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Ethnomedicines in Antiviral Drug Discovery

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ABSTRACT

This review is an attempt to portray the discovery and development of ethnomedicine and its phytophores against some important viral diseases from galenical to genomical period. Natural resource, particularly the plants and animals have been the basis of traditional treatment since the dawn of human civilization and the modern medicine (Allopathy) has gradually developed, over the years, by scientific and observational efforts from traditional practice. However, with the advent of antibiotics the role of traditional medicaments in infectious diseases was sidelined. Interestingly after the 1980's, society realized the problem of drug resistance, emerging and reemerging pathogens, adverse drug reactions of many antimicrobials, particularly the antivirals. Hence, the lag phase for plant medicine is changing as impressive successes have been achieved with many botanicals like artemisinin, baccosides, curcumine, phyllanthins, quinghaosu, rauwolfia alkaloids, psoralens, picrosides, withanolides, steroidal lactones etc against many chronic and difficult-to-treat diseases. A whole range of chronic and lifestyle related diseases including HIV/AIDS, SARS, and Herpesvirus infection require new effective drugs. Considerable research has been carried out on pharmacognosy, chemistry, pharmacology and clinical therapeutics on Indian Ayurveda, Chinese traditional medicine, and traditional medicines of Africa in the last few decades. Many of the major pharmaceutical companies have renewed their strategies for drug development where there are no effective drugs or vaccine. Hence, many new compounds have entered the international pharmacopoeia through ethno-pharmacology and traditional medicine. Traditional knowledge-driven drug development can reduce both time and cost following a reverse pharmacology path. The automated separation techniques, high-throughput screening and combinatorial chemistry can help ethnomedicines to serve as a powerful search engine to facilitate intentional, focused and safe natural products research and to rediscover the drug discovery process.

Keywords: antivirals, drug development, ethnopharmacology, naturaceuticals

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INTRODUCTION

Ethnomedicine is the study of traditional medicines of diverse culture, its knowledge and practices that transmitted orally over the centuries, and evolved over the millennia of human existence. It was exhibited by the use of specific plant or plant parts to relieve pain, supplement diet, and help cure diseases. As a multidisciplinary subject ethnomedicine covers sociology, biology and medicine on a cultural framework, sometimes based on countries or regions of its origin, like Chinese Traditional Medicine (CTM), Taji and Qi Gong of China, Ayurveda and Yoga of India, Traditional Tibetan Medicine (TTM) and Buddhist believes of Tibet, medical traditions of Europe, Africa and the Americas. The traditionally used naturaceuticals (natural pharmaceuticals) and cosmeceuticals are important reservoir of chemical diversity is now aimed for new drug discovery. Around 80% of modern drugs including paclitaxel, vincristine, vinblastine, artemisinin, camptothecin, podophyllotoxin etc. are of plant origin, and the market share of naturaceuticals is expanding at a rate of 20% per year globally (Patwardhan *et al.* 2004). Hence, global efforts are made to monitor quality and regulate the growing business of herbal drugs and traditional medicine.

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Invited Review

Throughout the age's mankind have relied on nature for their food, clothing, shelter, and medicaments. People have long applied poultices and imbibed infusions of indigenous plants for cures or relief symptom. The oldest record of ethnomedicinal practice dates back to 2600 BC from Mesopotamia describing the use of cedar wood (*Cedrus* spp.) and chalmugra oil in leprosy, cypress (*Cupressus sempevirens*), licorice (*Glycyrrhiza glabra*), myrrh (*Commiphora* spp.) and poppy (*Papaver somniferum*) juice for coughs and colds to parasitic infections and inflammation (Newman *et al.* 2000). Egyptian '*Ebers Papyrus*' of 1500 BC documented over 700 medicaments and formulae, while the Chinese *Materia Medica* (1100 BC) contained formulations described in *Shennong* and *Tang Herbal* (659 AD). On the other hand, the Indian Ayurveda (1000 BC) include the classics *Atharvaveda* (1200 BC), *Charak Samhita* and *Sushrut Samhita* (1000-500 BC) describe the use of 857 preparations from 700 herbs (Dev 1999; Das and Sharma 2001). However, the substantial contribution for the rational development of ethnomedicine was made by the Greek philosopher Theophrastus (~300 BC) who described the medicinal properties of many herbs and their chemical variation in his book '*History of Plants*', while the Greek physician Galen (130-200 AD) devised the first pharmacopoeia describing the use of hundreds of plants with prescriptions and formulae. During the 5th to 12th C AD, the monasteries in England, Ireland, France and Germany practiced ethnomedicinal knowledge of Greeks and Roman tradition. However, the Persian physician Avicenna compiled the Greco-Roman knowledge and expertise with Chinese and Indian tradition in *Canon Medicinae*, which was later superseded by the *Corpus of Simples* written by Ibn al-Baitar of Spain. In 1618 all these Informations were compiled in the *London Pharmacopoeia*. However, the foundations of modern pharmaceutical industry come with the idea of 'pure' compounds as drugs in early 1800, by the isolation of the active principles strychnine, morphine, atropine and colchicine from plants (Chattopadhyay and Naik 2007), which initiated the foundation of Natural products chemistry with the work on morphine from opium poppy (*Papaver somniferum*) by Serturner, and marketed by E. Merck in 1826 (Grabley and Thiericke 1999). Similarly, quinine isolated from the Indian fever bark *Cinchona officinalis* L. is originated in the royal households of the South American Incas. In the early 1500s, Indian fever bark infusion was used by the native people of the Andes and Amazon highlands to treat fevers, but in early 16th century Jesuit missionaries brought these bark to Europe (Patwardhan and Hooper 1992). In Andean cultures, the leaves of *Erythroxylum coca* (coca in Aymara word means "tree") were chewed for a euphoric sense of happiness and increased energy. Later in 1860, German chemist Carl Koler isolated cocaine from coca, and cocaine as a local anesthetic in surgery and dental procedures can paralyzed nerve endings responsible for transmitting pain (Grabley and Thiericke 1999). The alkaloid-rich aromatic oil pilocarpine secreted by the jaborandi tree *Pilocarpus jaborandi* is the only weapon against the blinding disease, glaucoma. Similarly, in 1891 a protein breaking enzyme bromelin was isolated from the pineapple (*Ananas comosos*) juice that breaks down blood clots, from the traditional practice of the American Indians of Guadeloupe Island, who used pineapple poultices to reduce inflammation of wounds and injuries, to aid digestion and cure stomachache. Other pharmaceuticals such as atropine, hyoscine, digoxin, colchicine and emetine also had their origin from ethnomedicinal practice. The anti-hypertensive alkaloid reserpine of *Rauwolfia serpentina* was isolated by Ciba-Geigy in India, while the first semi-synthetic drug aspirin was developed by Bayer in 1899 (Patwardhan and Hooper 1992; Grabley and Thiericke 1999). Though many of these ethnomedicinal drugs act as poison at higher doses, the natural products (plants, animals and mineral origin) were the basis of treatment since the dawn of civilization and the modern medicine (allopathy) has gradually developed over the years by scientific and observational efforts from the traditional wisdom. Thus, the ancient wisdom, the very basis of modern medicine, is an important source today and will remain important for future medicine also. However, the future of ethnomedicinal drug discovery will be more holistic, and personalized with wise use of ancient and modern therapeutic skills in a complementary manner for maximum benefits (Patwardhan *et al.* 2008).

The term "*Ethnomedicinal Phytophore*" is used to define the phytochemicals of medicinal plants used by several ethnic communities ("*phyto*" means plant, and "*phore*' means molecules that can act selectively in living cell). Earlier the term *phytophore* was used to mention the release of various small molecular metabolites of plants during preservation of vegetable and fruits in bactericidal gas generator by Charles Illouze in 1969 (Patent No. GB1158571). While in 1988 M. François de Sarre used the term to describe the first land living minute (phytophores-type) vertebrates (SARRE de François 1997; http://www.persowandadoo.fr/initial.bipedalism/), and to describe the ideal ligand (like auxin)-binding protein (Jones 1994). However, in recent times several phytochemicals are used in the management of diverse diseases (Patwardhan *et al.* 2004; Khan *et al.* 2005; Chattopadhyay and Naik 2007; Patwardhan *et al.* 2008) and this term was used to describe the small molecular secondary bioactive metabolites of medicinal and food plants (Chattopadhyay 2006; Chattopadhyay and Naik 2007; Chattopadhyay and Khan 2008).

This review is an attempt to summarize the current knowledge of promising ethnomedicinal antivirals and their phytophores, to compounds tested against diverse virus families from galenical to genomical period. The antiviral properties and structure activity relationship (SAR) of some of these potentially useful ethnomedicines will also be addressed with a focus on how these ethnic knowledge can led to the development of useful antivirals for preclincal or clinical evaluation.

ETHNOMEDICINE IN DRUG DISCOVERY PROCESS

Earth is estimated to contain about 5,00,000 plant species, 10% of which is used as food and 10-15% as source of drugs (Borris 1996). Over the centuries, plant based medicaments of diverse ethnic communities formed the basis of treatment in China (Chang and But 1986), India (Dev 1999), Africa, and in many other cultures (Schultes and Raffauf 1990). An estimated 80% of the world's populations rely on plant based medicines for primary health care and 20% use plant products as ingredients of drugs (Farnsworth 1990). To date 119 drugs used in modern medicine are derived from 90 plant species, of which 74% are of ethnomedicinal plants. The ethnomedicines of China (CTM), India (Ayurveda), Tibet (TTM) and Africa, is ancient but still alive with sound philosophical and experiential basis (Dahanukar and Thatte 2000; Chopra and Doiphode 2002), representing medical pluralism with holistic approach and are useful, especially for chronic diseases. Several recent work identified hypolipedemic agent from *Commiphora*, hepatoprotective from *Picrorhiza*, memory enhancer from *Bacopa*, anti-inflammatory from *Curcuma* and cardiotonic from *Asclepias* (Jain 1994) used in Ayurveda. Combining the strengths of ethnomedicinal knowledge with the dramatic power of combinatorial sciences and high throughput screening (HTS) scientists can generate structure-activity libraries; while the experiential database can provide the new functional leads that reduce time, money and toxicity, the three main hurdles in drug development. For example, the development of standardized herbal formulations is undertaken by many countries like India (Golden Triangle approach by the Council of Scientific and Industrial Research, Government of India, 2003), China (TCM Literature Database 1997), Canada (Canadian AIDS Treatment Information Exchage 2005), Brazil (Botsaris 1997), etc. having ethnomedicinal databases (Patwardhan 2005; Balik 2006; Sharma *et al.* 2007). Globally, in drug discovery and therapeutics, there is

a positive trend towards holistic health, integrative sciences, and systems biology approaches. Thus, a golden triangle consisting of ethnomedicine, modern medicine and modern science can converge to form a real discovery engine that can result in newer, safer, cheaper and effective therapies.

Clinical virologists are looking for plant extracts as most of the viral diseases are intractable to the orthodox antivirals, and the effective life span of most antiviral drug is limited. Furthermore, the problems of viral resistance, latency and recurrence, rapid spread of emerging and re-emerging viral diseases like human immunodeficiency virus (HIV), severe acute respiratory syndrome (SARS) forced them to look into the nature, especially for people having little or no access to expensive antivirals (De Clercq 1995; Chattopadhyay and Naik 2007). Additionally the rapid rate of species extinction leads to irretrievable loss of structurally diverse and potentially useful phytochemicals (Lewis and Elvin-Lewis 1995; Borris 1996). Hence, ethnomedicine can play a pivotal role in antiviral drug discovery by utilizing the impressive array of knowledge and wisdom of indigenous peoples about their generation old medicaments. Plant can produce far more compounds (secondary metabolites) than are necessary for their survival and propagation (primary metabolites). These secondary metabolites are species/strain specific with diverse structures and bioactivities (like flavors, colors, dyes, fragrances, insecticides, drugs), synthesized mainly for defense against predators as toxic, foul-tasting nasty chemicals, the natural version of chemical warfare. These diverse metabolites are broadly grouped into phenolics (anthocyanins, coumarins, flavonoids, quinones and tannins), terpenoids (essential oils, saponins, sterols and cucurbitacins), alkaloids, proteins, peptides, etc.

Problems and prospects of ethnomedicinal drug discovery

The Pharmaceutical research took a major turn as natural products chemists, pharmacologists, microbiologists and biochemists began to unravel the chemistry of ethnomedicines. This scientific advancement led to the identification of many key molecules as novel compounds. Many new drugs against infections, cancers, ulcers, heart diseases are resulted from sharp-eyed observations; while many developed through random screening. Studies on new drugs for neglected diseases like malaria, trypanosomiasis, filariasis, tuberculosis, schistosomiasis, leshmaniasis and amoebiasis came almost to a standstill; while there is no suitable drug to stop the emerging and re-emerging drug resistant microbes, including viruses. On the other hand, the clinical efficacy of many ethnomedicine was not yet evaluated and the composition of many traditional preparations was only crudely analysed (Patwardhan *et al*. 2008). Pharmaceutical scientists are experiencing difficulties in identifying new lead, templates and scaffolds in the finite world of chemical diversity as most synthetic drugs have unacceptable side effects. On the other hand, ethnomedicinal molecules like quinghaosu, artemisinin, rauwolfia alkaloids, psoralens, holarrhena alkaloids, guggulsterons, mucuna pruriens, piperidines, baccosides, picrosides, phyllanthins, curcumine, withanolides, steroidal lactones and glycosides showed impressive successes (World Medicine situation, 2004, a WHO Report; Patwardhan 2005; Sharma *et al*. 2007). A whole range of chronic and difficult-to-treat diseases such as cancers, cardiovascular disease, diabetes, rheumatism and AIDS, as well as neglected diseases require new effective drugs.

A major problem with traditional medicine is its reliability and use. In many parts of the world the use of indigenous medicine is broken down, where the indigenous population has been marginalized or limited to small tribal group or a small geographical area, as in Africa. The CTM and Ayurveda are 'great traditions', while the traditions of African, Tibet, CTC (Chakma Tilaka Chikitsa of Chakma tribes, Bangladesh) are an excellent repository of knowledge. However, researchers mainly exploited poisonous natural sources, because it is relatively easy to demonstrate poisonous characteristics that spread by word of mouth. On the otherhand, it is difficult to screen vast number of plants for pharmaceutical development, and a considerable time is required to demonstrate true medicinal activities with proven safety profile. As the "great traditions" have relatively organized database with more descriptive material and is easy to test by modern methods, thus, Ayurveda and TCM have an important role in bioprospecting of new medicines (Patwardhan *et al*. 2004).

Ethnomedicine in the genomic age

Drugs have been developed either on the basis of therapeutic need or of scientific opportunities. The antibiotics, diuretics, muscle relaxants, L-dopa, recombinant proteins and monoclonal antibodies were developed chemically due to scientific opportunities. However, the new informational paradigm "genomic science" is now changing the therapeutic science in two ways: Firstly, it unveils the complex human genomes and their functionality; and secondly, symptomatic drug therapies can targets closer to the causes of diseases (Patwardhan *et al*. 2004). Thus therapeutic progress is more directed, definitive and intentional and the future discovery will be based on intent rather than coincidence. The exploration of structural databases (a wide variety of chemotypes), with databases on target genes and proteins, will facilitate the creation of new chemical entities through computational modelling for pharmacological evaluation. The unveil of Human Genome pave the way of applications of genomics in drug discovery, that help in understanding the scientific basis of individual variation in response to a drug. Now, medicine is more scientific, predictive, individualistic and customized while medical practice will continue to remain an art (Ghosh *et al*. 2007). For hundreds of years physicians have noticed the individual differences during therapeutic intervention, and now pharmacogenetics (the study of the hereditary basis populations for differences in response to a drug), can tell us why some patients will respond well to the drugs, while others will not; a drug might show adverse effects in some patients, but not in others; why the same dose of a drug will result in elevated plasma concentrations for some patients but low for others? A population's variation, enzyme polymorphisms, differences among racial groups for glutathione *S*-transferase (GST, an enzyme that detoxifies environmental toxins) is now known. Phase I enzyme cytochrome P4502D6 (CYP2D6) and the phase II isoenzymes GST-M1 and GST-T1 are subject to genetic polymorphism, resulting in absent of enzyme function. CYP2D6 metabolizes toxic alkaloids of plants and about 40 common drugs consumed by humans (Ellenhorn and Barceloux 1997; Yan *et al*. 2003), and shows great variability between individuals, e.g., 5-10% Blacks and Caucasians, and few Asian are poor metabolizers; while Ethiopians and Saudi Arabian are rapid metabolizers. Furthermore, GST-M1 and GST-T1 provide a secondary defence by conjugating environmental toxins and/or reactive endobiotic compounds. In Caucasians, the proportion of individuals deficient in these enzymes is approximately 7% for CYP2D6 (Wolf and Smith 1999), 50% for GST-M1 and 20% for GST-T1 (Thomson *et al*. 1998). These differences affect the susceptibility of individuals to various forms of cancer (Ghosh *et al*. 2007). Similarly phenylthiourea related taste blindness is reported to be heritable and could serve as a tool of distinguishing between individuals. African Blacks had an incidence of 6%, American Blacks 2-23%, American Whites 30%, Chinese 6% and Eastern Eskimos 40% (Very and Iacono 2006). These studies indicated that the differences in response to disease and drugs differ not only from population to population, and truly from individual to individual. The importance of such individual variations in health and disease is an important principle of ethnomedicines like CTM and Ayurveda as underlined by Charaka (4000 years ago) as: "*Every individual is different from another and hence should be con-*

Table 1 Viral and cellular targets for antiviral agents.

Virus	Viral target	Cellular target
Parvovirus	DNA polymerase	-
Polyomavirus	DNA polymerase	-
Papillomavirus	DNA polymerase	-
Adenovirus	DNA polymerase	Cellular factors
α-Herpesvirus	DNA polymerase, Thymidine kinase, Helicase-primase	-
β-Herpesvirus	DNA polymerase, Protein kinase, Terminase	-
γ-Herpesvirus	DNA polymerase	-
Poxvirus	DNA & RNA polymerase	4 enzymes*
Hepadnavirus	DNA polymerase (RT)	-
Picornavirus	Capsid RNA polymerase	-
Flavivirus	RNA polymerase	-
Arenavirus	RNA polymerase	4 enzymes*
Bunyavirus	RNA polymerase	-do-
Togavirus	RNA polymerase	-do-
Rhabdovirus	RNA polymerase	-do-
Filovirus	RNA polymerase	-do-
Hepacivirus	RNA polymerase, RNA helicase, viral protease	-
Orthomyxovirus	Matrix protein, Neuraminidase	-
Paramyxovirus	Fusion polypeptide	4 enzymes*
Coronavirus	Spike (S) protein, RNA polymerase (replicase), RNA helicase, viral protease	-
Reovirus	-	4 enzymes*
Retrovirus	gp41, RT, Protease, gp120, Integrase, Transcription transactivator (TAT)	Integration- Transcription factors

*Inosine 5' monophosphate (IMP) dehydrogenase, S-adenosylhomocysteine (SAH) hydrolase, Oritidine 5'-phosphate (OMP) decarboxylase, Cytosine 5'-triphosphate (CTP) synthetase. [Reproduce from De Clercq, E. (2004) *Nature Review* 2, 710-720].

sidered as a different entity" (Dash 2001). Ayugenomics (Ghosh *et al*. 2007) describes the basis of individual variation and has clear similarities with the pharmacogenomics which can be the basis of designer medicine (Ferguson 2009). Understanding the relationship between Prakriti (nature) and genome can help in creation of human constitution (genotype), disease constitution (phenotype) and drug constitution databases that are capable of intelligently communicating with each other to give a customized prescription.

Virus and virus infection control

Viruses are actually the *acellular parasites of a cellular host*. The virus particles are ultramicroscopic, acellular, metabolically inert nucleoprotein particles containing either RNA or DNA as genetic material, with or without a lipid envelope (Chattopadhyay *et al*. 1999). Unlike free-living bacteria, viruses are obligate intracellular parasites, can utilize the host cell machinery to propagate and cause ailments as benign as a common wart, as irritating as a cold, or as deadly as the bloody African fever. The viruses that cause AIDS, Lassa and Ebola fever spread easily kill swiftly and have no cure or vaccine. The genetic variation, variety of transmission, efficient replication and the ability to persist within the host are the major evolutionary advantage of viruses. As a consequence viruses have adapted to all forms of life and have occupied numerous ecological niches resulting in widespread diseases in almost all living organisms (Wagner and Hewlett 1999; Chattopadhyay and Naik 2007). Viral infections, one of the leading cause of death globally, can be controlled either by prophylactic or therapeutic measures. As a metabolically inert particle virus require metabolic pathway of living cells to replicate, which makes it difficult to design a treatment that attack the virion or its replication, without affecting the host (Chattopadhyay *et al*. 1999). Although numerous compounds have been tested on different viruses, only 37 licensed antivirals are in the market (**Table 1**). But the development of antivirals from natural source is less explored, probably because there are very few specific viral targets for small molecules to interact with. Fortunately, many viruses have unique features in their structure or replication cycles that can be the potential target, as evident with nucleoside analogue acycloguanosine (acyclovir) which specifically blocks thymidine kinase enzymes of herpes viruses (Wagner and Hewlett 1999; De Clercq 2004) that play the key role in triggering disease.

ANTIVIRAL ACTIVITIES OF ETHNOMEDICINES OF DIVERSE CULTURE

The highly diverse plant kingdom ranges from unicellular microscopic plants to long-lived huge trees, and screening of each and every plant or their parts for the identification of bioactive compound is impossible. In the past many ethnomedicinal plants may have been used to treat viral diseases, however, first documented effort for the development of anti-Influenza agents from plants was made by the Boots Drug Company, Nottingham, England (Chantrill *et al*. 1952). Later studies have reported the inhibitory effects of various plant extracts on the replication of several viruses, particularly herpes simplex virus HSV) (Debiaggi *et al*. 1988), hepatitis B virus (HBV) (Kwon *et al*. 2005; Huang *et al*. 2006), human immunodeficiency virus (HIV) (Vermani and Garg 2002; Asres and Bucar 2005), poxvirus and severe acute respiratory syndrome (SARS) virus (Kotwal *et al*. 2005). Most of these studies used water or alcoholic extracts and limited efforts have been directed for the identification of active antiviral molecules. Moreover, several recent studies showed antiviral potential of plant extracts against viral strains resistant to conventional antivirals (Serkedjieva 2003; Tolo *et al*. 2006) which not only challenged the modern drug discovery practices, but forced the scientists to look carefully toward the antiviral components of medicinal plants. Presently the demand for new antiviral strategies has increased mainly for the increasing prevalence of chronic viral infections like HSV, HBV, hepatitis C virus (HCV) and HIV, and the emergence of SARS coronavirus, bird flu and swine flu viruses. Numerous reports throughout the world in last 25 years indicated that the crude extracts of hundred of ethnomedicinal plants of different culture have antiviral activity (Newman *et al*. 2000; Jassim and Naji 2003; De Clercq 2004; Chattopadhyay and Naik 2007; Naithani *et al*. 2008), that can inhibit many DNA and RNA viruses and can be useful in primary health care.

DNA viruses

1. Herpes viruses

There are six groups of major DNA viruses that contain DNA polymerase (**Table 2**), of which human herpesviruses (HHV), mainly the herpes simplex virus are known from antiquity and hence, extensively studied for therapeutic

Table 2 Members of Human Herpesviridae (HHV).

Type	Synonym	Subfamily	Pathophysiology
HHV-1	Herpes simplex virus-1	*Alphaherpesvirinae*	Oral and/or genital herpes (orofacial)
HHV-2	Herpes simplex virus-2	α (Alpha)	Oral and/or genital herpes (genital)
HHV-3	Varicella zoster virus	α (Alpha)	Chickenpox and Shingles
HHV-4	Epstein-Barr virus Lymphocryptovirus	*Gammaherpesvirinae* γ (Gamma)	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma (in AIDS patients), Post-transplant lymphoproliferative syndrome, Nasopharyngeal carcinoma
HHV-5	Cytomegalovirus	*Betaherpesvirinae*	Infectious mononucleosis-like syndrome, retinitis etc.
HHV-6, 7	Roseolovirus	β (Beta)	Roseola infantum or *exanthem subitum*
HHV-8	Kaposi's sarcoma-associated herpesvirus (a rhadinovirus)	γ (Gamma)	Kaposi's sarcoma, primary effusion lymphoma, some multicentric Castleman's disease

Herpes simplex virus 1 (HSV-1); Herpes simplex virus 2 (HSV-2); Varicella zoster virus (VZV); Epstein-Barr virus (EBV); Cytomegalovirus (CMV); Kaposi's sarcoma associated herpesvirus (KSAHV)

intervention, particularly against HSV-1 and HSV-2. Although infections are often subclinical, HSV can cause mild to severe diseases, especially in immunocompromised patients, and establish latency in the nuclei of neuronal cells that may reactivate, with or without symptoms, throughout the host's lifetime. Over one third of the world's population suffer from recurrent HSV infections several times a year and are thus capable of transmitting HSV by close personal contact. To date there are only a few drugs licensed for the treatment of HSV infections that target the viral DNA polymerase, and acyclovir remains the reference treatment even 30 years after its discovery. Both *herpes labialis* (HSV-1) and *herpes genitalis* (HSV-2) are lifelong infection with recurrent episodes, and are under diagnosed due to mild and asymptomatic nature. HSV-2 spread silently through sex, is a high risk factor for acquisition of HIV-1 infection (Cowan *et al*. 2003), and is a major opportunistic pathogen in immunocompromised patients, and thus, a serious disease in HIV/AIDS prevalent areas. The extensive use of acyclovir resulted in the development of HSV drug resistant strains globally, has further compounded this situation, highlighting the crucial need for new drugs that can inhibit both wild-type and drug-resistant virus strains. Hence, scientists are looking towards ethnomedicines for novel antiviral agents. Several alkaloids, phenols, polyphenols, flavonoids, terpenoids and sugar-containing compounds showed promising anti-herpetic activities (Khan *et al.* 2005), having potential viral and cellular target against HSV has been reviewed (Greco *et al*. 2007; Chattopadhyay and Khan 2008). A list of important ethnomedicinal plants and some of the important phytophores having antiviral activities against genetically diverse group of viruses are presented in **Table 3**. The earlier studies on ethnomedicinal plants was directed towards anti-HSV drug development, e.g., podophyllotoxin, isolated from the aqueous extract of *Podophyllum peltatum* L. inhibited HSV-1 (Bedows and Hatfield 1982). Similarly, the *Azadirachta indica* leaf extract inhibit DNA viruses like poxviruses (smallpox, chicken pox) and HSV (Rao *et al*. 1969), while *Cardamine angulata*, *Conocephalum conicum*, *Polypodium glycyrrhiza* showed anti-HSV-1 activity (McCutcheon *et al*. 1995). The aqueous extracts of *Nepeta nepetella*, *Dittrichia viscosa* and *Sanguisorba minor magnolii* of Iberian Peninsula inhibit vesicular stomatitis virus (VSV) and HSV-1 (Abad *et al*. 2000), while strong anti-HSV activity was reported with *Byrsonima verbascifolia* extract (Glatthaar-Saalmuller *et al.* 2001). Interestingly, the Chinese antipyretic and antiinflammatory medicament *Rheum officinale* and *Paeonia suffruticosa* prevent HSV attachment and penetration (Hsiang *et al.* 2001). The hydrolyzable tannin casuarinin (**1**) from *Terminalia arjuna* bark is virucidal and inhibit HSV-2 attachment and penetration (Cheng *et al.* 2002). The Taiwan folk remedy *Boussingaultia gracilis* and *Serissa japonica* extract can inhibit HSV and adenoviruses (ADV) 3, 8 and 11; while *Ardisia squamulosa* and *Artemisai princeps* can block ADV-8 replication (Chiang *et al.* 2003). Interestingly the adsorption, replication and transcription of HSV-1 were inhibited by *Ceratostigma willmattianum*, an ethnomedicine of China (Chen *et al.* 2004); while the extracts of *Senna petersiana*, a folk remedy for sexually transmitted diseases, have strong anti-HSV activity (Tshikalange *et al.* 2005).

On the other hand, isoborneol (**2**), a monoterpene essential oils from *Melaleuca alternifolia* inactivate HSV-1 replication within 30 min of exposure by inhibiting glycosylation of viral glycoprotein gB without hampering the host cell glycosylation process (Armaka *et al.* 1999), indicating isoborneol as an interesting anti-HSV agent. The anti-HSV activity was also reported with C-4 sulfated isoflavone torvanol A and steroidal glycoside torvoside H of *Solanum torvum* fruits (Arthan *et al.* 2002); isoquercitrin of *Waldsteinia fragarioides*, cinnamoylbenzaldehyde and lawinal of *Desmos* spp. (Wu *et al.* 2003), and mulberroside C of *Morus alba* root (Du *et al.* 2003). Similarly, organic solvents extracts of various plants have shown anti-HSV activity, suggesting varied nature of antivirals present in medicinal plants (Chattopadhyay and Naik 2007; Chattopadhyay and Khan 2008). Interestingly the sandalwood (*Santalum album*) oil had a dose dependent anti-HSV-1 activity, but essential oil of Italian food plant *Santolina insularis* inhibit cell-to-cell transmission of HSV (De Logu *et al.* 2000); The terpinen-4-ol (**3**) and 1,8-cineole of *Melaleuca alternifolia*, *M. officinalis* and *M. armillaris* used as antimicrobial preservative, exhibited strong virucidal activity against HSV-1 and HSV-2 by inhibiting adsorption and replication (Allahverdiyev *et al.* 2004; Farag *et al.* 2004). The diterpenes putranjivain A (**4**), isolated from *Euphorbia jolkini* inhibit viral attachment and penetration and significantly reduced infectivity (IC_{50} = 6.3 μM) by interfering at late stage of HSV-2 replication (Cheng *et al.* 2004). Although the active antiherpes components of these oil are not very clear but their application in recurrent herpes infection is promising. Recently it was reported that *ent*-epiafzelechin-(4α→8)-epiafzelechin (EEE, **5**) isolated from fresh leaves of *Cassia javanica* L. inhibit HSV-2 replication in a dose-dependent manner (IC_{50} = 83.8 and 166.8 μM), at non-cytotoxic concentration by blocking the viral penetration and replication (Cheng *et al.* 2006). The tetracyclic triterpene lupenone from *Euphorbia segetalis* inhibit plaque formation of HSV-1 and HSV-2 (Madureira *et al.* 2003); while harmine (**6**) isolated from *Ophirrhoza nicobarica*, a folklore of Little Andaman Islands, India, inhibit plaque formation and delayed the eclipse phase of HSV replication at 300 μg/ml (Chattopadhyay *et al.* 2006). Recently it was found that geraniin and 1,3,4,6-tetra-*O*-galloyl-β-D-glucose, isolated from the acetone extract of *Phyllanthus urinaria*, suppresses HSV-2 and HSV-1 (Yang *et al*. 2007).

There has always been a quest for antiviral which can overcome resistant strains of viruses or suppress the emergence of viral resistance. The eugeniin (**7**) and eugenol from *Geum japonicum* and *Syzygium aromaticum* block viral DNA polymerase and thereby inhibit acyclovir-resistant and thymidine kinase-deficient HSV-1, wild HSV-2, as well as Epstein-Barr virus (Kurokawa *et al.* 1998). Interestingly, triterpene betulinic acid (**8**) and moronic acid (**9**) of *Rhus javanica* inhibit acyclovir-resistant thymidine kinase-deficient and wild-type HSV-1 strains (Kurokawa *et al.* 1999). The oral administered of moronic acid to cutaneously infected mice with HSV-1 significantly retarded skin lesions,

Table 3 Antiviral activities of some important ethnomedicinal plants.

Virus	Name of plant(s)	Chemical group	References
HSV-1, HSV-2	*Aglaia odorata*, *Moringa oleifera*, *Ventilago enticulata*	Polyphenols	Lipipun *et al.* 2003
	Solanum torvum	Torvanol, torvoside (flavonoid)	Arthan *et al*. 2002
	Morus alba	Mulberoside (flavonoid)	Du *et al*. 2003
	Melia azedarach	Meliacine (peptide)	Alche *et al*. 2002
	Plantago major	Caffeic acid and derivative	Khan *et al*. 2005
	Ophirrhiza nicobarica	Harmon (alkaloid)	Chattopadhyay *et al*. 2006
	Carissa edulis Vahl.	*In vitro* and *in vivo*	Tolo *et al*. 2006
	Phyllanthus urinaria L.	Geraniin, 1346TOGDG	Yang *et al*. 2007
	Rhus javanica	Betulinic acid, Moronic acid (triterpene)	Kurokawa *et al*. 1999
	Myrica rubra	Prodelphinidin-di-*O*-gallate	Cheng *et al*. 2003
	Melissa officinalis, *M.. armillaris*, *Melaleuca alternifolia*	Terpinen-4-ol 1,8-cineole	Allahverdiyev *et al*. 2004; Farag *et al*. 2004
	Geum japonicum, *Syzygium aromaticum*	Eugenin and eugenol	Kurokawa *et al*. 1998
	Vaccinium vitis-ideaea	Proanthocyanidins A1	Cheng *et al*. 2005
	Ephorbia jolkini	Putranjivain A	Cheng *et al*. 2004
	Cassia javanica	Ent-epiafzelechin-(4α-8)- epiafzelechin (EEE)	Cheng *et al*. 2006
	Podophyllum peltatum L.	Podophyllotoxin	Bedows and Hatfield1982
	Rheum officinale, *Paeonia suffruticosa*	Podophyllotoxin	Hsiang *et al*. 2001
	Melalenca alternifolia	Isoborneol (essential oil)	Armaka *et al*. 1999
	Ephorbia segetalis	Lupenone (triterpenoid)	*Madureira et al.* 2003
	Melia azedarach	Cinnamoyl-dihydroxymeliacarpin	Alche *et al*. 2003
	Pelargonium sidoides	Coumarins, catechin, phenolics	Schnitzler *et al*. 2008
	Melissa officinalis	Lemon balm oil, *Citronella* oil	Schnitzler *et al*. 2008
	Prunella vulgaris, *Pippermint*, *Rosemary*	Rosmarinic acid, apigenin	Reichling *et al*. 2008
	Swertia chirata	HSV-1 plaque fusion	Verma *et al*. 2008
	Bambuseae sasa	Tricin	Sakai *et al*. 2008
	Anise oil, Chamomile oil	HSV adsorption	Koch *et al*. 2008
	Waldsteinia fragarioides, *Merus alba*	Isoquercitrin, linnamolbenzaldehyde	Wu *et al*. 2003
RSV, Influenza virus	*Aglaia* sp.	Dummarenolic acid, aglanol niloticin	Esimone *et al*. 2008
	Blumea laciniata, *Elephantopus scaber*	Polyphenols	Li *et al.* 2004
	Aesculus chinensis	Flavonoid	Wei *et al*. 2004
	Radix glycyrrhizae	Flavonoid	Dong *et al*. 2004
	Geranium sanguineum L.	*In vitro* and *in vivo*	Pantev *et al*. 2006
	Elderberry (*Sambucus* Sp) extract	Randomized, double-blinded placebo-controlled	Zakay-Rones *et al*. 2004
SARS	*Camellia sinensis*	Tannic acid, theaflavin3-gallate	Chen *et al*. 2005
RV, Coronavirus	*Camellia sinensis*	Theaflavin	Clark *et al*. 1998; Leung *et al*. 2003
HBV	*Boehmeria nivea* L.	Root extract reduced HBV production *in vivo*	Huang *et al*. 2006
	Phyllanthus nanus	Expression of annexin 7 gene	Lam *et al*. 2006
	Phyllanthus urinaria	Ellagic acid	Shin *et al*. 2005
	Herpetospermum caudigerum	Lignan	Yuan *et al*. 2006
	Sophora tonkinensis	Sophoranol, cytisine	Ding *et al*. 2006
	Alisma orientalis	Alisol-acetate, antyhydroalisol, β-epoxyalisol	Jiang *et al*. 2006
	Alisma orientalis	Alismorientol A	Jiang *et al*. 2007
	Ardisia chinensis	Phenolics	Leung *et al.* 2006
	Oenanthe javanica Blume	Flavonoids	Wang *et al.* 2005
	Sophorae flavescentis	Flavonoids	Li *et al*. 2006
	Paeonia lactiflora PALL		Lee *et al*. 2006
HCV	*Acacia nilotica*, *Boswellia carterii*, *Syzygium aromaticum*	Silybin, oxymatrine	Hussein *et al*. 2000; Liu *et al*. 2003
	Amebia euchroma, *Thlaspi arvense*, *Poncirus trifoliata*	Flavonoids	Ho *et al*. 2003
	Stylogne cauliflora	Oligophenol	Hegde *et al*. 2003; Liu *et al*. 2003
HIV	Olive leaf extract	Acute infection, cell-to-cell transmission	Lee-Huang *et al*. 2003
	Drymaria diandra	Drymaritin (alkaloid)	Hsieh *et al*. 2004
	Brazilian propolis	Moronic acid (triterpenoid)	Manfredi *et al*. 2001
	Glycyrrhiza lepidota, *G. glabra*	Diprenyl bibenzyl, glycyrrhizin (flavonoid)	
	Maesa lanceolata	Maesasaponin	Apers *et al*. 2001
	Desmos spp.	Cinnamoylbenzaldehyde	Wu *et al*. 2003
	Maclura tinctoria	Macluraxanthone (phenolics)	Groweiss *et al*. 2000
	Ailanthus altissima	Flavonoids	Chang and Woo 2003
	Begonia nantoensis	Oleanoic, catechin (flavonoid)	Wei *et al*. 2004
	Momordica charantia L.	Lectin MAP30	Cos *et al*. 2004
	Listeria ovata	Ribosome inactivating proteins	
	Gelonium multiflorum	GAP 31 (lectin)	Bourinbair and Huang 1996
	Urtica dioca	N-acetyl glucosamine (lectins)	Chattopadhyay and Khan 2008
	Tieghemella heckelii	Arganine (saponin)	Gosse *et al*. 2002
HIV-1 entry	*Stephania cepharantha*	Cepharanthine (alkaloid)	Ma *et al*. 2002
	Prangos tschimganica	Coumarine	Shikishima *et al*. 2001
	Vatica cinerea	Vaticinone (triterpenes)	Zhang *et al*. 2003
	Leucojum vernum	Alkaloid	Szlavik *et al*. 2004

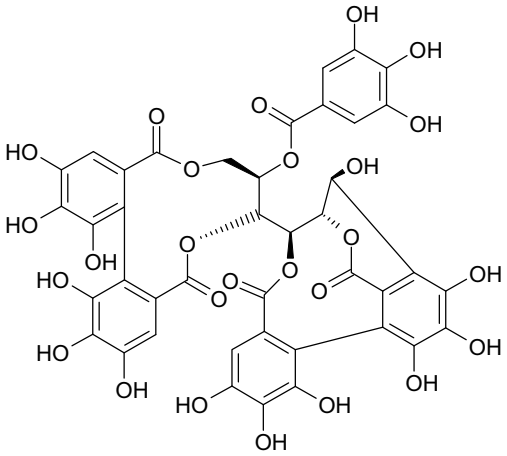
Table 3 (Cont.)

Virus	Name of plant(s)	Chemical group	References
Replication	*Scutellaria baicalensis*	Baicalein, baicalin	Wu *et al*. 2001
	Phyllanthus amarus	Flavonoids	Notka *et al*. 2004
HIV-1 RTase	*Callophyllum lanigerum*	Calonides (coumarins)	Cos *et al*. 2004
	Dryopteris crassirhizoma	Kaempferol	Min *et al*. 2001
	Momordica charantia	MRK 29 (polypeptide)	Jiratchariyakul *et al*. 2001
	Shepherdia argentea	Shephagenin, strictinin (tannin)	
	Phyllanthus amarus	Geraniin (gallotannins)	Notka *et al*. 2003
HIV-1 Protease	*Geum japonicum*	Ursolic acid (triterpene)	Clark *et al*. 1998
	Camellia japonica	Camelliatannin (tannin)	Park *et al*. 2002
HIV-1 Fusion	*Prunella vulgaris*	Polyphenol	Liu *et al*. 2002
	Rhizoma cibolte	Tannin	
Integrase, Protease	*Curcuma linga* L.	Curcumin	Cos *et al*. 2004
	Larrea tridentata L.	Lignan	
CXV- B3	*Loranthus yadoriki*	Camp B, C (polyphenol)	Wang *et al*. 2000
PV 2, 3	*Dianella longifolia*	Chrysophenate (anthraquinone)	Semple *et al*. 2001
Picorna, Rhino	*Pterocaulas sphaedatum*	Chrysophenol	
	Psiadia dentata	Kaempferol (flavonoids)	Robin *et al*. 2001
Poliovirus	*Guazuma ulmifolia* Lam.	Replication, viral antigen synthesis in infected cell	Felipe *et al*. 2006
Junin Virus	*Lippia junelliana*, *L. turbinata*, *Heterotheca latifolia*, *Tessaria absinthides*	Essential oil	Garcia *et al*. 2003
EBV	*Syzygium aromaticum*	Ellagitannin (tannin)	Jassim and Naji 2003
Dengue-2	*Artemisia douglasiana*, *Eupatorium patens*	Flavonoids	
	Azadirachta indica	*In vitro* and *in vivo*	Parida *et al*. 2002
SARS-CoV	*Stephania cepharantha*, *Glycyrrhiza glabra*	Isoquinoline alkaloid, glycyrrhizin	Liu *et al*. 2004
	Lycoris radiata	Lycorine	Li *et al*. 2005
Rotavirus, Coronavirus	*Camellia sinensis*, *Eleutherococcus senticosus*	Theaflavin, Catechin (flavonoid)	Clark *et al*. 1998 Turan *et al*. 1996
ADV-1	Black soybean extract	ADV-1, CXV- B1	Yamai *et al*. 2003
Haemorrhagic septicaemia virus	*Olea europaea* L.	Leaf extract Inhibit replication	Micol *et al*. 2005

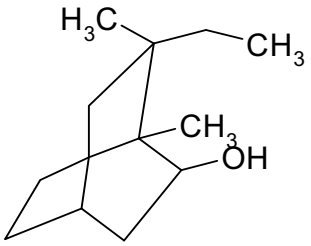
ADV, Adenovirus; CXV, Coxsakie virus; EBV, Epistein-Brrar virus; HSV, Herpes simplex virus; VSV, Vesicular stomatitis virus; VZV, Varicella zoster virus; PRV, Pseudorabies virus; PV, Poliovirus; RSV, Respiratory sychetrial virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; SARS-CoV, Sevier acute respiratory sychetrial Coronavirus; RV, Rotavirus.

prolonged the mean survival times of infected mice without toxicity by suppressing virus yields to the brain and therefore, can be a new anti-HSV agent with different mechanism of action than that of acyclovir. Similarly, the extracts of *Aglaia odorata*, *Moringa oleifera* and *Ventilago denticulate* of Thailand, inhibit thymidine kinase-deficient and phosphonoacetate-resistant HSV-1 and delayed the development of skin lesions, increase the mean survival times and reduced the mortality of infected mice similar to acyclovir (Lipipun *et al.* 2003). The polyphenol of *Agrimonia pilosa* and *Punica granatum* showed anti-HSV-1 activity, as observed with prodelphinidin-di-*O*-gallate from *Myrica rubra* bark that inhibits HSV-2 attachment and penetration (Cheng *et al.* 2003). As a whole plant polyphenols and proanthocyanidins had remarkable anti-HSV-1 activity (Erdelmeier *et al.* 1996; Shahat *et al.* 2002) as they nonspecifically bind proteins, but selectively inhibit NFkB-dependent gene expression, as reported with proanthocyanidin C1 (**10**) that modulates apoptosis and inhibits NFkB activities (Cos *et al.* 2004); while proanthocyanidins A1 (**10**) of *Vaccinium vitis-idaea* specifically block HSV-2 attachment and penetration (Cheng *et al.* 2005). An interesting SAR is noted with dimeric procyanidins and related polyphenols (**10, 11**), where epicatechin dimers (**11**) showed pronounced anti-HSV activities, as the ortho-trihydroxyl groups in B-ring and the double interflavan linkages significantly increase of the antiviral effects (Cowan *et al.* 2003). The aqueous extract of *Plantago major*, used in Ayurveda, TCM and Chakma Talika Chikitsa (Chakma tribes, Chittagong Hill, Bangladesh) inhibit HSV-1 and HSV-2 due to caffeic acid and its derivatives (**12**) (Khan *et al.* 2005). The SAR studies revealed that chlorogenic and caffeic acid (**12**) can be developed as an improved antiherpes agent. Similarly, xanthohumol (**13**)-enriched *Humulus lupulus* (hop) extract with anti-HSV-2 and HSV-1 activity might serve as a lead for synthesizing more active anti-HSV agent (Buckwold *et al.* 2004). The aqueous extract of a Kenyan plant *Carissa edulis* (Forssk.) Vahl (Apocynaceae) roots showed remarkable anti-HSV activity *in vitro* and *in vivo* against both wild type and resistant strains (Tolo *et al*. 2006), by inhibiting 100% plaque formation in Vero E6 cells infected with the wild type HSV-1 (7401H), HSV-2 (Ito-1262), and resistant HSV-1 strains (TK(-) 7401H and AP(r) 7401H) at 50 µg/ml *in vitro* with minimal cytotoxicity (CC_{50} 480 µg/ml); while an oral dose of 250 mg/kg significantly delayed the onset of symptoms, increased the mean survival time and reduced the mortality rate of cutaneously infected Balb/C mice with wild type or resistant strains (Tolo *et al.* 2006).

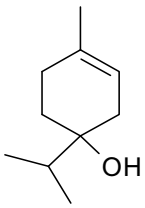
A recent study with the aqueous root extract of African plant *Pelargonium sidoides* showed that combinations of coumarins (**14**), phenolics, flavonoid and catechin derivatives (**11**) inhibit plaque formation (99.9%) of both HSV-1 and HSV-2 *in vitro*, when pretreated with the extract or the extract was added during adsorption, unlike acyclovir that acted intracellularly during replication. Thus, this extract affected the virus before penetration into the host cell; indicating that it might be a candidate for topical use (Schnitzler *et al*. 2008). The essential oil of *Melissa officinalis* containing monoterpene aldehydes citral a, citral b and citronellal and lemon balm oil showed *in vitro* anti-HSV-1 and HSV-2 activity (IC_{50} = 0.0004% for HSV-1 and 0.00008% for HSV-2). At noncytotoxic concentrations plaque formation was significantly reduced (98.8% for HSV-1 and 97.2% for HSV-2), while at higher concentrations viral infectivity was completely abolished, as the oil affected the virus before adsorption, and thereby exerting a direct antiviral effect. Moreover, the high selective index and lipophilic nature of oil help to penetrate the skin, indicating its suitability for topical use (Schnitzler *et al*. 2008). Rosmarinic acid (**15**), and phenolics like apigenin (**16**) and luteolin-derivatives isolated from the Lamiaceae plants *Prunella vulgaris* (self-heal), *Mentha piperita* (peppermint), *Rosmarinus officinalis* (rosemary) and *Thymus vulgaris* (thyme) exhibited high and concentration-dependent antiviral acti-



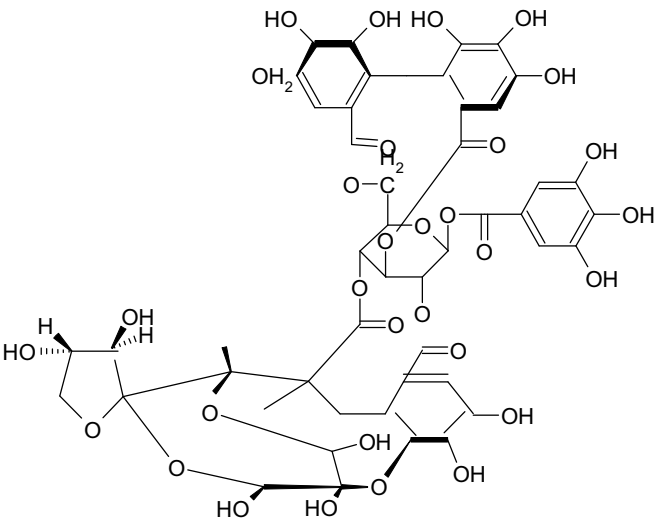
1. Casuarinin



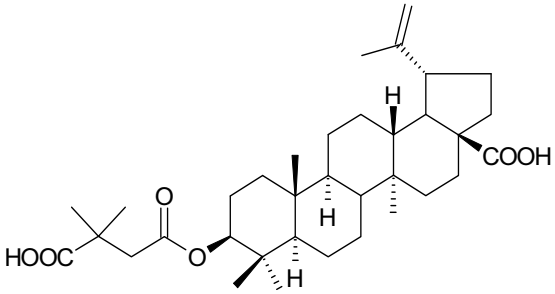
2. Isoborneol



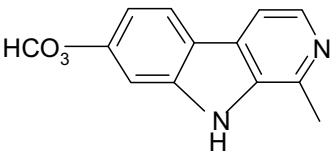
3. Terpinen-4-ol



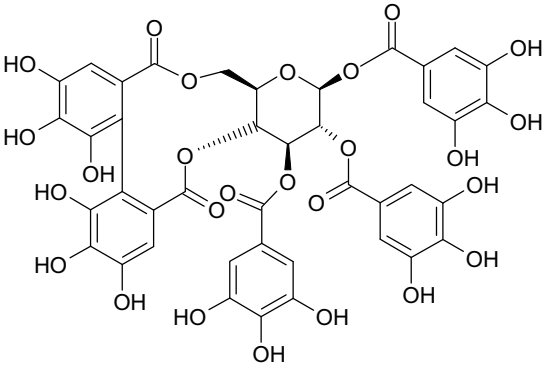
4. Putranjivain A



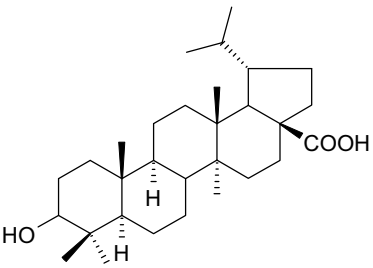
5. ent-Epiafzelechin



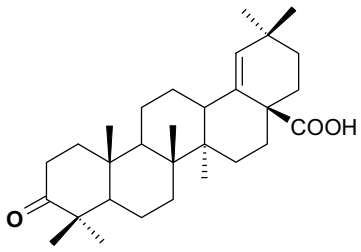
6. Harmine (*O. nicobarica*)



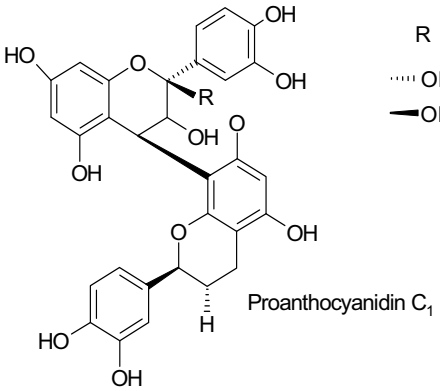
7. Eugenin



8. Betulinic acid

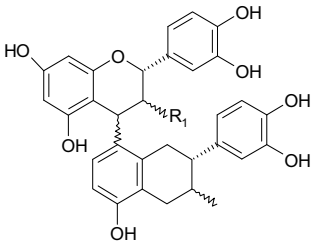


9. Moronic acid



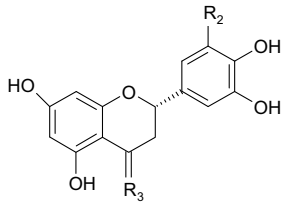
R	Name
····OH	Proanthocyanidin A_1
▬OH	Proanthocyanidin A_2

Proanthocyanidin C_1



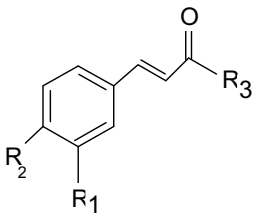
R_1	R_2	Interflavan bond	Name
····OH	▬OH	▬	Procyanidin B_1
····OH	····OH	▬	Procyanidin B_2
▬OH	▬OH	·····	Procyanidin B_3
▬OH	····OH	·····	Procyanidin B_4

10.Structure activity relationships of Proanthocyanidins



R_1	R_2	R_3	Name
····OH	H		(-) Epicatechin
▬OH	H	H_2	(+) Catechin
····OH	OH	H_2	Epigallocatechin
▬OH	H	O	(+) Taxifolin
▬OH		OH	Aromadendrin

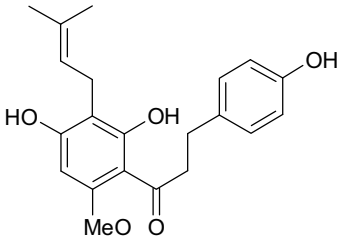
11. Epicatechin and its dimers



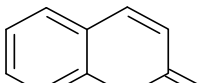
Name	Functional Groups R_1	R_2	R_3
Caffeic Acid	-OH	-OH	-OH
Chlorogenic Acid	-OH	-OH	X*
p-Coumaric Acid	-OH	-H	-OH
	-OH	-OCH	

*1, 3, 4, 5-tetrahydroxycyclohexane carboxylic acid

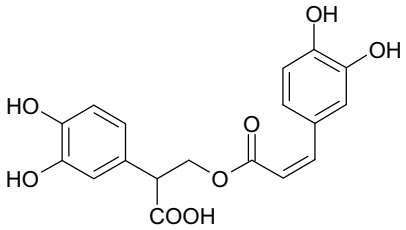
12. Structure activity of Chlorogenic acid and its derivatives



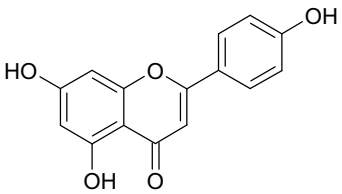
13. Xanthohumol



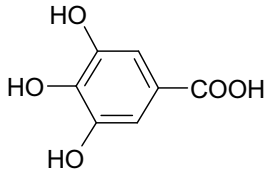
14. Coumarins



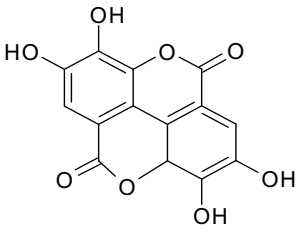
15. Rosmarinic acid



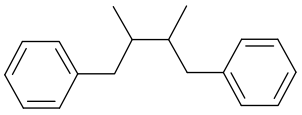
16. Apigenin



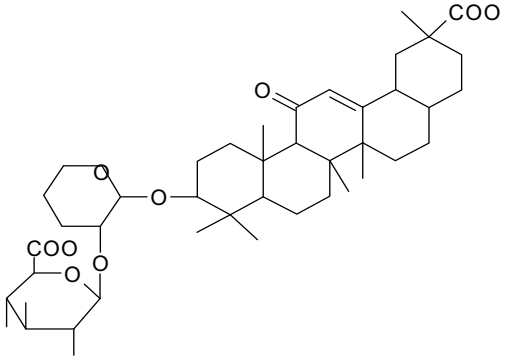
17. Gallic acid



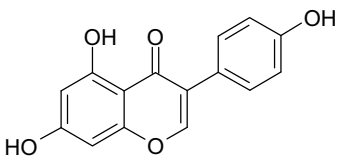
18. Ellagic acid



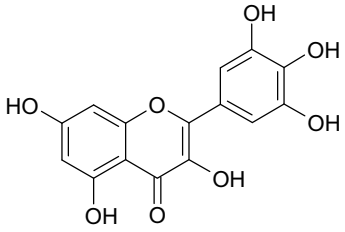
19. Lignan



20. Glycyrrhizin



21. Genistein



22. Myricetin
(3,3′,4′,5,5′,7-Hexahydroxy Flavones

vity against acyclovir-sensitive and acyclovir-resistant HSV-1 (IC_{50} 0.05-0.82 µg/ml). Studies revealed that 80% ethanol extract of *Prunella* and *Peppermint* at maximum non-cytotoxic concentrations exert antiviral effect against free HSV virions and block virus attachment to host cell, reduced plaque formation drastically, indicating its dual mode of action. Thus, *Prunella* and peppermint extracts are promising topical agents in recurrent herpes infections (Reichling *et al*. 2008). The crude extract of Indian *Swertia chirata* inhibits HSV-1 plaque formation at 1 gm/mL by inhibiting viral dissemination but failed to block gene amplification (Verma *et al*. 2008). On the otherhand, the tricin (4',5,7-trihydroxy-3',5'-dimethoxyflavone) from the crude hot water extract of Japanese bamboo tree *Sasa albo-marginata* (*Bambuseae sasa*) showed dose dependent cytopathic effect with reduced IE and late antigen of human CMV with an IC_{50} of 0.17 µg/ml and Selective index of 1205.8, indicating its further evaluation (Sakai *et al*. 2008). Again the anise oil, dwarf-pine oil and chamomile oil exhibited high levels of antiviral activity against aciclovir-sensitive HSV (KOS strain), aciclovir-resistant clinical isolates. At maximum noncytotoxic concentrations plaque formation was reduced (96.6-99.9%) when viruses were preincubated with extract before attachment, indicating that these oils interrupt HSV adsorption (direct effect), which might be useful in the treatment of drug-resistant viruses. Furthermore, chamomile oil is non-irritating on chorioallantioic membrane of hen's egg, have highest selectivity index and was highly active against aciclovir-resistant HSV-1 (Koch *et al*. 2008).

2. Hepatitis viruses

Viral hepatitis is caused by hepatitis A, B, C, D and E viruses. Although exposure to any of these viruses leads to acute infection, type B, C, and D are unique in causing chronic infection. Hepatitis B virus (HBV) is known to be associated with hepatitis, cirrhosis, chronic liver disease and primary hepatocellular carcinoma, and more than 200 million people worldwide are HBV carriers, of which many are asymptomatic (Ghendon 1987). Although a safe and effective HBV vaccine exists there is no effective therapy for carriers. Traditionally the genus *Phyllanthus* has been used against liver disease like jaundice retrospectively caused by HBV, hence *in vitro* studies of the aqueous extracts of several *Phyllanthus* species like *P. amarus*, *P. debilis*, *P. fraternus*, *P. niruri*, *P. urinaria* and *P. mimicus* was found to inhibit DNA polymerase of Hepadnaviruses (Venkateswaran *et al.* 1987; Wang *et al*. 1995). Clinical studies with *P. amarus* L., *P. niruri* L. and *P. urinaria* L. (Wang *et al*. 1995), and molecular studies with *P. amarus* L. showed that these extracts inhibit HBV polymerase activity and mRNA transcription due to interactions with viral enhancer I and C/EBP alpha and beta transcription factors (Lee *et al*. 1996; Ott *et al*. 1997). Microarray analyses revealed the anti-HBV activity of *Phyllanthus nanus* is due to over expression of genes like annexin 7 (Lam *et al*. 2006). A recent report showed that *Boehmeria nivea* root extract significantly reduce HBV activity by reducing HBsAg, HBVe antigen, inhibiting viral DNA replication and RNA expression at 100 mg/L dose (Huang *et al.* 2006). Due to the lack of smaller animal model the screening of anti-HBV compounds has been snagged, but duck hepatitis B virus (DHBV) model was found to be an excellent screening system for human HBV infection, as found with the screening of plants like *Phyllanthus* sp., revealed that *Phyllanthus amarus* has no significant inhibitory effect on viral DNA replication *in vivo* (Niu *et al*. 1990). Comparative studies with *P. amarus*, *P. maderas* (Munshi *et al*. 1993a), and *P. maderaspatensis* (Munshi *et al*. 1993b) in DHBV model revealed that these plants do not have any therapeutic potential against human HBV, although *P. nanus* showed strong inhibitory effect on DHBV in primary cell culture (Lam *et al*. 2006). Such controversial data need further investigation at molecular level to validate initial data. To date, DHBV model is found to be very helpful in identifying a number of candidate therapeutics for clinical trials, like *Ardisia chinensis*, and *Pithecellobium clypearia*, as evident from screening of 56 Chinese herbs for the identification of two potentials anti-DHBV extracts, *Ardisia chinensis*, and *Pithecellobium clypearia* (Leung *et al*. 2006). Again the identification of *Oenanthe javanica* Blume DC flavones as a strong inhibitor of HBsAg and HBeAg secretion and reducing DHBV-DNA levels in the HBV-infected duck model is significant (Wang *et al*. 2005). In traditional system several medicinal plants are mixed for combination therapy and such combination for viral hepatitis, like, fermentation broth of *Ganoderma lucidum* supplemented with aqueous extract of Radix *Sophorae flavescentis* showed strong anti-HBV activity *in vitro* and *in vivo*, and co-fermentation of these plant showed superior antiviral effect (Li *et al*. 2006). The ethyl acetate fraction of *Paeonia lactiflora* PALL root extract containing 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (PGG) showed anti-HBV activity (IC_{50} 8.1 µg/ml), as PGG (4 µg/ml) inhibit HBV multiplication, decreased the level of extracellular HBV (IC_{50} 1.0µg/ml) in a dose-dependent manner and reduced the HBsAg level by 25% (Lee *et al.* 2006). The gallate (**17**) group of PGG may play a critical role in the inhibition of anti-HBV activity. Interestingly the flavonoid ellagic acid (**18**) of *Phyllanthus urinaria* effectively blocks HBeAg secretion (IC_{50} 0.07 µg/ml), but unable to inhibit HBV polymerase activity or HBsAg secretion. Since HBeAg is involved in immune tolerance during HBV infection, so ellagic acid may be a therapeutic candidate against immune tolerance of HBV-infected individuals (Shin *et al.* 2005). The lignan (**19**) present in the ethanol extract of *Herpetospermum caudigerum* seed coat, inhibit HBV significantly (Yuan *et al.* 2006); while the alkaloids (-)-14 β-hydroxyoxymatrine, (+)-sophoranol, and (-)-cytisine, isolated from the roots and rhizomes of *Sophora tonkinensis* Gapnep. (Leguminosae) showed anti-HBV activity by inhibiting HBsAg and HBeAg secretion (Ding *et al.* 2006). Interestingly, the triterpenoid alisol A 24-acetate, 25-anhydroalisol A, β-epoxyalisol A, alisol B 23-acetate, alisol F and alisol F 24-acetate of *Alisma orientalis* rhizomes (a folk medicine of Sichuan province, China) had *in vitro* inhibitory activity against HBsAg (IC_{50} = 2.3-15.4 µM), and HBeAg (IC_{50} = 5.1-41.0 µM) secretion (Jiang *et al.* 2006); while the sesquiterpenoids alismorientols A of the same rhizomes showed moderate *in vitro* anti-HBV (IC_{50} for HBsAg and anti HBeAg was 1.1 and 14.7 µM) activity (Jiang *et al.* 2007).

Ethnomedicinal plants have also been tested against hepatitis C virus (HCV), e.g., the methanolic extracts of *Acacia nilotica* L. Willd ex Delile, *Boswellia carterii*, *Embelia schimperi*, *Quercus infectoria*, *Trachyspermum ammi* L. and aqueous extracts of *Piper cubeba* L., *Q. infectoria* and *Syzygium aromaticum* L., inhibit HCV (Hussein *et al*. 2000). Moreover, catechin, glycyrrhizin (**20**), polysterols and silymarin have potentials as anti-HCV agents (Patrick 1999; Jassim and Naji 2003). Data from five Chinese and one Japanese studies, and from thirteen randomized clinical trials showed that only four have appropriate methodologies; and phytochemicals like silybin and oxymatrine used in these trials have clear HCV, by reducing serum aspartate aminotransferase and γ-glutamyl-transpeptidase levels (Liu *et al*. 2003). The Chinese folklore *Arnebia euchroma*, *Thlaspi arvense* and *Poncirus trifoliata* displayed strong anti-HCV activities (Ho *et al.* 2003), while the oligophenols of Peruvian folklore *Stylogne cauliflora* inhibit HCV nonstructural serine protease (Hegde *et al.* 2003), but the Chinese herbal mix consisting of Bing Gan Tang, Yi Zhu decoction, and Yi Er Gan Tang reduced viral RNA and normalize ALT (Liu *et al*. 2003). Such reports strongly suggest appropriate vigilance programs for assessing the benefits of herbal medicine. Due to lack of a good vaccine identification of anti-HCV phytophores screening programs are ongoing, particularly in the resource poor countries.

RNA viruses

RNA viruses are a major source of respiratory diseases, but the lack of effective therapeutical treatment underlines the need of new antiviral compounds, particularly against influenza and respiratory syncytial viruses (RSV).

1. Influenza viruses

The search for natural inhibitors against influenza virus is very ancient and several scientific efforts have been made toward identifying phytochemicals that inhibit influenza virus in the past (Cochran *et al*. 1966; May and Willuhn 1978). Earlier and recent literature suggests that a variety of phytochemicals inhibit influenza virus both *in vitro* (Prajoubklang *et al*. 2005; Mothana *et al*. 2006; Pantev *et al*. 2006) and *in vivo* (Prahoveanu *et al*. 1986; Ivanova *et al*. 2005). An intriguing observation is the anti-influenza activity of wide variety of phytochemicals, such as alkaloids, flavonoids, glucosides, polyphenols, saponins (Wang *et al*. 2006), so it is being hoped that in future, an effective phytochemical will be developed for controlling the influenza virus. Earlier study showed that *Sanicula europaea* extract inhibit influenza A virus by blocking RNA dependent enzymes (Turan *et al.* 1996); while a combination of *Verbascum thapsiforme* flower infusion with amantadine markedly inhibit H7N7 (Alche *et al.* 2000) like Nepalese ethnomedicine *Nerium indicum* (Rajbhandari *et al.* 2001). Bodinet *et al.* (2002) reported that the oral administration of *Thujae occidentalis*, *Baptisiae tinctoriae* and *Echinacea purpurea* extract significantly increase the survival rate and mean survival time with reduced virus titer in Influenza A virus infected Balb/c mice. Interestingly the isoquinoline alkaloid thalimonine from *Thalictrum simplex* inhibit influenza A virus replication by blocking viral neuraminidase, haemagglutinin, nucleoprotein, and virus-specific protein synthesis (Serkedjieva and Velcheva 2003); while the bioflavonoids arctiin, phillyrin, liquiritin, genistein (**21**), daidzein, myricetin (**22**) and chlorogenic acid (**12**) inhibit influenza virus replication (Shi *et al.* 2003). The extract of *Bergenia ligulata* rhizomes, inhibits influenza virus replication by blocking RNA and protein synthesis at 10 µg/ml in a dose-dependent manner due to tannin (**24**) (Rajbhandari *et al.* 2003), but polyphenol-rich fraction of *Geranium sanguineum* extract showed strong activity against influenza virus (Sokmen *et al.* 2005). Wei *et al* (2004) reported that the flavonoids of *Aesculus chinensis* seed had flavonoids had significant activities against influenza A virus with IC_{50} 24.5 µg/mL and SI 16.0 (Wei *et al.* 2004); while the methanol extracts of *Boswellia ameero*, *Boswellia elongata*, *Buxus hildebrandtii*, *Cissus hamaderohensis*, *Cleome socotrana*, *Dracaena cinnabari*, *Exacum affine*, *Jatropha unicostata* and *Kalanchoe farinacea* inhibit influenza virus A with IC_{50} = 0.7-12.5 µg/mL (Mothana *et al.* 2006). On the other hand the flavonoid glycosides 2"-*O*-(2-methylbutanoyl) isoswertisin, of *Trollius chinensis* Bunge, had moderate active against influenza virus A (Cai *et al.* 2006).

2. Severe Acute Respiratory Syndrome Coronavirus (SARS Cov)

Medicinal plants exhibiting broad antiviral effects can be used in antiviral drug discovery programs as in case of glycyrrhizin (**20**), a bioactive phytophore of *Glycyrrhiza uralensis* (liquorice), and lycorine of *Lycoris radiata* that showed strong anti-SARS-CoV activity (Li *et al*. 2005). Hence, plants previously shown to possess broad-spectrum antiviral effects could be screened for newly emerging/ resistant viral strains. The caffeine beverages green, black and oolong tea from *Camellia sinensis* contain many polyphenolics mainly the bioflavonoids. In green tea the leaves are dried, in black tea the leaves are fermented and then dried, but Oolong tea is partially fermented. Black tea, produced by a series of fermentation that oxidizes the catechin of green tea leaves into theaflavins (theaflavin, theaflavin-3-gallate, theaflavin-3'-gallate and theaflavin-3,3'-digallate, **23**) by dimerization and then into thearubigins by polymerization. Catechins make up 80% of the flavonoids in green tea, but 30-50% in black teas, as some catechins is converted into theaflavins (**23**). Tea catechins have two isomers, catechins and epicatechins (**11**), and each stereochemical isomer exists as two optical isomers: (+) and (-), and (-)-catechin can be esterifies with gallic acid (**17**). Tea polyphenols are strong antioxidants, with several bioactivities, mainly due to epigallocatechin gallate (EGCG, **25**), or a mixture of polyphenols. A recent study reported that water soluble tannic acid (**24**, IC_{50} = 10 µM), theaflavin-3'-gallate (IC_{50} = 3 µM) and theaflavin-3,3'-digallate (IC_{50} = 7 µM) inhibit chymotrypsin-like protease ($3CL^{PRO}$), an essential enzyme of SARS Coronavirus (CoV) maturation (Chen *et al.* 2005). The SAR studies revealed that theaflavin-3-3'-digallate with two gallate groups at 3 and 3' position and the gallate group at 3' position might be important for interaction with $3CL^{PRO}$ active site as catechins are less active ($IC_{50} \geq$ 100 µM) than theaflavins (**23**). It is interesting that both rotavirus and coronavirus replicate in human intestinal tract can be neutralize by theaflavins (Clark *et al.* 1998; Leung *et al.* 2003). So, whether drinking black tea can prevent coronavirus and rotavirus infections and theaflavins can used to design more active viral inhibitor is a subject of further study.

3. Respiratory Syncytial Virus

Although the global prevalence of respiratory syncytial virus (RSV) infection, especially among infants and young children is increasing, there are only limited therapeutic options for its treatment. The British Columbian ethnomedicines *Potentilla arguta* and *Sambucus racemosa* inhibit RSV; but luteoside (flavonol glycoside) of *Barleria prionitis* and *Markhamia lutea* root showed potent anti-RSV activity (Hudson 1990; Kernan *et al.* 1998); while *Radix glycyrrhizae* inhibit the replication of RSV in a dose-dependent manner (Dong *et al.* 2004). A flavonoid fraction of *Aesculus chinensis* seed showed significant activities against RSV with IC_{50} = 4.1-6.7 µg/mL and SI of 15.8-63.8 (Wei *et al.* 2004). Interestingly polyphenols of *Blumea laciniata*, *Elephantopus scaber* and *Scutellaria indica* inhibit RSV with an IC_{50} = 12.5-32 µg/ml (Li *et al.* 2004), but flavonoids of *Aesculus chinensis* seed extract inhibit both RSV and influenza A virus (Dong *et al.* 2004). Therefore, the search for novel inhibitors of RSV has become more intensive. In a pilot screening of compounds from various *Aglaia* species found that dammarenolic acid is the most potent and more cytotoxic anti-RSV compound. Time of addition studies reveal that both dammarenolic acid and aglaiol target the RSV replication at a post-entry stage (Esimone *et al.* 2008). Interestingly methylation of dammarenolic acid results in a complete loss of anti-RSV activity. By carrying out parallel anti-RSV screening with aphidicolin (a highly cytotoxic diterpenoid) and dammarenolic acid, it was observed that aphidicolin had no anti-RSV activity (Esimone *et al.* 2008).

Medicinal plants in miscellaneous viral infections

A variety of herbal preparations have shown potentials for inhibiting viruses causing serious infections such as measles viruses (Sindambiwe *et al*. 1999; Olila *et al*. 2002), human rotaviruses (HRV) (Husson *et al*. 1994; Takahashi *et al*. 2001), RSV, human rhinoviruses (Glatthaar-Saalmuller *et al*. 2001), coxsackie group of viruses (Evstropov *et al*. 2004: Su *et al*. 2006), neurotropic Sindbis virus (Paredes *et al*. 2001) and strains of poliovirus (Vilagines *et al*. 1985; Andrighetti-Frohner *et al*. 2005; Melo *et al*. 2006). To prove or disprove antiviral effect of herbal preparation molecular study is essential. Very few studies have addressed this aspect relevant to the therapeutic development of phytochemicals. One such example is the molecular study with hot water extracts of *Stevia rebaudiana* L. that block entry of

various serotypes of HRV into the cells by an anionic polysaccharide (MW 9800) with uronic acid (Takahashi *et al*. 2001). Similarly an alkaloid extract of *Haemanthus albiflos* bulbs inhibited RNA synthesis of HRV propagated in MA-104 cells (Husson *et al*. 1994). The antiviral activity of many plants against multiple viruses is also reported. For e.g., *Melia azedarach* L., a deciduous tree native to India contain a number of potent pharmaceutical limonoids and triterpenoids (Lee *et al.* 1991) has long been used for its medicinal and insecticidal properties (Bohnenstengel *et al.* 1999) and for the treatment of a variety of diseases including dermatitis and rubella. It was found that the leaf extracts inhibit the multiplication of HSV, Junin virus, Sindbis virus, VSV, poliovirus, pseudorabies virus and Tacaribe virus *in vitro* with no toxicity to host cells (Wachsman *et al.* 1982, 1987; Descalzo and Coto 1989; Castilla *et al.* 1998), and its antiviral activity was ascribed to meliacine (Andrei *et al.* 1988; Alché *et al.* 2002). Recently, a tetranortriterpenoid limonoid 1-cinnamoyl-3, 11-dihydroxymeliacarpin from this plant (ethyl acetate extract of leaf), shown to reduced infectivity of VSV (IC_{50} = 6 μm) and HSV-1 (IC_{50} = 20 μm) by inhibiting viral multiplication (Alché *et al.* 2003), and block VSV entry and the intracellular transport of VSV-G protein to the plasma membrane (Barquero *et al.* 2004). Topical administration of meliacarpin in the corneas of HSV-1-infected mice can reduce the viral load and abolish the ocular inflammation (Alché *et al.* 2003), prevent the development of herpetic stromal keratitis, and impede NFkB activation in HSV-1-infected conjunctival cells that lead to the accumulation of p65 NFkB subunit in the cytoplasm of Vero cells. Hence, meliacarpin is a pleiotropic agent that inhibits the multiplication of DNA and RNA viruses by the same mechanism and also modulates the NFkB signaling pathway (Barquero *et al.* 2006).

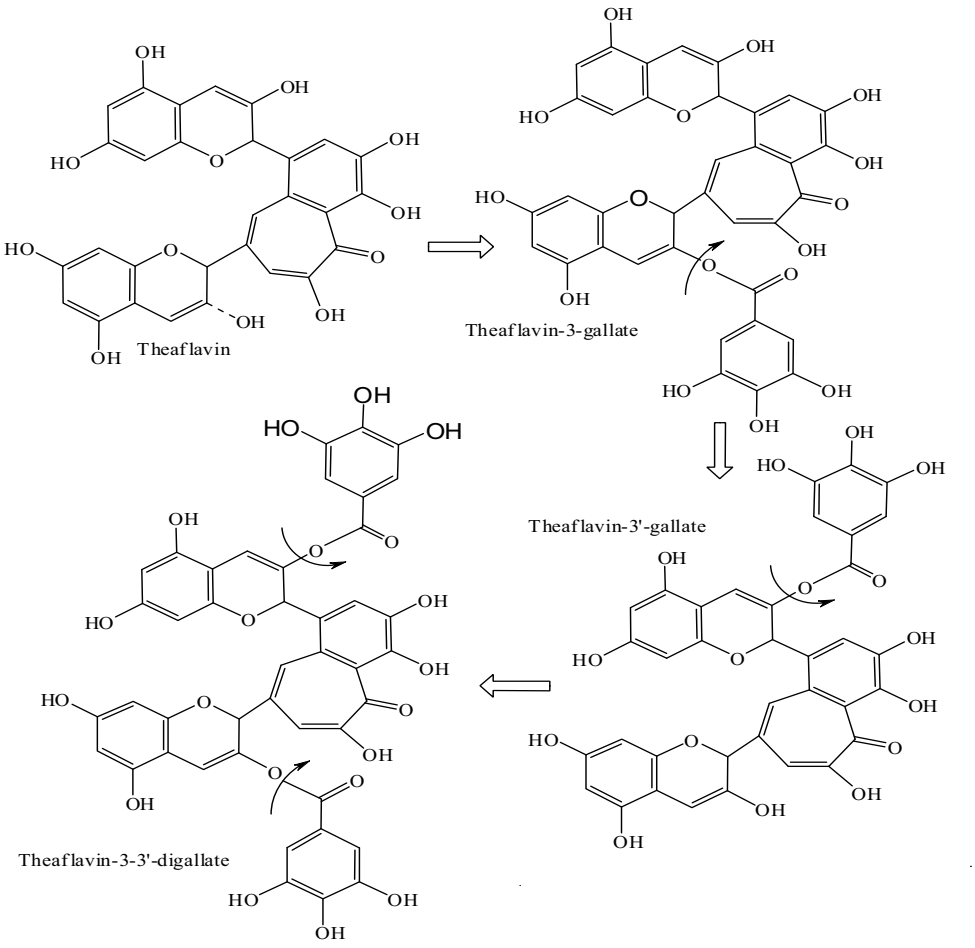
The caffeic acid, chlorogenic acid (**12**) and rosmarinic acid (**15**) derivatives of many ethnomedicines can inactivate HSV-1, varicella zoster virus (VZV), pseudorabies and influenza viruses (Sydiskis *et al.* 1991). The antiviral activities of grape, apple and strawberry juices were reported against HSV, poliovirus 1, coxsackievirus (CV) B5 and echovirus 7 (EV7). It is reported that the virucidal activity of *Loranthus yadoriki* extract against coxsackievirus B3 is better than ribavirin (Wang *et al.* 2000). Robin *et al.* (2001) found that 3-methylkaempferol (**26**) present in *Psiadia dentata* is the most potent inhibitor of genomic RNA synthesis of poliovirus, but skimmianine isolated from *Zanthoxylum chalybeum* seed inhibit *Edmonston* and *Swartz* strains of measles virus (Olila *et al.* 2002). Pulegone of *Minthostachys verticillata* inhibit HSV-1 and pseudorabies virus replication (Primo *et al.* 2001). The essential oil of *Lippia junelliana* and *L. turbinata* of San Luis, Argentina is virucidal (VC_{50} = 14-20 ppm) against Junin virus; while saikosaponins and iridoid glycosides of *Bupleurum rigidum* and *Scrophularia scorodonia* inhibit VSV (Bermejo *et al.* 2002), but essential oils of *Artemisia douglasiana* and *Eupatorium patens* inhibit HSV-1 and Dengue 2 (Garcia *et al.* 2003). On the other hand, *Senecio ambavilla*, a folk remedy of La Reunion Island had inhibitory activity against HSV-1 and poliovirus 2 (Fortin *et al.* 2002); while the furanoditerpenes caesalmin of *Caesalpinia minax* seed inhibit parainfluenza Virus 3 (Yogeeswari and Sriram 2005). The antiinflammatory, anticancer, neuroprotective and antioxidant monoflavonoid wogonin have rapid tissue distribution and prolonged plasma elimination rate and is reported to have broad spectrum of antiviral activity (Tai *et al.* 2005), thus be a potential candidate for designing anti-rabies and or anti-encephalitis drugs. The aqueous and ethanolic extract of *Ocimum basilicum*, sweet basil showed strong activity against HSV-1, CV B1, ADV-8 and EV 71 due to Apigenin (**16**), linalool and ursolic acid (**27**). Of these ursolic acid (**27**) showed the strongest activity (EC_{50}) against HSV-1 (6.6 mg/L), ADV-8 (4.2 mg/L), CVB1 (0.4 mg/L) and EV 71 (0.5 mg/L); while apigenin had highest activity against HSV-2, ADV-3, HBsAg and HBeAg. Again the antiviral activity of ursolic acid against coxsackievirus and Enterovirus is evident during the infection process and the replication phase, indicating that the ursolic acid can be a potential candidate against these RNA viruses (Chiang *et al.* 2005). A recent study showed that raoulic acid, principal ingredient of *Raoulia australis* Hook F, possessed strong activity against human rhinovirus (HRV) 2 with IC_{50} <0.1 μg/ml, HRV3 with 0.19 μg/ml, CB3 virus with 0.33 μg/ml, CB4 virus with 0.40 μg/ml, and enterovirus EV71 virus with IC_{50} <0.1 μg/ml (Choi *et al*. 2009a). Based on all the above information, it can be fairly concluded that medicinal plants offer a variety of anti-infectious compounds, particularly antiviral agents.

Antiviral activity of mixture of compounds and mixed formulations

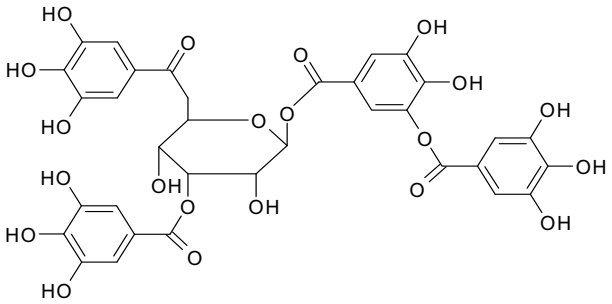
Traditionally ethnomedicines rely on both single-plant or mixed formulations with many plants. Propolis, a crude extract of the balsam of various trees inhibits hemagglutination activity of influenza A virus, acyclovir-resistant HSV-1, ADV-2, VSV, and poliovirus due to the synergistic action of a mixture of terpenoids, flavonoids, benzoic acid esters, and phenolic acid esters; while flavone (**28a**) and flavonol (**28b**) present in propolis were active against HSV-1 (Amoros *et al*. 1992). The methyl ester dehydrochebulic acid (**29**) and methyl brevifolin carboxylate from *Phyllanthus urinaria* showed anti-HBV activity (Zhong *et al*. 1998). Similarly the mixture of flavonoids, triterpenoids and their glycosides of *Azadirachta indica* leaf inhibit plaque formation in six antigenic types of coxsackievirus by interfering early steps of replication (Badam *et al*. 1999). The stem bark extract of *Juglans mandshurica* showed potent inhibitory activity on HIV-1 RTase due to 1,2,6-trigalloglucopyranose (IC_{50} = 0.067 μM) and 1,2,3,6-tetra galloyl glucopyranose (IC_{50} = 0.04 μM), respectively. Free hydroxyl group of galloyl residues inhibits RNase H activity (IC_{50} = 39 μM), and RTase inhibition is increased by the increase in the number of free hydroxyl on the galloyl residue (Min *et al*. 2000). The asiaticoside of *Centella asiatica* and mangiferin of *Mangifera indica*, used as herpesvirus remedy in Thailand, have anti-HSV activities; and combinations of any of these extracts with acyclovir resulted synergistic inhibition of HSV-2 (Yoosook *et al*. 2000). Again the mixture of compounds of *Artemisia capillaris* inhibits HIV replication (Wu *et al.* 2001). The kaempferol (crassirhizomoside and sutchuenoside) from *Dryopteris crassirhizoma* inhibit RT-associated DNA polymerase and RNaseH activities (Min *et al*. 2001), while diprenylated bibenzyl of *Glycyrrhiza lepidota* leaf inhibits HIV-1 (Manfredi *et al*. 2001). Extract of ajoene (**30**) from fresh garlic protect CD4 cells from HIV attack early in the viral life cycle and its anti-HIV activity is 45 times more powerful than dextran sulfate, as garlic impairs the activities of liver enzymes which processes protease inhibitors and thereby raises the protease inhibitor levels in the blood (Cos *et al*. 2004). Recent study revealed that despite highly active antiretroviral therapy (HAART) viral reservoirs can persist when HAART is ceased. Hence, prostratin (**31**), an anti-HIV phorbol ester (**32**) from Samoan medicinal plant *Homolanthus nutans*, was used with 12-deoxyphorboI 13-phenylacetate, a non-tumor promoting phorbol ester of *Euphorbia poissonii* to eliminate persistent viral reservoir in HIV-patients. This combined therapy is reported to induce HIV-1 gene expression in latently infected T-cells at concentrations 20 to 40-fold lower than prostratin alone (Bocklandt *et al*. 2003).

HIV/AIDS and medicinal plants

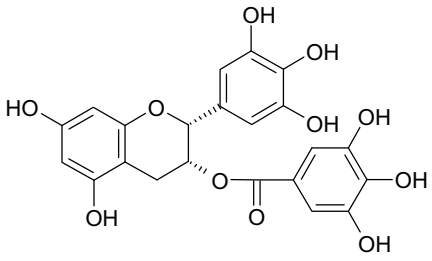
Numerous studies for the last two decades tried to identify an effective anti-HIV agent (Hudson 1990; Zhang *et al*. 1991; Nakamura *et al*. 1992; Decosterd *et al*. 1993; Rimando *et al*. 1994; Sun *et al*. 1996; Bukovsky and Gottlinger 1996; Boyd *et al*. 1997; Barthelemy *et al*. 1998; McDougall *et al*. 1998; Buckheit *et al*. 1999; Esser *et al*. 1999; Matthee *et al*. 1999; Zhu *et al*. 1999; Abad *et al*.



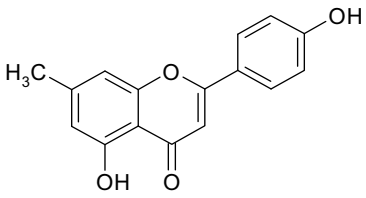
23. Structure activity relationship of theaflavin and its antiviral activity



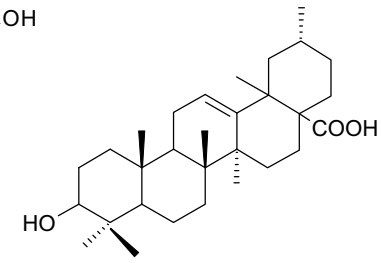
24. Tannic acid



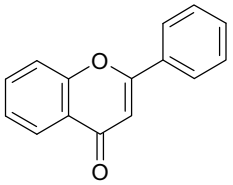
25. (-) Epigallocatechin-3-O-Gallate



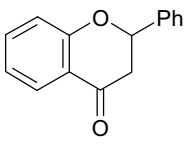
26. 3,methyl Kaempferol



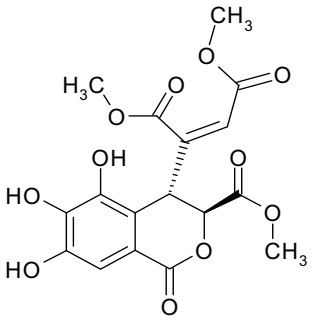
27. Ursolic acid



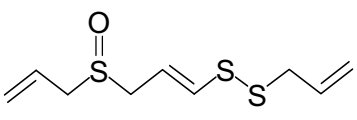
28a. Flavones



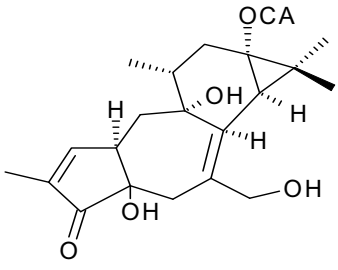
28b. Flavanols



29. Dehydrochebulic acid



30. Ajoene



31. Prostratin

2000; Labrosse *et al*. 2000; Jiratchariyakul *et al*. 2001; Liu *et al*. 2002; Yu *et al*. 2003a; Cos *et al*. 2004; Asrees *et al*. 2005; Kostova 2006; Fu *et al*. 2006; Chattopadhyay and Naik 2007; Saklani and Kutty 2008; Naithani *et al*. 2008; Lee *et al*. 2009). Over the past 28 years, since the first case of HIV/AIDS in 1981, AIDS has become the most devastating public health pandemic that has infected nearly 80 million people and 30 million dead. Around the world, the number of people living with HIV is now 40.3 million. The exploration and identification of natural products for controlling HIV/AIDS and co-infections is necessary because the efforts to find an effective cure for HIV infection has failed, and development of vaccine for HIV pandemic seems a far-fetched dream, and the most effective therapeutic regimen for HIV-infected individuals is a combination of protease inhibitors and nucleoside or non-nucleoside reverse transcriptase inhibitors called as highly active antiretroviral therapy (HAART), that can only control HIV infection among individuals continuously on therapeutic regimen, as withdrawal of medication leads to reemergence of the diseases. Furthermore, based on viral pathogenesis aim is to target every step of viral life cycle starting from entry to viral morphogenesis, though none of these strategies have led to cure. The introduction of HAART targeting HIV reverse transcriptase (RTase) and protease has dramatically improved survival and quality of life for HIV/AIDS patients. Despite the effectiveness of HAART, the emergence of drug-resistant viruses in infected patients and the severe side effects of HAART drug regimen necessitate continued search for new inhibitors targeted toward other viral proteins (Cos *et al*. 2004; Chattopadhyay and Naik 2007; Saklani and Kutty 2008; Naithani *et al*. 2008).

A class of antiviral compounds known as HIV entry inhibitors, interact either with viral envelope or host cell receptors mediating viral entry. Both cyanovirin and baicalin (**33**), interacts with chemokine receptors and inhibits HIV-1 entry (Zhang *et al*. 1991; Kitamura *et al*. 1998; Li *et al*. 2000; Wang *et al*. 2004). A recent study compared various plants and plant parts (stem, leaves, roots, etc.) in inhibiting viral RTase and integrase, the two essential enzymes in HIV infection (Bessong *et al*. 2006) and reported that *n*-butanol fraction of the *Bridelia micrantha* (Hochst) had highest anti-RT activity. RT inhibitors are already in the anti-HIV armamentarium, as it blocks viral infectivity and replication, and many medicinal plants can inhibit RT activity (Woradulayapinij *et al*. 2005; Fu *et al*. 2006; Kostova 2006). Medicinal plants have also inhibited viral protease, an enzyme essential for proteolytic processing of polyprotein precursor into essential proteins for the virus assembly. Triterpene derivatives from a many medicinal plants showed inhibitory effects on protease (Huang and Chen 2002; Park *et al*. 2005; Yu *et al*. 2005; Yu *et al*. 2006). *Prunella vulgaris* spike inhibit adsorption, replication and reverse transcriptase (RTase) of HIV-1, that lead to reduce the copies of proviral DNA (Kageyama *et al.* 2000), while the Korean ethnomedicines *Agrimonia pilosa* and *Mallotus japonicus* significantly inhibit HIV-1 RTase and RNase H (Min *et al.* 2001), but Korean folklore *Ailanthus altissima* inhibit HIV-1 fusion (Chang and Woo 2003). Interestingly fractionation of an antivirally inactive extract of *Tithonia diversifolia* yielded an aqueous fraction with a high anti-HIV-1 activity (Cos *et al.* 2004) indicating that the cytotoxicity of some ethnomedicines may mask the antiviral properties of the active compounds. On the other hand, *Homalium cochinchinensis* root bark extract can inhibit HIV-1 due to tremulacin and cochinchiside B (Ishikawa *et al.* 2004). Ongoing efforts are crucial toward further development of previously characterized protease inhibitors and identification of new compounds with such activity, as naturally occurring RT and protease inhibitors of various plants offer a reserve of unexplored antiviral compounds (**Table 4**).

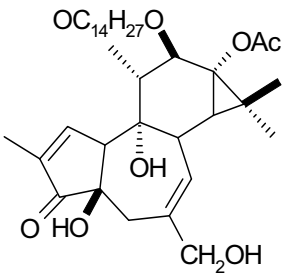
Another promising target for antiretroviral therapy is HIV-1 integrase, which catalyzes the integration of viral cDNA into the host DNA, a two-step process essential for HIV replication (Brown 1997). The efficient integrase inhibitors possess a strong antiviral potency *in vivo* (Hazuda *et al.* 2004). The most potent compounds, entering phase III clinical trial, are inhibitors of the strand transfer which constitutes the second step of the integration process (Hazuda *et al.* 2002, 2004). Evidence suggests that inhibitors of the first integration step, or 3′ processing, is also an interesting lead (Bonnenfant *et al.* 2004). Furthermore, integrase also affects viral particle formation, particle release, infectivity, the particle-associated RTase activity, and nuclear localization of the preintegration complex (Bukovsky and Gottlinger 1996; Dvorin *et al.* 2002). Interestingly integrase has no known counterpart (homolog) in mammalian cells. Hence, due to the pleiotropic activity and specificity integrase represents an attractive target for chemotherapy that could affect multiple steps in viral replication (Gulick 2003; Pluymers *et al.* 2004). Many different classes of compounds like polyhydroxylated flavonoids and phenolics have been reported to inhibit HIV-1 integrase, hence, can be a source for development of potent lead compounds of HIV-1 integrase inhibitors. Flavonoids are inhibitors of many essential enzymes of viral replication, like RTase (Kitamura *et al.* 1998), integrase (Kim *et al.* 1998) and protease, and can form complex with proteins (Xu *et al.* 2000). It can partly interfere with virus-cell binding, as found with glycyrrhizin (De Clercq 2000). Taxifolin, a flavanone with an OH group at C-3′ inhibit viral protease, RTase, and CD4/gp120 interaction by binding to the V3 loop of gp120; while aromadendrin (flavanone lacking OH group at C-3′) are more specific inhibitor of CD4/gp120 interaction (Hudson 1990). Similarly the epicatechin inhibit HIV-1 protease (IC_{50} = 70 μg/ml); while the (-)-epigallocatechin 3-0-gallate (EGCG, **25**) inhibit protein, RTase and blocks the post-adsorption entry of HIV-1 with a nonspecific destruction of virions (Yamaguchi *et al.* 2002), while dihydroxyolean-oic acid, indole-3-carboxylic acid and (-)catechin of *Begonia nantoensis* inhibit HIV replication (Wu *et al.* 2004). The green tea flavonoid, EGCG binds to CD4 (the cell surface receptor for HIV-1 entry) with extraordinary high affinity (binding constant 10 ηM/L), thereby preventing the HIV-1 surface glycoprotein gp120 from binding to human $CD4^+$ T cells, the first stage in gaining entry to the cells. Another study showed that green and black tea polyphenols block the formation of 'fusion bundle' by the HIV-1 gp41, at micromolar concentrations, a hundredth of those that kill cancer cells, similar to tannin from *Prunella vulgaris* that inhibit HIV-1 entry to CD4 cells by blocking gp41 six-helix bundle formation, a critical step of membrane fusion between HIV and target cell (Liu *et al.* 2002). The most effective green tea polyphenol, 2',2"-bisepigallocatechin digallate had an EC_{50} of 0.64 mM, while EGCG was 3.44 mM, black tea epitheaflavin-3'-gallate was 1.28 mM, and theaflavin digalate was 1.96 mM (Liu *et al*. 2005). The antiinflammatory flavonoids baicalein and baicalin (**33**) from *Scutellaria baicalensis* markedly inhibit HIV-1RTase and its replication in a dose dependent manner (De Clercq 2000), interact with envelope proteins and chemokine co-receptors to block the HIV-1 entry to the CD4 cells (Li *et al.* 2000). Most of the potent anti-HIV flavonoids like baicalein (**33**), quercetin (**34**), myricetin (**22**) not only block RTase but also the DNA/RNA polymerase of HIV, where the degree of inhibition depends on the structure and side chain (Hudson 1990; Bunyapraphatsara *et al.* 2000). It has also been reported that several anti-HIV flavonoids like quercetin, chrysin, epicatechin and (-)-epigalIocatechin gallate had kinase II inhibitory activity (Critchfield *et al.* 1997; Haneda *et al.* 2000). The triterpenes ursolic acid (**27**), oleanolic acid, betulinic acid (**8**) and their derivatives (**35**-**36**) inhibit HIV-1 protease (Mattheé *et al.* 1999; Mengoni *et al.* 2002; Cos *et al.* 2003) and the stability of gp120/gp41 complex (Labrosse *et al.* 2000; Yogeeswari and Sriram 2005). Betulinic acid (**8**) isolated from *Syzigium claviflorum*, exhibited anti-HIV activity (EC_{50} = 1.4 μM), while dihydrobetulinic acid (**35**, EC_{50} = 0.9 μM) by esterification in C-3 hydroxyl group resulted in more potent anti-HIV compound 3-*O*-(3,3′-dimethylsuccinyl) betulinic acid (DSB, **36**) with an $EC_{50} < 3.5 \times 10^{-4}$

μM. The DSB block a key step in viral capsid formation in wild and drug-resistant HIV strains *in vivo*, and is suitable for use in combination therapy, and thus is under phase II clinical trial (Kashiwada *et al.* 1996). The betulinic acid, its methyl ester and guaiane sesquiterpenoids from the roots of *Saussurea lappa* also showed protein tyrosine phosphatase 1B inhibitory activity (Choi *et al*. 2009b). The protostanes and garcisaterpenes isolated from *Garcinia speciosa* had anti-RTase and syncytium formation of HIV-1 (Rukachaisirikul *et al.* 2003); while secocycloartene triterpenoid nigranoic acid from *Schisandra sphaerandra* inhibit RTase of both HIV-1 and HIV-2 (Sun *et al.* 1996).

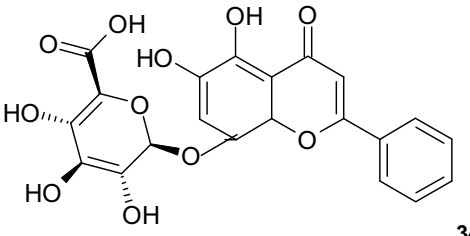
The most exciting non-nucleoside inhibitor 4-propyldipyrano coumarins from tropical rainforest tree *Calophyllum lanigerum* and *C. inophyllum* of Sarawak, Borneo, Malaysia (Buckheit *et al.* 1999). The *Calophyllum* coumarins are calanolides (**37**), inophyllums, and cordatolides (**37**), substituted with *n*-propyl, phenyl, and methyl groups respectively on the basis of C-4 substituent on the lactone ring (Ishikawa 2000). The SAR studies revealed that methyl groups at C-10 and C-11 and a hydrogen bond acceptor at C-12 are responsible for anti-HIV activity (Dharmaratne *et al.* 2002). In calanolides the C-12 hydroxyl group is S configured, while the C-12 hydroxyl of inophyllums is either S or R configured, hence (+)-calanolide A is 50 times more active viral RTase inhibitor (Yu *et al.* 2003). But the modifications of suksdorfin (**38**) at the 3′,4′-position yielded more improved ((EC_{50} 0.0004 μM) anti-HIV compound 3′-R,4′-R-di-*O*-(-)-camphanoyl-(+)-*cis*-khellactone (**39**) (Yu *et al*. 2003a). Further modifications led to more potent 4-MeDCK (**40**) with $EC_{50} = 1.6 \times 10^{-7}$ μM; but a preclinical candidate 3-hydroxymethyl-4-methyl DCK (**41**) is found to inhibit both primary and drug resistant HIV-1 isolates with minimal toxicity (Yu *et al.* 2003). The antiviral action of tannin is due to inactivatation of adsorption, transport proteins, polysaccharides and RTase (Kaul *et al.* 1985; Cowan *et al.* 2003), as evident with HIV-1 RTase inhibitors shephagenins A and B, hippophaenin A and strictinin, the hydrolysable tannins while gallotannin geraniin from *Phyllanthus amarus* inhibit HIV-1 RTase in a dose-dependent manner (Notka *et al.* 2003). The hydrolyzable tannin camelliatannin H from the Korean folklore *Camellia japonica* pericarp inhibit HIV-1 protease (Park *et al.* 2002). A Japanese group showed that tannins can suppress promoter gene in HIV and structure-activity relationship study revealed that, 3-phenylcoumarins, isoflavones, and chalcones suppressed 12-0-tetradecanoylphorbol-13-acetate-induced HIV promoter activity more effectively than tannic acid (Uchiumi *et al.* 2003). Repandusinic acid and nuriside (**42**) isolated from *Phyllanthus niruri*, Phyllamyricin B and its lactone retrojusticidin B from *Phyllanthus myrtifolius* and *P. urinaria* demonstrated strong anti-HIV-1 RTase activity (Liu *et al.* 1999). The dibenzylbutadiene lignans, anolignan A (**43a**) and anolignan B (**43b**) isolated from *Anogeissus acuminata*, showed HIV-1 RTase inhibitory activity and in combination they act synergistically (IC_{50} = 60.4 μg/ml), even against drug-resistant HIV-1 RTase with an IC_{50} of 106 μg/ml (Rimando *et al.* 1994). Recently, globoidnan A isolated from buds of *Eucalyptus globoidea* inhibited HIV integrase (Ovenden *et al.* 2004). Cyanovirin N, an 11-kDa protein of the cyanobacteria *Nostoc ellipsosporum*, possesses broad-spectrum activity including HIV-1 (Boyd *et al*. 1997; De Clercq 2005; Witvrouw *et al*. 2005), specifically interact with the envelope glycoprotein gp120 (Esser *et al*. 1999; Barrientos *et al*. 2003), that plays a major role in the infectivity and mediates interactions with CD4 receptors in concert with chemokine receptors (CXCR4, CCR5). A recent study suggested that 1-deoxynojirimycin blocked HIV envelope glycoprotein-mediated membrane fusion at the CXCR4 binding step (Papandreou *et al.* 2002). It was reported that the biphenolic depsides (bis-catechol) 3,5-dicaffeoylquinic acid (DCQA, **44**) and dicaffeoyltartaric acid (DCTA) demonstrated a 10-100-fold higher preference for HIV integrase inhibition than RTase, and l-chicoric acid (a DCTA), was the most active Inhibitor of HIV integrase (McDougall *et al.* 1998). This inhibition is irreversible and independent of divalent cations and the primary target of L-chicoric acid is the HIV-1 gp120 (Zhu *et al.* 1999). The SAR studies showed that D- and L-chicoric acid had similar anti-integrase activity (**45a, 45b**). The transregulatory protein *Tat*, secreted by HIV-1 infected cells, play an important role in the dysregulation of cytokines and regulate pathogenesis of AIDS, as its can be taken up by non-infected cells (Kim *et al.* 2004). The morphine related compound and FK-3000 (**46**) isolated from *Stephania cepharantha* root tuber is reported to inhibit HIV-1 (7.8 μg/ml) (Ma *et al.* 2002) while its biscoclaurine alkaloid cepharanthine (**47**) inhibit NFk-B (nuclear factor kappa-light-chain-enhancer of activated B cells), a potent inducer of HIV-1 gene expression (Liu *et al.* 2004), along with SARS Coronavirus, HSV-1, coxsackievirus B3 and have *in vivo* anti-tumor, antiinflammatory, anti-allergic and immunomodulating activity (Szlavik *et al.* 2004).

Curcuminoids from *Curcuma longa* rhizome, a century old Indian spice that inhibit eicosanoid biosynthesis (Aggarwal and Shishodia 2004), induce apoptosis in cancer cells and inhibit lipid peroxidation and oxidative DNA damage, can block HIV-1 and HIV-2 replication by inhibiting HIV integrase, protease and virus-cell fusion (Roth *et al.* 1998), and is a potent inhibitor of TNF induced NFkB activation (Singh and Aggarwal 1995). At 10-100 nM dose curcumin (**48**) and its derivatives inhibit *Tat*-mediated transactivation of HIV-1 long terminal repeat (LTR)-directed gene expression (Barthelemy *et al.* 1998) like caffeic acid phenethyl ester (**49**), an active component of propolis of honeybee hives having antiviral, anticancer, antiinflammatory and immunomodulatory activities (Hiebert *et al.* 1999). Curcumin can also interfere with the activity of the transcription factor NFκB, that linked to inflammatory diseases like cancer and when 0.2% curcumin is added to carcinogen challenged rat or mice diet, it significantly reduces colon carcinogenesis (Yang *et al.* 2005), may suppress the oncogene MDM2 (Aggarwal and Shishodia 2004), inhibit the accumulation of β-amyloid in the brains of Alzheimer's patients and also break up existing plaques (Ng *et al.* 2006). Recent report indicated that even 2 g of curcumin, if eaten and absorbed, resulted in undetectable serum levels, while curcumin when co-supplemented with 20 mg of piperine its absorption was significantly increased (Bisht *et al.* 2007). The nanoparticle-based drug delivery approaches showed that "nanocurcumin" can bypass the shortcomings of free curcumin, like poor solubility and bioavailability (Bisht *et al*. 2007).

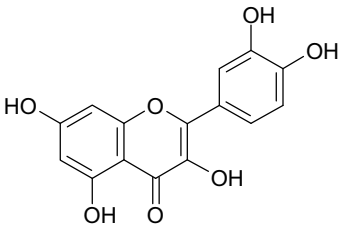
Since anti-retroviral multi-drugs treatment has severe side effects, hence, one of the strategies is to block the HIV-1 entry and its replication by natural compounds that target lipid rafts (lipid microdomain of plasma membrane is the site of entry and budding of HIV-1). A recent review on composition/structure and formation of plasma membrane lipid rafts, interaction of HIV-1 with lipid rafts and the interaction of phytocompounds that can target lipid rafts, showed that it could have potential preventive or therapeutic values against the progression of AIDS. The review emphasizes to the roles of omega-3 fatty acids and terpenes (**50**; especially euphane triterpenes from Neem tree) that target lipid rafts and cholesterol (Verma 2009). Similarly the andrographolide (**51**) from *Andrographis paniculata* can reduce the HIV-1 viral load and increase CD+ count in nine weeks of treatment (**Table 5**). The CH_2Cl_2 extracts of *Erythrina senegalensis* yielded 8 compounds, namely, the prenylated isoflavone 8-prenylluteone, auriculatin, erysenegalensein O, erysenegalensein D, erysenegalensein N, derrone, alpinumisoflavone, and 6,8-diprenylgenistein, and showed dose-dependent inhibitory activities on HIV-1 protease (IC_{50} = 0.5-30 μM). First five compounds contain two hydroxy groups in 2' and 4' positions of the B ring, potently inhibited HIV-1 protease activity. In addition, 6,8-diprenylgenistein with two prenyl groups in the 6 and 8 positions of A ring and one hydroxy group in the 4' position of B-ring was the most potent HIV-1 protease inhibitor (Lee *et al.*



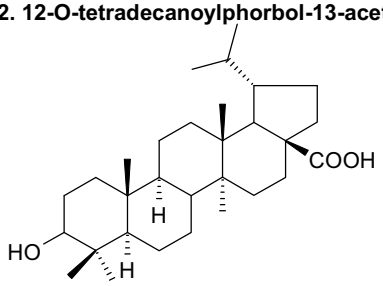
32. 12-O-tetradecanoylphorbol-13-acetate



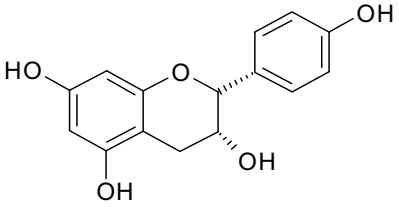
33. Baicalin



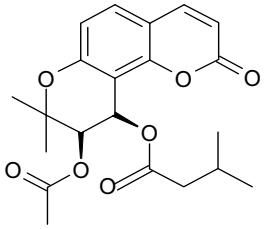
34. Quercetin (3,3′,4′,5,7-Pentahydroxy Flavone)



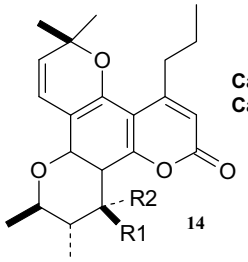
35. Dihydrobetulinic acid



36. 3-O-(3-3'-dimethylsuccinyl) betulinic acid

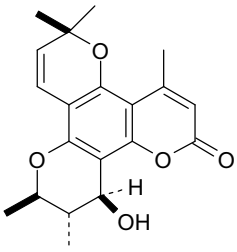


38. Suksdorfin

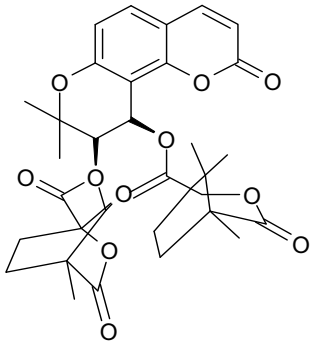


Calanolide A $R_1 = OH,\quad R_2 = H$
Calanolide B $R_1 = H,\quad R_2 = OH$

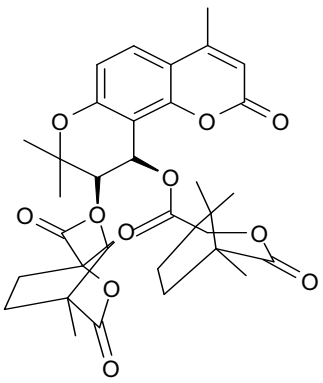
37. Calanolides and Cordatolide



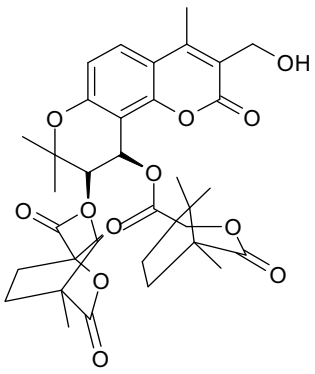
Cordatolide A



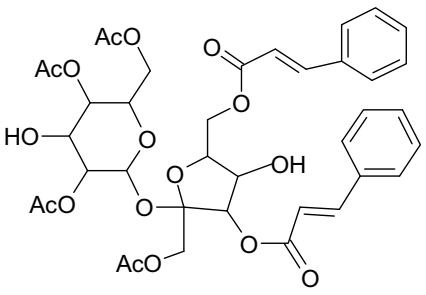
39. Cis-Khellactone



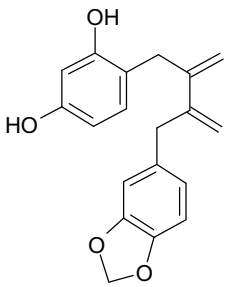
40. 4-MeDCK



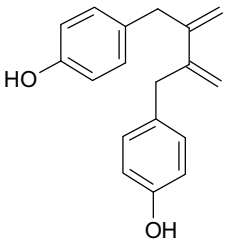
41. 3-Hydroxymethyl-4-methyl-DCK



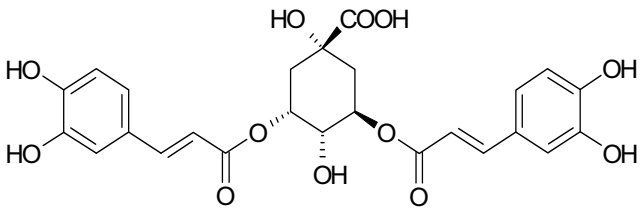
42. Niruriside (*P. niruri*)



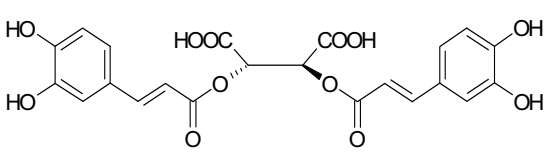
43a. Anolignan A



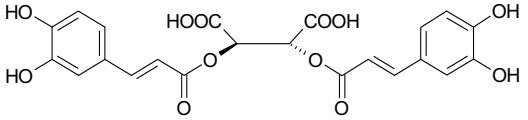
43b. Anolignan B



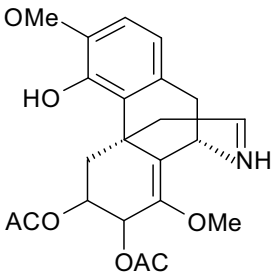
44. 3,5- Dicaffeoylquinic acid (DCQA)



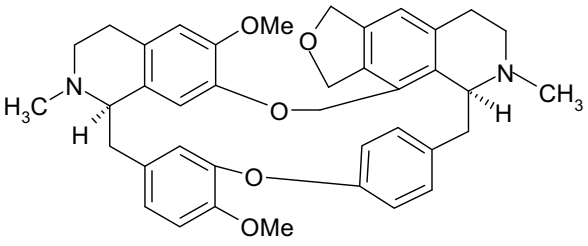
45a.D-Chicoric acid



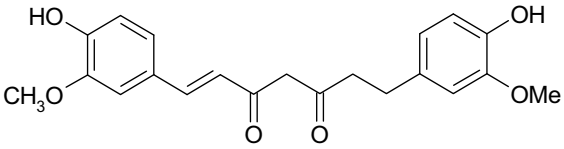
45b. L-Chicoric acid



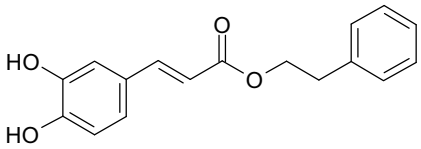
46. FK- 3000



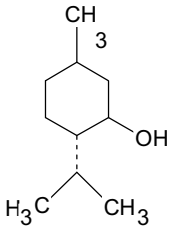
47. Cepharanthine



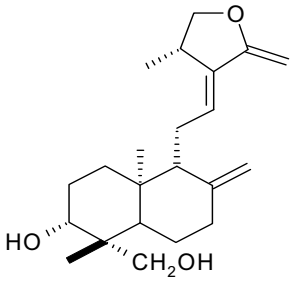
48. Curcumin



49. Caffeic acid phenyl ester (CAPE)



50. Terpenoid (Menthol)



51. Andrographolide

2009). Interestingly three new galloyl arbutins, hyemalosides isolated from the evergreen tree *Eugenia hyemalis* was found to inhibit HIV-1 RNase H in *vitro* (IC_{50} = 1.46, > 18, and 1.19 μM, respectively). The most important initiative is the establiahment of HIV/AIDS Research Initiative on Traditional Healthcare in Africa, to develop controlled clinical trial protocols for evaluating the safety and efficacy of potential phytomedicines for HIV/AIDS. Another major effort by the Canadian AIDS Treatment Information Exchange (CATIE) for improving the health and quality of life for people living with HIV/AIDS. A list of medicinal plants having beneficial effects for HIV-infected individuals (**Table 4**) is published in "Practical Guide to Herbal Therapies for People Living with HIV" is very informative, however, those information's are anecdotal, lack scientific validity and do not have appropriate clinical trials for validating medicinal usage among humans.

Isolation and characterization of bioactive plant components

The basic step towards evaluating the therapeutic potential of medicinal plant is the preparation of crude cellular lysate of the plant matrix followed by extraction of various components of medicinal value. There are several books and reviews describing standardized extraction procedures, most of these classical isolation procedures have limitations of reproducibility and quality, thus compromising the safety and efficacy of preparations. Hence, there is an urgent need to refine and further develop classical methodologies to obtain procedural consistency and highly pure plant components exhibiting medicinal value. Therefore, increased interest in traditional medicine has complemented quality awareness and refinement in extraction methodologies and standardization of procedures isolation (Atta-ur-Rahman and Choudhary 1998; Ong 2004). To ensure high quality herbal preparations, efforts are ongoing to replace traditional methodologies with modern sample preparation and extraction procedures. Classical solvent separation is being complemented with modern techniques like microwave-assisted extraction, pressurized-liquid extraction, matrix-assisted laser desorption/ionization mass spectrometry (Wu *et al*. 2007) and several others. To further facilitate plant-based drug discovery efforts are also being directed toward standardization of methodologies for pharmacokines/pharmacodynamics behavior of phytomedicinal products (Lin *et al*. 2005).

Studies on the mechanism of action

Compounds can also be evaluated for activity when challenged with different amounts of viruses ranging from very low to very high multiplicity of infection. *Time of addition and time of removal:* Compounds are added or removed from cultures at various times pre- and post-infection. By comparison with other known virus inhibitors, which allows to determine the relative point in the virus life cycle that is being inhibited (immediate early, early, late functions, DNA polymerization, etc.). This standard technique typically used early during the process of determining mechanism of action as it allows one to narrow in on a smaller target window of activity for further experimentation. It also allows for an easy way to determine if a compound is acting by a unique or novel mechanism compared to other known inhibitors. Furthermore, time of removal studies allow one to determine the reversibility of a compounds activity. *Analysis of viral genome:* The effect of compounds on the production of viral genome can be evaluated using various hybridization techniques, PCR or TaqMan PCR or RT PCR. *Analysis of viral proteins:* The effect of compounds on the production of immediate early, early and late viral proteins can be evaluated using Western blots and/or Flow cytometry. *Selection and characterization of drug-resistant virus isolates:* Resistant virus isolates are selected in tissue culture by serial passage of the virus in the presence of gradually increasing concentrations of the compound. Resistance evaluations can be performed in any of the available cell lines with a variety of virus isolates. In addition, resistance

Table 4 Plants and their products used among HIV-infected individuals.

Scientific name [common name]	Activity
Aloe vera [Aloe]	Acemannan (complex sugar) and leave paste with Jelly-like substance improves skin problems associated with HIV and anti-HIV drugs
Andrographis paniculata (Burm.f.) Nees. [Andrographis]	Anti-HIV effect, Increased $CD4^+$ counts, 30% decrease in viral load after 9 weeks treatment
Withania somnifera (L.) Dunal. [Ashwagandha leaves]	Rejuvenate immune system, have *in vivo* immuno-stimulatory properties
Astragalus membranaceus Bunge. [Astragalus]	Bone marrow stimulant, have anti-HIV activity
Atractylodes macrocephala Koidz. [Atractylodes]	Improve body weight, muscle strength, diarrhea, immune function
Uncaria tomentosa Willd. [Cat's claw inner bark]	Increase in CD4+ counts, antioxidant and immunomodulatory activity
Allium sativum L. [Garlic]	Amerliorate fungal and parasitic infections (cryptosporidium)
Zingiber officinale Roscoe. [Ginger]	Stop nausea associated with antiretroviral therapy
Gingko biloba L. [Gingko seeds]	Prevent HIV-associated memory loss
Panax ginseng C Meyer; *Panax quinquefolium* L.; *Eleutherococcus senticosus* Maxim [Ginseng roots]	Improves cell-mediated immunity of HIV-infected people. Contraindicated in pregnancy
Hydrastis canadensis L. [Goldenseal roots]	Alkaloid Berberine control diarrhea and weight loss
Chelidonium majus L. [Greater Celandine flower]	Prevent HIV-associated Kaposi sarcoma
Hyssopus officinalis L. [Hyssop leaves, flowers]	*In vitro* inhibition of HIV replication
Melissa officinalis L. [Lemon balm]	*In vitro* activity against HIV and HSV
Glycyrrhiza glabra L. [Licorice roots]	Glycyrrhizinais immunostimulant, inhibit viral production
Lomatium dissectum Mathias & Constance, *L. suksdorfii* [Lomatium]	Inhibit HIV *in vitro*
Cannabis sativa L. [Marijuana]	Prevent nausea and stimulating appetite
Olea europaea L. [Olive leaf]	Anti-HIV-1 and antioxidant activity
Plantago ovata Forssk. [Psyllium seed and husk]	Fiber prevents diarrhea of protease inhibitors therapy
Sanguinaria canadensis [Sanguinaria]	Prevent *Pneumocystis carinii* pneumonia in HIV-infected people
Asparagus racemosus Willd. [Shatvari]	Stimulate macrophages *in vivo*, to control microbes.
Hypericum perforatum L. [St. John's Wort]	Photosensitive component inactivate antiretrovirals, contraindicated for HIV patients on other medications
Melaleuca alternifolia [Tea tree oil]	Controls HIV-associated thrush (fungal infections)

Table 5 Mechanism of antiviral actions of some ethnomedicinal compounds.

Class	Subclass	Compounds	Antiviral mechanism
Polyphenols	Phenols, phenolic acids	Caffeic, rosmarinic, chlorogenic acid	Clumping, inhibiti adsorption, RTase, RNA polymerase
	Anthocyanins	Proanthocyanidins	HIV-RT inhibition
	Coumarins	Calanolides	Inhibit entry, RTase, integrase
	Flavones, flavonols	Taxifolin, torvanol, amentoflavone	Inactivate protease, RTase, gp120 interaction, protein
	Flavonoids	Chrysin, quercetin, morin, myricetin, catechin, glycyrrhizin, baicalin	Inhibit adsorption, entry, binding, RTase, integrase, protease, DNA-RNA polymerase, proteins
	Quinones, fluroquinone	Hypericin, chicoric acid, chrysophlenol C	Inhibit integrase, replication, protein inactivation
	Tannins	Ellagitannin, geraniin, shephagenin, strictinin, casuarinin, camelliatannin	Inhibit adsorption, RTase, protease, DNA polymerase, transport protein, polysaccharide, attachment , penetration
Terpenoid	Terpens, Essential Oils	Caesalmin, capsaicin, terpinen-4-ol	Inhibit adsorption, cell-to-cell transmission, multiplication
	Triterpenes	Betulinic acid, arginine, ursolic acid	Inhibit virus entry, protease, replication
	Other terpenoids	Swertifrancheside	Inactivate protein
Alkaloids		Cepharanthine, michellamine B, solamargine, harman, skimmianine	Inhibit viral genome, replication, protein synthesis, interfere with cellular factors
Sulfated poly saccharides/ polypeptides	Mannose specific lectins	MAP 30, GAP 31, MRK 29, fabatin	Block fusion, adsorption, RTase, and form disulfide bridges
	Polypeptides	Xylanase, trichosanthin	Fusion, RTase, cellular factors
	Polysaccharide	Jacalin, prunellin, RAP, RMP	Block viral replication and budding

RT, reverse transcriptase; MAP30, a 30 kDa protein of *Momordica charantia*, GAP31, a 31 kDa protein of *Gelonium multiform*; MRK 29, a 29 kDa protein of *Momordica charantia*; RAP, *Rhizophora apiculata* polysaccharides; RAM, *Rhizophora mucronata* polysaccharides.

selection can be evaluated using combinations of anti-viral agents to evaluate the relative ability of the virus to become resistant to multiple agents (Chattopadhyay *et al*. 2009).

The molecular mechanisms associated with the antiviral effects of plant extracts may vary among different viruses (**Table 5**). However, the common pathways might involve the boosting of inherent antiviral defense of human body. A number of studies have explored immunomodulatory properties of antiviral plant extracts, as evident from the root extracts of *Heracleum maximum* Bartr. (Umbelliferae), which possess antiviral, antifungal and antibacterial properties, by stimulating Interleukin 6 (IL-6) production in the macrophage (Webster *et al*. 2006). Furthermore, *Plantago major* and *P. asiatica* Linn. (Plantaginaceae), used for the treatment of infections in Taiwan, exhibited lymphocyte proliferation and secretion of gamma interferon (IFN-γ), the indicators of cell-mediated immune response modifier (Chiang *et al*. 2003). Similarly, sambucol, from *Sambucus nigra* L., showed anti-influenza activity by boosting immune responses through the secretion of inflammatory cytokines IL-1 β, TNF-α, IL-6, and IL-8 (Barak *et al*. 2001). Similarly, the broad-spectrum antiviral activity of a single phytochemical, or a different phytophores (Pompei *et al*. 1979) as observed with Secomet-V from *Trifollium* species against human papillomavirus (HPV), Marburg, influenza, HIV, HBV and HCV (Kotwal *et al*. 2005). Again pandanin, a lectin from *Pandanus amaryllifolius* Roxb. leaves inhibit HSV-1 and influenza virus H1N1 (Ooi *et al*. 2004); while the crude extract of hop showed antiviral effect against a diverse group of viruses, suggesting the presence of broad-spectrum antiviral phytochemicals in different parts of the plants (Buckwold *et al*. 2004). The reactive oxygen species, antioxidants, transcription factors, and cytokines are essential for life and are a part of large human defense network that behaves like a black box. The evidence of oxidative stress in virus-infected cell indicates that antioxidants like flavonoids proanthocyanidins, etc. with low oral availability may have some role in controlling viral disease progression (Cos *et al.* 2004). Hence, the evaluation of *in vivo* antioxidants effect on viral diseases need monitoring of oxidative stress, as excessive antioxidant protection could lean over the balance from oxidative stress to "oxidative deficit".

Table 6 Etnomedicinal phytophores and its derivatives in Clinical trials.

Compound	Disease	Principal Sponsors
Artemisinin from *Artemisia annua* (Asteraceae)	CMV infection	Hadassah Medical Organization, Israel
Calanolides (coumarin) from *Calophyllum lanigerum* var *austrocoriaceum* (Guttiferae)	HIV-1 infection	Sarwak Medicem Pharmaceuticals
Crofelemer (oligomeric proanthocyanidin) From *Croton lecheri* latex (Euphorbiaceae)	HIV/AIDS related diarrhoea	Trine Pharmaceuticals Inc, AsiaPharm Group Ltd
DCK (3-hydroxymethyl-4-methyl khellactone from *Lomatium suksdorfii* (Apiaceae)	HIV-1 infection	Panacos Pharmaceutical
3,5-di-0-cafeeoylquinic acid from *Inula britannica* (Asteraceae), inhibit integrase enzyme	HIV-1 infection Hepatitis C	China's Academy of Military Sciences
6-0-butanoyl castanospermine from *Castanospermum australe* (Fabaceae)	Chronic Hepatitis C	MIGENIX, Canada
4-methylumbelliferone (7-hydroxycoumarins) from Manna ash, sweet woodruff, German chamomile, celery, parsley	Hepatitis B and C	M T Medical Institute of Health, University of Texas Health Science Center, San Antonio; BioMonde Preparations Limited
Polyphenol E (catechin derivative) from green tea *Camellia sinensis*	Wart (Genital and Perianal) caused by Human Papilloma virus (HPV)	MediGene AG, Germany

Thus, controlled clinical trials with antioxidants, along with oxidative stress measurement can help to determine the clinical significance of oxidative stress on viral diseases; and antioxidant food could be an inexpensive alternative to the existing antiviral treatment strategies.

FUTURE DIRECTIONS IN ANTIVIRAL POTENTIALS OF MEDICINAL PLANTS

Many of the viral diseases are either fatal or are not yet curable and do not have vaccine yet. Hence, development of safe, effective and inexpensive antivirals is among the top global priorities. Furthermore, the long-term combination therapies for herpes and retroviruses yielding drug-resistant mutants. Hence, scientists are investigating ethnomedicinal plants, with an eye to their antiviral usefulness. WHO estimates that about 80% of the global population used phytochemicals to fulfill their healthcare needs this shows that the medicinal plants are still an important area for drug development. Improved separation technologies offer potentials to screen anti-infectious/antiviral nature of medicinal plants. Several problems related to screening of antiviral plants like incidental infection to the workers are now overcome by vector-based assay techniques, i.e. recombinant viral vectors mimicking the infection and expressing firefly luciferase marker gene are widely used to screen a variety of antivirals (Esimone *et al*. 2005). Intelligent usage of plants for the production of vaccines and protein-based therapeutics is also encouraging, as several reports suggest that plant can be a good source for the production of pharmaceutical grade peptides/proteins (Koprowski and Yusibov 2001; Glenz and Warzecha 2006). Since the expression of first subunit vaccine for HBsAg in 1992, several other vaccine antigens have been successfully and safely expressed in plants (Ma *et al*. 2003; Thanavala *et al*. 2005; Glenz and Warzecha 2006). While considering plants for treating human viral diseases we have to be careful, as majority of viral vaccines are constituted with attenuated or inactivated viral particles. Hence, to overcome these limitations efforts are made toward expressing viral coat proteins that can assemble as virus-like-particles in plants and are antigenic. Other issues like appropriate processing of protein to be expressed in plants and isolation of active ingredients are to be considered. In China, India etc crude plant extracts are used in healthcare and their efficacy is well-documented. Though it is hard to get these extracts approved through FDA, but for countries with limited resources, government sponsored explorations will serve as a gateway for merging of modern drug discovery with conventional medicine. Moreover, considering the problems faced by drug resistance and failure in finding an effective vaccine for deadly viruses like HIV/AIDS, phytomedicinal products may provide a hope (**Table 6**), e. g., trials of calanolide A by Sarawak MediChem Pharmaceuticals (Saklani and Kutty 2008), Panacos Pharmaceuticals trials with 3-hydroxymethyl-4-methyl DCK and DSB (Yu *et al*. 2006a; Saklani and Kutty 2008), polyphenon E from green tea catechin agaist human papilloma virus wart by Medi Gene AG (http://www.drugs.com/newdrugs/; Saklani and Kutty 2008), artemisinin in CMV infection by Hadassah Medical Organization, Israel (Corson and Crews 2007). Moreover, a number of plant extracts can block virus entry into host cells and or specific cellular enzymes, which is very important in the context of viral drug resistance and limited life span of antiviral drugs. The compounds having alternative mechanism of action can be the potential candidates to tackle the threats posed by emerging, reemerging and drug resistant viruses, as it is quite difficult to eliminate most of the viral diseases by the available antivirals. Although, herbal preparations are widely used in several parts of the world, individually or in combination, data about their interactions on living system is non-existent. It is only experience of the indigenous people using a particular plant product for treating an ailment. Results of clinical finding of using combination of plant or plant products like co-administration of kava-kava and St. John's Wort lead to hepatotoxicity (Musch *et al*. 2006), should be available to the healthcare providers practicing traditional medicine. Herbal remedies are perceived as harmless; however, several reports suggest hepatotoxicity associated with herbal medication (Schiano 2003; Pak *et al*. 2004). Publication of scientific reports relevant to the cytotoxicities of medicinal plants usage should be encouraged and incorporated into a universal database system. Moreover, larger randomized, double-blind, placebo-controlled multicenter clinical trials should be conducted before incorporation of a particular herbal remedy in treating people.

Though medicinal plants have been used throughout the world, however, their wide usage had been limited to China, India, Japan, Pakistan, Sri Lanka, Thailand and some African countries (Hoareau and da Silva 1999); and now developed countries are also turning towards the usage of plant-based medicines in their healthcare systems, as observed in Canada (Siow *et al*. 2005). Traditional medicine was developed during of limited access to technological variability and standardization. Today many such species might have been extinct and the properties of many phytocompounds as recorded in classics may undergo change due to time and environmental factors. Hence the process of standardization needs a flexible approach due to complex nature of natural remedies. Recently, WHO, European Agency for the Evaluation of Medicinal Products and European Scientific Cooperation of Phytomedicine, US Agency for Health Care Policy and Research, European Pharmacopoeia Commission, Department of Indian System of Medicine have started creating new mechanisms to induce and regulate quality control and standardization of these time tested remedies. The standardization of multi-component formulations may include DNA fingerprinting, HPTLC, liquid chromatog-

raphy, mass spectroscopy, etc. New technologies such as combinatorial chemistry and high-throughput screening allow synthesis of billions of compounds and an unimaginably large and diverse 'chemical landscape'. So it needs to introduce a variety of computational techniques that allow chemists to reduce by virtual screening huge molecular libraries to a more manageable size. Preclinical studies on ethnomedicines are required for validating drug safety, while suitable animal models are needed in understanding the mechanism of action and pharmacodynamics, especially where there are no good animal models. The clinical basis of ethnomedicine is presumptive; hence systematic clinical trials are necessary. In ethnomedicine research, clinical experiences, observations or available data becomes a starting point. Thus, the drug discovery based on ethnomedicine follow a '*reverse pharmacology*' and the critical pharmacopoeial tests such as dissolution time, microbial, pesticide and heavy m*etal*s contamination must be in accordance with global standards.

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