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Plant as a Source of Natural Antiviral Agents

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ABSTRACT

Viruses are one of the main hazards for both humans and animals. They enter in the living body and redirect body's metabolism to produce large copies of their genome and proteins. Diseases caused by these viruses are difficult to tackle with the help of currently available antiviral drugs. So the aim of this study was to explore the plants with reported antiviral activity, to get understanding for better control of these viruses. Herpes virus, Human Immunodeficiency Virus (HIV), influenza and hepatitis virus were at top among all studied viruses. Prominent modes of action against these viruses were inhibition of viral entry and its replication in host cell. Against RNA viruses plants mainly targeted their Reverse Transcriptase (RT) enzyme (like HIV) or protease (mostly found against hepatitis C virus). A range of active compounds have been identified which could be the potential antiviral agents for future drug development. Some plants like *Allium sativum, Daucus maritimus, Helichrysum aureonitens, Pterocaulon sphacelatum* and *Quillaja saponaria* emerged to have broad spectrum antiviral activity. Detail study of their phytochemicals and mode of action against these viruses could be help full for more effective control of hazardous viruses.

Key words: Antiviral, herpes virus, influenza, hepatitis, *Allium salivum, Dauucus maritimus*

INTRODUCTION

Virus "a piece of bad news wrapped in a protein coat" has been defined by Peter Medawar (Oldstone, 1993). It appears as the perfect definition after considering the list of top ten causes of death in low, middle and high income countries. Lower respiratory infections, diarrhoeal diseases and HIV/AIDS are the common death causes among low and middle income countries (WHO, 2011b). All of these three health disorders are directly or indirectly caused by viruses. Except lower respiratory infections none of the above mentioned factors are prevalent among high income countries. It clearly indicates that how severely these viral diseases are affecting the people health in low and middle income/developing countries.

Our planet contains nearly 10^{31} viruses and their ubiquity also invaded the marine environment, where in every 200 liter of water nearly 5000 viral genotypes are present (Breitbart and Rohwer, 2005; Suttle, 2005). Moreover viruses are moving between the environments and they are present almost everywhere e.g. deep sea, polar ice, alkaline, hot and saline waters and more than 2000 m deep in terrestrial environment. There are almost 20 families of viruses that actually

infect humans (Harvey *et al*., 2006) and some of them also cause diseases in animals (Mahzounieh *et al*., 2006). The diseases they cause in human include chickenpox, influenza, skin rash, hepatitis, bronchiolitis, acquired immunodeficiency syndrome, liver infection and many others. Virus particles enter in the living system and if they overwhelm the body's immune system then it is almost impossible to stop their spread in body. They direct the host metabolic pathway for the sake of their repeated replication; this makes their treatment difficult. But fortunately, it is now well known that viruses are unique in their mode of replication, which can be easily targeted (Selisko *et al*., 2007; Syed *et al*., 2010). They use specific enzymes to infect and replicate, whose inhibition could arrest their metabolism. For example, the proteolytic enzyme promotes virus maturation by separating the viral polyprotein precursor, whose inhibition will stop its maturation (Wapling *et al*., 2007). So the virus metabolism or replication can be stopped by specific inhibitors.

Today many synthetic antiviral drugs e.g. moroxydine, ganciclovir, valganciclovir, valaciclovir etc. are used, which inhibit the virus replication via different mechanisms (Biron, 2006; Czeizel *et al*., 2006). But difficulty in drug treatment arises due to their low efficiencies, cytotoxicity and development of viral resistance against them. Another antiviral treatment; vaccination, can be applied but they are still under development, as they often provide incomplete protection against virus and their reliability needs more research (Pervez, 2000b; Subbarao and Joseph, 2007). Thus the treatment through antiviral synthetic drugs and vaccines need more scientific investigation. Nature provides another, more reliable source of antiviral agents; viz. plants phytochemicals; almost 40% of currently available drugs are direct or indirect derivatives of plants. A number of ethnobotanical studies aiming to identify potential therapeutic plants for more effective control of health issues demonstrate the importance of plant species in health care system (Shinwari and Khan, 2000; Heneidy and Bidak, 2004; Appidi *et al*., 2008; Ky *et al*., 2009; Ansari and Inamdar, 2010; Makambila-Koubemba *et al*., 2011). Plants are rich source of phytochemicals like alkaloids, anthocyanins, carotenoids, flavonoids, isoflavones, lignans, monoterpenes, organosulfides, phenolic acids, saponins and many more (Al-Yahya, 2005; Hassan *et al*., 2006; Anitha and Ranjitha Kumari, 2006; Akomo *et al*., 2009; Rahman *et al*., 2009; Amabeoku and Kinyua, 2010; Ndjonka *et al*., 2010). These phytochemicals have been proved to be responsible for their antimicrobial (Sampathkumar *et al*., 2008; Krishnan *et al*., 2010), antihypertensive (Amalia *et al*., 2008), anti-diabetic (Qureshi *et al*., 2009), antioxidant (Momtaz and Abdollahi, 2010), hepatoprotective (Mahalakshmi *et al*., 2010; Ansari *et al*., 2011), cardioprotective (Ojha *et al*., 2008; Fard *et al*., 2008) and other therapeutic activities. Thus this study is aimed to analyze the previously reported antiviral plants and identify potential mode of action and compounds that are responsible for their antiviral activity. Better understanding of natural antiviral agent's mode of action and identification of responsible compounds will be helpful to provide a new insight for the development of new antiviral drugs for more effective viral control.

Basic viral structure and its mode of action: Viruses are organic objects, which are metabolically inactive outside the host body but become active on their entry into the host cell (Dupre and O'Malley, 2009). These are mainly composed of proteins and nucleic acid; the proteins majorly contribute to their specific shape and form a coat called capsid (Andersson, 2010). Thus viruses are of various shapes e.g. simple, helical, icosahedral or complex and some viruses are surrounded by a lipid bilayer, derived from host membrane, which is called as envelope (Geng *et al*., 2007; Raja *et al*., 2003). Some capsid proteins are also associated with virus nucleic acid and called as nucleocapsid, while nucleic acid proteins, are the direct part of the nucleic acid, known as nucleoproteins. The nucleic acid of virus is either made up of DNA or RNA, is the basic

source of information required for the regulation of its metabolic activities. Theses DNA and RNA can be further divided into two types depending upon the number of strands i.e. single stranded or double stranded DNA/RNA (Firth *et al.*, 2010; Pichlmair *et al.*, 2006). The single stranded RNA viruses can be further distinguished depending upon the sense of strand as some RNA viruses have positive-sense RNA (+VE ssRNA) and some viruses have negative-sense RNA (-VE ssRNA) (Gorbalenya *et al.*, 2006). The shape of nucleic acid (DNA/RNA) is also an important source of differentiation, because all the viruses did not contain same-shape nucleic acid (Gao and Hu, 2007). It can be either in circular, linear or coiled form.

Virus (either DNA or RNA) life cycle can be divided into some predefined stages; adhesion, adsorption (entry), replication, maturation and release, which involve some enzymes and proteins. For example, the process of virus entry is carried out by cell surface proteins; HCV entry involves claudin-1, occludin, tetraspanin as main receptors proteins (Burlone and Budkowska, 2009). Its entry is also mediated by some other lipoproteins and an enzyme; lipoprotein lipase. On the other hand the influenza virus infection is mediated by protease enzyme, which activates the viral surface protein haemagglutinin (Zambon, 2001). The protease enzyme is also important in the expression of viral proteins; it splits the proteins into groups depending upon their structural and nonstructural functions (Appel *et al.*, 2006). But the RNA viruses need two additional enzymes for their survival; reverse transcriptase and integrase, former transcribes the viral RNA into DNA at the time of replication (Briones *et al.*, 2010; Sluis-Cremer and Tachedjian, 2008). While the second enzyme is used to incorporate the viral DNA into host genome, furthermore it is also needed for proper uncoating of virus core proteins. Thus virus is needy of enzymatic and non-enzymatic proteins, which can be targeted to stop their replication and infection.

Antiviral plants: In this review a total of 105 plant species have been identified that were reported for their potential antiviral activities (Fig. 1). Maximum number of plants were reported for their activity against herpes viruses, indicating that herpes viruses were the highly studied viruses with respect to antiviral plants. After herpes virus, HIV, influenza and hepatitis were among other viruses that were addressed in most of the studies in order to discover the plant with antiviral properties. In next sections a brief description with respect to the available antiviral plants against some important viruses has been provided.

Plants with antiviral activity against herpes virus: An enveloped double stranded DNA virus with linear genome; it belongs to the family Herpesviridae, which is recently reclassified to separate the mammal's virus from other non-mammalian viruses (Davison *et al.*, 2009). It is also

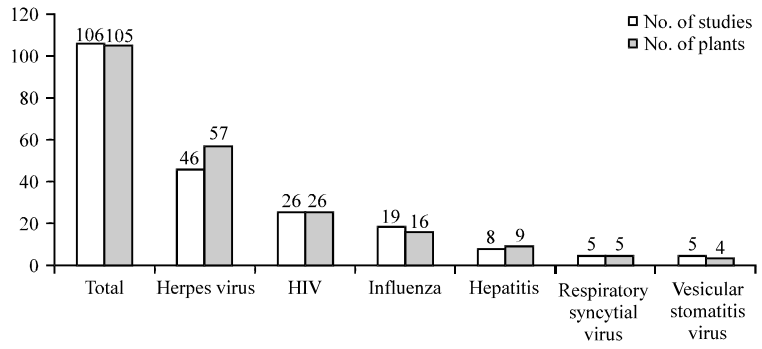

Fig. 1: Mostly studied viruses found during current review

known as human herpesvirus and Varicella-zoster virus. It is highly infectious and prevalent disease especially in developing countries with almost 50 % prevalence in adults, disease symptoms are often unnoticeable (WHO, 2001). It is a sexually transmitted disease and highly prevalent in females as they often get infected with it before the age of fertility (Ziyaeyan *et al*., 2007). It also causes febrile rash and graft-versus-host disease in humans, who got hematopoietic stem cell transplantation (Pichereau *et al*., 2011). It is also the casual agent of genital herpes disease; vaccines against it are currently under developmental stages (Soleimanjahi *et al*., 2007).

Total 57 plants were identified with antiviral activity against herpes virus (Table 1). Binns *et al*. (2002) reported that h-hexane extracts of *Echinacea purpurea* showed in vitro antiviral activity against herpes virus in another study polysaccharide and cichoric acid were found among the active phytochemicals of various plant parts extracts (Vimalanathan *et al*., 2005). Another compound of *Phyllanthus urinaria* from its acetone extract (hippomanin A) showed its activity against herpes simplex virus type 2 (Yang *et al*., 2007); in another study Cheng *et al*. (2011) identifies a compound (excoecarianin) from this herb with same activity. Anthraquinones has been identified as potential compound responsible for antiviral properties of *Rhamnus frangula*, *Rhamnus purshianus* and *Rheum officinale* (Sydiskia *et al*., 1991). This organic compound has also been reported in many studies to be responsible for positive health attributes of many medicinal plants (Kumar *et al*., 2007; Hussein *et al*., 2010; Karou *et al*., 2011; Mbaya and Ibrahim, 2011; Sonibare *et al*., 2011). Kurokawa *et al*. (1999) reported the antiviral activity of *Rhus javanica* against herpes virus and found moronic acid as potential active agent from its herbal extract. Plants mainly showed activities like restriction of entry host into cell (Weber *et al*., 1992; Zandi *et al*., 2007), reduced viral replication (Duarte *et al*., 2001; Chiang *et al*., 2003; Alche *et al*., 2003) and partial destruction of viral envelope (Sydiskia *et al*., 1991). Active compound present in most of the plants were anthraquinones, terpenes, quercetin, lectins and phenolics (Amoros *et al*., 1987; Sydiskia *et al*., 1991; Chiang *et al*., 2003; Ooi *et al*., 2004; Kan *et al*., 2009). *Allium sativum* is a medicinal plant with a lot of health benefits (Ishtiaq *et al*., 2007; Sukandar *et al*., 2010; Abdelaziz and Kandeel, 2011; Weber *et al*., 1992) found its extract effective against this virus. The extract of *Aloe vera* another important medicinal plant (Alqasoumi *et al*., 2008; Semalty *et al*., 2010) has been reported to be effective against this virus by inhibiting the viral entry and replication into the host cell(Zandi *et al*., 2007).

Plants with antiviral activity against HIV: HIV is highly infectious enveloped virus of family Retroviridae; it has liner ssRNA positive sense genome and cause high morbidity. During year 2004, HIV infection was one of the leading factors responsible for almost 2.65 million deaths in low income countries (Patton *et al*., 2009). It is also prevalent in high income countries, as in United States almost 55400 new HIV cases were observed each year from 2003-06 (Hall *et al*., 2008). It increases the chances of bacteria and other viruses infections, which poorly effects the health; transmission of HIV from mother to child could lead to the death (Corbett *et al*., 2003; Ahasan *et al*., 2004; Ilboudo *et al*., 2007; Abongo *et al*., 2008). Its chemo-treatments are scarce, because of their potential side effects on human body, non-significant efficiencies and increased divergence in HIV genome (Fokunang *et al*., 2006; Jaffary *et al*., 2007; Kagone *et al*., 2011). But a nutrient rich food can reduce the HIV caused decreased weight and help in improving the patient's health (Oguntibeju *et al*., 2007).

In present study 26 plant species were found effective against HIV. Terpenoids, lectins, alkaloids and flavonoids were common among the active compound of these plants (Table 2). Roja and Heble (1995) reported the positive activity of an alkaloid (castanospermine) isolated from seeds

Table 1: Detail description of studies focusing on antiviral plant activities against herpes virus

Plant name	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Achyrocline flaccida	n/a	Aqueous extracts	n/a	*In vitro*, inhibits viral replication	Garcia *et al.* (1995)
Allium sativum	Ajoene, Allicin, Allyl methyl thiosulfinate and Methyl allyl thiosulfinate	Oil-macerates and fresh garlic extract	HeLa /Vero cells	Interfere with virus adsorption and penetration	Weber *et al.* (1992)
Aloe barbadensis	Anthraquinones: Aloe emodin	Hot glycerin extracts	Vero cells	Partially destroy the viral envelope and inactivate them	Sydiskia *et al.* (1991)
Aloe vera	n/a	Leaves' crude hot glycerin extract	Vero cells	Inhibits virus attachment, entry and replication	Zandi *et al.* (2007)
Anagallis arvensis	Triterpene saponin	n/a	n/a	*In vitro*; inhibits the virus replication	Amoros *et al.* (1987)
Andrographis paniculata	Diterpenes: Andrographolide, Neoandrographolide and 14-deoxy-11,12-didehydroandrographolide	n/a	n/a	n/a	Wiart *et al.* (2005)
Bergenia ciliata	n/a	Methanolic extracts	Vero cells	n/a	Rajbhandari *et al.* (2009)
Bostrychia montagnei	Sulfated polysaccharides	Cold and Hot water extracts	Vero cell	Inhibits the virus replication	Duarte *et al.* (2001)
Caesalpinia pulcherrima	Quercetin derivatives	Aqueous extracts of fruit, stem, leaf, fruit and seed	Human skin basal cell carcinoma cell line (BCC-1/KMC)	Inhibits the virus replication at early stages of cycle	Chiang *et al.* (2003)
Canavalia ensiformis	Lectins	n/a	n/a	*In vitro*; inhibits virus penetration	Marchetti *et al.* (1996)
Cassia angustifolia	Anthraquinones	Hot glycerin extracts	Vero cells, WI-38 cells	Partially destroy the viral envelope and inactivate them	Sydiskia *et al.* (1991)
Cedrela tubiflora	Acidic polysaccharides	Leaves fraction extracts	n/a	Inhibits virus replication	Craig *et al.* (2001)
Cicer arietinum	Phenolic compounds	Seed, fruit skin and aerial parts	Madin-darby Bovine Kidney/Vero cells	n/a	Kan *et al.* (2009)
Clerodendrum Inerme	n/a	Methanol extracts	n/a	Reduce the viral cytopathic effect	Vimalanathan *et al.* (2009)
Cocos nucifera	Catechin, epicatechin and B-type procyanidins	Husk fiber' water extract	n/a	n/a	Esquenazi *et al.* (2002)
Conyza canadensis	n/a	Ethyl acetate, chloroform, butanol and methanol extracts of the aerial parts	Human diploid embryonic lung fibroblasts (MRC-5)	n/a	Edziri *et al.* (2011)
Dianthus caryophyllus	n/a	Seed crude extracts	Vero and HepG2 cells	n/a	Barakat *et al.* (2010)

Table 1: Continued

Plant name	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Echinacea purpurea	alkenes and amides	Root's n-hexane extracts	*In vitro*	n/a	Binns *et al.* (2002)
Echinacea purpurea	Polysaccharide, Cichoric acid and others	Stems, leaves and flowers water, ethyl acetate, ethanolic and other fractions	Vero cells	n/a	Vimalanathan *et al.* (2005)
Geum japonicum	n/a	Hot water extract	Immunosuppressed mice; it suppressed the activity of reverse transcriptase enzyme	n/a	Kageyama *et al.* (1996)
Glyptopetalum sclerocarpum	Sesquiterpene: Sclerocarpic acid	Sesquiterpene extraction	n/a	n/a	Sotanaphun *et al.* (1999)
Hamamelis virginiana	Oligomeric to polymeric proanthocyanidins	Ultrafiltered crude hydroalcoholic extract	n/a	n/a	Erdelmeier *et al.* (1996)
Hancornia specios	n/a	Ethanolic extract	n/a	n/a	Brandao *et al.* (2011)
Helichrysum aureonitens	Galangin	Shoots extracts	n/a	n/a	Meyer *et al.* (1997)
Himatanthus phagedaenica	n/a	Ethanolic extract	n/a	n/a	Brandao *et al.* (2011)
Hyssopus officinalis	n/a	Leaves methanolic extracts	Mice and Vero E6 cells; reduce the virus cell number via different mechanism than commercially used drug, acyclovir	n/a	Behbahani (2009)
Maclura cochinchinensis	Morin	Ethyl acetate and methanol extracts	*In vitro*	n/a	Bunyapraphatsara *et al.* (2000)
Melia azedarach	Meliacarpin	Ethyl acetate extract of leaves	Vero cells	Inhibits the virus replication	Alche *et al.* (2003)
Melissa officinalis	n/a	Volatile oils	HEp-2 cells	Inhibits virus replicaiton	Allahverdiyev *et al.* (2004)
Momordica charantia	n/a	n/a	Vero cells	n/a	Praseno and Rintiswati (1997)
Myrica rubra	Tanin (prodelphinidin B-2 3,3'-di- O-gallate)	Bark	Vero cell	Inhibits the viral attachement with cell	Cheng *et al.* (2003)
Ocimum americanum	n/a	Dichloromethane extract	Green monkey kidney cells	n/a	Yucharoen *et al.* (2011)
Ocimum basilicum	n/a	Dichloromethane extract	Green monkey kidney cells	n/a	Yucharoen *et al.* (2011)

Table 1: Continued

Plant name	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Ocimum sanctum	n/a	Dichloromethane and methanol extract	Green monkey kidney cells	n/a	Yucharoen *et al.* (2011)
Ouratea castaneafolia	n/a	Ethanolic extract	n/a	n/a	Brandao *et al.* (2011)
Ouratea semisrrata	n/a	Ethanolic extract	n/a	n/a	Brandao *et al.* (2011)
Ouratea spectabilis	n/a	Ethanolic extract	n/a	n/a	Brandao *et al.* (2011)
Pandanus amaryllifolius	lectin (pandanin)	Saline extract of the leaves	n/a	n/a	Ooi *et al.* (2004)
Phyllanthus orbicularis	n/a	Aqueous extract of leaves and stems	n/a	Inhibition of viral entry	Del Barrio and Parra (2000)
Phyllanthus urinaria	Excoecarianin	Acetone extract	n/a	n/a	Cheng *et al.* (2011)
Phyllanthus urinaria	Hippomanin A	Acetone extract	n/a	n/a	Yang *et al.* (2007)
Podophyllum peltatum	Podophyllotoxin	Aqueous extract	n/a	n/a	Bedows and Hatfield (1982)
Polygonum spectabil	n/a	Ethanolic extract	n/a	n/a	Brandao *et al.* (2011)
Pterocaulon sphacelatum	Lactone (acanthoaustralide-1-O-acetate) and flavonoids (quercetin and chrysosplenol D)	Hydroethanol extract	n/a	n/a	Rocha Martins *et al.* (2011)
Punica granatum	Tannin	Pericarp	n/a	n/a	Zhang *et al.* (1995)
Quillaja saponaria	Triterpenoid saponins	Aqueous extracts	n/a	n/a	Roner *et al.* (2007)
Rhamnus frangula	Anthraquinones	Glycerin extracts	n/a	n/a	Sydiskia *et al.* (1991)
Rhamnus purshianus	Anthraquinones	Glycerin extracts	n/a	n/a	Sydiskia *et al.* (1991)
Rheum officinale	Anthraquinones	Glycerin extracts	n/a	n/a	Sydiskia *et al.* (1991)
Rhinacanthus nasutus	Naphthoquinones [rhinacanthin-C and rhinacanthin-D]	n/a	n/a	n/a	Sendl *et al.* (1996)
Rhus aromatica	n/a	Aqueous extract of root/stem bark	Cell culture	Prevent viral penetration in host cell	Reichling *et al.* (2009)
Rhus javanica	Moronic acid	Herbal extract	Mice	n/a	Kurokawa *et al.* (1999)
Saponaria officinalis	n/a	Lyophilized infusion	n/a	n/a	Serkedjieva *et al.* (2006)
Sclerotium glucanicum	Scleroglucan	n/a	n/a	Inhibits virus binding	Marchetti *et al.* (1996)
Spirulina platensis	n/a	Phosphate buffer and water extracts	n/a	n/a	Shalaby *et al.* (2010)
Syzgium aromatic	Eugeniin	Bud	n/a	n/a	Takechi and Tanaka (1981)

n/a = not available

Table 2: Detail description of studies focusing on antiviral plant activities against HIV

Plant name	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Agastache rugosa	Rosmarinic acid	Root's aqueous methanolic extract	*In vitro*	Inhibits virus integrase enzyme	Kim *et al.* (1999)
Calophyllum brasiliense	Apetalic acid, Calanolides B and C	Hexane extract of the leaves	n/a	Inhibitory effect on reverse transcriptase	Cesar *et al.* (2011)
Calophyllum cerasiferum	Inophyllum, Calanolide A and Coumarins	n/a	n/a	Inhibitory effect on reverse transcriptase	Saeed and Hussain (2006)
Calophyllum inophyllum	Inophyllum B and P	Leaves	n/a	n/a	Laure *et al.* (2008)
Calophyllum teysmannii	Costatolide	Latex	n/a	n/a	Fuller *et al.* (1994)
Castanospermum australe	Alkaloid: Castanospermine	Seeds	n/a	n/a	Roja and Heble (1995)
Corydalis yanhusuo	Gossypol and alkaloids	n/a	n/a	Inhibitory effect on reverse transcriptase	Wang and Ng (2001)
Daucus maritimus	n/a	Seeds	n/a	Inhibitory effect on reverse transcriptase	Miladi *et al.* (2011)
Gelonium multiflorum	Protein (GAP31)	Protein	T-lymphocytes	Inhibits the viral DNA integration to the host DNA and viral replication	Lee-Huang *et al.* (1995)
Geum japonicum	n/a	Hot water extract	Immunosuppressed mice	Inhibitory effect on reverse transcriptase	Kageyama *et al.* (1996)
Kadsura heteroclita	Triterpenoid and lignans (dibenzocyclooctadiene-type)	Stems	n/a	n/a	Pu *et al.* (2008)
Monotes africanus	Flavonoids	Organic extract	n/a	Inhibitory effect on reverse transcriptase	Meragelman *et al.* (2001) and Reutrakul *et al.* (2007)
Panax ginseng	Protein panaxagin	n/a	n/a	Inhibitory effect on reverse transcriptase	Ng and Wang (2001)
Phaseolus lunatus	Trypsin inhibitors	n/a	n/a	Inhibitory effect on reverse transcriptase	Wang and Ng (2001)
Phaseolus vulgaris	Lectin	n/a	n/a	Inhibitory effect on reverse transcriptase	Ye *et al.* (2001) and Fang *et al.* (2010)
Prunella vulgaris	n/a	Aqueous extracts	n/a	Interference of early, post-virion binding events	Oh *et al.* (2011)
Quillaja saponaria	Triterpenoid saponins	Aqueous extracts	n/a	n/a	Roner *et al.* (2007)
Rhizophora apiculata	Polysaccharide extracted from the leaf	n/a	Cell culture systems	Blocked the binding of HIV-1 virions	Premanathan *et al.* (1999b)
Rhizophora mucronata	Polysaccharide bark	Alkaline extract	n/a	Inhibited the viral binding to the cell	Premanathan *et al.* (1999a)
Rhus succedanea	Flavonoids	n/a	n/a	Inhibitory effect on reverse transcriptase	Lin *et al.* (1997)

Table 2: Continued

Plant name	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Ricinus communis	Lectin	n/a	n/a	Inhibitory effect on reverse transcriptase and the N-glycohydrolases	Wang and Ng (2001)
Shepherdia argentea	Tannins (shephagemins A and B)	Leaf extract	n/a	Inhibitory effect on reverse transcriptase	Yoshida *et al.* (1996)
Terminalia chebula	n/a	Methanol	Virus-infected baby hamster kidney	n/a	Lee *et al.* (2011)
Trichosanthes kirilowii	Trichosanthes anti-HIV protein	Protein	n/a	n/a	Lee-Huang *et al.* (1991)
Vigna unguiculata	Unguilin	Seed protein	n/a	Inhibiting effect on reverse transcriptase and the glycohydrolases α- and β-glucosidases	Ye *et al.* (2000) and Ye and Ng (2001)

n/a: Not available

of *Castanospermum austral* against this virus. Wang and Ng (2001) reported that gossypol and alkaloids of *Corydalis yanhusuo* might be responsible for it inhibitory activity on HIV virus. Ethanolic extract of *Monotes africanus*, which is a rich source of various flavonoids has been reported for its antiviral activity against HIV (Meragelman *et al*., 2001; Reutrakul *et al*., 2007). Most of the plants mainly affect the Reverse Trancriptase (RT) activity or penetration of virus particles into host cell. Calanolides which exhibits potential RT inhibitory activity have been found in the hexane extract of *Calophyllum brasiliense* leaves (Cesar *et al*., 2011). The hexane extract of this plant was found to have inhibitory effect on RT enzyme of HIV. Lectins derived from *Phaseolus vulgaris* are reported for their potential inhibitory effect on HIV RT activity (Ye *et al*., 2001; Fang *et al*., 2010). Another seed protein isolated from *Vigna unguiculata* possesses the same effect on RT activity in addition to inhibitory effect on glycohydrolases α- and β-glucosidases (Ye *et al*., 2000; Ye and Ng, 2001). Oh *et al*. (2011) reported that aqueous extract of *Prunella vulgaris* interferes with the viron post binding events. Extract of *Rhizophora mucronata* and *Rhizophora apiculata* (a rich source of polysaccharides) blocks the viral binding to the cell surface (Premanathan *et al*., 1999a; Premanathan *et al*., 1999b). In another study Lee-Huang *et al*. (1995) studied the effect of a protein isolated from *Gelonium multiflorum* and found that it reduces the virus replication by inhibiting the integration of viral DNA into host genome. *Panax ginseng*, which is also effective against cardiovascular diseases (Jun *et al*., 2007) has been reported to be effective against HIV by inhibiting the RT activity (Ng and Wang, 2001). *Ricinus communis* an important medicinal plant (Onwuliri and Anekwe, 2001) showed inhibitory effect on RT and N-glycohydrolases of HIV (Wang and Ng, 2001). Another plant *Terminalia chebula*, which has been proven to have many beneficial medicinal properties (Gupta *et al*., 2008a, b; Shinde *et al*., 2009; Anam *et al*., 2009) posses significant anti-HIV activity (Lee *et al*., 2011). Its methanolic extract showed antiviral activity against HIV when tested on virus infected baby hamster kidney cells.

Plants with antiviral activity against influenza virus: It is a single stranded RNA virus with negative sense linear fragmented genome enclosed in a capsid, it belongs to family Orthomyxoviridae and infects both mammals and birds. It has seasonal epidemiology and mainly spread through air when the environment is dry and cold (Lowen *et al*., 2007). The hospitalization and death rate associated with influenza vary with the age and type of virus, as influenza virus A-caused infection rate is higher than type-B (Thompson *et al*., 2004). Influenza virus, especially of avian origin is highly virulent disease causing agent in humans and birds; it has long history, put huge burden on human health since 1580 (Farooq *et al*., 2006; Lazzari and Stohr, 2004). It is responsible for deaths of millions of people; its pandemic nature is due to its variable strains which develop via the reassortment of genetic information. Thus the development of vaccine against it is difficult both in humans and birds.

Sixteen plants were identified which showed antiviral activity against influenza virus. Anthocyanin and polyphenols were among the commonly found active phytochemicals in these plants (Table 3). *Camellia sinensis* is an important herbal plant having significant antioxidant, photochemoprotective, hyperglycemic, antibacterial and many other beneficial heath benefits (Adiloglu and Adiloglu, 2006; Bakar *et al*., 2006; Shokrzadeh *et al*., 2006; Hassani *et al*., 2008; Mohamed and Metwally, 2009; Amutha *et al*., 2010; Chakraborty and Chakraborti, 2010; Kaur and Saraf, 2011; Obaid *et al*., 2011). Catechin derivatives obtained from the tea of this plant showed significant inhibitory effect on influenza strains (Song *et al*., 2005). Ehrhardt *et al*. (2007)

Table 3: Detail description of studies focusing on antiviral plant activities against influenza virus

Plant name	Active compounds	Extract type	Model organism	Mode of action	Reference
Agrimonia pilosa	n/a	n/a	MDCK cells, embryonated chicken eggs	Inhibits RNA synthesis and react with viral membrane	Shin *et al.* (2010)
Aloe barbadensis	Anthraquinones: Aloe emodin	Hot glycerin extracts	Vero cells	Partial destruction of viral envelope	Sydiskia *et al.* (1991)
Aronia melanocarpa	Anthocyanins	Fruit juice	n/a	n/a	Valcheva-Kuzmanova and Belcheva (2006)
Bergenia ciliata	n/a	Methanolic extracts	MDCK (Madin-Darby Canine Kidney) cells	n/a	Rajbhandari *et al.* (2009)
Camellia sinensis	Catechin derivatives	Tea	MDCK cell	Inhibits virus replication and hemagglutination	Song *et al.* (2005)
Cistus incanus	Polyphenol; CYSTUS052	n/a	A549 or MDCK cells; Human patients	Inhibits the viral cell entry by modulating the viral surface structures	Ehrhardt *et al.* (2007) and Kalus *et al.* (2009)
Clinacanthus siamensis	n/a	Leaf's ethanolic extracts	MDCK cells and mouse	Produce antibodies against virus	Wirotesangthong *et al.* (2009)
Commelina communis	Alkaloids	n/a	Mice and Madin-Darby canine kidney cells	Inhibits the virus growth and reduce viral titres in lungs	Bing *et al.* (2009)
Echinacea purpurea	n/a	Commercial extract; Echinaforce®	H-1 (subclone of HeLa cells) cells	Resists virus entry by inhibiting receptor biding and replication	Vimalanathan *et al.* (2005) and Pleschka *et al.* (2009)
Geranium sanguineum	Polyphenols	Methanolic extracts	Murine model	Effect the expression of virus proteins on cell surface	Serkedjieva (1996) and Sokmen *et al.* (2005)
Narcissus tazetta	Protein (Narcissus tazetta lectin)	Bulbs	n/a	n/a	Ooi *et al.* (2010)
Pandanus amaryllifolius	Lectin (pandanin)	Saline extract of the leave	n/a	n/a	Ooi *et al.* (2004)
Rhinacanthus nasutus	Lignans [rhinacanthin E and rhinacanthin F]	Aerial parts	n/a	n/a	Kernan *et al.* (1997)
Saponaria officinalis	n/a	Lyophilized infusion	n/a	n/a	Serkedjieva *et al.* (2006)
Scutellaria baicalensis	Isoscutellarein-8-methylether	Roots	n/a	Inhibit viral replication	Nagai *et al.* (1995)
Toddalia asiatica	n/a	Extract	n/a	n/a	Lu *et al.* (2005)

n/a = Not available

found that *Cistus incanus* possess the antiviral activity by modulating the viral surface in order to inhibit its entry into Madin-Darby Canine Kidney (MDCK) cells. Inhibitory effect against influenza virus has also been reported in human patients (Kalus *et al*., 2009). Another herb *Echinacea purpurea* also restrict the viral entry by inhibiting the binding of viral receptors to the host cells surface (Pleschka *et al*., 2009). *Geranium sanguineum*, a rich source of polyphenols showed antiviral activity by effecting the expression of viral proteins on cell surface (Serkedjieva, 1996; Sokmen *et al*., 2005). A lectin isolated from bulbs of *Narcissus tazetta* showed significant antiviral activity against various strains of influenza virus (Ooi *et al*., 2010). In another study Ooi *et al*., 2004) reported the anti-influenza activity of a lectin isolated from saline extract of *Pandanus amaryllifolius* leaves. *Scutellaria baicalensis* an important medicinal plant (Yeh *et al*., 2010) possess a compound (isoscutellarein-8-methylether) which is thought to be responsible for it antiviral activity against influenza virus (Nagai *et al*., 1995).

Plants with antiviral activity against Hepatitis C Virus (HCV): Hepatitis C is an enveloped virus with +VE single stranded linear RNA, which belongs to the family Flaviviridae. It cause mild-chronic liver disease infecting more than three million people each year, which results in almost 350 000 deaths (WHO, 2011a). It has worldwide spread with 4.8% infection rate in Pakistan. It is a global problem nearly affecting 130 million people; moreover, alone it is responsible for about 27% of cirrhosis and almost 25% of world's hepatocellular carcinoma (Alter, 2007). Its high spread is attributed to poor moral and health conditions, use of drugs, alcohol and contaminated syringes (Roshandel *et al*., 2007; Zakizad *et al*., 2009). It is detectable through serum proteins and blood analysis; its chemotherapeutic treatment is difficult but can be treated through herbal products (Ansari *et al*., 2011; Joseph and Raj, 2011; Pervez, 2000a; Moundipa *et al*., 2007; Tabassum *et al*., 2000).

In current study six plants have been identified with proved antiviral activity against HCV. Mainly plant showed inhibitory effect on HCV protease. Hussein *et al*. (2000) reported the inhibitory effect of *Trachyspermum ammi* and *Embelia schimper* methanol extract on HCV protease. *Solanum nigrum* which also exhibits hepatoprotective activity (Subash *et al*., 2011) has also been reported to have inhibitory effect on HCV (Javed *et al*., 2011). Cannabis a commonly used drug (Richardson, 2010) is a phytochemical of *Cannabis sativa* a medicinal plant with many beneficial health effects (Arshad and Khan, 2000; Qureshi *et al*., 2001; Tehranipour and Ebrahimpour, 2009). *Acacia nilotica* has remained the focus of many studies for its multipurpose applications (Shirazi *et al*., 2001; Banerjee *et al*., 2004; Ghosh *et al*., 2004; Elkhalifa *et al*., 2005; Emtehani and Tabari, 2007) its acetonic and methanolic extracts have sown anti-HCV effect on liver cells (Rehman *et al*., 2011). Sylvestre *et al*. (2006) reported the anti-HCV activity of cannabis in human patients. Mainly these plants showed their activity against HCV by targeting its protease (Table 4).

Plants with antiviral activity against respiratory syncytial virus: It belongs to the family Paramyxoviridae and is single stranded RNA virus, which is enclosed in an envelope. It is a highly prevalent virus throughout the world with large variation in its genome (Trento *et al*., 2010). It cause bronchiolitis and other respiratory problems and is a major cause of lower respiratory tract infections; it mostly infects the children under age of six months and also responsible for asthma problems (Mohapatra and Boyapalle, 2008). It causes an infection in 3-7% of healthy adults and 4-7% in the non-healthy adults, who already suffers from lung and heart diseases (Falsey *et al*.,

Table 4: Detail description of studies focusing on antiviral plant activities against hepatitis, respiratory syncytial virus and vesicular stomatitis virus

Plant name	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Hepatitis A Virus					
Spirulina platensis	n/a	Phosphate buffer and water extracts	n/a	n/a	Shalaby *et al.* (2010)
Dianthus caryophyllus	n/a	Seed crude extracts	Vero and HepG2 cells	n/a	Barakat *et al.* (2010)
Hepatitis B Virus					
Phyllanthus urinaria	Methyl ester dehydrochebulic acid and methyl brevifolin carboxylate	n/a	n/a	n/a	Zhong *et al.* (1998)
Hepatitis C Virus					
Trachyspermum ammi	n/a	Methanol	n/a	Inhibitory HCV proteases	Hussein *et al.* (2000)
Embelia schimper	Benzoquinones (embelin (I) and 5-O-methylembelin (II))	Methanol	n/a	Inhibitory HCV proteases	Hussein *et al.* (2000)
Solanum nigrum	n/a	Methanol and chloroform extracts of seeds	n/a	Inhibitory effect on NS3 protease	Javed *et al.* (2011)
Acacia nilotica	n/a	Acetonic and methanolic extract	Liver cells	n/a	Rehman *et al.* (2011)
Cannabis sativa	Cannabis	n/a	Human patients	n/a	Sylvestre *et al.* (2006)
Daucus maritimus	n/a	Seeds	n/a	Inhibits the reverse transcriptase activity	Miladi *et al.* (2011)
Respiratory Syncytial Virus					
Narcissus tazetta	Protein (Narcissus tazetta lectin)	Bulbs	n/a	n/a	Ooi *et al.* (2010)
Selaginella sinensis	Amentoflavone	Ethanol extract	n/a	n/a	Ma *et al.* (2001)
Schefflera heptaphylla	3,4-Di-O-caffeoylquinic acid and 3,5-di-O-caffeoylquinic acid	n/a	n/a	inhibition of virus-cell fusion	Li *et al.* (2005)
Barleria prionitis	Iridoid: 6-O-trans-p-coumaroyl-8-O -acetylshanzhiside methyl ester and its cis isomer	n/a	n/a	n/a	Chen *et al.* (1998)
Markhamia lutea	Luteoside, verbascoside and isoverbascoside	Roots	n/a	n/a	Kernan *et al.* (1998)
Vesicular Stomatitis Virus					
Allium sativum	Ajoene, allicin and allyl methyl thiosulfinate	Oil-macerates and Fresh garlic extract	HeLa /Vero cells	interfere with virus adsorption and penetration	Weber *et al.* (1992)
Cedrela tubiflora	Acidic polysaccharides	Leaves fraction extracts	n/a	Inhibits virus replication	Craig *et al.* (2001)
Justicia procumbens	Justicidins A-B and diphyllin derivatives	Aerial parts; methanolic extract	Cultured rabbit lung cells (RL-33)	n/a	Asano *et al.* (1996)
Melia azedarach	Meliacarpin; Tetranortriterpenoid: 1-cinnamoyl-3, 11-dihydroxymeliacarpin	Ethyl acetate extract of leaves	Vero cells	Inhibits the virus replication; inhibits viral nucleocapsid uncoating and stops the movement of G-protein thus stop exocytosis of virus	Alche *et al.* (2003), Barquero *et al.* (2004)

n/a: Not available

2005). Moreover it cause burden on population equal to that of influenza A virus, as the patients needs more health facilities and care. Ma *et al.* (2001) found that ethanol extract of *Selaginella sinensis* possess significant activity against respiratory syncytial virus. They further elaborated that this activity of plant could be due to the presence of a biflavonoid (amentoflavone) in its plant extract. A lectin isolated from *Narcissus tazetta* also showed antiviral activity against this virus (Ooi *et al.*, 2010). Li *et al.* (2005) reported the *Schefflera heptaphylla* antiviral activity against respiratory syncytial virus and concluded that this activity was due to the inhibition of fusion of viral particles to the host cell.

Plant with broad spectrum antiviral activity: Based on the data presented in Table 1-5 plant with broad spectrum antiviral activity (plants reported for their antiviral activity against two or more than two viruses) were identified. Total 24 plants were found that were resistant to two or more than two viruses (Fig. 2). Two plant species showed antiviral activity against four viruses.

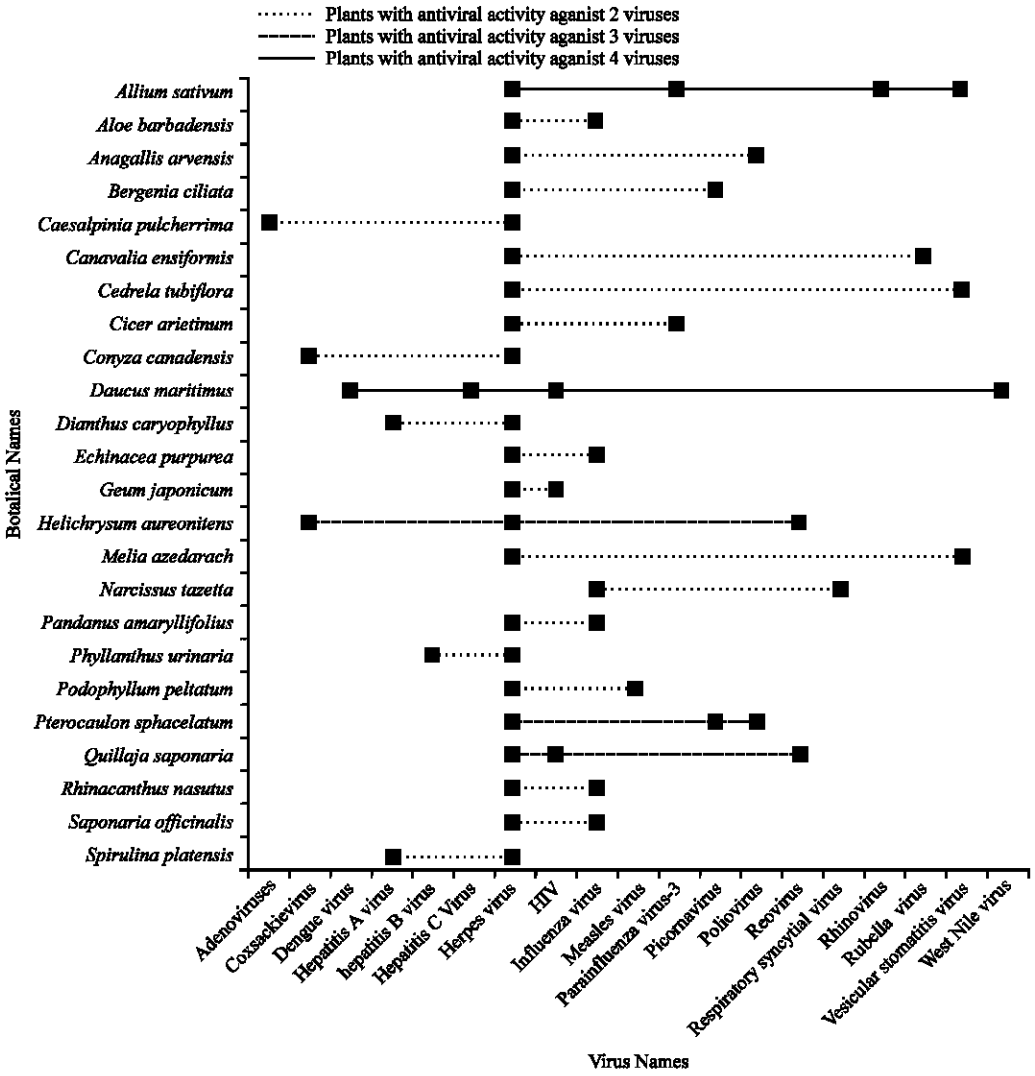

Fig. 2: Plant with broad spectrum antiviral activity

Table 5: Detail description of studies addressing rarely studied viruses

Plant name	Virus	Active compounds	Plant part/Extract type	Model organism	Mode of action	Reference
Aegle marmelos	Human coxsackieviruses	Marmelide	Leaf, root, stem and fruit extracts	Vero cells	Inhibits viral replication at various steps e.g. adsorption penetration etc.	Badam *et al.* (2002)
Allium sativum	Parainfluenza virus-3 and Human rhinovirus-2	Ajoene, allicin and allyl methyl thiosulfinate	Oil-macerates and fresh garlic extract	HeLa / Vero cells	Interfere with virus adsorption and penetration	Weber *et al.* (1992)
Anagallis arvensis	Poliovirus	Triterpene saponin	n/a	n/a	Inhibits the virus replication	Amoros *et al.* (1987)
Azadirachta indica	Dengue virus	n/a	Leaves' aqueous extract	Aedes albopictus' larval cells and Mice	Inhibits virus replication	Parida *et al.* (2002)
Caesalpinia pulcherrima	Adenoviruses	Quercetin derivatives	Aqueous extracts of fruit, stem, leaf, fruit and seed	Human skin basal cell carcinoma cell line (BCC-1/KMC)	Inhibits the virus replication at early stages of cycle	Chiang *et al.* (2003)
Canavalia ensiformis	Rubella virus	Lectins	n/a	n/a	Inhibits replication	Marchetti *et al.* (1996)
Cicer arietinum	Parainfluenza-3 virus	Phenolic compounds	Seed, fruit skin and aerial parts	Madin-Darby bovine kidney/Vero cells	n/a	Kan *et al.* (2009)
Conyza canadensis	Coxsackie B virus type 3	n/a	Ethyl acetate, chloroform, butanol and methanol extracts of the aerial parts	Human diploid embryonic lung fibroblasts (MRC-5)	n/a	Edziri *et al.* (2011)
Daucus maritimus	Dengue virus and West Nile virus	n/a	Seeds	n/a	Inhibits the reverse transcriptase	Miladi *et al.* (2011)
Glycyrrhiza glabra	Japanese encephalitis virus	Glycyrrhizin and licorice	n/a	Porcine stable kidney (PS) and Human cervical carcinoma (HeLa) cell	n/a	Badam (1997)
Helichrysum aureonitens	Coxsackie B virus-1 and Reovirus	Galangin	Shoots extracts	n/a	n/a	Meyer *et al.* (1997)
Hibiscus sabdariffa	Measles virus	n/a	Leaves ethanol extract	Hep-2 cells	n/a	Sunday *et al.* (2010)
Podophyllum peltatum	Measles virus	Podophyllotoxin	Aqueous extract	n/a	n/a	Bedows and Hatfield (1982)
Prunus mume	Human rhinovirus	n/a	Fruit juice	n/a	n/a	Song *et al.* (2010)
Pterocaulon sphacelatum	Picornavirus	Flavonoid (chrysosplenol C)	Ethanolic extract of aerial parts	n/a	n/a	Semple *et al.* (1999)
Pterocaulon sphacelatum	Poliovirus	n/a	Hydroethanol extract	n/a	n/a	Rocha Martins *et al.* (2011)
Quillaja saponaria	Reovirus	Triterpenoid saponins	Aqueous extracts	n/a	n/a	Roner *et al.* (2007)
Sophora flavescens	Coxsackievirus B3	Sophoridine	n/a	Primarily cultured myocardial cells	n/a	Zhang *et al.* (2006)
Zingiber officinale	Rhinovirus	Beta-sesquiphellandrene	Dried rhizomes	n/a	n/a	Denyer *et al.* (1994)

n/a = Not available

Allium sativum showed resistance against Herpes virus, Parainfluenza virus-3, Rhinovirus and Vesicular stomatitis virus. *Daucus maritimus* has been reported for its activity against Dengue virus, Hepatitis C virus, HIV and West Nile virus. *Helichrysum aureonitens*, *Pterocaulon sphacelatum* and *Quillaja saponaria* have been reported for their antiviral activity against three viruses each. As shown in figure 2 *Helichrysum aureonitens* is effective against Coxsackievirus, Herpes virus and Reovirus. *Pterocaulon sphacelatum* showed antiviral activity against Herpes virus, Picornavirus and Polio virus. *Quillaja saponaria* has been reported for its activity against Herpes virus, HIV and Reovirus. Almost all plants with broad spectrum activity were effective against herpes viruses. Moreover five plants which were effective against Herpes virus, also showed antiviral activity against Influenza virus. In the same way three plant species showed resistance against both Herpes virus and Vesicular stomatitis virus.

CONCLUSION

Majority of the studied viruses belongs to the Flaviviridae, Herpesviridae and Picornaviridae family. A large number of plants are available in nature which could act as a source of lead antiviral compounds. Mainly these plants target the enzymes that are involved in replication and integration of virus into host cell. In case of DNA viruses restricted entry of viral particles into host cell or inhibition of viral replication into the host cells were most frequent mode of actions. Destruction of viral envelop was also one of the identified mode of action against DNA viruses. RT plays a significant role in replication of RNA viruses and most of the plants restrict the activity of RT enzyme of virus. In order to design effective drugs against viruses their enzymes that are involved in the key metabolic activities (integration, replication) should be focused. A lot of plant population with possible potential is still uncovered as few plants have been studied in detail in order to identify the active phytochemicals against these viruses. More detailed studies in future will help not only to identify the potential antiviral compounds but also in better understanding of their mode of action for more effective control of these lethal viruses.

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