Antivirals of Ethnomedicinal Origin: Structure-activity Relationship and Scope

Debprasad Chattopadhyay[1] and Trailokya N. Naik[2,*]

[1]*ICMR Virus Unit, I.D. & B.G. Hospital Campus, GB 4, (East Wing, First Floor), 57 Dr Suresh C Banerjee Road, Beliaghata, Kolkata 700 010, India;* [2]*Division of Virology, National Institute of Cholera and Enteric Diseases, P-33, CIT Road Scheme XM, Beliaghata, Kolkata 700010, West Bengal, India*

Abstract: Ethnomedicinal plants have been used as source of candidate drugs for almost all diseases, but the number of compounds having antiviral activity is scarce. Irrespective of type of viruses and the cells they infect, there are a very few specific viral targets for the natural molecules to interact. Most of the available antiviral drugs often lead to the development of viral resistance coupled with the problem of side effects, recurrence and viral latency. A wide array of ethnomedicinal plants showed high level of antiviral activities and many of them have complementary and overlapping mechanism of action, either inhibiting viral replication, or viral genome synthesis. Hence, there is an urgent need to develop new antivirals of natural origin. This review will cover some of the promising antiviral compounds isolated from ethnomedicinal plants with proven *in vitro* and some documented *in vivo* activities, along with their structure activity relationship.

Key Words: Ethnomedicine, antivirals, structure activity relationship (SAR), HSV, HIV.

INTRODUCTION

Mankind has always relied on nature for their basic needs including medicine. People of all continents have long applied poultices and imbibed infusions of indigenous plants with mixed therapeutic results, quite often it cures or relief symptom but sometimes poisoning of the subjects occurs. The oldest record of ethnomedicine (2600 BC) describe the use of oil of cedar (*Cedrus* Spp.*)* wood and cypress (*Cupressus sempevirens)*, juice of licorice (*Glycyrrhiza glabra*), myrrh (*Commiphora* Spp.) and poppy (*Papaver somniferum*) for the treatment of coughs and colds to parasitic infections and inflammation [1]. Thousands of herbal formulations were described in the Egyptian 'Ebers Papyrus' (1500 BC), the Chinese *Materia Medica* (1100 BC) and Ayurved, the Indian System of Medicine (1000 BC) [2], which combines with the work of Theophrastus (~300 BC) and Galen (130–200 AD) of Greece leads to the rational development of herbal medicine. But the idea of 'pure' compounds as drugs originates from the isolation of the active principle morphine from opium poppy by E. Merck in 1826 and the first semi-synthetic drug aspirin by Bayer in 1899 [3].

ETNOMEDICINES AND DRUG DISCOVERY

Over the centuries phytomedicines formed the basis of traditional medicaments in China [4], India [2], Africa and in many other civilizations [5]. Even today 80% of the world's populations rely on phytochemicals for primary health care while the rest 20% use plant products as ingredients of several drugs [6]. Out of 119 drugs of modern medicines 84 are of ethnomedicinal origin but none are used against viruses, although the traditional healers have long used plant based medicaments to prevent or cure infectious diseases/conditions. The Clinical virologists are interested in antiviral plant extracts as (i) the effective life span of any antiviral drug is limited, (ii) viral diseases remain intractable to most of the orthodox antiviral drugs and (iii) the problems of viral resistance, latency and recurrence in immunocompromised hosts. Moreover, the rapid spread of emerging and reemerging diseases like human immunodeficiency virus (HIV)/AIDS, severe acute respiratory syndrome (SARS) etc has spurred intensive investigation into the ethnomedicines, especially for people having little or no access to expensive antiviral drugs. Additionally the rapid rate of species extinction [7] leads to the irretrievable loss of structurally diverse and potentially useful phytochemicals. Hence, ethnopharmacology can play a pivotal role in drug discovery by utilizing the impressive array of knowledge and wisdom of indigenous peoples about their generation old medicaments. Phytomedicines are the secondary metabolites of plants and are species/strain specific with diverse structures and bioactivities, synthesized mainly for defense against predators, as the natural version of chemical warfare.

This review will summarize the prospective bioactive molecules of ethnomedicinal plants (Table **1**) of various communities tested against diverse virus families and the structure-activity relationship (SAR) of some of these potential compounds with proven *in vitro* and documented *in vivo* activities (Table **2**).

VIRUSES: THE UNIQUE PARASITES!

Viruses are ultramicroscopic nucleoprotein particles containing gene strands of either RNA or DNA, with or without a lipid envelope. They are obligate intracellular parasites capable of utilizing the host cell machinery to replicate and cause ailments as benign as a common wart, as irritating as a cold, or as deadly as haemorrhagic fever. The viruses that

*Address correspondence to this author at the Division of Virology, National Institute of Cholera and Enteric Diseases, P-33, CIT Road Scheme XM, Beliaghata, Kolkata 700010, India; Tel: +91-33-23701176; Fax: +91-33-23705066; E-mail: tnaik@satyam.net.in; tnaik@sify.com; tnnaik@gmail.com

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Table 1. Ethnomedicinal Antivirals from Diverse Chemical Groups

Natural Product	Source	Antiviral Activity (μg ml^{-1})	Reference
Phenolics			
Asiaticoside	*Centella asiatica*	HSV*	[173]
Caffeic acid (1)	*Plantago major*	HSV-1(15.3) [b], VZV*, IV* HSV-2 (87.3) [b]	[10]
Chicoric acid (9)	*Echinacea purpurea*	HIV-1(40-60μM) [a, g]	[18, 21]
Chlorogenic acid (1)	*Aloe barbadensis*	HSV-1 (47.6) [a], HSV-2 (86.5) [a,] PRV*	[10,161]
Curcumin (10)	*Curcuma longa*	HIV-1(100μM)[a,g, f, j]	[24-26]
Diprenylated bibenzyl (93)	*Glycyrrhiza lepidota*	HIV-1*	[172]
Mangiferin (95)	*Mangifera indica*	HSV-1*, HSV-2*	[173]
Procyanidin A1 (4)	*Vaccinium vitis-idaca*	HSV-2*[l]	[16]
Procyanidin C1 (4)	*Crataegus sinaica*	HSV-1*[d]	[17,18]
Prodelphinidine-o-gallate	*Myrica rubra*	HSV-2 (5.3)[a,d,l]	[14]
Rosmarinic acid (2)	*Plantago major*	Influenza*, HIV (10mM), VZV*	[10, 19]
Xanthohumol (6)	*Humulus lupulus*	HSV*[h]	[20]
Coumarins			
(+)-Calanolide A (14)	*Callophyllum lanigerum*	HIV-1 (0.2 μM)[b,e,h, k]	[31,32]
(–)-Calanolide B (14)	*C. lanigerum*	HIV (0.2 μM)[b,h,k]	[31,35]
Cordatolide A (15)	*C. cordato-oblongum*	HIV (19.3 μM)[a,d]	[32,33]
Coriandrin (20)	*Coriandrum sativum*	HIV*	[34]
Suksdorfin (16)	*Lomatium suksdorfii*	HIV (2.6 μM)[b, d]	[37]
Flavonoids			
Amentoflavone (30)	*Rhus succedanea*	HSV*, IV*,HIV (65 μM)[a,e]	[57]
Baicalein, Baicalin (33)	*Scutellaria baicalensis*	HIV-1 (0.5)[a,d, e, i]	[42, 59]
Catechin (5)	*Eleutherococcus senticosus* *Orange, Grape* *Begonia nantoensis*	Coronavirus RSV, HSV-1* HIV[d]	[55] [47] [47]
Cinnamoylbenzaldehyde	*Desmos sp.*	HIV (0.22)[b], HSV-1	[61]
Diandroflavone (C-glycoside flavo-noid)	*Drymaria diandra*	HIV (10)[a]	[143]
Dihydroxyolean-oic acid	*Begonia nantoensis*	HIV-1[d]	[49]
Epicatechin (5)	*Xanthoceras sorbifolia*	HIV (70)[a, f]	[43]
Galangin (25)	*Helichrysum aureonitens*	HSV, CVB1	[45]
Glycyrrhizin (22)	*Glycyrrhiza glabra*	HSV-1, SARS, HIV-1	[46, 42]
Hesperidin (27)	*Orange, Grape*	HSV, PV, PIV, RSV	[47]
Luteoside	*Markhamia lutea*	RSV	[56]

(Table 1. Contd….)

Natural Product	Source	Antiviral Activity (μg ml^{-1})	Reference
Mulberroside C	*Morus alba*	HSV-1	[62]
Oxyresveratrol	*Millettia erythrocalyx*	HSV, HIV-1	[50]
Robustaflavone (31)	*Garcinia multiflora*	Measles, VZV	[46]
Theaflavin (29)	*Camellia sinensis;*	Rotavirus	[55]
Torvanol A,	*Solanum torvum*	HSV-1 (9.6)[a]	[44]
Torvoside H	*Solanum torvum*	HSV (23.2)[a]	[44]
Wikstrol B (32)	*Wikstroemia indica*	HIV-1*	[58]
Terpenes/sterols			
Andrographolide (54)	*Andrographis paniculata*	HIV*[d,k]	[89]
Apigenin (38)	*Ocimum basillicum*	HSV-1, ADV-8	[70]
Betulinic acid (41)	*Ocimum basilicum* *Syzygium claviflorum*	HSV (2.6)[b], HIV, CVB1, EV71 HSV, HIV 13 μM[a]	 [76-78] [81]
Caesalmin	*Caesalpinia minax*	PIV-3[*]	[80]
Chlorophyll (Pheophorbide)	*Vatica cinerea*	HIV -1 (1.5)[a]	[92]
Dihydrobetulinic acid (42)	*S. claviflorum*	HIV (13 μM)[a]	[81]
Epiafzelechin (44)	*Cassia javanica*	HSV-2[*]	[71]
Isoborneol (46)	*Melaleuca alternifolia*	HSV-1, 2 (0.06)[a, d]	[73]
Limonin (55)	*Citrus* spp.	HIV-1 (60 μM)[b,f]	[90]
Lupenone	*Euphorbia segetalis*	HSV-1, HSV-2	[91]
Maslinic acid (49)	*Geum japonicum*	HIV (17.9) [a,f]	[83]
Moronic acid (48)	*Myrceugenia euosma* *Rhus javanica*	HIV (< 0.1)[b], HSV (3.9)[b] HIV-1, HSV-2	 [84] [75]
Nigranoic acid (51)	*Schisandra sphaerandra*	HIV*	[86]
Nomilin (56)	*Citrus* spp.	HIV (52 μM)[b,f]	[90]
Oleanolic acid (40)	*S. claviflorum*	HSV, HIV (21.8)[d]	[82]
Ovatodiolide	*Anisomeles indica*	HIV*	[93]
Prostratin (52)	*Homalanthus nutans*	HIV (< 0.132 μM)[b]	[88]
Pulegone	*Minthostachys verticillata*	HSV-1(10), PRV(9.5)[c]	[97]
Putranjivain A (47)	*Euphorbia jolkini*	HSV-2, (6.3μM) [a, d, l]	[74]
12-*O*-Tetradecanoyl phorbol-13-acetate (53)	*Croton tiglium*	HIV-1(0.48 ng/ml)[a,h]	[88]
Ursolic acid (39)	*Geum japonicum* *Crataegus pinatifida*	HSV, ADV,CV, EV (18 μM)[a,f]	[82] [92]
Vaticinone	*Vatica cinerea*	HIV-1(6.5)[a, d]	
Quinones			
Chrysophanic acid (64)	*Pterocaulum sphacelatum*	PV-2(0.21)[b], PV-3(0.02)[b,d]	[110]
Chrysoplenol C (63)	*Dianella longifolia*	Picorna, Rhino, Polio	[110]

(Table 1. Contd….)

Natural Product	Source	Antiviral Activity (μg ml^{-1})	Reference
Conocurvone (67)	*Conospermum incurvum*	HIV (0.02 μM)[b,h]	[113]
Hypericin (62)	*Hypericum perforatum*	HSV, HIV*[e]	[108]
Saponins			
Actein (60)	*Cimicifuga racemosa*	HIV,0.375 mg/ml[b]	[103]
Arganine C	*Tieghemella heckelii*	HIV-1[n]	[93]
Escins	*Aesculus chinensis*	HIV*	[105]
Maesasaponin	*Maesa lanceolata*	HSV-1, HIV-1(50)[a]	[95]
Iridoid-Saikosaponin (57)	*Bupleurum nigidum* *Scrophularia scorodonia*	HSV-1(500)[a] VSV[*]	[94]
Saponin B1	Soybean seeds	HIV-1 (0.5) [d, j]	[104]
Xanthones			
Macluraxanthone B (59)	*Maclura tinctoria*	HIV-1*	[102]
Swertifrancheside (58)	*Swertia franchetiana*	HIV (43 μM)[a,e]	[101]
Tannin			
Camelliatannin H	*Camellia japonica*	HIV (0.9 μM)[a,e,f]	[121]
Casuarinin (71)	*Terminalia arjuna*	HSV-2 (1.5μM)[a,l]	[120]
Chebulic acid	*Terminalia chebula* *Phyllanthus urinaria*	HIV[*] HBV[*]	[114] [171]
Eugeniin (70)	*Geum japonicum*	HSV-1, HSV-2, EBV	[117]
Geraniin, Corilagin	*Phyllanthus amarus*	HIV-1(1.8)[d, e]	[119]
Phyllamyricin B (75)	*Phyllanthus myrtifolius* *Phyllanthus urinaria*	HIV[e] HBV[*]	[124] [154]
Retrojusticidin B (76)	*Phyllanthus urinaria*	HIV-1[e]	[124]
Samaragenin B	*Limonium sinensi*	HSV-1	[116]
Shephagenin, Strictinin	*Shepherdia argentea* *Syzgium aromaticum*	HIV-1[*e]	[115]
Lignans			
(–)-Arctigenin (81)	*Arctium lappa*	HIV*[m]	[132]
Anolignan A (79)	*Anogeissus acuminata*	HIV-1(60.4)[a,e]	[131]
Anolignan B (80)	*A. Acuminata*	HIV-1(1072)[a,e]	[131]
Globoidnan A (82)	*Eucalyptus globoidea*	HIV (0.64)[a, g]	[134]
Gomisin	*Kadsura interior* *Ipomoea cairica*	HIV (0.006)[b] HIV-1*	[133] [132]
Nordehydroguanoferate	*Larrea tridentata* *Terminalia belerica*	HIV-1*[d] HIV-1*	[127,130] [135]
Alkaloids			
Aromoline (90)	*Stephania cepharantha*	HIV-1 (31.3) [h]	[146]
Castanospermine (91)	*Castanospermium australe*	HIV*	[148]

(Table 1. Contd….)

Natural Product	Source	Antiviral Activity (μg ml^{-1})	Reference
Cepharanthine (89)	*Stephania cepharantha*	HIV-1(0.028) [a, d,m] SARS, HSV, CVB3*	[144]
Drymaritin (87)	*Drymaria diandra*	HIV (0.699) [b]	[143]
FK-3000 (88)	*Stephania cepharantha*	HIV, HSV-1(7.8) [a, h]	[144]
Harmine (85)	*Symplocos setchuensis*	HIV (0.037μM) [b,d]	[138]
Isoquinoline	*Stephania cepharantha*	SARS-CoV*	[146]
Michellamine B (84)	*Ancistrocladus korupensis*	HIV 1 μM[b, e, j, k]	[136]
Piperidines (92)	*Euphorbia poissonii*	HIV Gene expression	[150]
Skimmianine	*Zanthoxylum chalybeum*	Measles	[140]
Solamargine (83)	*Solanum khasianum*	HIV-1(1μM)[b,e,j,k]	[136]
Thalimonine	*Thalictrum simplex*	IV-A[d]	[141]
Triptonine A	*Trypterigium hypoglaucum*	HIV (2.54) [b]	[137]
Triptonine B	*Trypterigium hypoglaucum*	HIV (<0.1) [b]	[137]
Carbohydrates			
Galactofucan	*Undaria pinnatida*	HSV-1, HSV-2*	[162]
Niruriside	*Phyllanthus niruri*	HBV, HIV (3.3 μM)[a]	[94]
Stevian	*Stevia rebaudiana*	HRV, HSV-1[*]	[163]
Proteins & Peptides			
Griffithsin	*Griffithsia Sp*	HIV-1	[166]
MAP30	*Momordica charantia*	CMV, HIV-1(0.3 nM)[b,d,e,k]	[157]
Meliacine	*Melia azedarach*	HSV-1, JV*	[152,153]
MRK29	*M. Charantia*	HIV (18)[a,e]	[155]
NAG	*Urtica dioca*	HIV*[j]	[156, 18]
TAP29	*Trichosanthes kirilowii*	HIV (0.2–0.3 nM)[b,d,e,k]	[160]
Trichosanthin	*Trichosanthes kirilowii*	HIV-1*[d, g, k]	[159,160]
GAP31	*Gelonium multiflorum*	HIV (0.3 nM) [b, g]	[157]
Xylanase	*Panax notoginseng*	HIV (10μM)[a, e]	[154]

[a]IC_{50}, [b]EC_{50}, [c]ED_{50}, Inhibit: [d]replication, [e]reverse transcriptase, [f]protease, [g]integrase, [h]virus-induced cytopathic effects, [i]virus entry, [j]cellular fusion, [k]syncytium formation, [l]attachment and penetration, [m]infected cell polypeptide/proviral DNA/gene expression. *IC_{50}/EC_{50}/ED_{50} not available

ADV, Adenovirus; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIV, Human immunodeficiency virus; IV, Influenzavirus; PIV, parainfluenzavirus; PV, Poliovirus; RSV, Respiratory sychetrial virus; PRV, Pseudorabiesvirus; HRV, Human Rota virus; SARS-CoV, Severe acute respiratory syndrome-Coronavirus; JV, Juninvirus; VZV, Varicella zoster virus; RIP, ribose inactivating proteins; NAG, n-acetyl glucosamine.

Table 2. Mechanism of Antiviral Actions of Some Plant Derived Compounds

Class	Subclass	Compounds	Antiviral Mechanism
Phenolics	Simple phenols & Phenolic acids	Caffeic, Rosmarinic & Chlorogenic acid	Virus clumping, inhibition of virus adsorption, RTase, RNA polymerase
	Anthocyanins	Proanthocyanidins	HIV-RT inhibition
	Coumarins	Warfarin, Calanolides	Inhibit virus entry, RTase, integrase
	Flavones, Flavonols	Taxifolin, Torvanol Amentoflavone	Inactivate protease, RTase, gp120 interaction, protein binding

(Table 2. Contd….)

Class	Subclass	Compounds	Antiviral Mechanism
	Flavonoids	Chrysin, Quercetin, Morin, Myricetin, Catechin, Glycyrrhizin, Baicalin	Inhibit adsorption, virus entry, virus binding, RTase, integrase, protease, DNA & RNA polymerase, and form complex with proteins.
	Quinones, Fluroquinone	Hypericin, Chicoric acid, Chrysophlenol C	Integrase inhibition, protein inactivation, replication inhibition
	Tannins	Ellagitannin (Eugeniin), Shephagenin, Strictinin, Geraniin, Casuarinin, Camelliatannin	Inhibit adsorption, RTase, protease, DNA polymerase, transport protein, polysaccharide, Attachment & penetration
Terpenoid	Terpenoid & Essential Oils	Caesalmin, Capsaicin, Pulegone, terpinen-4-ol	Inhibit adsorption, cell-to-cell transmission, multiplication
	Triterpenoids	Betulinic acid, Arginine, Vaticonine, Ursolic acid	Inhibit virus entry, protease, replication
	Other terpenoids	Faicalein, Swertifrancheside	Inactivate protein by binding
Alkaloids		Cepharanthine, Michellamine B, Solamargine, Harman, Skimmianine, Triptonine	Inhibit viral gene expression, viral replication, protein synthesis, and 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	Meliacin, 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 Thai bitter gourd *Momordica charantia*; RAP, *Rhizophora apiculata* polysaccharides; RAM, *Rhizophora mucronata* polysaccharides.

cause AIDS, Marburg, Ebola and Lassa fever spread easily kill swiftly and have no cure or vaccine. They have numerous invasion strategies and each strain has its own unique configuration of surface molecules [8,9], enabling them to enter into host cells by precisely fitting their surface molecules with the molecules of target cell. The genetic variation, efficient replication, variety of transmission and ability to persist within the host cell help viruses to adapt in all forms of life and occupy numerous "ecological niches", and to cause widespread diseases in humans and other living organisms [9].

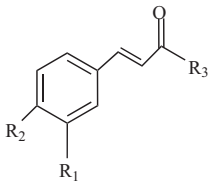
VIRAL INFECTION CONTROL

In spite of continuous advances have been made in the development of antiviral, infection with therapy viral diseases become the leading cause of death globally. The viral infections can be controlled either through prophylactic or therapeutic measures. As a metabolically inert particle virus requires metabolic pathway of living cells to replicate, which makes it difficult to design a treatment modalities to attack the virion or its replication, without affecting the host [8,9]. Although numerous compounds have been tested on different viruses, only 37 licensed antiviral drugs are in the market. On the other hand, development of antiviral drugs from natural source is less explored, probably because there are very few specific viral targets are available for small molecules to interact with. Fortunately, many viruses have unique features in their structure or replication cycles that can be the potential targets as evident with nucleoside analogue acycloguanosine (acyclovir) which specifically blocks certain viral enzymes of herpes viruses [9] that play the key role in triggering clinical manifestation of the diseases.

Due to the amazing structural diversity and broad range of bioactivities the ethno medicines can be explored as a source of complementary antivirals, as many of them are reported to inhibit several steps of replication cycle and certain cellular factors of many DNA and/or RNA viruses. A list of some potential ethnomedicinal plants along with the compounds having antiviral activities are presented in Table **1**.

PHENOLICS AND POLYPHENOLS

The simplest bioactive phytochemicals with a single substituted phenolic ring belongs to a wide group of phenylpropane that are in the highest oxidation state and have wide range of antiviral activities. The caffeic acid, chlorogenic acid (Fig. **1**) and rosmarinic acid (Fig. **2**) derivatives

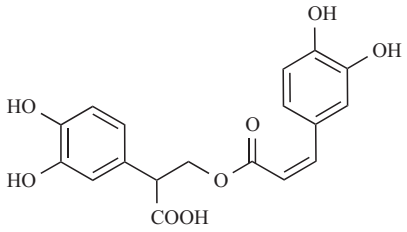


	Functional Groups			Anti-HSV activities (EC_{50}, µl/ml)	
Name	R_1	R_2	R_3	HSV-1	HSV-2
Caffeic Acid	-OH	-OH	-OH	15.3	87.3
Chlorogenic Acid	-OH	-OH	X*	47.6	86.5
p-Coumaric Acid	-OH	-H	-OH	>200	32.8
Ferulic Acid	-OH	$-OCH_3$	-OH	>100	>100

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

1. SAR of Caffeic acid and Chlorogenic acid

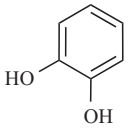
Fig. (1).



2. Rosmarinic acid

Fig. **(2)**.

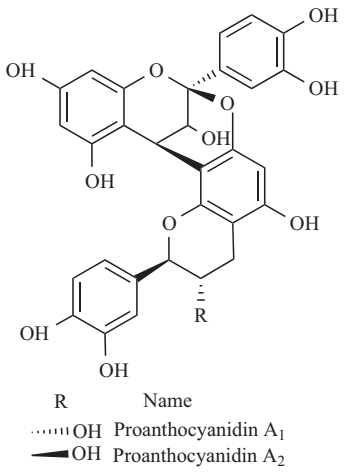
present in many ethnomedicinal plants can inactivate herpes simplex virus 1 (HSV-1), varicella zoster virus (VZV), pseudorabies virus (PRV) and influenza viruses [10]. The polyphenol rich extract of *Agrimonia pilosa* and *Punica granatum* of southern Mainland China, showed anti-HSV-1 activity; while oligophenols isolated from the Peruvian folklore *Stylogne cauliflora* inhibit hepatitis C virus (HCV) non-structural serine 3 (NS3) protease [11]. Interestingly polyphenols extracted from *Blumea laciniata*, *Elephantopus scaber* and *Scutellaria indica* inhibit respiratory syncytial virus (RSV) activity with an IC_{50} of 12.5-32 μg/ml [12]. The most pronounced *in vitro* anti-herpes and anti-influenza activity of polyphenol was reported with Bulgarian folklore *Geranium sanguineum*; but the broad *in vitro* antiviral activity does not correspond to their *in vivo* activities [13]. The polyphenols often showed virucidal effect in several viral systems by attaching to the proteins and/or host cell surfaces, resulting in reduction or prevention of viral adsorption; inhibit reverse transcriptase (RTase) of HIV-1 and RNA polymerase of influenza virus [13]. The SAR studies revealed that the site(s) and number of hydroxyl groups on phenols are responsible for their antiviral activity as reported with the pyrogallol and catechol (Fig. **3**). The prodelphinidin-di-*O*-gallate isolated from *Myrica rubra* bark demonstrated *in vitro* anti-HSV-2



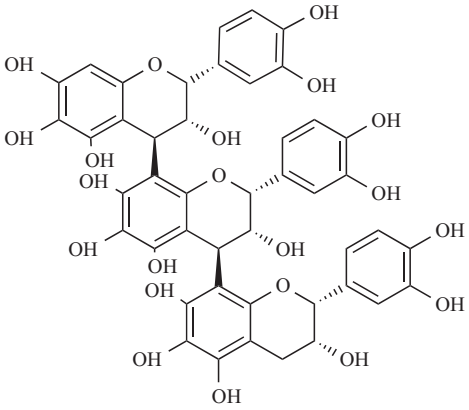
3. Catechol

Fig. **(3)**.

activities by inhibiting viral attachment and penetration, reducing viral infectivity and affecting the late stage of infection cycle [14]. Polyphenols and proanthocyanidins isolated from *Hamamelis virginiana* bark had remarkable anti-HSV-1 activity [15] while proanthocyanidins A1 (Fig. **4**) isolated from *Vaccinium vitis-idaea* block HSV-2 attachment and penetration to the host cell [16], but oligomeric procyanidins of *Crataegus sinaica* significantly inhibit HSV-1 [17]. Though proanthocyanidins nonspecifically bind proteins, but selectively inhibit nuclear factor kappa B (NFKB)-dependent gene expression, as reported with procyanidin C1 (Fig. **4**) that modulate apoptosis and inhibit NFKB activities [18]. An interesting SAR is noted with dimeric proanthocyanidins and related polyphenols, where epicatechin (Fig. **5**)-containing dimers showed pronounced anti-HSV activities, as the ortho-trihydroxyl groups in the B-ring and the double interflavan



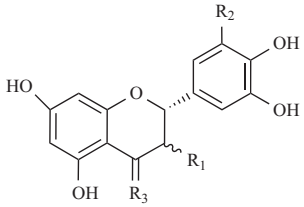
R	Name
····OH	Proanthocyanidin A_1
◄OH	Proanthocyanidin A_2



4. Proanthocyanidin C_1

Fig. **(4)**.

linkages lead to a significant increase of the anti-HSV effects [19]. The aqueous extract of *Plantago major*, a popular ethnomedicine used in Ayurveda (the Indian system of medicine), traditional Chinese medicine and Chakma Talika Chikitsa (system of "Chakma" tribes of Chittagong Hill, Bangladesh), for treating several ailments showed antiherpes

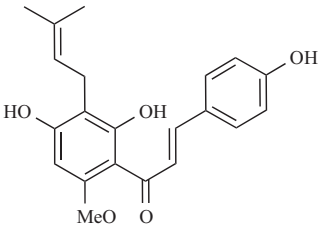


R_1	R_2	R_3	Name
····OH	H	H_2	(-) Epicatechin
◄OH	H	H_2	(+) Catechin
····OH	OH	H_2	Epigallocatechin
◄OH	H	O	(+) Taxifolin
◄OH		OH	Aromadendrin

5. Epicatechin

Fig. **(5)**.

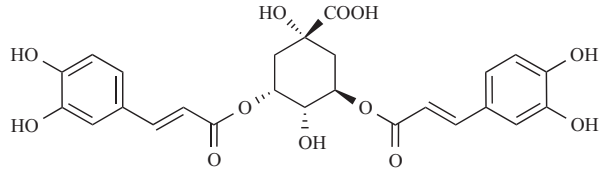
activity against HSV-1 and HSV-2 due to caffeic acid and its derivatives. The SAR studies revealed that chlorogenic acid and caffeic acid can be developed as an improved antiherpes agent. A xanthohumol (Fig. **6**)-enriched *Humulus lupulus* (hop) extract having moderate activity against HSV-2 and



6. Xanthohumol

Fig. (6).

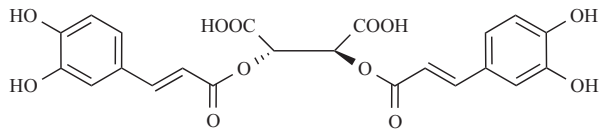
HSV-1 might serve as a lead for synthesizing more active anti-HSV agent [20]. McDougall *et al.* [21] reported that the biphenolic depsides (bis-catechol) 3, 5-dicaffeoylquinic acid (DCQA) (Fig. **7**) and dicaffeoyltartaric acid (DCTA) demonstrated a 10-100-fold higher preference for HIV integrase



7. 3,5-Dicaffeoylquinic acid (DCQA)

Fig. (7).

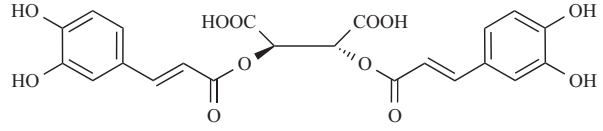
inhibition than RTase, and d-chicoric acid (Fig. **8**), a DCTA, was the most active Inhibitor of HIV integrase [21].



8. d-Chicoric acid

Fig. (8).

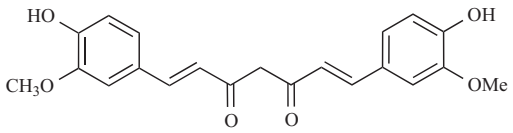
The inhibition of HIV integrase by DCQAs was irreversible and independent of divalent cations and the primary target of I-chicoric acid is the HIV-1 envelope glycoprotein gp120 [21, 22]. The SAR studies on DCTA's showed that l-chicoric acid (Fig. **9**) and d-chicoric acid (Fig. **8**) had similar anti-integrase activity, and removal of its carboxylic groups do not affect its activity, but bis-catechol moieties are essential



9. l-Chicoric acid

Fig. (9).

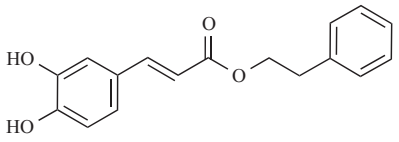
[18]. The transregulatory protein *Tat*, secreted by HIV-1 infected cells, is reported to play an important role in the deregulation of cytokines and regulate pathogenesis of AIDS, as its can be taken up by non-infected cells [23]. Curciminoids, the yellow pigment of turmeric *Curcuma longa* rhizome, a century old Indian spice having antiinflammatory, anticancer and antioxidant activities can block HIV-1 and HIV-2 replication *in vitro* by inhibiting HIV integrase, protease and virus-cell fusion [24], and is a potent inhibitor of TNF induced NFKB activation [25]. At 10-100nM dose Curcumin (Fig. **10**) and its derivatives inhibit *Tat*-mediated transactivation of HIV-1 long terminal repeat (LTR)-directed



10. Curcumin

Fig. (10).

gene expression [26] like caffeic acid phenethyl ester (CAPE) (Fig. **11**), an active component of propolis from honeybee hives having antiviral, anticancer, antiinflammatory and immunomodulatory activities [27]. Reduced curcumin, tocopheryl curcumin and allyl curcumin showed greater antiviral activity than curcumin, but ineffective in clinical trial [26]. The antiviral activities along with SAR of common isoprenoidal glycosides of folk medicines were recently reviewed by Nohara [28].

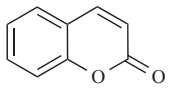


11. Caffeic acid phenethyl ester

Fig. (11).

COUMARINS

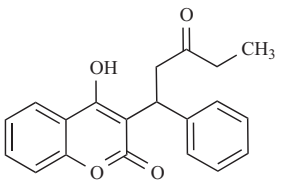
Coumarins are phenolics with fused benzene and α-pyrone rings (Fig. **12**) that can stimulate macrophages and thereby exert an indirect effect on viral infections, as found



12. Coumarin

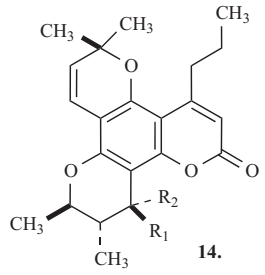
Fig. (12).

with oral anticoagulant warfarin (Fig. **13**), which prevent recurrences of cold sores caused by HSV-1 [29]. The coumarins of *Prangos tschimganica* have anti-HIV activity [30], but the most exciting antiviral coumarins are non-nucleoside inhibitor 4-propyldipyrano coumarins, isolated from tropical rainforest tree *Calophyllum lanigerum* and *C. inophyllum* found in Sarawak of Borneo, Malaysia [31]. The *Calophyllum* coumarins are classified into calanolides (Fig. **14**), inophyllums, and cordatolides (Fig. **15**), substituted with n-propyl, phenyl, and methyl groups respectively on the basis



13. Warfarin

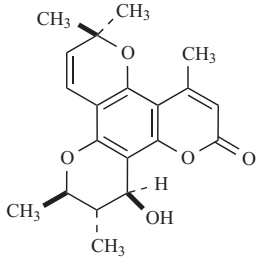
Fig. **(13)**.



14.

R_1 = OH, R_2 = H (+)Calanolide A
R_1 = H, R_2 = OH (-)Calanolide B

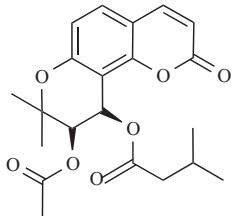
Fig. **(14)**.



15. Cordatolide A

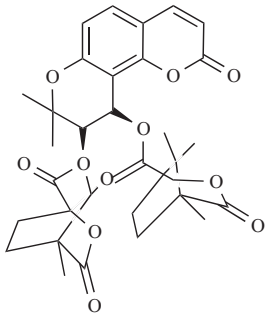
Fig. **(15)**.

of C-4 substituent on the lactone ring [32]. 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 [33]. 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 (Fig. **14**) is 50 times more active viral RTase inhibitor, indicating the importance of C-4 substituent [18,34]. Calanolides are treated as novel antiretroviral agent due to its potent RTase activity, unique sensitivity profile against non-nucleotide RTase inhibitor resistant viruses and producing synergism in combination with lamivudine and nelfinavir [35], as well with AZT [36] in clinical trials. Khellatone coumarins, pyranocoumarin suksdorfin (Fig. **16**) isolated from *Lomantium suksdorfii* can suppress HIV replication with an EC_{50} values of 2.6 μM [37]. Modifications at 3′,4`-position yielded 3`-R,4`-R-di-O-(-)-camphanoyl-(+)-cis-khellactone (Fig. **17**) with improved anti-HIV activity (EC_{50} 0.0004 μM). Steriochemical studies showed that R,R isomer was 10,000 times more active than R,S, S,R and S,S isomers. Further modifications led to more potent 4-MeDCK (Fig. **18**) with EC_{50} 1.6 $X10^{-7}$ μM and recently, a preclinical candidate 3-hydroxymethyl-4-methyl DCK (Fig. **19**) inhibit both primary and drug resistant HIV-



16. Suksdorfin

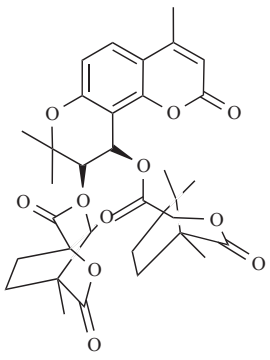
Fig. **(16)**.



17. cis-Khellactone (DCK)

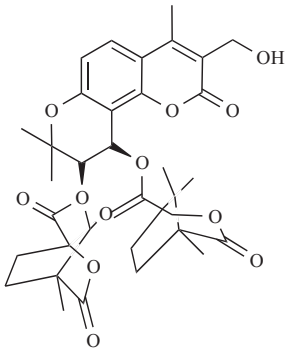
Fig. **(17)**.

isolates at nanomolar concentration with minimal toxicity [34]. Coriandrin (Fig. **20**) an isocoumarin of *Coriandrum*l



18. 4-MeDCK

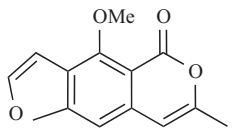
Fig. **(18)**.



19. 3-hydroxyymethyl-4-methyl DCK

Fig. **(19)**.

sativum possessed anti-HIV and other antiviral activities [34]. A recent review by Curini *et al.* [38] may be consulted for more detailed.



20. Coriandrin

Fig. (20).

FLAVONES, FLAVONOIDS, AND FLAVONOLS

Flavones (Fig. **21**) are hydroxylated phenolics containing one carbonyl group instead of two in quinones, while the

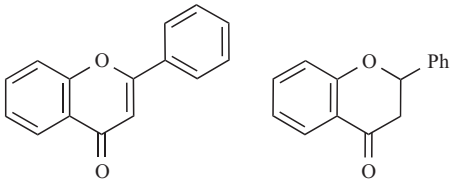
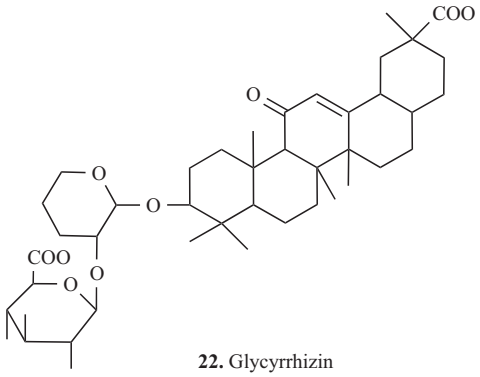


Fig. (21).

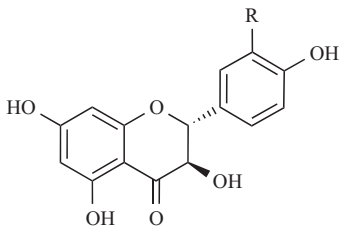
addition of a third hydroxyl group yields a flavonol. Flavonoids occur as a C_6-C_3 unit linked to an aromatic ring and are synthesized in response to microbial infections, hence has broad spectrum of antimicrobial activity. Flavonoids are well-known inhibitors of many essential enzymes of viral replication, such as viral RTase [39], Integrase [40] and protease [41], and form complex with extracellular and soluble proteins. It can partly interfere with virus–cell binding, as found in glycyrrhizin (Fig. **22**) [42]. Taxifolin (Fig. **23**), a flavanone with an OH group at C-3´inhibit viral protease,



22. Glycyrrhizin

Fig. (22).

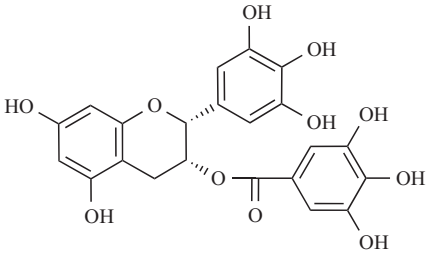
RTase, and CD4/gp120 interaction by binding to the V3 loop of gp120; while flavanones lacking OH group at C-3´ (aromadendrin) (Fig. **23**), are more specific inhibitor of CD4/gp120 interaction [18]. Similarly the epicatechin of *Xanthoceras sorbifolia* inhibit HIV-1 protease at IC_{50} of 70 µg/ml; while the antioxidant (-)-epigallocatechin 3-0-gallate



23. Taxifolin R = OH
Aromadendrin R = H

Fig. (23).

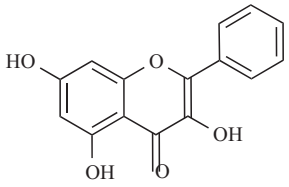
(EGCG) (Fig. **24**) blocks the post-adsorption entry and inhibits viral protease and RTase with a nonspecific destructive



24. (-)Epigallocatechin 3-*O*-gallate

Fig. (24).

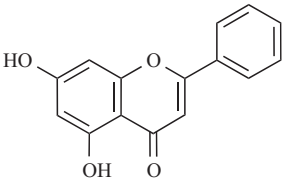
effect on HIV-1 particles [43]. The C-4 sulfated isoflavone torvanol A and the steroidal glycoside torvoside H, isolated from *Solanum torvum* fruits, had strong anti-HSV-1 activity [44]. But antibacterial galangin (3,5,7-trihydroxy-flavone) (Fig. **25**) isolated from *Helichrysum aureonitens* had significant activity against HSV-1 and coxsackie B virus



25. Galangin

Fig. (25).

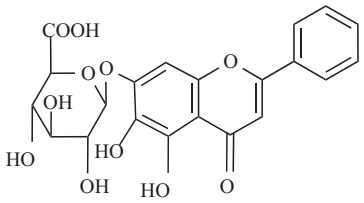
(CVB1) type 1 [45]. Similarly the isoquercitrin of *Waldsteinia fragarioides* have anti-HSV activity, while glycyrrhizin (Fig. **22**), chrysin (Fig. **26**) and swertifrancheside (Fig. **58**) have anti-HIV activities [46]. Kaul *et al.* [47]



26. Chrysin

Fig. (26).

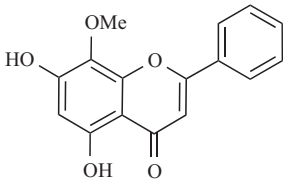
reported that hesperidin (Fig. **27**) of orange and grape inhibit replication of HSV, poliovirus 1, parainfluenza 3 and



27. Hesperidin

Fig. **(27)**.

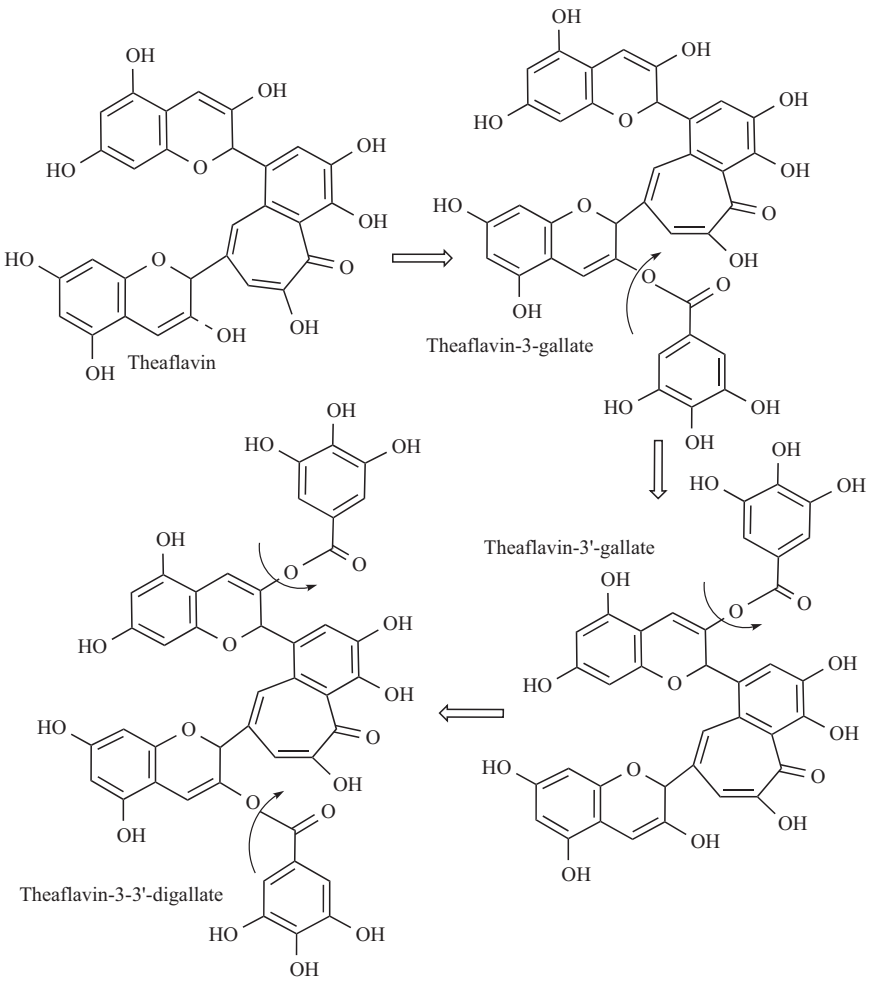
RSV but catechin (Fig. **5**) inhibits infectivity of RSV and HSV-1, while quercetin (Fig. **36**) inhibit all, as the small structural differences of these compounds are critical to their activity. Robin *et al.* [48] found that 3-methylkaempferol of *Psiadia dentata* is the most potent inhibitor of genomic RNA synthesis of poliovirus; while dihydroxyolean-oic acid, indole-3-carboxylic acid and (-) catechin of *Begonia nantoensis* inhibit HIV replication [49]. Interestingly oxyresveratrol of *Millettia erythrocalyx* and *Artocarpus lakoocha* inhibit both HSV and HIV-1 [50] and flavone glycoside dihydroxytrimethoxyflavone-β-D-xylopyranosyl-β-D-glucopyranoside of *Butea monosperma* seed had broad antiviral spectrum [51]. A natural monoflavonoid wogonin (Fig. **28**) with anti-inflammatory, anticancer, neuroprotective and antioxidant activity have rapid tissue distribution and prolonged plasma elimination rate and is reported to have broad spectrum of antiviral activity [52], thus be a potential candidate for designing anti-rabies and or anti-encephalitis drugs.



28. Wogonin

Fig. **(28)**.

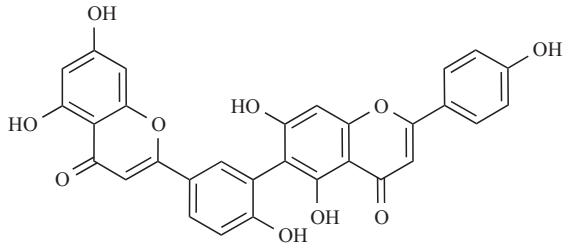
Considerable number of evidence suggests that bioflavonoids, the basis of many folk remedies, are health promoting, disease-preventing dietary compounds and some of which are applied in therapy or used as prototypes for specific drug development. The antiviral activities of plant bioflavonoids have been evaluated and reviewed [46,53,54] earlier. Black tea, a popular beverage, produced by a series of fermentation through which catechin (30%) of green tea leaves oxidized into theaflavins (4%) (Fig. **29**) like theaflavin (0.8%), theaflavin-3-gallate (0.31%), theaflavin-3'-gallate (0.11%) and theaflavin-3,3'-digallate (1.5%) by dimerization and into thearubigins (17%) through polymerization. A recent report indicated that water soluble polyphenols tannic acid (IC_{50}3μM), theaflavin-3'-gallate (IC_{50}10μM) and theaflavin-3,3'-digallate (IC_{50}7μM) can inhibit chymotrypsin-like protease ($3CL^{PRO}$), an essential enzyme of SARS Coronavirus (CoV) maturation [55]. The SAR studies indicated that theaflavin-3-3'-digallate contain two gallate groups attached to the 3 and 3' position, in contrast to one in theaflavin 3-gallate or no gallate group in theaflavin. The gallate group attached to 3' position might be important for interaction with $3CL^{PRO}$ active site as catechins are less active ($IC_{50}\geq$100μM) than theaflavins. It is interesting to note that both coronavirus and rotavirus replicate in intestinal tract [56] and both can be neutralize by theaflavins of black tea [57]. Hence, whether drinking black tea can prevent coronavirus and rotavirus infections and theaflavins can used as a starting point of designing more active SARS inhibitor is a subject of further study. Theaflavin (Fig. **29**) of black tea neutralize bovine rotavirus and coronavirus [55]; while the flavonol glycoside luteoside of *Barleria prionitis* and *Markhamia lutea* root have potent anti-RSV activity [46, 56]. The amentoflavone (Fig. **30**) and robustaflavone (Fig. **31**) isolated from *Rhus succedanea* and *Garcinia multiflora* inhibit HSV, influenza virus and HIV-1 RTase *in vitro* while measles and VZV were inhibited by rhusflavanone and succedaneflavanone [57]. Another bioflavonoid wikstrol B (Fig. **32**) isolated from *Wikstroemia indica* root showed good anti-HIV-1 activity [58]. The antiinflammatory flavonoids baicalein and baicalin (Fig. **33**) from *Scutellaria baicalensis* of China markedly inhibit RTase and the replication of HIV-1 in a dose dependent manner [42], interact with envelope proteins and chemokine co-receptors to block the HIV-1 entry to the CD4 cells [59]. The bioflavonoids arctiin, phillyrin, liquiritin, genistein (Fig. **34**), daidzein (Fig. **35**) and chlorogenic acid (Fig. **1**) inhibit influenza virus [60]; while cinnamoylbenzaldehyde and lawinal of *Desmos* spp. [61], mulberroside C and leachianone G of *Morus alba* root inhibit HSV-1 [62]. The flavonoids of *Aesculus chinensis* seed extract inhibit RSV and influenza A [63]. Unlike morin pentaacetate the morin, a flavonoid group, isolated from *Maclura cochinchinensis* have powerful anti-HSV-2 activity, as the free hydroxyl groups are responsible for antiviral activity [21]. Most of the potent anti-HIV flavonoids like baicalein, quercentin (Fig. **36**), myricetin etc. not only block viral RTase but also the cellular DNA/RNA polymerase of HIV, where the degree of inhibition depends on the structure and side chain [46,64]. The citrus polymethoxylated flavonoids inhibit the release of TNF-R from monocytes *in vitro* by elevating cAMP level through inhibition of cAMP cleavage enzyme phosphodiesterase [65]. Since tyrosine kinase is essential for the activation of NFKB, so kinase inhibitors like genistein (Fig. **34**) and staurosporine (Fig. **37**) can inhibit TNF release, both *in vitro* and *in vivo* [66]. Several anti-HIV flavonoids like quercetin, chrysin, epicatechin and (-)-epigallocatechin gallate showed inhibitory activity against kinase II [67,68]. However, further research is needed to fully understand the biological significance of casein kinase II in viral replication and its inhibition by flavonoids. The evidence of oxidative stress in virus-infected individuals indicates that antioxidants like polyphenolics flavonoids and proanthocyanidins with oral availability may have some role on viral disease progression [69]. The evaluation of *in vivo* effect of antioxidants on viral diseases need monitoring of oxidative stress as excessive antioxidant protection could lean over the balance from oxidative stress to "oxidative deficit". The reactive oxygen species (ROS), antioxidants, transcription factors, and cytokines are part of a large human defense network that behaves like a black box, essential for



29. SAR of Theaflavin and its derivatives

Fig. (29).

life. Hence, controlled clinical trials with antioxidants, along with oxidative stress measurement will help to determine the clinical significance of oxidative stress on viral diseases; and dietary intervention with antioxidants could be an inexpensive alternation to the existing antiviral treatment strategies.

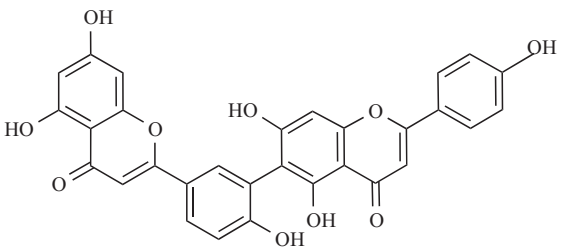


30. Amentoflavone

Fig. (30).

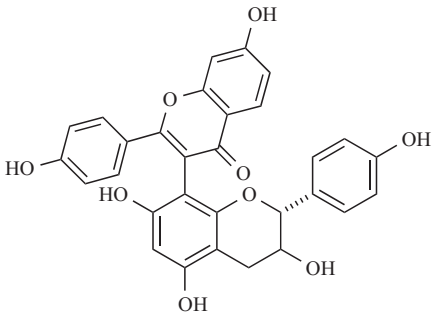
TERPENOIDS AND ESSENTIAL OILS

Essential oil (*quinta essentia*), the fragrance of plants, are the phenolic compounds with a C_3 side chain and at a lower level of oxidation without oxygen. The oils that are highly enriched in isoprene structure are called terpenes; and when contain additional elements like oxygen; they are termed as terpenoids that are active against many viruses [18,19,46]. Chiang *et al.* [70] recently reported the broad spectrum antiviral activity of *Ocimum basilicum*, sweet basil of Indian and Chinese medicine, against diverse virus families. The aqueous and ethanolic extract alogwith purified apigenin (Fig. **38**), linalool and ursolic acid (Fig. **39**) showed strong activity against HSV-1, Adenovirus 8 (ADV-8), CVB1 and



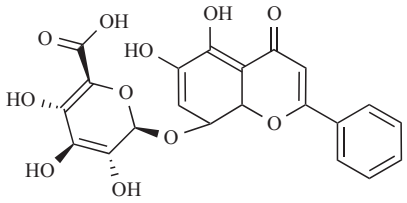
31. Robustaflavon

Fig. (31).



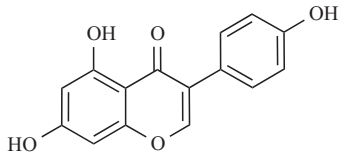
32. Wikstrol B

Fig. **(32)**.



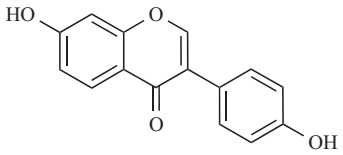
33. Baicalin

Fig. **(33)**.



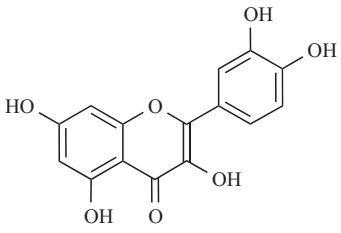
34. Genistein

Fig. **(34)**.



35. Daidzein

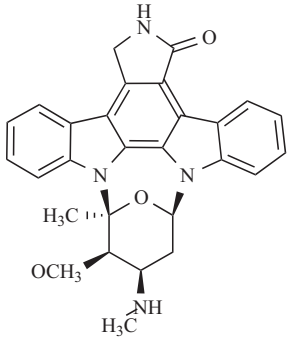
Fig. **(35)**.



36. Quercetin

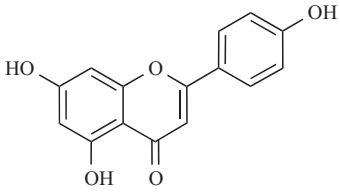
Fig. **(36)**

Enterovirus 71 (EV71). Of these ursolic acid showed the strongest activity against HSV-1 with an EC_{50} of 6.6 mg/L; ADV-8 (4.2 mg/L), CVB1 (0.4 mg/L) and EV71 (0.5 mg/L), apigenin showed the highest activity against HSV-2, ADV-3,



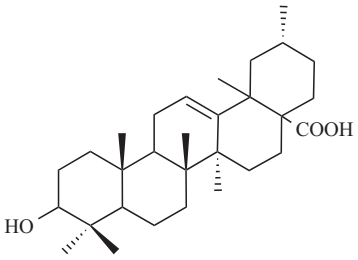
37. Staurosporine

Fig. **(37)**.



38. Apigenin

Fig. **(38)**.

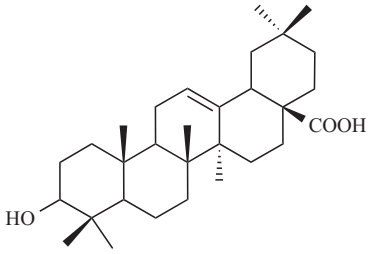


39. Ursolic acid

Fig. **(39)**.

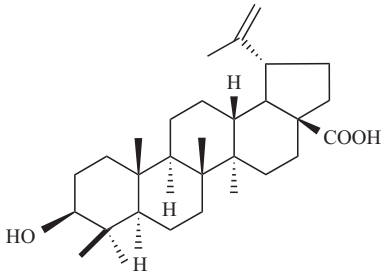
hepatitis B surface antigen and hepatitis B e antigen; while linalool showed strongest activity against AVD-II. The antiviral activity of ursolic acid against CVB1 and EV71 is evident during the infection process and the replication phase, indicating that the ursolic acid can be a potential candidate against these RNA viruses [70], which merits further investigation. Recently Cheng *et al.* [71] reported that *ent*-epiafzelechin-(4α->8)-epiafzelechin (EEE) (Fig. **44**) isolated from fresh leaves of *Cassia javanica* L. *agnes* de Wit inhibit HSV-2 replication in a dose-dependent manner with an IC_{50} value of 83·8±10·9 and 166·8±12·9 μM for XTT and plaque reduction assays, respectively at non cytotoxic concentration. Further study demonstrated that EEE prevented HSV-2 from penetration and replication at the late stage of life cycle [71]. The volatile oil 1,8-cineole and terpinen-4-ol (Fig. **45**) of Egyptian plants *Melaleuca armillaris* was more effective virucidal [72]. On the other hand, isoborneol (Fig. **46**), a monoterpene of essential oils isolated from *Melaleuca alternifolia* exhibited anti-HSV-1 activity by inactivating HSV-1 replication within 30 min of exposure. At non-cytotoxic dose it specifically inhibits glycosylation of viral

polypeptides without changes in the glycosylation pattern of cellular polypeptides and affecting the glycosylation of gB [73], indicating isoborneol (Fig. **46**) as an interesting anti-HSV agent. Diterpene putranjivain A (Fig. **47**), isolated from *Euphorbia jolkini* significantly reduced infectivity of HSV-2 *in vitro* with an IC_{50} of 6.3-7.9 μM and IC_{90} of 14.5 μM, affecting late stage of replication, inhibit viral attachment and cell penetration [74]. Triterpene Moronic acid (Fig. **48**) of *Rhus javanica* have activity against acyclovir-resistant, thymidine kinase-deficient and wild-type HSV-1 strains with EC_{50} of 3.9 μg/ml and betulonic acid (Fig. **41**) with 2.6 μg/ml against wild-type HSV-1 [75]. Oral administered of moronic acid to cutaneously infected mice with HSV-1 significantly retarded skin lesions and/or prolonged the mean survival times of infected mice without toxicity by suppressing virus yields to the brain more efficiently and therefore, it can be a major anti-HSV agent with a different mechanism of action than that of acyclovir. The triterpenes ursolic acid (Fig. **39**), oleanolic acid (Fig. **40**), betulinic acid (Fig. **41**) and their derivatives isolated from many plants inhibit HIV-1 protease [76-78] and the stability of



40. Oleanolic acid

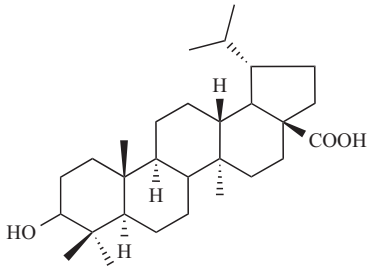
Fig. **(40)**.



41. Betulinic acid

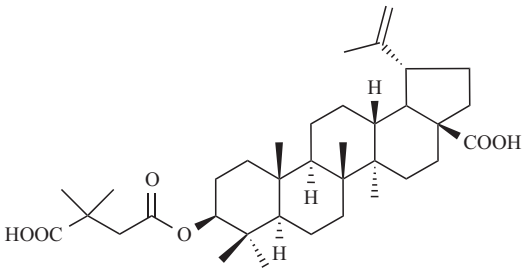
Fig. **(41)**.

gp120/gp41 complex [79, 80]. Betulinic acid (Fig. **41**) and oleanolic acid (Fig. **40**) isolated from *Syzigium claviflorum*, exhibited anti-HSV and anti-HIV activity; but betulinic acid is more active with an EC_{50} value of 1.4μM. Dihydrobetulinic acid (Fig. **42**) has an EC_{50} of 0.9 μM, while the esterification at C-3 hydroxyl of those acids resulted in more potent antiviral compound 3-*O*-(3,3′-dimethylsuccinyl) betulinic acid (DSB) (Fig. **43**) with an EC_{50}<3.5 x 10^{-4}μM [81], can block a key step in the processing of a viral core protein capsid. The DSB is very active against drug-resistant virus, effective in an animal model of HIV infection and suitable



42. Dihydrobetulinic acid

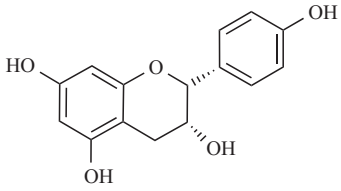
Fig. **(42)**.



43. 3-*O*-(3,3'-dimethylsuccinyl) betulinic acid (DSB)

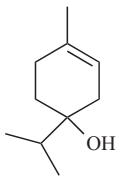
Fig. **(43)**.

for use in combination therapy and is under phase II clinical trial. Oleanolic acid isolated from many plants, including



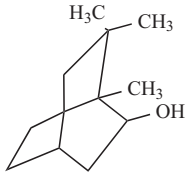
44. Epiafzelechin

Fig. **(44)**.



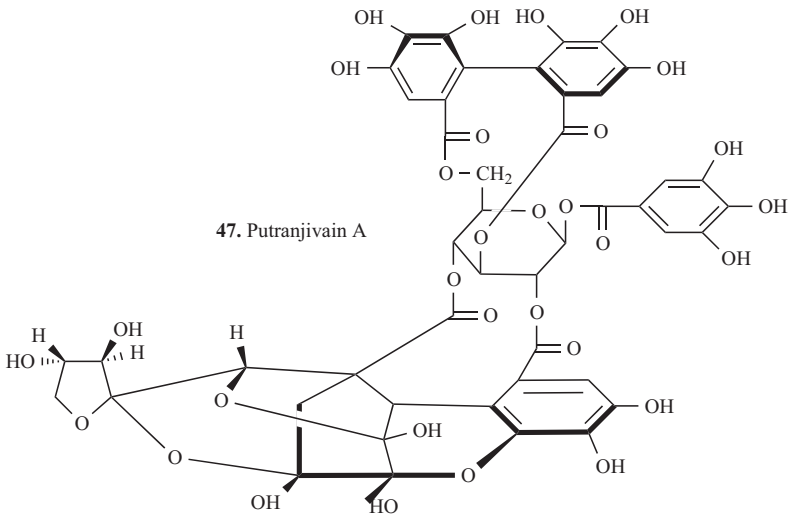
45. Terpinen 4-Ol

Fig. **(45)**.



46. Isobornoel

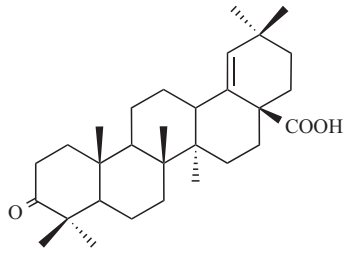
Fig. **(46)**.



47. Putranjivain A

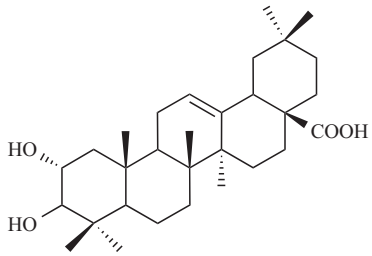
Fig. **(47)**.

Xanthoceras sorbifolia wood, inhibit herpes and HIV virus replication, but esterification at C-3 hydroxyl position resulted in 3-oxotirucalla-7,24-dien-21-oic acid with improved antiviral activity(EC_{50} 0.0039 μg/ml) and also block HIV protease with an IC_{50} of 10 μg/ml. Ursolic acid isolated from *Crataegus pinatifida* leaves showed potent action against HIV-1 protease activity at 100 μg/ml [82]. Maslinic acid (Fig. **49**) isolated from *Geum japonicum* can inhibit HIV-1 protease at 17.9 μg/ml [83]; while Moronic acid (Fig. **48**) extracted from *Myrceugenia euosma* showed significant anti-HIV activity with therapeutic index greater than 186 [84].



48. Moronic acid

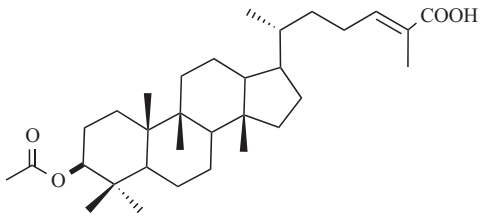
Fig. **(48)**.



49. Maslinic acid

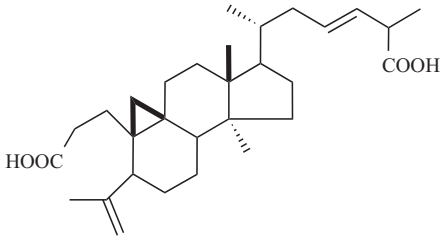
Fig. **(49)**.

The protostanes, garcisaterpenes A (Fig. **50**) and C isolated from *Garcinia speciosa* showed significant inhibitory activities against HIV-1 RTase and in the syncytium formation assay [85]; while secocycloartene triterpenoid, nigronoic acid (Fig. **51**) from *Schisandra sphaerandra* inhibit RTase of both HIV-1 and HIV-2 [86]. Kaurane diterpenoid, 16-β,17-dihydroxy-*ent*-kauran-19-oic acid isolated from fresh fruits of *Annona squamosa* L. significantly inhibited HIV with an EC_{50} value of 0.8 μg/ml [87].



50. Garcisaterpenes A

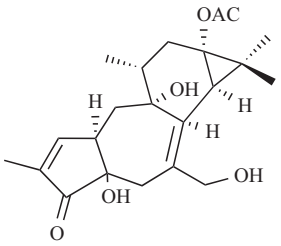
Fig. **(50)**.



51. Nigronoic acid

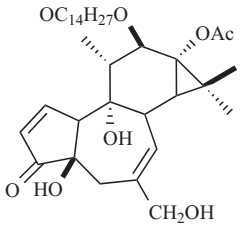
Fig. **(51)**.

Phorbol ester, prostratin (Fig. **52**) extracted from *Homalanthus nutans* showed potent HIV inhibitory activity; while phorbol diester, 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (Fig. **53**) isolated from *Croton tiglium* inhibited HIV-1-induced cytopathic effects [88]. Diterpene lactone, andrographolide (Fig. **54**) from *Andrographis paniculata* inhibited HIV-infected cells from arresting in G2 phase in which viral replication is optimal and is reported to inhibit cell-to-cell



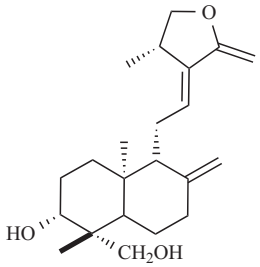
52. Prostratin

Fig. (52).



53. 12-*O*-tetradecanoylphorbol-13-acetate (TPA)

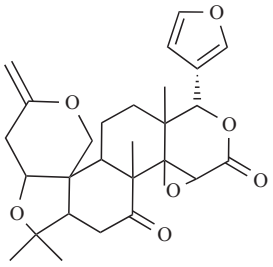
Fig. (53).



54. Androgropholide

Fig. (54).

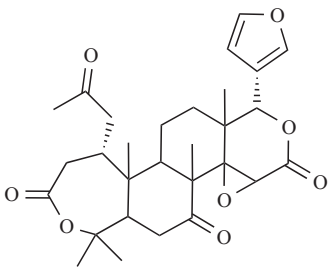
transmission, viral replication and syncytia formation in HIV-infected cells [89]. Limonin (Fig. **55**) and nomilin (Fig. **56**) isolated from *Citrus* spp. exhibited anti-HIV-1



55. Limonin

Fig. (55).

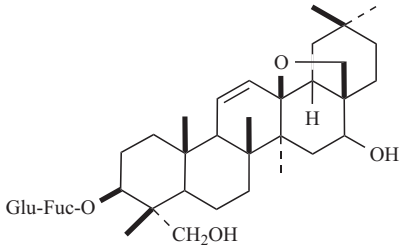
activity and a dose dependent inhibition of viral replication was observed in PMBC from healthy donors and infected with HIV-1 strain after incubation with limonin and nomilin due to inhibition of the production of p24 antigen in infected monocytes/macrophages by blocking HIV-1 protease [90].



56. Nomilin

Fig. (56).

The triterpenoid saponin of oleanane group inhibits DNA synthesis, while the ursane group inhibits capsid protein synthesis of HSV-1 [80]. *Euphorbia segetalis* exhibit strong viral plaque inhibitory effect against HSV-1 and HSV-2 due to tetracyclic triterpene lupenone [91]. The furanoditerpenes caesalmin isolated from *Caesalpinia minax* seed reported to inhibit Parainfluenza Virus 3 (PIV3)[80], but tetracyclic furanoditerpenoids caesalmin is more potent than the lactone caesalmin. The triterpenes vaticinone from *Vatica cinerea* of Vietnam inhibit HIV-1 replication [92]; arganine C, a triterpene saponin from *Tieghemella heckelii* fruits inhibits HIV entry into host cell suggesting their usefulness as potential antiviral agent, while ovatodiolide and triterpenoid betulinic acid (Fig. **41**) of *Anisomeles indica* had anti-HIV [93]. The inhibition of vesicular stomatitis virus (VSV) by saikosaponins (Fig. **57**) and iridoid glycosides from *Bupleurum rigidum* and *Scrophularia scorodonia* [94], and the virucidal

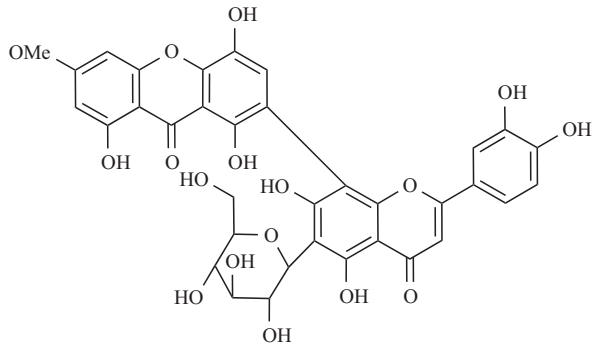


57. Saikosaponin

Fig. (57).

activity of iridoid maesasaponin of *Maesa lanceolata* against HSV-1 are due to diacylation [95]. 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 herpes viruses [96]; while pulegone of *Minthostachys verticillata* inhibit HSV-1 and pseudorabies virus (PRV) replication [97]. The terpinen-4-ol (Fig. **45**) of tree tea *Melaleuca alternifolia* oil used as antimicrobial preservative in many cosmetics, exhibited strong virucidal activity against HSV-1 and 2, while Eucalyptus oil reduced HSV titers from 57.9-75.4% [98], as both the oils affect HSV before or during adsorption. The essential oil of *Lippia junelliana* and *L. turbinata* of San Luis province of Argentina is virucidal (VC_{50} 14-20 ppm) against Junin virus, while essential oils of *Artemisia douglasiana* and *Eupatorium patens* inhibit HSV-1 (65-125 ppm) and Dengue virus 2

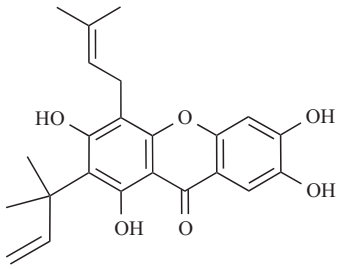
(150 ppm) [99] but *Melissa officinalis* oil inhibit HSV-2 replication [100]. Although the active antiherpes components of tea tree and eucalyptus oil are not very clear but their application in recurrent herpes infection is promising. Swertifrancheside (Fig. **58**), a flavonone–xanthone glucoside isolated from *Swertia franchetiana* was found to inhibit HIV-1



58. Swertifrancheside

Fig. (58).

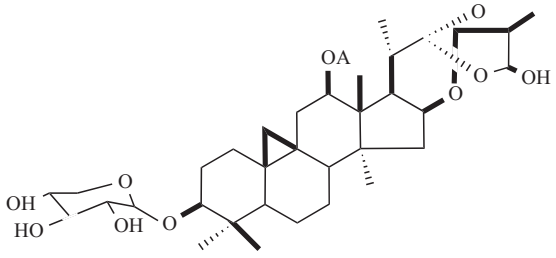
RTase by binding with DNA, and may explain why it is also an inhibitor of several other polymerases, including DNA polymerase, and thus not a selective HIV-1 RTase inhibitor [101]. The prenylated xanthone, macluraxanthone B (Fig. **59**) isolated from *Maclura tinctoria* exhibited moderate



59. Macluraxanthone B

Fig. (59).

anti-HIV activity [102]. Actein (Fig. **60**), a tetracyclic triterpenoid saponin isolated from *Cimicifuga racemosa* rhizome,



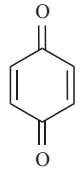
60. Actein

Fig. (60).

showed potent anti-HIV activity [103] whiles Soybean saponins inhibited HIV-1 replication without inhibiting HIV-1 RTase; but inhibits HIV-induced cell fusion [104]. Escins, the triterpenoid saponin mixture extracted from *Aesculus chinensis* seed was found to show moderate anti-HIV-1 protease activity [105].

QUINONES

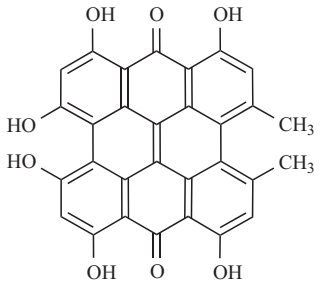
Quinones (Fig. **61**) are coloured compounds having aromatic rings with two ketone substitutions, and are highly



61. Quinone

Fig. (61).

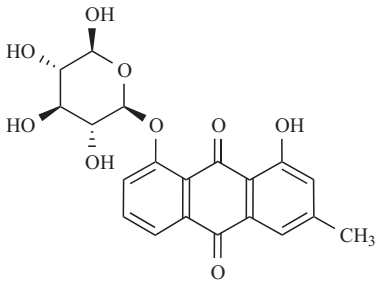
reactive. These compounds are responsible for the browning reaction in cut or injured fruits and vegetables, dying of henna, and are an intermediate of melanin synthesis pathway [106]. The switch between diphenol (hydroquinone) and diketone (quinone) occurs easily through oxido-reduction reactions and hence, individual redox potential of particular quinone-hydroquinone pair is very important in biological systems. Quinones provide a source of stable free radicals, and also irreversibly bind with nucleophilic amino acids leading to the inactivation and loss of function of proteins [107]. Therefore, quinone have wide antiviral spectrum, probably targeting the virus attachment site along with some viral enzymes. A polycyclic aromatic dianthroquinone hypericin (Fig. **62**), an antidepressant isolated from *Hypericum perforatum* (St. John's wort) showed antiviral activity against non-human and human retroviruses by inhibiting



62. Hypericin

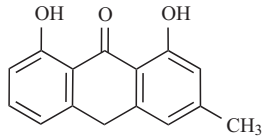
Fig. (62).

HIV-1 RTase [108], while chrysosplenol C is a potent and specific inhibitor of picornaviruses and rhinoviruses [109], causing common cold. Chrysophanol C and its glycoside (Fig. **63**) isolated from Australian folklore *Dianella longifolia* and chrysophanic acid (Fig. **64**) from *Pterocaulon sphacelatum* inhibits the replication of poliovirus type 2 and 3 due to hydrophobic C-6 group and methyl group at C-3 [110]. The introduction of an aryl group at the piperazine moiety of fluoroquinolone (Fig. **65**) yielded antiviral activity, specifically on HIV transcription and *tat* functions. Substitution of the fluorine at position 6 with an amine group



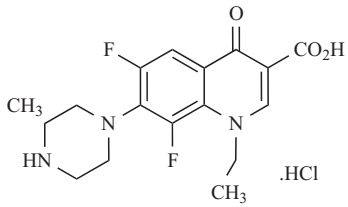
63. Chrysophanol 8-glucoside

Fig. (63).



64. Chrysophanic acid 9-anthrone

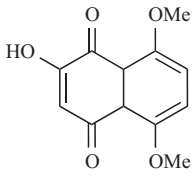
Fig. (64).



65. Fluoroquinolone (Lomefloxacin)

Fig. (65).

yielded aryl-piperazinyl-6-amino-quinolones, a selective and potent inhibitor of HIV-1 replication by interfering with *tat-TAR* interaction [111]. This relationship can be useful for rational drug design with optimized antiviral activity. Several naphthoquinones such as 1,4-naphthoquinone (Fig. **66**), vitamin K3, juglone and plumbagin showed HIV- inhibitory



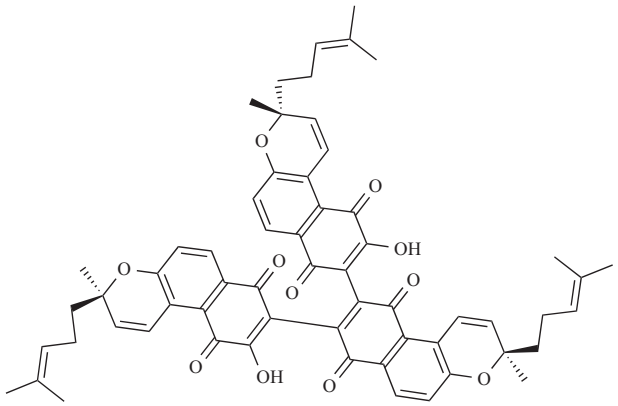
66. 1,4-Napthoquinone

Fig. (66).

activity [112]. A trimeric naphthoquinone, conocurvone (Fig. **67**) isolated from *Conospermum incurvum* showed potent anti-HIV activity by a novel mechanism in the late phase of viral replication cycle. Conocurvone added 48 h after infection, protected T-cells from cytopathogenic effect of HIV-1 [113].

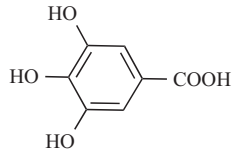
TANNINS

A group of polymeric plant phenolics (MW 500-3000) is capable of tanning leather or precipitating gelatin from solution (astringency) is called 'tannin', which is grouped into hydrolyzable and condensed tannins. Hydrolyzable tannins are based on gallic acid (Fig. **68**), while the condensed tannins proanthocyanidins are derived from flavonoid monomers. Several hydrolysable tannins such as chebulagic acid,



67. Conocurvone

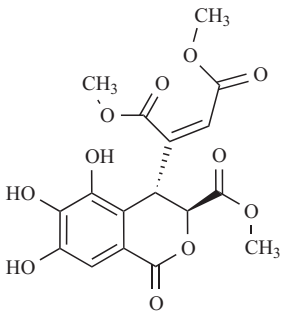
Fig. (67).



68. Gallic acid

Fig. (68).

dehydrochebulic acid (Fig. **69**), punicalin and punicalagin from *Terminalia chebula* show anti-HIV activity. The consumption of tannin-containing beverages, like green teas and

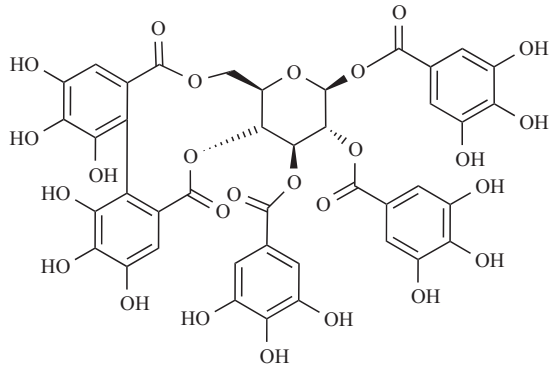


69. Dihydrochebulic acid

Fig. (69).

red wines, can cure or prevent a variety of illnesss as tannins can stimulate phagocytic cells, inhibit tumor and wide range of microbes by forming complex with microbial proteins through hydrophobicity, hydrogen and covalent bonding [114]. Thus, the mode of antiviral action of tannin is to inactivate virus adsorption, transport proteins, polysaccharides and viral RTase [19,46,47], as evident with HIV-1 RTase

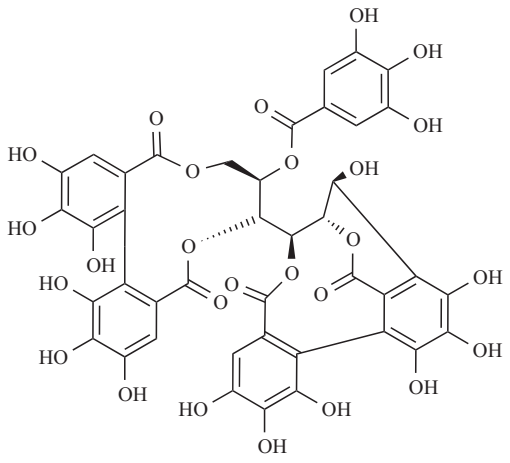
inhibitors shephagenins A and B, hippophaenin A and strictinin, the hydrolysable tannins of *Shepherdia argentea* [115]. The phenolic samaragenin B of *Limonium sinensi* suppress HSV-1 replication by regulating macromolecular synthesis [116]; while eugeniin (Fig. **70**) and eugenol from *Geum japonicum* and *Syzygium aromaticum* block viral



70. Eugeniin

Fig. (70).

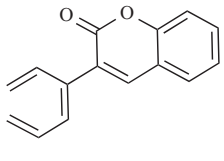
DNA polymerase and thereby inhibit acyclovir-resistant and thymidine kinase-deficient HSV-1, wild HSV-2, and Epstein-Barr virus [117]. The extract of *Bergenia ligulata* rhizomes, a Nepalese ethnomedicine, inhibits influenza virus replication by blocking RNA and protein synthesis at 10 μg/ml, in a dose dependent manner due to tannin [118]; while gallotannins geraniin from *Phyllanthus amarus* inhibit HIV-1 replication by inhibiting RTase in a dose-dependent manner [119]. Hydrolyzable tannin casuarinin (Fig. **71**) from *Terminalia arjuna* bark is virucidal and inhibit HSV-2



71. Casuarinin

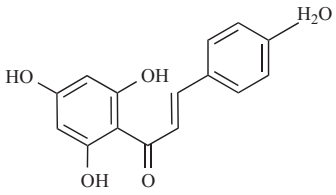
Fig. (71).

attachment and penetration [120], but camelliatannin H from the Korean folklore *Camellia japonica* pericarp inhibit HIV-1 protease [121]; while tannin from *Prunella vulgaris* and *Rhizoma cibotte* 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 [122]. A Japanese group showed that tannins can suppress promoter gene in HIV and structure-activity relationship study revealed that 3-phenylcoumarins (Fig. **72**), isoflavones, and chalcones (Fig. **73**) suppressed 12-0-tetradecanoylphorbol-13-acetate (TPA)-induced HIV promoter activity more effectively than



72. 3-Phenylcoumarin

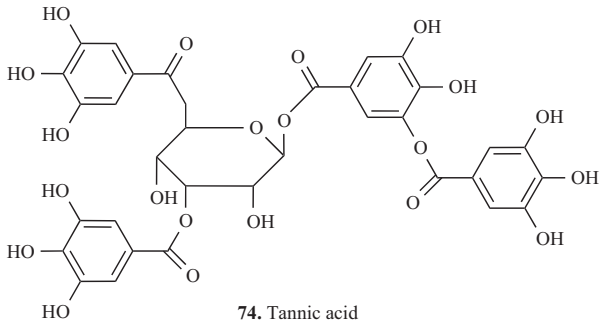
Fig. (72).



73. Chalcones

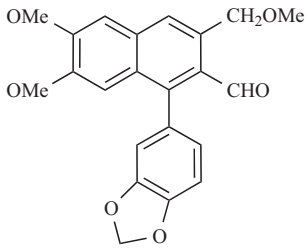
Fig. (73).

tannic acid (Fig. **74**) [123]. Phyllamyricin B (Fig. **75**) and its lactone retrojusticidin B (Fig. **76**) isolated from *Phyllanthus myrtifolius* and *P. urinaria* demonstrated strong inhibition of HIV-RTase [124]. Repandusinic acid isolated from *Phyllanthus niruri* inhibited HIV-1 RTase while gossypol (Fig. **77**) and 1, 1′-dideoxygossylic acid, yellow pigments from the cotton plant are also reported to have anti-HIV activities [125].



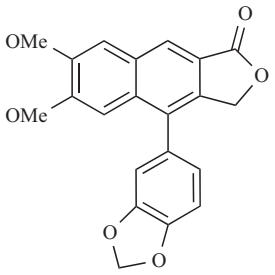
74. Tannic acid

Fig. (74).



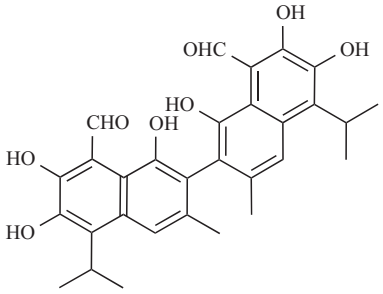
75. Phyllamyricin B

Fig. (75)



76. Retrojusticidin B

Fig. (76).

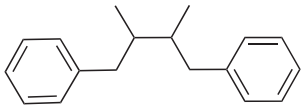


77. Gossypol

Fig. (77).

LIGNANS

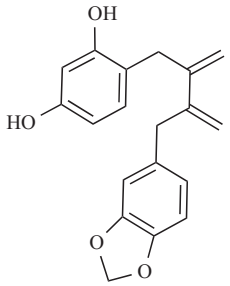
Lignans are cinnamic acid derivatives with two C-6, C-3 units, linked with β, β′ (Fig. **78**), widely distributed in plants and reported to possess antiviral activities [126]. The



78. Lignan

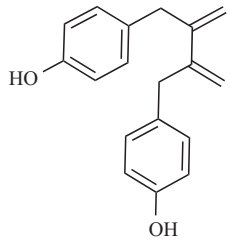
Fig. (78).

nordehydroguanoferate isolated from the extracts of *Larrea tridentates*, *Rhinacanthus nasutus* and *Kadsura matsudai* had anti-HIV, anti-influenza and anti-herpes activities [127, 128]; while lignans of *Rhus javanica* exhibit anti-HSV-2 activity similar to acyclovir [129]. The lignan 3'-O-methylnordihydro-guaiafetic acid isolated from *Larrea tridentata* was able to suppress HIV-1 replication by blocking the promoter activity of HIV-1LTR [130]. Dibenzylbutadiene lignans, anolignan A (Fig. **79**) and anolignan B (Fig. **80**) isolated from *Anogeissus acuminata*, showed HIV-1 RTase inhibitory activity and in combination they act synergistically with an IC_{50} of 60.4 μg/ml. Anolignan also showed activity against drug-resistant HIV-1 RTase with an IC_{50} of 106 μg/ml [131]. Dibenzylbutyrolactone lignanolide, (–)-arctigenin (Fig. **81**) isolated from *Ipomoea cairica* and *Arctium lappa* can inhibit HIV proviral DNA [132]; while the lignans isolated from *Kadsura interior* (–) gomisin inhibit HIV replication [133]. Recently, globoidnan A (Fig. **82**), a



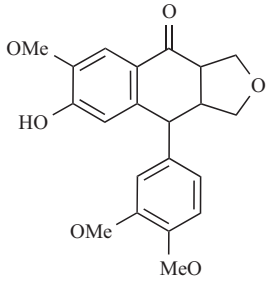
79. Anolignan A

Fig. (79).



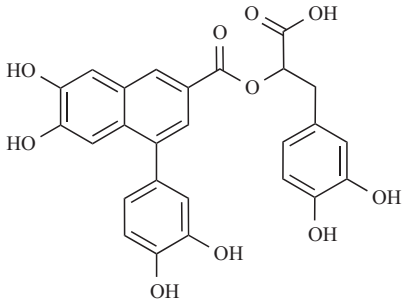
80. Anolignan B

Fig. (80).



81. (-)Arctigenin

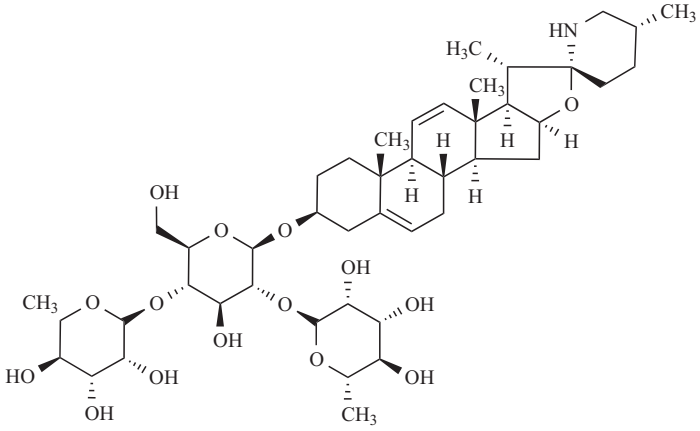
Fig. (81).



82. Globoidnan A

Fig. (82).

lignan isolated from buds of *Eucalyptus globoidea* by bioassay-guided fractionation, inhibited HIV integrase [134]. The ethanolic extract of the fruit rind of *Terminalia bellerica*, a commonly used plant in the Indian traditional systems of



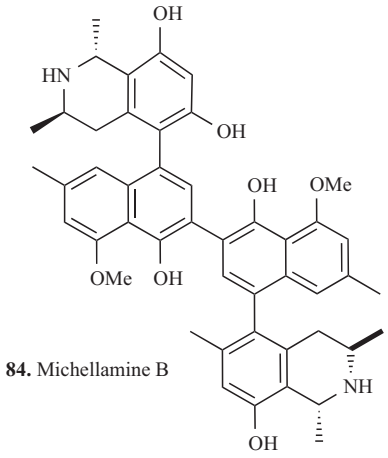
83. Solamargine

Fig. **(83)**.

medicine, yielded anolignan B and other lignans, showed demonstrable anti-HIV activity *in vitro* [135].

ALKALOIDS

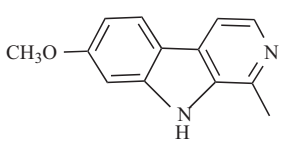
Alkaloids, the heterocyclic nitrogen compounds, have been found to possess antiviral activities against many viruses. Solamargine (Fig. **83**) and michellamine B (Fig. **84**), the atropisomeric naphthylisoquinoline alkaloid dimmers isolated from *Solanum khasianum* berries and *Ancistrocladus korupensis* leaves, the plant from Khasia hills of



84. Michellamine B

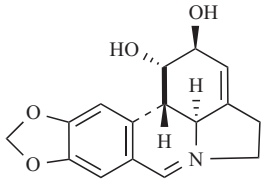
Fig. **(84)**.

North Eastern India and Korup of Cameroon inhibit HIV reverse transcriptase as well as cellular fusion and syncytium formation, while berberine inhibits intestinal infections associated with AIDS [136]. Duan *et al.* [137] reported that the sesquiterene pyridine alkaloids triptonine A and B isolated from *Tripterygium hypoglaucum* and a clinically used extract of T. wilfordii exhibited potent *in vitro* anti-HIV activity. Matairesinol and harmine (Fig. **85**) isolated from *Symplocos setchuensis* was found to inhibit HIV replication, and its derivatives N-butylharmine was most potent with an EC_{50} of 0.037 μM [138] while the harman isolated from *Ophirrhoza nicobarica*, a folklore of Little Andaman, inhibit plaque formation and delayed the eclipse phase of HSV replication [139]; but skimmianine isolated from *Zanthoxylum chalybeum* seed inhibit Edmonston and Swartz strains of measles virus [140]. The isoquinoline alkaloid thalimonine from *Thalictrum simplex* inhibit influenza A virus replication by reducing the expression of viral neuraminidase, haemagglutinin, nucleoprotein, and virus-specific protein synthesis [141]. Lycorine (Fig. **86**), homolycorine and acetyllycorine haemanthamine of *Leucojum vernum* possess high antiretroviral activities with low therapeutic indices [142]; but the



85. Harmine

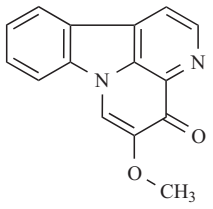
Fig. **(85)**.



86. Lycorine

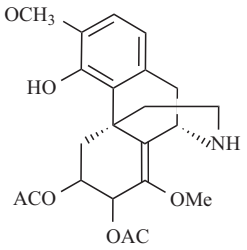
Fig. **(86)**.

drymaritin (Fig. **87**) isolated from *Drymaria diandra* had anti-HIV activity [143]. The morphine related compound aromoline and FK-3000 (Fig. **88**) isolated from Chinese and Mongolian folklore *Stephania cepharantha* root tuber is reported to inhibit the cytopathic effect of HIV-1 at 31.3 and 7.8μg/ml respectively [144] while the biscoclaurine alkaloid cepharanthine (Fig. **89**) of the same plant inhibit kappa B, a potent inducer of HIV-1 gene expression [145]; and also



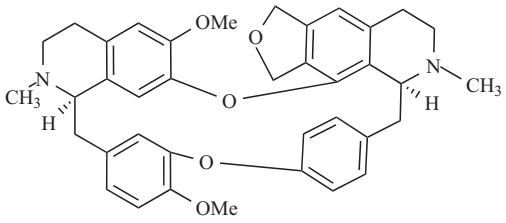
87. Drymaritin

Fig. (87).



88. FK-3000

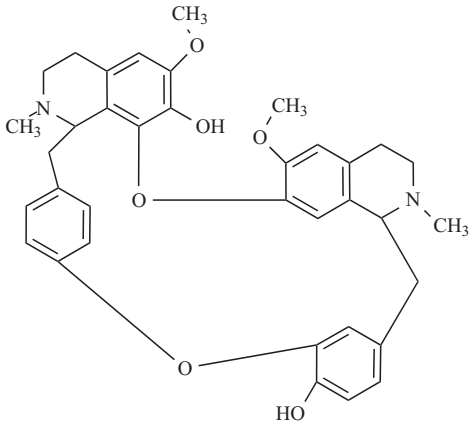
Fig. (88).



89. Cepharanthine

Fig. (89).

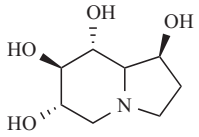
inhibit SARS Coronavirus, HSV-1, CVB3 along with *in vivo* anti-tumor, antiinflammatory, antiallergic and immuno-modulating activity [144]; while aromoline (Fig. **90**) of the same species inhibit HIV-1 [146] replication. As cepharanthine



90. Aromoline

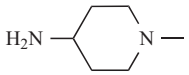
Fig. (90).

had strong antiviral activity against both RNA and DNA viruses and hence, be a source of potential lead for new antivirals. A number of alkaloids including indolizidines, castanospermine (Fig. **91**), a tetrahydroxy indolizidines of Australian plant *Castanospermium australe* [147] and piperidines (1-deoxynojirimycin) (Fig. **92**) inhibit HIV replication [148,149]; and as there is a good correlation between anti-HIV potency and R-glucosidase I inhibitory activity [149], it is presumed that anti-HIV activity is related to their inhibition of R-glucosidase I. A recent study suggested that 1-deoxynojirimycin blocked HIV envelope glycoprotein-mediated membrane fusion at the CXCR4 binding step [150].



91. Castanospermine

Fig. (91).



92. Piperdines

Fig. (92).

LECTINS, POLYPEPTIDES AND SUGAR-CONTAINING COMPOUNDS

The antimicrobial peptides are often positively charged and contain disulfide bonds. Meliacine isolated from *Melia azedarach* leaves and many common plants have potent anti-HSV-1 *in vitro* and *in vivo* activity by inhibiting infected-cell polypeptides, DNA synthesis, assembly of nucleocapsids and affecting late event in virus life cycle [151]. Ultrastructural analysis of infected cells revealed that meliacine treatment results accumulation of unenveloped nucleocapsids instead of mature virus particle in cytoplasmic vesicles, suggesting that meliacine block the syntheses of viral DNA and its maturation. Meliacine is also reported to inhibit replication of Junin virus and foot and mouth disease virus by blocking virus fusion [46,152]. Xylanase, a 15 kDa protein from *Panax notoginseng* inhibit HIV-1 RTase at IC_{50} 10μM [153] and 5 kDa peptides of *Phaseolus vulgaris* and *P. coccineus* (pinto and red bean) inhibit HIV-1 RTase [154]. Thai bitter gourd protein MRK29, isolated from *Momordica charantia*, inhibit HIV-1 RTase and its salt precipitated fraction strongly reduced viral p24 expression in HIV-infected cells with increased TNF activity [155] indicating its immunomodulatory role.

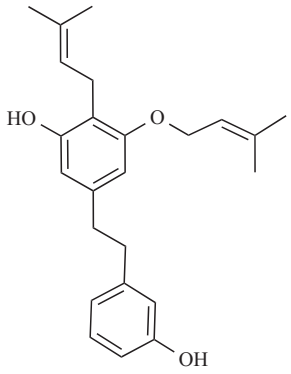
The mannose specific lectins of *Cymbidium, Epipactis helleborine, Hippeastrum* and *Listeria ovata*, and the N-acetylglucosamine (NAG)-specific lectins of *Urtica dioca* inhibit HIV infection by blocking viral fusion [18]. These lectins are plant proteins having a non catalytic domain that bind irreversibly to specific carbohydrates, through a monosaccharide-specific mechanism [156] and likely interfere with the virus-cell fusion. It is assumed that mannose- and NAG-specific lectins interact with specific glycosylation sites within the viral glycoproteins gp120 and/or gp41, particularly the sites rich in mannose or *N*-acetylglucose. The

larger mannose-specific lectins MAP30, a 30 KDa protein of *Momordica charantia*, have RNA N-glycosidase and DNA glycosylase/apurinic lyase activity and thereby inhibit integrase and DNA gyrase of HIV-1; while GAP31, a 31KDa protein of *Gelonium multiflorum* and jacalin (a multimeric plant lectin interact with CD4 receptor) inhibits integrase of HIV and proliferation of cytomegalovirus (CMV) by inhibiting host-viral interaction [18,157]. Another group of integrase inhibitors are the ribosome inactivating proteins (RIPs) or RNA N-glycosidases of plants that inactivate ribosomes through specific deadenylation of large rRNA [158]. Trichosanthin and TAP29, single-chain RIP of Chinese ethnomedicine *Trichosanthes kirilowii* root can inhibit HIV ribosome activity and interfere with HIV integrase [159,160]. Consequently, the DNA glycosylase/apurinic lyase activity of MAP30 and RIPs suggested that RIPs have anti-HIV activity independent of their ribosome inactivating activity.

The antiviral polysaccharides from *Rhizophora apiculata* (RAP) leaf and *R. mucronata* (RMP) bark prevent HIV budding by blocking capsid protein p24 expression [46]. On the otherhand, aloe polymannose of *Aloe barbadensis* potentiate antibody production against capsid protein epitopes of nonenveloped picornavirus and enhance antibody concentrations against enteroviruses and poliovirus vaccine strains [161]. Recently Thompson and Dragar [162] reported that galactofucan, a sulfated polysaccharide from aqueous extract of seaweed *Undaria pinnatida* exhibits anti-HSV activity at noncytotoxic dose by inhibiting viral binding and entry into the host cell against clinical strains of HSV-1 and HSV -2, with a median IC_{50} values of 32 and 0.5 μg/ml respectively, demonstrating its significant activity against HSV-2 (P<0.001). Stevian, the heterogeneous anionic polysaccharide with different ionic charges, extracted from *Stevia rebaudiana* and *Achyrocline flaccida* inhibit the replication of four serotypes of human rotavirus and HSV-1 by blocking the virus attachment to cell surface [163]; while the acidic polysaccharides of *Cedrela tubiflora* inhibit HSV-2 and VSV replication [164], indicating that the antiviral activity of polysaccharides correlates with molecular weight and sulfate content. Sulfated polysaccharide on the otherhand exerts antiviral activity by shielding off the positively charged amino acids in the V3 loop of gp120 of HIV [165]. The anionic polysaccharide of Japanese medicine *Prunella vulgaris* had specific anti-HSV activity (IC_{50} 10μg/ml) by competing for cell surface receptor, unlike other anionic carbohydrates [166]. It can also inhibit HIV RTase, replication and absorption [167]. Recently Mori *et al.* [168] reported that Griffithsin (GRFT), a 121-amino acid protein, isolated from an aqueous extract of the red alga *Griffithsia* sp. displayed potent activity against primary isolates of T- and M-tropic HIV-1 with EC_{50} 0.043 to 0.63 nM by aborting cell-to-cell fusion and transmission of HIV-1. GRFT blocked CD4-dependent gp 120 binding to receptor-expressing cells and bound to viral coat glycoproteins gp120, gp41, and gp160 in a glycosylation-dependent manner; but preferentially inhibit gp120 binding of the monoclonal antibody, which binds to CD4-induced epitope, and interfered with the binding of gp120 to sCD4. GRFT is a new lectin that binds to various viral glycoproteins in a monosaccharide-dependent manner and could be a potential candidate for prevention of the sexual transmission of HIV/AIDS [168].

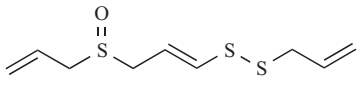
MIXTURES & OTHER COMPOUNDS

Traditionally Ayurveda, the Indian traditional medicine, Chinese traditional medicine, African folk medicine and other ethnomedicines rely on both 'pure' single-plant preparations and mixed formulations with many plants. Propolis, a crude extract of the balsam of various trees inhibits hemagglutination activity of influenza virus, acyclovir-resistant HSV-1, ADV 2, VSV, and poliovirus. As propolis is a mixture of terpenoids, flavonoids, benzoic acids and esters, and phenolic acid esters, which act synergistically, while flavone and flavonol were active in isolation against HSV-1 [169]. The stem bark extract of *Juglans mandshurica* showed potent inhibitory activity on HIV-1 RTase (IC_{50} 0.067 and 0.040μM) due to a mixture of naphthalenyl glucopyranosides 1,2,6-trigalloglucopyranose and 1,2,3,6-tetra galloyl glucopyranose (TTGP) respectively. TTGP also inhibited RNase H activity (IC_{50} 39μM). The RTase inhibition is increased by the increase in the number of free hydroxyl on the galloyl residue [170]. The kaempferol crassirhizomoside and sutchuenoside of *Dryopteris crassirhizoma* inhibit RT-associated DNA polymerase and RNase H activities [171]. 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 [172], while the mixture of *Artemisia capillaris* inhibit HIV replication [173]. The methyl ester dehydrochebulic acid (Fig. **69**) and methyl brevifolin carboxylate from *Phyllanthus urinaria* have anti-HBV activity [174], while *Glycyrrhiza lepidota* leaf inhibits HIV-1 due to a diprenylated bibenzyl (Fig. **93**) [175]. Extract of fresh garlic, called ajoene (Fig. **94**), can protect CD4 cells from HIV attack early in the viral life cycle and its anti-HIV activity is



93. Diprenylated bibenzyl

Fig. (93).

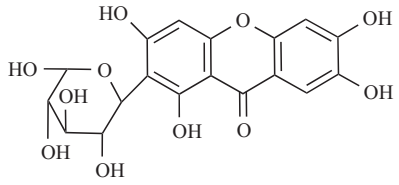


94. Ajoene

Fig. (94).

45 times more powerful than dextran sulfate, as garlic impairs the activities of liver enzymes that process protease inhibitors and thereby raises the protease inhibitor levels in

the blood [18]. The free hydroxyl of galloyl residues of tertagalloyl-glucopyranose from *Juglans mandshurica* inhibits RTase and RNase H activity; while asiaticoside of *Centella asiatica* and mangiferin (Fig. **95**) of *Mangifera indica*, used as herpesvirus remedy in Thailand, have anti-HSV activities; and combinations of any of these extracts with acyclovir resulted additive or synergistic inhibition of HSV-2 [46,176]. Recent study revealed that despite highly active antiretroviral therapy (HAART) viral reservoirs can persist when HAART is ceased. When prostratin (Fig. **52**), a phorbol ester from Samoan medicinal plant *Homolanthus* nutans, having *in vitro* anti-HIV activity by interacting with protein kinase C [88], was induced in HIV-1 patients using HAART an inductive adjuvant therapy with 12-deoxyphorboI 13-phenylacetate, a non-tumor promoting phorbol ester isolated from *Euphorbia poissonii* with a goal is to eliminate persistent viral reservoirs in HIV-infected persons. This agent was found to induce HIV-1 gene expression in latently infected T-cells at concentrations 20- to 40-fold lower than prostratin [177].



95. Mangiferin

Fig. **(95)**.

HUMAN CLINICAL TRIALS

Phytomedicines have been used for centuries to treat infections in aboriginal or ethnic community, but controlled clinical studies are scarce. Some randomized clinical trials of plant antivirals have been reported till date [46]. In a clinical trial Provir, the proprietary compounds of tropical plants, used to treat respiratory viral infections and a topical antiherpes agent Virend were tested, but only the efficacy and safety of Virend have been established [178]. A trial of andrographolide from *Andrographis paniculata* on 13 HIV patients and 5 uninfected healthy volunteers showed a significant rise in the mean $CD4^+$ lymphocyte level with 10 mg/kg andrographolide. However, no significant change in mean plasma HIV-1 RNA levels was found as andrographolide dysregulate HIV-induced cell cycle, leading to a rise in $CD4^+$ levels [179]. In a hepatitis B clinical trial *Phyllanthus amarus* extract eliminate detectable HBV antigen from the sera of 59% treated human carriers as compared to 4% of placebo controls [180,181]. A review on randomized trials on *Phyllanthus* in chronic HBV patients by Liu *et al.* [182] showed that *Phyllanthus* species had positive effect on clearance of serum HBsAg in chronic hepatitis compared with placebo or no intervention, and is better than nonspecific or other herbal treatment. Another review on randomized clinical trials showed that the aqueous extract of *Sophorae flavescentis* (matrine) have anti-HBV activity with protective effect on liver function in chronic HBV patients. However, *Phyllanthus* or matrine can not be recommended for routine clinical use due to low methodological quality and the variations of the herb [183]. Martin and Ernst [184] found that hundreds of herbal preparations have antiviral activity, but extracts from only 11 species met the inclusion criteria. Out of 33 randomized and 8 nonrandomized trials 14 with *Phyllanthus* sp yielded 7 positive results and 27 trials with other 10 herbs yielded six positive results. Tani *et al.* [185] conducted a long-term (1992-2000) treatment of pediatric AIDS patients with Romanian folk medicine and found that the 92 months treatment helps to drop HIV-RNA below the measurable level in 90% cases, but at lease 1-3 years is required to get the beneficial effects of the treatment without any side effects and emergence of drug-resistant strains. A controlled study with Japanese Oriental medicine Mao-to in 18 chronic hepatitis C patients showed the side effect of interferon (IFN) was relieved [186]. In another study 12 chronic HCV patients treated with a combination of IFN-beta and Mao-to or Dai-seiryu (groups A and B), and 16 with IFN alone (group C). Mao-to was administered to 8 and Dai-seiryu-to 4 in A and B groups respectively. In all patients, HCV-RNA was negative and serum alanine aminotransferase levels were normal at the end of the treatment, indicating that these phytomedicines reduce adverse effects of IFN treatment in chronic HCV patients [185]. Recently a placebo-controlled double-blind pilot study conducted by Emerit *et al.* [186] on 30 HCV patients with a phenol-rich antioxidant grain food showed that antioxidant food considerably improved defense, in 11 of the 15 patients (received 6g food powder thrice daily for 3 months) liver enzymes decreased and the viral load remained unchanged, compared to placebo (who received an herbal extract with no antioxidant). After 3 month treatment a sustained response was observed in 5 of 9 antioxidant pretreated patients when they received interferon and ribavirin treatment even 6 month after discontinuation of the 12 month antioxidant therapy [187].

CONCLUSIONS

Many of the viral diseases are still fatal and or are not yet curable, although some can be kept under control with life-prolonging drugs, but those expensive drugs are beyond the reach of majority of population. Therefore, development of safe, efficacious and inexpensive antiviral drugs is among the top global priorities of drug development. Furthermore, the long-term combination therapies for retroviruses and herpes viruses may yield drug-resistant mutants. Therefore, scientists from divergent fields are investigating ethnomedicinal plants, with an eye to their usefulness of antiviral drugs. Extensive research for last 50 years on ethonomedicine resulted in the discovery of antivirals especially anti-HSV and potent anti-HIV agents from nature. A number of purified molecules have been used as lead compounds because of their specific activity and low toxicity and significant structure activity relationship. Many of them have potential to interfere with particular viral targets like RTase, protease, integrase, cellular fusion and target cell binding, result in mechanisms of action complementary to those of existing antiviral drugs. Although no plant-derived drug is currently in clinical use to treat the dreaded viral diseases, promising activities have been shown by some natural product/ natural product-derived candidates of diverse class, particularly the phenolics, coumarins, flavonoids and alkaloids, in preclinical and clinical trials. Sarawak MediChem Phar-

maceuticals conducting phase II clinical trials of calanolide A for assessment of long-term anti-HIV activity in combination with other antiretroviral agents. While Panacos Pharmaceuticals have successfully completed preclinical studies and undergoing phase II clinical trial for 3-hydroxymethyl-4-methyl DCK and DSB. These clinical candidates have the potential to come up as drugs for treatment of HIV infection. Interestingly 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 self life of many antiviral drugs. The compounds having alternative mechanism of action, unlike synthetic antivirals, 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.

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