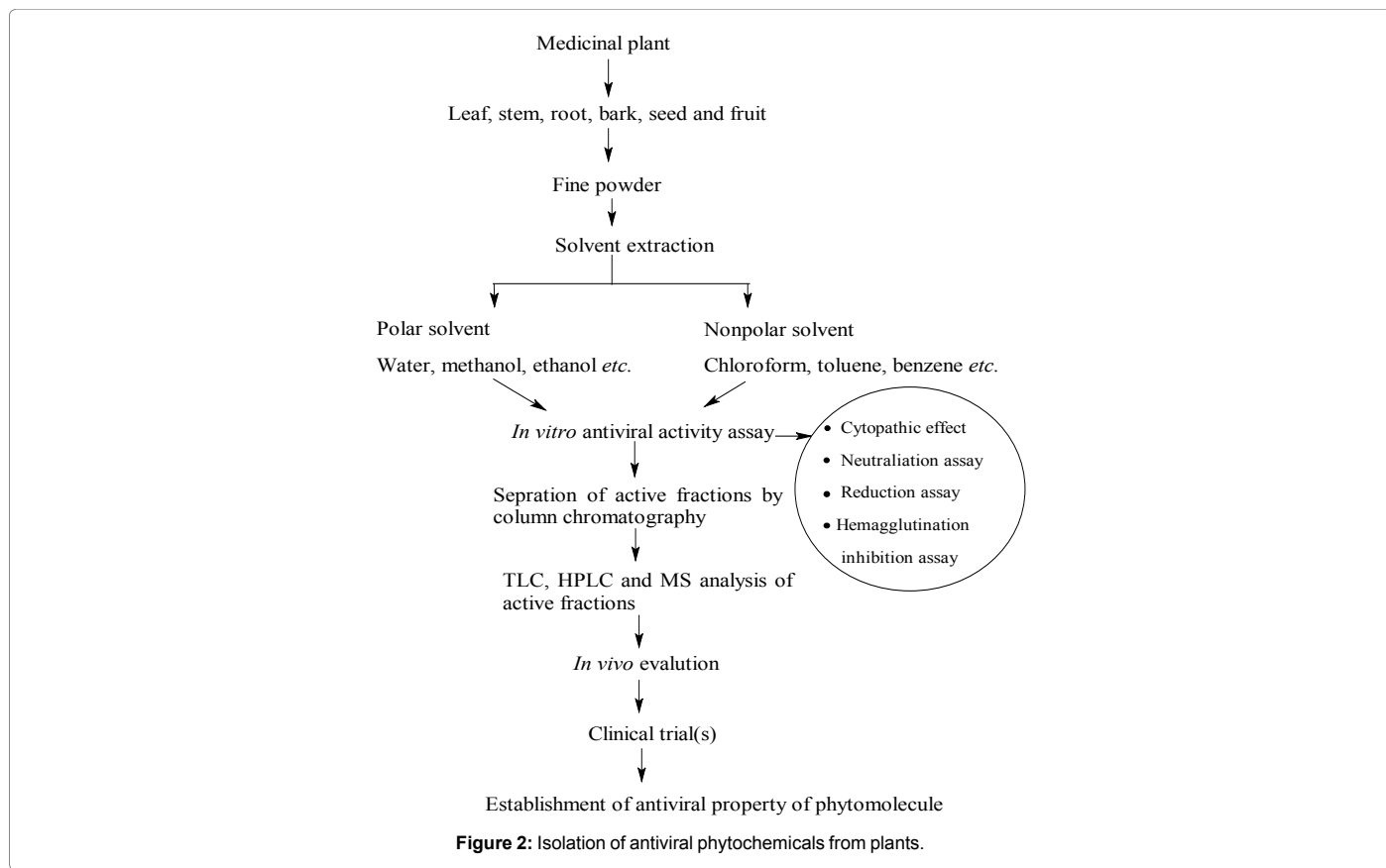
Phytochemicals	Class	Active against virus	Plant (part)	References
Baicalin	Flavonoid	DENV	<i>Scutellaria baicalensis</i> (roots)	[23]
Chalcones	Ketone	Influenza A (H1N1)	<i>Glycyrrhiza inflata</i> (roots)	[24]
Dammarenolic acid	Triterpenoid	Retroviruses	<i>Aglaia</i> sp. (bark)	[25]
Decanoylphorbol-13 acetate	Diterpene	CHIKV	<i>Croton mauritianus</i> (leaves)	[26]
Excoecarianin, Loliolide	Tannins	HSV- 2, HCV	<i>Phyllanthus urinaria</i> (whole plant)	[27,28]
Honokiol	Lignin	DENV-2	Magnolia tree (roots, bark)	[29]
Jubanines	Alkaloids	PEDV	<i>Ziziphus jujuba</i> (roots)	[30]
Limonoids	Lignin	HCV	<i>Swietenia macrophylla</i> (stem)	[31,32]
Oleanane	Triterpenes	PDEV	<i>Camellia japonica</i> (flowers)	[33]
Quercetin	Flavonoid	HCV	<i>Embelia ribes</i> (seeds)	[34]
Saikosaponins	Terpenoid	HCV	<i>Bupleurum kaoi</i> (roots)	[35]
Sennoside A	Glycoside	HIV-1	<i>Rheum palmatum</i> (roots)	[36]
Silvestrol	Benzofuran	Ebola virus	<i>Aglaia foveolata</i> (leaves, bark)	[37]
SJP-L-5	Lignin	HIV-1	<i>Schisandra micrantha</i> (roots)	[38]
Spiroketalenol	Ether	HSV-1 HSV-2	<i>Tanacetum vulgare</i> (rhizome)	[39]
Swerilactones	Lactones	HBV	<i>Swertia mileensis</i> (whole plant)	[40]
Xanthohumol	Chalcone	BVDV	<i>Humulus lupulus</i> (whole plant)	[41]

Table 1: Some antiviral phytochemicals from plants.

extract the desired bioactive molecules/phytochemicals. The traditional practices in isolation of these bioactive molecules/phytochemicals using different separation techniques such as TLC, column chromatography, flash chromatography, HPLC, FTIR, NMR and MS have been extensively exploited to obtain and facilitate the identification of the bioactive molecules/phytochemicals. The ability to identify bioactive molecules/phytochemicals from large chemical libraries accurately and rapidly has been the ultimate goal in developing high throughput screening assays (Figure 2). To firmly establish the antiviral activity and adverse reactions like reagentogenicity or toxicity of the purified phytomolecules, appropriate *in vivo* studies (animal models) and subsequent clinical trials are necessary. A bioactive flavonoid 'Baicalein' isolated from Chinese medicinal plant *Scutellaria baicalensis* Georgi showed antiviral properties using high-speed counter-current chromatography (HSCCC) technique [42-58].

Virus attacks the host cells specifically through adsorption to

receptors, penetrating through cell wall where there is uncoating of virus, the genetic material liberates out and integrates or episomally exists inside the nucleus with genetic material of host cell, interfere with their transcription, replication and translation process, respectively, assembles there and releases out during host cell lysis. Various steps of virus interaction with the host cell till the release of the virions from the host cells have been depicted schematically (Figure 3). Plant produces a diverse array of more than 100,000 secondary metabolites and can be classified, on the basis of composition and the pathway through which they are synthesized [59]. Enormously improved methods of genetically engineering the structural complexity of natural products from plants have been successfully mastered now [60-62]. Herpes simplex virus 1 and 2 (HSV-1 and HSV-2) which have double-stranded linear DNA genome and icosahedral protein [63] show symptoms of infection including blisters on the skin, lips, nose or genitals [64]. HSV enter into the host cell through interaction with glycoproteins present



on the surface of the virus envelope and trans-membrane receptors of the cell surface of host cell [64]. Plants preferred as impending sources of novel bioactive molecules for development of new antiviral drugs [65] often on the basis of their ethnomedicinal use. Compounds such as Spiroketalenol ether derivatives isolated from rhizome extract of *Tanacetum vulgare*, which function as cell entry inhibitors had been reported to block virus entry and also arrest the synthesis of HSV-1 gC and HSV-2 gG glycoproteins. Samarangenin B cut-off from roots of *Limonium sinense* exhibited inhibition of HSV-1 α gene expression. *Artocarpus lakoocha* plant with Oxyresveratrol compound was found to inhibit early and late phase of viral replication of HSV-1 and HSV-2, respectively (Figure 3). Pterocarnin A compound inaccessible from *Pterocarya stenoptera* inhibited HSV-2 from binding and penetration to the host cells. Hepatitis B (HBV), C (HCV) causes hepatic infectious diseases that affects the liver, out of which around 143 million people worldwide are estimated to be infected by Hepatitis C virus [64,66]. The primary route of their transmission through blood transfusions and unsafe medical procedures [67]. Saikosaponin b2 compound from *Bupleurum koi* roots has been reported to inhibit early HCV entry. Chalepin and Pseudane IX reported from *Ruta angustifolia* (Leaves) inhibited HCV at the post-entry step, RNA replication and viral protein synthesis. LPRP-97543 compound isolated from root part of *Liriope platyphylla* demonstrated to inhibit viral gene expression, replication and viral promoter activity by affecting the binding activity of NF- κ B to HBV surface gene CS1 element. The HIV virion enters macrophages and CD4⁺ T cells by the adsorption of glycoproteins on their surface to receptors on the target cell(s) followed by fusion of the viral envelope with the cell membrane leading to the release of the HIV capsid into the cell. Entry to the cell begins through interaction of the trimeric envelope complex (gp160 spike) to both CD4 and a chemokine receptor (generally either CCR5 or CXCR4) present on the host cell surface. The gp160 spike contains binding domains for both CD4 and chemokine receptors [68,69]. Considerable advancement has been made on the use of natural products of plant origin as anti-HIV agents which could assist in the prevention of the disease. Jatrophane esters interfered with viral entry by inducing internalization and down regulation of HIV receptors (CD4, CXCR4 and CCR5). RSV (Respiratory syncytial virus) has a linear negative-sense RNA genome with F and G lipoproteins which are the only two that target the cell membrane, and are highly conserved among RSV isolates [70]. Tangeretin and Nobiletin (Polymethoxylated flavones) isolated from pericarps of *Citrus reticulata* (Pericarps) affected the intracellular replication of RSV. Tangeretin down regulated the expression of RSV phosphoprotein (P protein). The reports through inhibition of virus-cell fusion in the early stage, and the inhibition of cell-cell fusion at the end of replication cycle. Dicafeoylquinic acids from *Schefflera heptaphylla* inhibited the replication of RSV. An inhibitory effect of Manassantin B isolated from the root part of *Saururus chinensis* towards Epstein-Barr virus (EBV) lytic replication has been reported. The first step of entry of EBV into the host cell is inhibited by the Glycirrhizic acid. EBV infects B cells of the immune system and epithelial cells. Once EBV's initial lytic infection is brought under control, EBV latency persists in the individual's B cells for the rest of the individual's life [71]. Some of the other examples of antiviral compounds with their mode of action have been summarized in Table 2.

Challenges and future avenues

Plants possessing minute amount of invaluable natural compounds are great source for pharmaceuticals invention. Modern drug discovery which has its roots in traditional medicine provides avenues to newer

phytomolecules-based therapies [72]. Now a days major pharmaceutical industry are reducing their research focus and are indulging towards profit-making venture by extracting and selling phyto-constituents [73]. Various challenges appear during the drug discovery or identification of natural compound from plants or their extracts. The isolation of active biological compound(s) starts primarily with their isolation, purification and characterization involving multistep procedures with low yields. In addition, reduction of biological activity of compound in each step during fractionation of extracts leads to the loss of synergistic effects between analogue constituents [74]. In modern time, many efforts have been focused on the production of bioactive natural compounds/products from plants through metabolically engineered process using versatile *E. coli* to sustain the availability of potential drug candidates; however, it has one possible drawback that is non-functionality of many key plant enzymes [75]. Metabolic engineering of plant derived natural products/compounds no doubt has high potential but with a little success rate. A gene encoded Hyoscyamin 6 β -hydroxylase isolated from *Hyoscyamus niger* and incorporated into *Atropa belladonna* resulted in the accumulation of high value of end-product Scopolamine but this compound was however, overexpressed in *Hyoscyamus muticus* hairy roots. So, along with large amount of Scopolamine, high level of Hyoscyamine also accumulated in the hairy roots [76,77]. Alternative biotechnology tools to enhance the production of natural products/compounds using plant cell cultures are indeed needed. Such examples include skinonin production from *Lithospermum erythrorhizon* and berberine production by *Copis japonica* cell culture [78]. Another big challenge in natural compounds/drug development is that it hardly focuses on single site(s) of drug action and ignores the multiple pharmacological actions of many drugs and molecules. So, with the development of science of network pharmacology, which involves interpretation of mechanism of drug action, shifts one target or one drug to target a disease, considers multi-component plant mixtures (which contains 10-20 plants in the formula) has been expected as a significant alternative model for the drug discovery [79,80]. A number of electrophilic [81], nucleophilic [82] and scavengers [83] are commercially available now to avoid repeated purifications of the crude compound prior to final HPLC purification. Today, nanomedicine gained tremendous attention in pharmaceutical science [84]. Phytonanotechnology provides ecofriendly, simple, rapid, stable and cost effective new avenues for synthesis of nanoparticles. It has advantages including biocompatibility and has medical applicability [85]. As plant constituents, they act as capping and stabilizing agents [86]. Many natural compounds such as Quercetin (phytochemical) with low aqueous solubility and bioavailability is quickly metabolized in the body, which unfortunately reduces its efficacy in treating diseases [87]. The encapsulation of Quercetin into biodegradable and biocompatible nanoparticles might help in delaying its metabolism and maintaining adequate free Quercetin level in blood. But major hurdle is potential toxicity of nanoparticles. So, incorporation of targeted ligand on the surface of nanoparticles can increase delivery of encapsulated phytochemicals [88]. Data exist about and bioavailability of nanocarriers, and tissue specific pharmacokinetics are limited [89]. The precise mechanism and the components responsible for plant-mediated synthetic nanoparticles remain to be elucidated. The use of *in silico* information systems further provide avenues that might involve databases to relate constituents to their network profile in order to integrate networks which would decrease the exploitation of plants. Such strategies may also permit the development of new drug discovery from plants which have ubiquitous existence on all corners of earth.

Plant (part)	Phytochemicals	Target	Mode of action	References
<i>Artocarpus lakoocha</i> (Heartwood)	Oxyresveratrol	HSV-1 HSV-2	Inhibitory activity at the early and late phase of viral replication of HSV-1 and HSV-2. Inhibition of late protein synthesis	[44]
<i>Bupleurum kaoi</i> (Root)	Saikosaponin b2 (Terpenoid)	HCV	Inhibiting early HCV entry, including neutralization of virus particles, preventing viral attachment	[45]
<i>Citrus reticulata</i> (Pericarps)	Tangeretin and nobilletin (Polymethoxylated flavones)	RSV	Affected the intracellular replication of RSV. Tangeretin down regulated the expression of RSV phosphoprotein (P protein)	[46]
<i>Euphorbia amygdaloides</i> spp. and <i>semiperfoliata</i> (Whole plant)	*Compound 3 (Jatrophone esters)	CHIKV HIV-1 HIV -2	Selective inhibitor of the replication and inducing down regulation of HIV receptors (CD4, CXCR4 and CCR5)	[47]
<i>Glycyrrhiza radix</i> (Roots)	Glycyrrhizic acid (GL)	EBV	GL interferes with an early step of EBV replication cycle.	[48]
<i>Houttuynia cordata</i> (Aerial parts)	Quercetin 3rhamnoside (Q3R)	Anti-influenza A/WS/33 virus	Inhibit replication in the initial stage of virus infection by indirect interaction with virus particles	[49]
<i>Limonium sinense</i> (Root)	Samarangenin B	HSV-1	Inhibit HSV-1 α gene expression, including expression of the ICP0 and ICP4 genes, by blocking β transcripts such as DNA polymerase mRNA, and by arresting HSV-1 DNA synthesis and structural protein expression in Vero cells.	[50]
<i>Liriope platyphylla</i> (Root)	LPRP-Et-97543	HBV	Inhibit viral gene expression and replication. Inhibit viral promoter activity.	[51]
<i>Melia azedarach</i> L. (Leaves)	Tetranortriterpenoid 1-cinnamoyl-3, 11-dihydroxymeliacarpin (CDM)	VSV HSV-1	CDM blocks VSV entry and the intracellular transport of VSV-G protein and confined it only to the Golgi apparatus and also modulates the NF- κ B signaling pathway by slowing down its activation in HSV-1-infected conjunctival cells which leads to the accumulation of p65 NF- κ B subunit in the cytoplasm of uninfected treated Vero cells	[52]
<i>Prunella vulgaris</i> (Fruit spikes)	Lignin-carbohydrate complex (PPS-2b)	HSV-1 HSV-2	Block HSV-1 binding and inhibiting penetration into Vero cells	[53]
<i>Pterocarya stenoptera</i> (Bark)	Pterocarin A	HSV-2	Inhibit HSV-2 from attaching and penetrating into cells. It also actively suppressed HSV-2 multiplication in Vero cells even when added 12 h after infection	[54]
<i>Ruta angustifolia</i> (Leaves)	Chalepin and pseudane IX	HCV	Inhibited HCV at the post-entry step and decreased the levels of HCV RNA replication and viral protein synthesis	[55]
<i>Saururus chinensis</i> (Root)	Manassantin B (Dineolignans)	EBV	Inhibitory effects toward EBV lytic replication	[56]
<i>Schefflera heptaphylla</i> (Leaf stalks)	Dicaffeoylquinic acids	RSV	Inhibition of virus-cell fusion in the early stage and the inhibition of cell-cell fusion at the end of the RSV replication cycle.	[57]
<i>Scoparia dulcis</i> L. (Whole plant)	Scopadulcic acid B	HSV-1	Inhibit the viral replication.	[58]
<i>Scutellaria baicalensis</i> (Root)	5,7,4' trihydroxy-8-methoxyflavone (F36)	A/PR8 (mouse-adapted influenza virus)	Reduces single-cycle replication of A/PR8 from 4 h to 12 h after incubation by dose-dependent manner but did not inhibit the adsorption of A/PR8 to MDCK cells.	[59]
<i>Tanacetum vulgare</i> (Rhizome)	Spiroketalenol ether derivative	HSV-1 HSV-2	Block virus entry and arrested the synthesis of HSV-1 gC and HSV-2 gG glycoproteins. The viral glycoprotein reduction was due to the inhibition of Gc and gG coding mRNA synthesis.	[60]

* (2R,3R,4S,5R,7S,8R,13R,15R)-3,5,7,15-Tetraacetoxy-2-hydroxy-8-tigloyloxy-9,14-dioxojatropha-6(17),11E-diene

Table 2: Mode of action of specific phytochemicals with antiviral activity.

Conclusion

Viruses are obligate intracellular parasites that have evolved genetic variation, transmission, and replication, and have the ability to persist within the host for short or long period of time. By understanding the molecular mechanisms of viral invasion and replication in the host cell(s), researchers and scientists will get help to design effective and inexpensive antiviral drugs and target them to their specific site. Most of the known clinical essential antiviral drugs can specifically target a single viral enzyme (proteolytic viral enzymes, viral polymerase, integrase and reverse transcriptase) during different stages of viral replication. For new drug development, the replication inhibitors are mid of the top priorities as many virus diseases are yet non-curable. Acyclo-guanosine, popularly known as acyclovir is a nucleoside analogue that drastically slows down the Herpes virus infection [90,91]. Carbohydrate-binding agents might also act as inhibitors binds by masking the glycans present on the viral envelope. This step subsequently blocks virus entry and cause some deletions in the envelope glycan shield triggering the immune system to act against epitopes of the viral envelope. Glycans have been reported to be present on the HIV and HCV and often play important role in enabling an efficient entry of the

virus into permissive target cells [92]. For creative revelation of modern drug development, introduction of high-throughput technologies and traditional medicines together could play a crucial role to identify the potential plant derived compounds. They act against viral diseases but still have long way to cover for discovery, isolation and mechanistic studies before final utilization in the clinic. Considering vast range and complexity of bioactive molecules/phytochemicals present in plants, a strong unrelenting and persistent approach is needed to explore unknown phyto-constituents with potent antiviral activities. This obviously requires more investments, systematic exploration to prove the desired activity of the phyto-constituent in an *in vivo* and/or *in vitro* model in a reasonable period of time.

Conflict of Interest

The authors have no conflict regarding publication of this paper among themselves or with the parent institute.

Acknowledgement

The financial supports in the form of a Senior Research Fellowship [F. No. 17-4-/08(SA-1)] to Ms. Rita Kapoor from University Grants Commission, New Delhi, and DST Inspire-Senior Research Fellowship to Mr. Bhupender Sharma (IF 130378), Department of Science and Technology, Ministry of Science and Technology, Govt.

of India are gratefully acknowledged. The authors are thankful to the Department of Biotechnology, Himachal Pradesh University, Shimla for providing the basic infrastructure and other facilities to the authors.

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