**Review Article**

**Phytoconstituents as potential anti-HIV agents: A Systematic review**

Md. Abul Barkat¹, Md. Rizwanullah², Javed Naim³, Faheem Hyder Pottoo⁴ and Rakesh Kumar⁵

¹Faculty of Pharmacy, Jamia Hamdard, New Delhi-62  
²Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi-62  
³Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi-62  
⁴Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi-62  
⁵Research Scientist, Analytical Division, Jubilant Life Sciences, Sector-62 Noida, U.P, India

*Correspondence Info:  
Md. Abul Barkat  
(Ph.D Research Scholar)  
F/o Pharmacy, Jamia Hamdard, New Delhi-62  
E-mail: abulbarkat05@gmail.com

**Abstract**

HIV/AIDS pandemic is currently the most socio-economic challenge that is facing the world at immensely colossal as it affects mostly the adolescent and economically productive population. The utilization of phytomedicines to manage HIV/AIDS has recently gained public interest, albeit harmonization with official HIV/AIDS policy remains a contentious issue in many countries. Plants products present a sizable voluminous repertoire from which to isolate novel anti-HIV active compounds. The anti-HIV active compounds such as terpenoids, coumarins, polyphenols, tannins, proteins, alkaloids, and bioflavonoids inhibit sundry steps of the HIV life cycle. However, further studies are needed to determine their interactions with current regimes of antiretroviral drugs. More clinical trials of candidate drugs developed from these novel compounds are withal inspirited. The review presents evidence that several plant families and species contain anti-HIV active compounds that could be developed into more incipient drugs to manage HIV/AIDS. This evidence should persuade further research and public interest into the isolation of anti-HIV active compounds from plants.

**Keywords:** HIV/AIDS, Phytomedicines, Anti-HIV active compounds, Clinical trials

1. Introduction

The recommendation of World Health Organization (WHO) that, traditional rejuvenators be included in national replications to HIV/AIDS¹ In the early of 1989, WHO had already verbally expressed the desideratum to evaluate ethnomedicines for the management of HIV/AIDS. “In this context, there is desideratum to evaluate those elements of traditional medicine, particularly medicinal plants and other natural products that might yield efficacious and affordable therapeutic agents. This will require a systematic approach”, verbalized a memorandum of the WHO.²

In 2008, an estimated 2.7 million incipient HIV infections occurred worldwide; this was 30% lower than the 3.5 million incipient infections at the apex of the epidemic in 1996 (UNAIDS, 2009). Sub-Saharan Africa remains the most heavily affected region, accounting for about 71% of all incipient HIV infections in 2008. There are two cognate but distinct types of HIV: HIV-1 and HIV-2.³ HIV-1 is the most pathogenic and causes over 99% of HIV infections.⁴ HIV-2 is additionally kenned to cause AIDS but is much less prevalent, being present in fewer and isolated geographic locations such as West Africa. Therefore, most research is done on HIV-1.⁵

HIV/AIDS pandemic is currently the most socio-economic challenge that is facing the world at immensely colossal as it affects mostly the adolescent and economically productive population. A study has shown that majority of people living with HIV/AIDS are susceptible to fungal and bacterial opportunistic infections that result from immunosuppression and treatment of such infections is therefore one of the areas that traditional health accommodations for the control of the disease is prevalent.⁶ The World Health Organization (WHO) estimates that 4 billion people (80% of the World’s population) use herbal medicines for some aspect of primary healthcare.⁷ Treatment of diseases utilizing traditional remedies is an age old art which has been confined into the backstage due to access to western biomedicine, adequate inculcation, employment opportunities and economic magnification.⁸

The utilization of herbal medicine is increasingly becoming more popular in many countries.⁹ This practice has perpetuated to be a main source of health care in the rural communities especially in developing countries, since modern medicine has not been able to reach the majority of the populace. Withal, herbal medicines are still being commonly sold by practitioner and their agents without any restriction with most of the health care providers receiving little or no formal training in this area. This lack of congruous training may be associated with the inability of answer questions patients have about its efficacy either as a supplement to orthodox medicine or as a therapy to treat or avert disease. Their inability to answer questions may partly be linked to the fact herbal medicine involve a sophisticated theory or system, with the erudition that is often passed on, verbally or otherwise, from generation to generation.¹⁰¹¹¹² Notwithstanding, there have been a remarkable increase in the popularity of herbal preparations especially in developed countries, which has stimulated considerable public health concern among medicos who are sometimes dubious about the safety of herbs especially when used concomitantly with customary orthodox medications.¹³

1.1 Alkaloids

The michellamines A, B and C are atropisomeric naphthyl isoquinoline alkaloid dimers obtained from the leaves of Ancistrocladus korupensis belonging tofamly Ancistrocladaceae and these plant families being native to the Korup National Park in Cameroon’s southwest Province. They act at an early stage of the HIV life cycle by inhibiting reverse transcriptase as well as at later stages by inhibiting HIV-induced cellular fusion and syncytium formation.¹⁴ In addition, the michellamines were found to inhibit rat brain protein kinase C with IC50 values in the 15–35µM range.¹⁵ The michellamines D – F being obtained from the same plant exhibited *in vitro* HIV inhibitory activity comparable to michellamine B.¹⁶ Michellamine B underwent extensive preclinical characterization as a potential anti-AIDS drug, but had been found too toxic to allow it to proceed to clinical trials. Therefore, the option that we were left with were to develop synthetic drugs having less toxicity but more potent. Jozimine Cwas the synthetically prepared dimer of diconophylline C, showing a close structural similarity with the michellamines [Figure 1]. Its anti-HIV activity (HIV-1) was nearly as good as michellamine B, but it did show a distinct cytotoxicity, limiting its therapeutic range.¹⁷ Octadehydromichellamine; a fully
dehydrogenated structural analogue was the first synthetic michellamine without centrochirality. It showed some anti-HIV activity (HIV-1 IC$_{50}$ = 29 μM) comparable to michellamine B.$^{18}$

Nitrogen-containing sugar analogues, such as Castanospermine [Figure 1] is a tetrahydroxindolizidine alkaloid being isolated from Castanosperum austral belonging to family Fabaceae. It showed inhibition of HIV replication and formation of syncytium induced from the envelope glycoprotein of HIV. Glycosidase inhibitory activity was also reported with itand 1-deoxynojirimycin is yet another nitrogen-containing sugar analogues, capable of inhibiting N-linked oligosaccharide processing and inhibiting the replication of HIV.$^{19,20}$ The anti-HIV potency is in correlation with the α-glucosidase-I inhibitory activity, it leads the hypothesis regarding the anti-HIV activity is due to the inhibition of α-glucosidase-I.$^{21}$ However in due course of time more number of natural epimers of α-homonojirimycin and N-alkylated derivatives were isolated or synthesised and it was observed that α-homonojirimycinand N-methyl-α-homonojirimycin were more potent inhibitors of α-glucosidase-I than 1-deoxynojirimycin or castanospermine. Nevertheless, only the two latter compounds showed a significant HIV-1 inhibitory activity,$^{22}$ it suggests that the anti-HIV activity may be due to other factors than inhibition of α-glucosidase-I.

A quinoline, derivative Buchapine [Figure 1] possesses two isoprene units and 3-(3-methyl-2-butenyl)-4-(3-methyl-2-butenyl)oxy-2(1H)-quinolone is its structural isomer obtained from plant Euphorus burhiana, it is indigenous to Southeast Asia and Australia, acting by protecting CEM-SS cells from the cytopathic effects of HIV-lin vitro.$^{23}$ The alkaloids obtained from the root bark of Tripterygium hypoglaucaumand T. wilfordii namely Triptone, triptone Band hypoglauna are sesquiterpene pyridine derivatives exhibited the anti-HIV activity in vitro with a therapeutic index$^{24}$ of more than 1000. The IC$_{50}$ values against HIV replication were 2.54 and <0.10 μg/mL.

Nitidine [Figure 1] is obtained from the roots of Toddalia asiatica belonging to family Rutaceae showed significant anti-HIV activity in the cell-based assay and also HIV-reverse transcriptase inhibitory activity was reported.$^{25}$

A piperidine-flavone related alkaloid O-Demethyl-buchanaviamineobtinened from Buchenavia capistrat belonging to family Combretaceae also showed anti-HIV activity.$^{26}$

Cepharanthine ah bicosclareine alkaloid obtained from Stephania cepharantha is a morphone-related compound and can potentially inhibit replication of HIV-1.$^{8,27}$ It also exhibited anti-inflammatory, anti-inflammatoty, and immunomodulatory activities in vivo.$^{28,29}$ Its effects on mammalian cells, and the implications for cancer, shock, and inflammatory diseases have recently been reviewed.$^{30}$ That is known the several inflammatory cytokines affect the progress and HIV-1 infectious pathogens.$^{31}$ Therefore, the inhibitory action of cepharanthine on TNF-α and polymorphonuclear-13-aceate (PMA)-induced HIV-1 replication in chronically infected monocytes and T lymphocytic celllines were evaluated. Cepharanthine was a highly potent inhibitor of HIV-1 in the monocytic cell line, but not in the T-lymphocytic cell line.$^{32}$ It also suppressed HIV-1 long terminal repeat (LTR)-driven gene expression and increases inhibition of NF-kB activation.

Cycleanine [Figure 1] is the related bixbenylosiquinoline alkaloidswas evaluated against HIV-1 and HIV-2. It showed activity against HIV-2 with an IC$_{50}$ of 1.83 μg/mL but was at least 10-fold less active against HIV-1. The selectivity index of cycleanine against HIV-2 was 9, with an IC$_{50}$ of 15.68 μg/mL.$^{33}$ Various anti-HIV alkaloids were found to possess β-carboline skeleton. The well-known β-carboline alkaloid harmine [Figure 1] isolated from Symposocset chensui, indigenous in southern China, was found to inhibit HIV replication in H9 lymphocyte cells, (IC$_{50}$ = 10.73 μM, SI = 10.4). The more active derivative was N-butytharmine (IC$_{50}$ = 0.037 μM, and therapeutic index of 210.$^{34}$ Siamenol [Figure 1] the new carbazole alkaloids was obtained from the extract of Murraya siamensis. It showed the anti-HIV activity with an IC$_{50}$value of 2.6 μg/mL, reaching 50–60% maximum protection in the XTT-tetrazolium assay and was more active than the related β-carboline alkaloid mahanimbilisol isolated from the same source.$^{35}$

Carbazoles were obtained from Clausena excavata, used in Thai folk medicine showed Anti-HIV activity. O-Methylmekonal-3-formyl-2,7-dimethoxybenzaldehyde clausoline J appears anti-HIV-1 activity in a syncytial assay with IC$_{50}$ values of 12.29 and 34.2 μM, respectively, and with a selectivity index of 56.7, 8.0 and 1.6, respectively.$^{36}$ The methoxycanthinone [Figure 1] β-carboline derivative, is obtained from Leitneria floridana, a rare tree or shrub restricted to scattered wet sites in the southern Atlantic and Gulf coastal plains of the United States, was a potent anti-HIV agent (IC$_{50}$0.26 μg/mL; SI >391).$^{37}$ Also the canthin-4-one drymaritin, obtained from Drymaria diandra from Taiwan, showed anti-HIV activity (IC$_{50}$0.69 μg/mL; SI 20.6), indicating the potential of canthinones as anti-HIV leads.$^{38}$

The 18-methoxyconcuridine congener of Iboga alkaloid showed in vitro leishmanicidal and in vivo anti-addiction properties and also inhibited the replication of HIV-1 in human peripheral blood mononuclear cells and in monocyte-derived macrophages.$^{39}$ According to the test system, IC$_{50}$ values in the range of 9.5 to 23 μM, were obtained, with an SI of 14.5 to 34.5. In this concentration range, 18-methoxyconcuridine moderately reduced the polymerase activity of recombinant HIV-1 reverse transcriptase (IC$_{50}$ = 69.4 μM). The in vitro antileishmanial activity of 18-methoxyconcuridine may be exploited for treating patients who co-infected with HIV-1 Leishmania.$^{40}$

Lycorine [Figure 1] an amaryllidaceae alkaloids had been reported to show antiviral properties.$^{41}$ More recently in lycorine, homolycorine, trisphaeridine and haemanthamine the anti-HIV activity was observed. IC$_{50}$ values in the range of 0.4–7.3 μg/mL were obtained, but similar in cytotoxicities, leading to a low SI for all alkaloids (1.3–1.9).$^{42}$

Figure 1: Anti-HIV alkaloids from plants

1.2 Coumarin

The naturally derived dipyrano coumarins, Calanolides and Inophyllins had been established as non-nucleoside-specific inhibitors of HIV reverse transcriptase. These are isolated from various species of Callophyllum belonging to family Clusiaceae and genus primarily found in Malaysia.$^{43}$ Calanolides and inophyllins are representatives of a distinct class of NNRTIs and its HIV sensitivity/resistance profile is different from other NNRTIs. (+)-
Calanolide A, (−)-calanolide Band its dihydro-derivative, (−)-7,8-dihydrocalanolide B obtained from the fruits and twigs of C. lanigerum, a tropical rainforest tree, significantly affect the cytopathic effects of HIV-1 in T-cell lines, including both MT-2 cell and CEM-SS cells. These calanolides inhibits the laboratory-adapted HIV-1 variants, the clinical viral isolates, inclusive of the diverse clades (A–F), syncytium-inducing and non-syncytiuminducing isolates, and T-tropic and monocytotropic isolates. The exclusive worldwide license was provided by the National Cancer Institute to the Sarawak MedChem Pharmaceuticals, Malaysia for the study of calanolide class of compounds. They have successfully completed clinical trial phase III on 48-subject for calanolide A in combination therapy for HIV, and evaluated the effect of therapy on pharmacokinetic profile and safety. Trials result showed the combination therapy was effective in increasing the plasma concentration of calanolide in human volunteers. As such there is no serious adverse effect were seen in any human volunteers. Calanolide A is currently in phase II clinical trials, focused on assessment of its anti-HIV activity in combination with other anti-HIV agents and an assessment of the long-term durability of such drug combinations, the two structural analogues of calanolides Cordaladole A and B, obtained from Cypholium cordato-oblongum inhibits replication of HIV-1 in a novel green fluorescent protein-based reporter cell assay.

In addition Kellactone are also naturally derived coumarins, which shows a number of biological activities like anti-HIV, anti-tumour promoting and anti-platelet aggregation. About 50 or more naturally derived kellactonecoumarins have been discovered. Suksdorfin [Figure 2], chalconyis ita dihydroesin-type angular pyranocoumarin obtained from alcoholic extract of Lonatium suksdorffii, suppressed viral replication in eleven separate acute HIV-1 infections of H9 lymphocyte cells with an average EC50 value of 2.6 μM. It also suppressed acute HIV-1 infections in fresh peripheral blood mononuclear cells, monocyte/macrophages and U-937 cells, a promonocytic cell line.

Imperatorina furanosocoumarin which is isolated from alcoholic extracts of dried roots of Fehula sambil, family Umbelliferae, showed anti-HIV activity with IC50 > 100 μg/ml, EC50 < 0.10 μg/ml and TI > 1000. Chiandrori [Figure 2]an isocoumarin obtained from the of coriander Coriandrum sativum, family Umbelliferaeashowed anti-HIV and other anti-viral activities. Mesuol [Figure 2]also naturally derived coumarins shows basic ring 4-phenylocoumarin, which inhibits the replication of HIV-1 by targeting the NF-κB pathway. It also inhibited the phosphorylation and the transcriptional activity of the NF-κB p65 subunit in TNF-α-stimulated cells.

**Figure 2: Anti-HIV coumarin from plants**

1.3 Flavonoids

Several critical enzymes involved in the HIV life cycle is inhibited by the flavonoids, such as reverse transcriptase, viral protease and integrase.

Casein kinase-II that is responsible for HIV replication is a cAMP, GMP, and Ca2+/phospholipid-independent serine/threonine protein kinase that phosphorylates several enzymes in HIV-infected cells and was found to be inhibited by Quercetin, chrysin, and (−)−epigallocatechin 3-O-gallate naturally derived flavonoids. The biological significance of casein kinase-II in the replication of HIV-1 and its inhibition mechanism by flavonoids are not completely understood yet.

The antiviral activity of various flavonoids against several viruses in cell cultures and in animal models had been done. Prenylated flavonoids, 6,8-diprenylalmoniradendrin 6,8-diprenylkaempferol obtained from the Monote safricans showed anti-HIV activity in the XTT-based, whole-cell screen. Quercetin 3-O-(2-galloyl) α-L-arabinopyranose and flavonoid gallate ester is naturally derived flavonoids isolated from the extract of Acer okamotoaunobius belonging tofamiliar Aceraceae, which inhibits the activity of HIV-1 integrase with IC50 values of 18.1 ± 1.3 and 24.2 ± 6.6 μg/ml respectively.

The chalcone 2-methoxy-3-methyl-4,6-dihydroxy-5-(3′-hydroxy)-innamoylbenzaldehyde naturally derived from the roots of Desmos spp. is known for its powerful anti-HIV activity, but actually it is known for their cytotoxic activity. The compound was isolated from the Caribbean sea grass Thalassia testudinum which inhibits HIV integrase. Some prenylated flavonones and flavones showed moderate anti-HIV activity, but actually it is known for their phytoestrogenic activity. Xanthohumol [Figure 3], a naturally derived prenylated flavonoid with multiple biofunctions, isolated from hops (Humulus lupulus),showed to inhibit cytopathic effects (CPE) induced by HIV-1, as well as production of viral p24 antigen and reverse transcriptase in C8166 lymphocytes at non-cytotoxic levels. The IC50 values were, respectively, 0.82, 1.28 and 0.50 μg/ml and an SI of about 10.8. The target of xanthohumol on HIV-1 may be on the steps post reverse transcription.

Robustaflavone [Figure 3] and hinokiflavone [Figure 3] are biflavonoidsisolated from alcoholic extracts of twigs and leaves of plant Rhus succedanea, family Anacardiaceae. These types of biflavonoids contain two apigenin units. It inhibits strongly the polymerase of HIV-1 reverse transcriptase in in vitro assay with IC50 values of 65 and 62μM. Wickstrøm Bis another biflavonoid isolated from the extracts of roots of Wikstroemia indigoca, family Thymelaeaceae, reputed good activity against HIV-1 in vitro studies.

Recently about five new flavonoidal glycosides which have weak anti-HIV activity and isolated from the plant Ochna integerrima. Along with two other biflavonoids is known such as ochnaflavone 7′-4-methyl etherand 2,3-dihydroochnaflavone 7′-O-methyl etherhaving significant anti-HIV-1 action as reported in the syncytium assay with IC50 values of 2.0 and 0.9μg/ml, respectively. The HIV-1 reverse transcriptase inhibition with IC50 values are comparable to the syncytium assay values as a potential mechanism of action.

Genistein is derived from soybeans showing promising action against HIV infection, and is a “tyrosine kinase inhibitor” that works by blocking the communication from a cell’s surface sensors to its interior. Found on a cell's surface, these sensors tell the cell about its environment and also communicate with other cells. HIV uses some of these surface sensors to trick the cell to send signals inside. These signals change cell structure so that the virus can get inside and spread infection.

Bunifensin blocks the signal and stops HIV from finding a way inside the cell. It takes a different approach than the standard antiretroviral drug used to inhibit HIV. Instead of directly acting on the virus, genistein interferes with the cellular processes that are necessary for the virus to infect cells, Wu says. "Thus, it makes the virus more difficult to become resistant to the drug."
The antiviral activity of lignans was reviewed by Charlton, and most of the products were found to be having moderate antiviral activity. Lignans act by diverse mechanisms of action which includes tubulin binding, inhibition of reverse transcriptase, integrase, and topo-isomerase. Podophyllotoxin a lignan obtained from podophyllum was found to be most prominent representatives of the tubulin-binding. Also dibenzylbutyrolactones dibenzylbutanes, dibenzylcyclooctadienes, and aryltetralins the other classes of lignans also showed the inhibition of the reverse transcriptase. The lignan compound isolated from the roots of North American Podophyllum peltatum Linnaneus, the Tibetan P. emodi Wall, or the Taiwanese species Podophyllum pleinthum is Podophyllotoxin. Clinically useful anti-cancer drugs, like etoposide and teniposide is obtained by extensive structural modification and anti-tumour studies of podophyllotoxin. Recently, the several derivatives podophyllotoxin were synthesised that showed potent inhibitory effects on HIV-1.

Anolignan A and anolignan B obtained from Anogeissus acuminate, possesses HIV-1 reverse transcriptase inhibitor activity. Anolignan A and anolignan B are shown to act by synergistic effect with an IC50 value of 60.4 µg/ml and 1073 µg/ml for HIV-1 reverse transcriptase. Anolignan A and anolignan B are isolated from the leaves of Arctium lappa as a meager class of drug candidate for the following reasons:

1. Potency as an inhibitor of HIV-1 reverse transcriptase.
2. Efficacy of antitumour activity.
3. Good bioavailability.
4. Easy procurement.
5. Chemical stability.

Also HIV-RT strong inhibition was shown by Phyllamyricin Band its lactone retrojusticidin, isolated from chelidonic acid. It is a rare type of lignan, which act by associating with proteins of viral particles and/or host cell surfaces, resulting in reduction or prevention of viral adsorption. Naturally derived phenolics, like Dicaffeoylquinic acids (DCQAs) and dicaffeoyltartaric acids (DCTAs) on HIV-1 integrase, an enzyme which catalyses the insertion of viral DNA into the genome of the host cell. DCQAs like 3,5-dicaffeoylquinic acid and DCTAs such as L-chicoric acid is suggested a 10-100 fold higher suitability for the inhibition of HIV integrase in enzymatic assays than that of HIV reverse transcriptase. The bis-catechols, L-chicoric acid was the most active against HIV integrase and the phenolic acids such as caffeic acid and chlorogenic acid were not active against HIV integrase. The DCQAs inhibit HIV integrase irreversibly and not dependent on divalent cations. A single glycine-to-serine substitution at position 140 of integrase was resistant to L-chicoric acid in HIV-1 mutant, which indicates pathway of mechanism of action of this compound is likely to interact at residues near the catalytic triad in the integrase active site. The replication of viral strains is not inhibited by the L-chicoric acid resistant to polyanionic compounds, like dextran sulphate. Therefore, the primary action of L-chicoric acid and its analogues against HIV could be the envelope glycoprotein gp120. However, still the dicaffeoylquinic acids (DCQAs), dicaffeoyltartaric acids (DCTAs), and diketo acids (DKAs) is the most potent classes of integrase inhibitors with anti-HIV activity. According to Veber's bioavailability criteria and Lipinski's rule of 5, L-chicoric acid is a meager class of drug candidate for the following reasons: a) due to the diacid moiety shows limited cell permeability, b) instability of the two ester linkages due to hydrolytic enzymes, c) two catechol moieties showed potential toxicity. The Repanduscinic acid found from an aqueous extract of Phyllanthus niruri belonging to family-Euphorbiaceae as inhibitors of HIV-1 reverse transcriptase.

The 8-C-ascorbyl (-)-epigallocatechins also naturally derived compound which showed potent activity against HIV with an adequate TI value of 9.5. Theaflavinins Dalsoe inhibited moderate-HIV activity. The yellow pigments gossypol and 1,1-dideoxygossypol, obtained from the cotton plant also exhibited activity against HIV.

Visniacia yennensis is a naturally derived compound obtained from Visniacia yennensis showed activity in the primary anti-HIV screen, while gutiflure A obtained from the Symphoniaglobalifera belonging to family Gutiferae which provided the cytotoxicity of CEM-SS cells from HIV-1 infection. The isomeric caffeic acid tetramer such as monosodium and monopotassium salts isolated from the aqueous acetone extract of Arnebi aechroma belonging to Boraginaceae, by bioactivity-guided fractionation, exhibited potent inhibitory activity against replication of HIV in H9 cells which is acutely infected, with EC50 values of 2.8, 4.0, and 1.5 µg/ml respectively, their TI values were 19.6, 12.5 and 33.3 respectively.
The 1,3,4,5-tetra-O-galloylquinic acid showed significant anti-HIV activity which is obtained from the stem bark of the Lepidobo trysstaedti belonging to family Lepidobotryaceae. It leads protection of CEM-SS cells from cytopathic effects of HIV-1p24. From Terminaliachebulifamily Combretaceae) gallic acid and galloyl glucoses was shown activity against HIV integrase, and also from the pericarp of Camellia japonica the camellia-tannin H is isolated showed potent action against HIV-1 protease.102

Curcumin a yellow pigment isolated from the ethyl acetate extract of rhizomes of Curcuma longa Linn. Family, Zingiberales103 which shows a wide variety of biological activities, including anti-inflammatory and antioxidant activities. But it also inhibit different enzymes as well as enzy-

matic activities, such as HIV-1 integrase, nuclear factor-kappa B activation and p300-specific HAT/acyetyltransferase activity.104,105,106

Phloroglucinol-pyrenezarnol, is isolated from the Helichry sumatralicum spp. Microphyllum, which yields a potent NF-kappa B inhibitor107, and also inhibited the replication of HIV-1 in T cells. Several phenylpropanoid glycosides were isolated from Clerodonton trichotomum, and showed activity against anti-HIV-1 integrase.108 There are two isomer like Acteoside and anacetiosidewhich showed the highest activity with IC fiftyvalues of 7.8 and 13.7µM, respectively. Ardimerindigallatea naturally derived dimeric lactone, was obtained from the whole plants of Ardisia japonica and showed activity against HIV-1 and HIV-2 RNase H vitro with IC fiftyvalues.

1.6 Saponins
Actein [Figure 6] is isolated from the rhizome of Cuminicufa racemosa (black cohosh), a tetracyclic triterpenoid saponin showed potent anti-HIV activity.110 Soybean saponins obtained from the soybean seeds inhibited the replication of HIV-1 in MT-4 cells but showed no inhibitory action on HIV-1 RTase with narrow therapeutic index. The saponins (B1) isolated from soybean seed which inhibits HIV-induced cell fusion in MOLT-4 cells.111 Escins the triterpenoid saponin obtained from the seeds of Aesculus chinesis belonging to family Hippocastanaceae, showed moderate activity against HIV-1 protease.112

1.7 Tannins
Hydrolysable and non-hydrolysable or condensed tannins are the two classes of tannins.113 The first group consists of polyesters of gallic acid and hexahydroxydiphenic acids (gallotannins and ellagitannins, respectively). The condensed tannins are oligomers and polymers composed of fla-
van-3-ol moieties, commonly referred to as proanthocyanidins.114 Antiviral activity against the retroviruses HIV and HTLV III B was shown by a proanthocyanidin polymer fraction (MW 1500–2000 Da) from Capparissa [IC fiftyvalues of 1.5 to 15µg/ml and 5 to 25 µg/ml, respectively.115 Epigallocatechin-(4a,8,2a-O-7)-epicatechin inhibited HIV-1 protease at 70µg/ml, but proanthocyanidin A2 was not active up to a concentration of 100 µg/ml.116 However, a structure-anti-HIV-1 activity relationship study of a series of proanthocyanidin oligomers showed that proanthocyanidin A2 was the most interesting compound with an SI of 24.117 Proanthocyanidin A1, which only differs from proanthocyanidin A2 in its terminal (+)-catechin unit, only had an SI of 10, which is still larger than procyanidins with a single linkage (the B-series). The two groups of natural polyphenols Catechins and theaflavins found in green and black tea, respectively. In a comparative study, the theaflavin derivatives showed the highest anti-HIV-1 activity.118 Tea polyphenols with a galloyl moiety were more active than those without a galloyl moiety and the number of galloyl groups was correlated with the anti-HIV-1 activity. Theaflavin 3,3-digallate inhibited HIV-1 replication, HIV-1-induced virus-cell fusion and cell-cell fusion, and gp41 six-helix bundle formation at lower micromolar concentrations. Computer-aided molecular docking studies indicated that theaflavin 3,3-digallate may fit in the hydrophobic pocket with its phenyl groups interacting with the hydrophobic residues in the pocket. The HIV-1 protease (IC fiftyvalues of 20.7 µM and 12.5 µM, respectively) was inhibited by twoellagitannins, corilagin out of six hydrolysable tanninsand repandusinic acid, which indicates the importance of the hexahydroxydiphenyl unit.119 The isolated ellagittannins, geraniin and corilagin from a gallotannin-containing fraction of Phyllanthusamuratus were shown to be the most active antiretroviral compounds.119 These tannins blocked the interaction of HIV-1 gp120 with its primary cellular receptor CD4 and inhibited the enzymes integrase, reverse transcriptase and protease at low µg/ml concentrations.

1.8 Quinones
The xantrhones/quinones were evaluated for their anti-HIV activity and being isolated from several plants.124,126,127,128 In general however most of the xantrhones appeared to have a weak or moderate activity against HIV, mostly owing to their toxicity. The vitamin K1, juglone and plumbagin are chemically 1,4-naphthoquinone which showed anti-HIV activity.129 The trimeric naphthoquinone concoumore obtained from Conospermum curvum belonging to family Proteacea showed potent anti-HIV activity, and acts by a novel mechanism which is different from any of the earlier known one, the inhibitory action happened in the late phase of viral replication cycle. After the 48 h of infection the concoumore is added which shows protection of T-cells from cytopathogenic effect of HIV-1. Concoumore has been taken up by the Australian company, AMRAD for further development.130 The polycyclic aromatic dianthoquinonel hypericin, which is obtained from Hypericum perforatum showed inhibitory effect on both like non-human retroviruses and human retroviruses in lymphocytes. It also showed activity against HIV-1 RTase.134

1.9 Terpenes
Anti-HIV activity was exhibited by Betulinic acid, platanic acid and olea-oil from the leaves of Syzigium claviflorum in H9 lymphocyte cell. Betulinic acid demonstrated an anti-HIV activity with an IC fiftyvalue of 1.4 µM and an IC ninetyvalue of 13 µM. Dihydrobetulinic acid showed an EC ninety and IC ninetyvalues of 0.9 and 13 µM respectively. However modification of betulinic acid and dihydrobetulinic acids has successfully increased anti-HIV potency. Esterification at C-3 hydroxyl resulted in more potent compounds with tremendously improved Tlvvalues. 3-O-(3,3-dimethylacrylyl) betulinic acid (DSB, PA-457) had an EC ninety< 3.5 × 10⁻¹ µM and TI > 20,000,128 DSB (PA-457), which was discovered by Panacos scientists, works by a mechanism
different from that of any approved drug or other drugs under development, by blocking a key step in the processing of a viral core protein called capsid. The maturation inhibitor was found out to be 3-O-[3,3-dimethyl succinyl]-butenolic acid. It is responsible for disruption of the late-stage viral maturation processes of the Gag protein, resulting in a defective core structure around the viral RNA, and a non-infectious virus. This compound was the first member of a new class of anti-HIV drug candidates. In a structure-activity relationship study on butenolic acid derivatives, RPR103611, a statin derivative, was found to be inactive against HIV-1 protease, reverse transcriptase, and integrase, but it acted as a fusion inhibitor. More recently, it was suggested that its antiviral activity was dependent on the stability of the gp120/gp41 complex. Gp120 was proposed as the primary target for the anti-HIV activity of a stereoismer of RPR103611, IC50. Both compounds were found to be equally potent in their anti-HIV-1 and anti-fusion activities. However, the drug development process of RPR103611 was stopped due to its poor pharmacodynamic properties. The combination of a 3,3-dimethyl succinyl side chain at C-3 and an aminoalkanoic side chain at C-28 resulted in very active bifunctional anti-HIV compounds with EC50 values in the nanomolar range. They showed antifusion activity as well as maturation inhibition. Preclinical studies have shown that PA-457 retains full activity against drug-resistant viruses, and is effective in an animal model of HIV infection and should be suitable for use in combination therapy with other drugs. Recently, Panacos announced positive results from a phase II/III clinical trial in HIV-infected patients, which may act as a reverse transcriptase, and integrase. The company recently completed a phase Ib clinical trial of PA-457, administered orally once a day for 10 days to uninfected volunteers. The drug candidate was well-tolerated and plasma concentrations of PA-457 reached levels significantly greater than those predicted to provide a therapeutic benefit in HIV-infected patients. Recently, Panacos Pharmaceuticals has started phase II clinical studies of PA-457.

The inhibition of HIV-1 replication in human peripheral mononuclear cells (IC50 values: 22.7-24.6 mg/l) and monocytes/macrophages (IC50 values: 57.4 μM), was demonstrated to be inhibited by the parent compound oleanolic acid isolated from methanol extract of wood of Xanthoceras sorbifolia Bge (family Myrtaceae), with therapeutic index value: 17.9 mg/ml. Significant anti-HIV activity was also shown by Moronic acid[Figure 7] isolated from Myrcygenia euosma belonging to family Myrtaceae, with therapeutic index of more than 186. Panectyclic triterpenes, 6b-hydroxyxyparpine 3-9-hydroxybenzoxa, and 2a-hydroxyxyparpine 2,3-bis-6-hydroxybenzoxa isolated from the roots of Maprounea africana Muell.(family-Euphorbiaceae), inhibited HIV-1 RTase with an IC50 value of 12.8 μM. Anti-HIV inhibition of the replication activity in H9 lymphocyte cells was shown by Celasdin B isolated from ethanolic extract of Celastrus hindii belonging to family Celastraceae in vitro.

HIV-1 induced cytopathic effects in MT-4 cells and HIV-1 protease inhibitory activity was shown by Oxycenetic triterpenes, such as ganoderic acid-a, ganoderol F, ganodermontriol, ganoderic acid B, ganoderol B, and ganoderic acid C1 isolated from methanolic extracts of Ganoderma lucidum belonging to family Polyporaceae. Anti-HIV replication activity in H9 lymphocyte cells was shown by Lanostane-type triterpene, suberosil isolated from ethanolic extract of the stems and leaves of Polylithia suberosa belonging to family Annonaceae. Significant inhibitory activities against HIV-1 RTase and in the syncytium assay was demonstrated by the proteasomes, garciserpenes A and Cisolated from ethyl acetate extract of bark and stems of Garcinia spectabilis. HIV-1 RTase and HIV-2 RTase Inhibitory activity was shown by a ring-seco-cycloartenol triterpenoid, nigracid acid isolated from the stems of Schisandra sphaerandra. Inhibitory activity against HIV replication in H9 lymphocytes, shown by triterpene lactone, linalactone Cisolated from stems and roots of Kadsura lancilimba.

Anti-HIV activity was also reported with Shinjalactone C, possessing unusual structure isolated from Brucia javanica and Brucetaeae dysernerica, with therapeutic index of more than 25 and also by Well-known antimalarial sesquiterpene lactone, artemisinin, isolated from Artemisia annua, with an IC50 of 100 mM and EC50 of 100 μg/ml. Kauranetditerpenoid, 1, 6b, 17-dihydroxy-ent-kaur-1-9-0ic isolated from methanolic extracts of the fresh fruits of Annona squamosa L. belonging to family Annonaceae, significantly inhibited HIV with an EC50 value of 0.8 mg/ml (TI = 5). Anti-HIV activity against HIV-1 replication in H9 lymphocyte cells was shown by Linearol[Figure 7], an ent-kauranetditerpenoid isolated from Sideritis akamii and its semisynthetic derivatives. Potent HIV inhibitory property was shown by Phorbol ester, prostatinsisolated from Homalanthus nutans to family Euphorbiaceae. HIV-1 induced cytopathic effects was shown to be inhibited by another phorbol diester, 12-O-tetradecanoylphorbol-1-3-acetate (TPA) isolated from methanolic extract of Croton tiglium belonging to family Euphorbiaceae.

HIV-1 RTase activity was reported in 12-Deoxyphorbol 13-(3E, 5E-decadienolate), isolated from leaves and stems of Excoecaria agallocha. Diterpene lactone, andrographolide, isolated from Andrographis Paniculata inhibited HIV-infected cells from arresting in G2 phase in which viral replication is optimal. Anti-HIV replication was then reported to be inhibited in HIV-1 infected cells. HIV replication in H9 lymphocytes was inhibited by another diterpene lactone, nortripterifordin[Figure 7] isolated from Tritypargum gironfordi. HIV-inhibitory activity in vitro screening was established with Diterpenes from Homalanthus cuminatus and Chryso balanumisco. Glycyrrhizin from licorice root has shown anti-HIV-1 activity in MT-4 cells. A limonoid, clausenolide-1-ethyl ether isolated from ethanol extract of rhizomes of Clausenae-cavata (family-Rutaceae), exhibited anti-HIV activity in cell-based assays anti HIV activity was demonstrated with Limonin and nonlimonins isolated from Citrus spp. Belonging to family Rutaceae. A dose-dependent inhibition of viral replication was observed in PMBC isolated from healthy donors and infected with HIV-1 strain after incubation with limonin and nonlimonins. This also inhibited the production of HIV-1-p24 antigen in infected monocytes/macrophages. The mechanism of anti-HIV-1 effect of limonoids was found to be inhibition of HIV-1 protease. HIV-1 reverse transcriptase was also seen to be inhibited also by a diterpene 8,10,18-triulohydo-2,6-dolabelladiene, isolated From the brownish injuries Dicyota pfluffii with an IC50 value of 16.5 μM. It also inhibited the replication of HIV-1 (IC50 = 2.1 μM). It was reported that this compound blocks replication of HIV-1 at a post-transcriptional step. The HIV-1 reverse transcriptase inhibitor was also inhibited by diterpenes which were isolated from the alga Dicyota membranoides. Therereplication of HIV-1(IC50 = 4.5 μM) with a SI of 71.4, was demonstrated to be inhibited by Lincalactone C which is isolated from the stems and roots of Kadsura lancilimba also from the Schisandra lancifolia, A trinorcycloartenoltriterpenoid, lancifolacton inhibited by e H, and the A ring secco-cycloartenol, lancifolacton inhibitory activity was isolated which is likely to be showed weak anti-HIV-1 activity, with EC50 of 16.6, 16.2 and 10.3 μM.

**Figure 7: Anti-HIV terpenes from plants**

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Structural Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maslinic acid</td>
<td><img src="image" alt="Maslinic acid" /></td>
</tr>
<tr>
<td>Moronic acid</td>
<td><img src="image" alt="Moronic acid" /></td>
</tr>
<tr>
<td>Linearol</td>
<td><img src="image" alt="Linearol" /></td>
</tr>
<tr>
<td>Nortripterifordin</td>
<td><img src="image" alt="Nortripterifordin" /></td>
</tr>
</tbody>
</table>
isolated from the methanolic extract of dried leaves of *Phyllanthus niruri* L.\(^{166}\) with an IC\(_{50}\) value of 3.3 \(\mu\)M. HIV-1 reverse transcriptase activity was shown to be inhibited by a polysaccharide fraction isolated from *Thuja occidentalis* belonging to family Cupressaceae.\(^{188}\) The HIV regulatory gene tat is quite essential for viral replication. The *tat* protein is released from HIV-1 infected cells, enters new cells in an active form, and stimulates the transcriptional activity of HIV-LTR.\(^{189}\) Thus anti-HIV-1 activity was shown in pentosan polysulphate\(^{190}\) and heparin\(^{191}\) by virtue of Inhibition of tat activity, selective 2'-O-, 6-O-, or N-desulfation of heparin prevented the interaction with tat.

Sulphated dextrin derivatives inhibited HIV-1 *tat*, whereas unsulphated dextrin did not.\(^{192}\) Sulphated polysaccharides have already been known for a long time as potentiators of HIV-1 and -2 replication *in vitro*.\(^{171,172}\) They are believed to exhibit the following properties: (1) broad activity against enveloped viruses, including HIV and HSV; (2) low induction of viral resistance in cell cultures; (3) inhibition of virus adsorption to the cells; and (4) inhibition of syncytium (giant cell) formation between HIV-infected and normal CD4+ T cells. The latter point may be important for the depletion of CD4+ T cells in AIDS patients.

Sulphated polysaccharides showing the anti-HIV activity is due to shielding off the positively charged amino acid residues in the V3 loop of the viral envelope glycoprotein gp120.\(^{126}\) In this way, viral attachment to cell surface heparin sulphate is prevented. This is a primary binding site, followed by a more specific binding to the CD4 receptor.

HIV-1 exhibited resistance to dextran sulphate which seemed to be located in the *env* genome of HIV, and specifically in the V3 loop domain.\(^{173}\) More than 15 years ago, the *in vivo* activity of dextran sulphate against HIV was found to be disappointing, both after oral or intravenous administration.\(^{174,175}\) This was due to its poor oral bioavailability, its short plasma half-life, partial inactivation by plasma components, and poor ability to penetrate infected cells.\(^{176}\) However, it was reported that dextran sulphate was absorbed rapidly in humans after oral administration and could be found in plasma, lymphocytes, and urine.\(^{177}\) A significant decrease in viral load was observed in an open phase III dose escalation study in which six AIDS patients were treated with intra-peritoneally administered dextrin 2-sulphate.\(^{178}\) The question if sulphated polysaccharides can be useful anti-HIV drugs after oral or parenteral administration, or as a gel formulation (e.g., on condoms) in the prevention of sexually transmitted HIV remains a matter of debate.\(^{179}\) The development of new drug delivery systems such as liposomes, niosomes may improve the therapeutic efficacy of sulphated polysaccharides. Potency against Herpes simplex virus type 1, human cytomegalovirus and HIV-1 was shown by a sulphated polysaccharide with fucose as the main component which was isolated from the water extract of a brown alga *Sargassum hornertii*.\(^{179}\) Time-of-addition experiments suggested that it inhibited not only the initial stages of viral infection, but also intracellular replication stages. Potency against Herpes simplex virus type 1, human cytomegalovirus and HIV-1 was also shown by rhumin sulphate, a natural sulphated polysaccharide isolated from the seaweed Monostroma latissimum, composed of large amounts of 1,2- and 1,3-linked 0-L-rhamnose residues with small amounts of their branching residues.\(^{180}\) Rhumin sulphate and AZT showed synergistic activity in their anti-HIV effect.\(^{182}\) The sulphated galactans with a galactose:3,6-anhydrogalactose sulphates molar ratio of 1:0.01:1.23, 1:0.04:0.47, and 1:0.01:1.13, respectively were obtained from the gametic, carposporic and tetr sporic reproductive stages of the Mediterranean red alga *Asparagopsis armata*. The carposporic polysaccharide with the lowest sugar ratio was ineffective against HIV-1 replication up to 100\(\mu\)g/ml, in contrast to the other galactans which inhibited HIV-1 replication at 10 and 8\(\mu\)g/ml, as measured by HIV-induced syncytium formation and reverse transcriptase activity in cell-free culture supernatant.\(^{181}\) From *Arthrospira platensis* (formerly *Spirulina platensis*) a sulphated polysaccharide called Calcium spirulan was obtained which consists mainly of two types of disaccharide repeating units, O-hexuronosylhexosamine and O-rhamnosyl-3-O-methylhexosamine. A broad spectrum of antiviral activity against herpes viruses, paramyxoviruses, influenza viruses, and HIV-1, was reported with calcium spirulan and spirulan like substances. With regard to herpes viruses, antiviral effects were most pronounced after preincubation prior to virus addition, indicating virus entry as the primary target. However, in the case of human cytomegalovirus, it was clearly demonstrated that intracellular steps also contributed to the antiviral effect. In the case of HIV-1, inhibition occurred at a stage later than viral entry.\(^{182}\)

![Figure 8: Anti-HIV carbohydrate from plants](image)

**Figure 8: Anti-HIV carbohydrate from plants**

2. **Miscellaneous**

The anti HIV activity was shown by the methanolic extracts of *Crinum asiaticum*, 183 *Tetrapanax macrocarpa*, 184 50% hydroalcoholic extract of *Hysopp officinalis*, aqueous extract of *Dictyria viscosa*, 185 *Jatropha curca*, *Chamaesyce hyssopifolia*, *Cordia spinescens*, *Hypis lanthanifolia* and extracts of *Tuberous hygrophila* and *Stagonospora minor magnolia*. The acetone fraction of *Combretum pauciflum* and the methanolic fraction of *Dodonea angustifolia* showed selective inhibition of HIV-1 replication with selectivity indices of 6.4 and 4.9, and afforded cell protection of viral-induced cytopathic effect of 100 and 99% respectively.\(^{186}\) The natural killer cell activity in HIV infected individuals was increased by the hydro-alcoholic extract of *Derris scandens*.\(^{187}\)

2.1 **Peptides**

Anti-HIV activity was shown to be exhibited by Small macrocyclic peptides, cycloviolins isolated from tropical plant *Leonia cymosa* and *circulins*, a group of cyclic peptides isolated from *Chassalia parvifolia* belonging to family Rubiaceae, HIV-1 gp120 infection of CEM-S3 cells.\(^{188}\) Was shown to be inhibited by Palicourea, a 37 amino acid cyclic polypeptide, isolated from organic extract of the tropical tree *Palicourea condensata* belonging to family Rubiaceae.

2.2 **Proteins**

Anti-HIV activity had been observed in some plants such as Ribosome inactivating proteins (RIPs) and lectins which are Proteins obtained from higher plants.\(^{189}\) RIPs are RNA N-glycosidases, that specifically interfere with eukaryotic protein translation. They inactivate ribosomes through a site-specific deactivation of the large ribosomal RNA.\(^{190}\) A high number of RIPs have been identified in plants belonging to various families, particularly *Caryophyllaceae*, *Sambucaceae*, *Cucurbitaceae*, *Euphorbiaceae*, *Phytolaccaceae* and *Poaceae* and also in bacteria and fungi. They vary greatly in their physical properties and cellular effects. Many of the plants from which RIPs are isolated are used medicinally in traditional Chinese medicine and the RIPs may account for some of the reported clinical efficacies of these plants.\(^{191}\) For some RIPs, sensitisation and IgE induction have been demonstrated, so their allergenic and cross-reactive potential should be considered when applying them in therapy.\(^{192}\)

MAP30 is a plant protein with a molecular weight of 30 kDa isolated from *Momordica charantia* showed Anti-HIV properties with Anti-tumour properties.\(^{193,194}\) MAP30 was active against tumour-transformed or HIV-infected cells, while it resulted in no adverse effect on normal cells. In also possessed RNA N-glycosidase activity, MAP30 acted as a DNA glycosylase/apurinic lyase.\(^{195}\) This may explain its apparent inhibition of HIV-1 integrase by rendering the HIV-LTR an unsuitable substrate for HIV integrase as well as DNA gyrase. The DNA glycosylase/apurinic lyase activity of MAP30\(^{196,197}\) and other RIPs suggested that the anti-HIV activity of RIPs was independent of their ribosome inactivation activity. Indeed, endoproteinase digestion of MAP30 and GAP31 resulted in the generation of peptide fragments with full antiviral and antitumour activity.\(^{200}\) These fragments remained fully active in HIV integrase inhibition and HIV-LTR topological inactivation, but not ribosome inactivation. Therefore, it could be concluded that the antiviral and antitumour activities of MAP30 and GAP31 are independent of their ribosome inactivation activity.

Md. Abul Barkat et al
Trichosanthin obtained from the root tuber of *Trichosanthes kirilowii* showed in vitro HIV inhibition.211 Trichosanthin also inhibited HIV replication in H9 and CEM-SS cells, and syncytium formation between infected H9 cells and uninfected Sup-T1 cells.213 However Clinical trials with trichosanthin showed that it induced anaphylactic reactions in AIDS patients after i.v.administration.214 In order to resolve the problem and reduce its antigenicity, the seven C-terminal amino acid residues were deleted, which resulted in a 2.7-fold decrease in antigenicity, but a 10-fold reduction in *in vitro* ribonuclease inhibition activity. Apoptosis induced by trichosanthin was demonstrated in a ribonuclease packed cell lysate which showed partial the antiviral action.215 Several plant RIPS, such as agrostin, gelonin, luffin, α-momorcharin, β-momorcharin, saporin, and trichosanthin were evaluated as inhibitors of HIV-1 replication.216 They exhibited a very weak suppressive effect on HIV-1 reverse transcriptase and HIV-1 protease, but apart from agrostin, all RIPS strongly inhibited HIV-1 integrase. However, it remains to be elucidated whether interference with integrase is the key mechanism for the anti-HIV activity of RIPS.

The entry of the virus into host cells is mediated by glycoproteins gp120 and gp41 which are present on the envelope of HIV. Both gp120 and gp41 are heavily glycosylated, surrounding the receptor binding regions. It is estimated that gp120 consists of N-linked glycans for almost 50% of its molecular weight. The N-glycans of gp120, 21% of the high-mannose type and 29% of the complex type, the latter being predominantly glycosylated and/or sialylated. Carbohydrate- binding agents (CBAs) specifically targeting HIV-1 glycan shields efficiently inhibit HIV infection and prevent virus entry into target cells. In contrast to other existing anti-HIV agents, resistance development of HIV against CBAs may allow efficient immunological suppression of virus replication and virus clearance from the systemic circulation because of the exposure of previously hidden immunogenic epitopes on HIV-1 integrase. They may therefore represent the first available drugs for which chemotherapeutics may act in concert with an immunological response.217

Synergistic activity between CBAs and 1-deoxymannojirimycin was recently described.218 1-deoxymannojirimycin (the α(1,2)-mannosidase I inhibitor was found to potentiate the inhibitory activity of CBAs against wild-type HIV-1. The susceptibility to the inhibitory effect of 1-deoxymannojirimycin was increased in cell cultures infected with mutant HIV-1 strains containing N-glycan deletions in the gp120 envelope. Moreover, it was able to partially reverse the phenotypic resistance of CBAs to the mutant virus strains. CBAs are almost exclusively of protein nature and can be divided into at least seven distinct groups of molecules depending on their origin: prokaryotes, sea corals, algae, fungi, plant lectins, and vertebrates.219

Antiviral activity, immunomodulation/repression/ anti-HIV activity was demonstrated with Plant lectins being the largest group of plant proteins with biological activities, including antiviral activity, immunomodulation/ repression and anti-HIV activity.219 Lecitins are proteins bearing a non-catalytic domain that binds irreversibly to specific carbohydrates, normally through a monosaccharide-specific mechanism. Most plant lectins with HIV activity are derived from the monocot families Alliaceae, Amaryllidaeae and Orchidaceae or the dicot families Cecropiaceae, Fabaceae, Moraceae and Urticaceae.

Plant lectins which form the vast majority of anti-HIV group are directed against mannos oligomers. *Galanthus nivalis* agglutinin (GNA) and *Hippeastrum* hybrid agglutinin (HHA) are two extensively studied mannose-specific plant lectins. Recently, a higher inhibitory activity of HHA compared to GNA was demonstrated for HIV adsorption to the epithelial cell line HEC-1A, HIV transcytosis through HEC-1A cell line monolayer, HIV adsorption to monocyte-derived dendritic cells (MDDC), and HIV transfer from MDDC to T cells.220,221 However the Systemic use of plant lectins to inhibit HIV infection may be questionable as they do show antigenic (immunogenic) properties and exhibit short plasma half-life. However, local (intravaginal) application as a gel or cream formulation may avoid these disadvantages and may open novel perspectives to develop plant lectins as microbicides. Therefore, Balarzini et al. investigated GNA and HHA for their potential as microbicides.222,223 Both proteins inhibited a wide variety of HIV of different strains and viral isolates in different cell types. Markedly decreased HIV infectivity and increased microbicidal activity of the plant lectins was demonstrated with short exposure of the lectins to cell-free virus particles or persistently HIV-infected HUT-78 cells. Selection of HIV-1 strains with different levels of resistance to the two mannose-specific lectins showed that there was no cross-resistance to any other HIV entry inhibitor, including T-20 and cyanovirin.224 They also exhibited desirable pharmacological properties for formulation studies, such as stability at high temperatures and low pH for prolonged time periods, odourless and tasteless, and they can be easily formulated in gel preparations.225 Pronounced anti-HIV activity was found in the only GlcNAc-specific plant lectin (*Urtica dioica* agglutinin or UDA) which was isolated from *Urtica dioica*. It ranks among the smallest plant lectins and is an 8.5-kDa monomeric protein having two carbohydrate- binding sites with different affinities. It inhibited HIV-1 and HIV-2-induced cytopathogenicity and syncytium formation of HIV-infected HUT-78 cells and CD4+ MOLT-4 cells.226 In contrast to the mannose-binding proteins, which had a 50- to 100-fold decreased antiviral activity against the UDA-exposed mutant viruses, UDA showed only a slightly lower antiviral activity, even against those mutant virus strains lacking about 40% of the glycosylation sites in their gp120 envelope.227 UDA was found to be of toxicity when given intravenously to mice at doses up to 25 mg/kg body weight. It has also been reported that UDA was poorly mitogenic and at high concentrations did not agglutinate human red blood cells.

The glycans of HIV gp120 consist to 33% of the high-mannose type and 67% of the complex type, the former being predominantly glucosylated and/or sialylated. Carbohydrate- binding agents (CBAs) specifically targeting HIV-1 glycan shields efficiently inhibit HIV infection and prevent virus entry into target cells. In contrast to other existing anti-HIV agents, resistance development of HIV against CBAs may allow efficient immunological suppression of virus replication and virus clearance from the systemic circulation because of the exposure of previously hidden immunogenic epitopes on HIV-1 integrase. They may therefore represent the first available drugs for which chemotherapeutics may act in concert with an immunological response.217

Potential anti-HIV activity was demonstrated with cyanovirin-N, originally isolated from an aqueous extract of the cyanobacterium *Nostoc ellipsosporum*, being the first prokaryotic mannose-specific lectin with a potent anti-HIV activity.219,220 This protein consists of a single chain containing 101 residues and its amino acid sequence shows obvious duplication. The protein is highly resistant to degradation and shows no loss of structural integrity or antiviral activity after treatment with detergents, denaturants, organic solvents, freezing and heating up to 100°C.227

The only CBA for which efficacy and safety was demonstrated in a chimeric simian immunodeficiency virus (SIV)/HIV-1 virus infection in monkey studies when applied intravaginally or rectally as a topical microbicide is cyanovirin-N.221,222 By exposing HIV-1 infected CEM cell cultures to increasing concentrations of cyanovirin-N, a total of eight different amino acid mutations exclusively located at N-glycosylation sites in the envelope surface gp120 were observed. The extent of the decrease of antiviral activity against the mutated virus strains was markedly less pronounced than observed for the (n1,3)- and (n1,6)-mannose-specific plant lectins, *Hippeastrum* hybrid agglutinin and *Galanthus nivalis* agglutinin, pointing to the existence of a higher genetic barrier for cyanovirin-N.223 Mannane reverses the antiviral and *in vitro* antiproliferative activity of cyanovirin-N but the pronounced antiretroviral activity of cyanovirin-N on peripheral blood mononuclear cells remained unaffected. Therefore, careful monitoring of potential side effects should be required if applied as a microbical drug. Nowadays, studies are ongoing to express and release cyanovirin-N in commensal lactobacilli or *Streptococcus gordonii* to create a microbicidal environment in the vaginal ecology.224,225 Other algal lectins with a significant anti-HIV activity are scytovirin, *Microcystis viridis* lectin, and griffithsin.226,227,228 Saporin and luffin, also exhibited anti- HIV integrase activity.224 *Myrianthus holstii* lectin (MHL), a 9284Da, cysteine-rich protein isolated from aqueous extract of *M. holstii* belonging to family Moraceae,229 showed anti-HIV activity with an EC50 value of 150 μM.

### 2.3 Xanthones

HIV-1 RTase was found to be inhibited by Swertiafranchetiana, a flavonone–xanthone glucoside isolated from *Swertia franchetiana*. Its mode of action was found to be related to its 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.230 While moderate anti-HIV activity26 was shown to be exhibited by the prenylated xanthone, maculaxanthone B isolated from *Maclura tinctoria* belonging family Moraceae.

IJBR (2014) 05 (05) www.ssjournals.com
3. Summary of plants with anti-HIV active compounds and their modes of action

Plants are an important source of anti-HIV chemical compounds, and several plant families and species contain anti-HIV active compounds that could be developed into newer drugs to manage HIV/AIDS. The details of the plant sources, active compounds, modes of action, and literature sources are listed in Table 1.

<table>
<thead>
<tr>
<th>Biological Sources</th>
<th>Active Constituents</th>
<th>Mode Of Action</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrographis paniculata (Acanthaceae)</td>
<td>Aqueous extracts of leaves</td>
<td>Inhibits HIV protease and reverse transcriptase</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td>Diterpene lactones (andrographolide)</td>
<td>Inhibit cell-to-cell transmission, viral replication and syncytia formation in HIV-infected cells</td>
<td>155</td>
</tr>
<tr>
<td>Acer o大宗商品um (Aceraceae)</td>
<td>Flavonoid gallocate</td>
<td>Anti-HIV-1 integrase Activity</td>
<td>54</td>
</tr>
</tbody>
</table>
| Lentina edodes (Berk., J. Singer (Aga
traceae) | Sulfated lentiman | Prevents HIV-induced cytopathic effect | 277 |
| Galanthus nivalis L. | Plant lectins: G. nivalis agglutinin (GNA), Hippeastrum hybrid agglutinin (HHA), and monocot mannose-binding lectins (MBLs) | Stops spread of HIV among lymphocytes; most prominent anti-HIV activity is found among MBLs; GNA has specificity for terminal α(1-3)- and internal α(1-3)- and α(1-6)-linked mannose residues; HHA recognizes both terminal and internal α(1-3)- and α(1-6)-linked mannose residues | 277 |
| Rhizoma sachiedama (Anarcardiaceae) | Biflavonoids, robustallavone and Hinokilavone | Inhibits HIV-1 reverse transcriptase | 35 |
| Ancistrocladus korupensis (Ancistrocladaceae) | Michellamines A and B | Inhibits reverse transcriptase, cellular fusion and syncytia formation | 277 |
| Polysiphonia suberosa (Annonaceae) | Lamostane-type triterpene, suberosol | Anti-HIV replication activity | 74 |
| Lamium neglectum (Asteraceae) | S Lukodrin | Suppresses HIV-1 viral replication | 277 |
| Agorothiella tenora (Areschougia
caeae) | Sulphonated polysaccharides | Inhibits HIV cytopathic Effect | 277 |
| Achyrocline aspera (Asteraceae) | Dicaffeoylquinic acids: 3,5-dicaffeoylquinic acid, and 1-methoxyxylol-3,5-dicaffeoylquinic acid | Irreversible inhibition of HIV-1 integrase | 277 |
| Arctium latum (Burdock) (Asteraceae) | Wedelolactone, a coumarin derivative; orobol (an isoflavone derivative) | Inhibits HIV-1 replication; blocks cell-to-cell transmission of HIV-1 | 277 |
| Acerba euchroma (Boraginaceae) | Monosodium and monoprotin salts of isomeric caffeic acid tetramer | Inhibits HIV replication | 277 |
| Humulus lupulus (Cannabinaceae) | Xanthohumol | Inhibits HIV-1-induced cytopathic effects | 78 |
| Celastrus hindsii (Celastraceae) | Celastrin B | Anti-HIV replication activity | 27 |
| Tripterygium wilfordii (Celastraceae) | Diterpene lactones (nortripterifordin) | Inhibits HIV replication | 277 |
| Calliopsis scopulorum (Chlo
caceae) | Cordiolide A and B | Inhibits HIV-1 replication | 277 |
| Martina lutea (Chlo
caceae) | Lantasanone | Inhibits reverse transcriptase | 277 |
| Symphyon glabratia (Chlo
caceae) | Gutifierone A | Inhibits cytopathic effects of HIV | 277 |
| Hypericum perforatum (Chlo
caceae) | Hypericin, 3-hydroxy auric acid | Inhibits HIV-1 replication | 277 |
| Combretum molle (Combretaceae) | Gallotannin | Inhibits HIV-1 reverse Transcriptase | 277 |
| Terminalia chebula (Combretaceae) | Gallic acid and galloyl glucose | Inhibits HIV reverse transcriptase and integrase | 277 |
| Vatica anobila (Dipterocarpaceae) | 6,8-diprenylaromadendrin and 6,8-diprenylkaempferol | Inhibits HIV-1 and entry | 277 |
| Peltophorum orienticum (Fabaceae) | Gallotannin | Inhibits HIV-1 reverse transcriptase | 277 |
| Siverina franclona (Gentianaceae) | Flavonone-sambubioside glucoside | Inhibits HIV-1 reverse transcriptase | 277 |
| Inonotus obliquus (Hymenochaetaceae) | Water-soluble lignans | Inhibits HIV-1 protease | 277 |
| Garcinia spectabilis (Hypericaceae) | Garciraterpenes A and C, Protostanes | Inhibits HIV-1 reverse transcriptase | 277 |
| Sideritis akani (Lamiaceae) | Sulphonated polysaccharides; Lincarol | Anti-HIV replication | 277 |
| Detarium microcarpus (Leguminosae) | Cathecins 1-5 | Inhibits HIV reverse transcriptase activity in a non-specific way | 277 |
| Magnolia spp. (Magnoliaceae) | Neuroglans e.g. magnolol 1 and honokiol 2 | Antioxidant; induces apoptosis in tumor cells, weak anti-HIV-1 activity | 277 |
| Stephania cepharantha (Menispermaceae) | Cepharanthine | Inhibits HIV replication | 277 |
| Musa acuminata (Musaceae) | BanLec, a jacalin-related lectin | Blocks HIV entry, hence is a good microbicide; potent inhibitor of HIV-1 replication | 277 |
| Myrothamnus flabellifolius (Myrothamnaceae) | Polypehons, gallostatins, 3,4,5-tri-O-galloylquinic acids | Polypehons protect cell membranes against free radical-induced damage; gallostatins have anti-bum properties; 3,4,5-tri-O-galloylquinic acids have anti-HIV reverse transcriptase/Activity | 277 |
| Flammelina velutin (Physalacriaceae) | Velutin | Inhibits HIV-1 reverse transcriptase | 277 |
| Physalacria americana (Physalacriaceae) | Pokeweed antiviral protein (PAP) | Broad spectrum microbicide | 277 |
| Cuscuta pinutifida (Rosaceae) | Uvaol and ursolic acid | Inhibits HIV-1 protease | 277 |
| Geum japonicum (Rosaceae) | Maslinic acid | Inhibits HIV-1 protease | 277 |

4. Conclusions

The plants are a consequential source of anti-HIV compounds, and that chemical compounds could be employed in the development of more incipient drugs to manage HIV/AIDS. The current literature survey provides an evidence-predicated contribution to our constrain of plant constituents or plants derived that can be utilized in the management of HIV/AIDS. The inclusion of traditional herbal rejuvenators in the health care system especially in primary healthcare team in developing countries could amend quality of life and safety standards and their utilization as a complimentary therapy could play
a role in the palliative care of people living with HIV/AIDS. This evidence should persuade further research and public interest into the isolation of anti-HIV active compounds from plants. There is need to increase the screening of plants predicated on ethnopharmacological data and indigenous erudition; this will quicken the search for novel anti-HIV compounds. There is additionally an exigent need to expeditious-track HIV/AIDS clinical tribulations of candidate drugs developed from novel compounds isolated from plants. Post-genomics, phylogenetic analysis and other bioinformatics may implement light on other cognate plants that may contain highly active compound.

References


Dicaffeoylquinic and dicaffeoyltartaric acids are selective inhibitors of human integrase. 

**References**


---

**IJBR (2014) 05 (05)**

www.ssjournals.com


