

Review

Structure-Activity-Relationship and Mechanistic Insights for Anti-HIV Natural Products

Ramandeep Kaur ^{1,†}, Pooja Sharma ^{1,2,†}, Girish K. Gupta ³ , Fidele Ntie-Kang ^{4,5,6,*}  and Dinesh Kumar ^{1,*}

¹ Sri Sai College of Pharmacy, Manawala, Amritsar 143001, India; poojasharmagndu@gmail.com (R.K.); pooja.sharma2007@yahoo.co.in (P.S.)

² Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, India

³ Department of Pharmaceutical Chemistry, Sri Sai College of Pharmacy, Badhani, Pathankot 145001, India; girish_pharmacist92@rediffmail.com

⁴ Department of Chemistry, Faculty of Science, University of Buea, P.O. Box 63 Buea, Cameroon

⁵ Institute for Pharmacy, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle (Saale), Germany

⁶ Institut für Botanik, Technische Universität Dresden, Zellescher Weg 20b, 01062 Dresden, Germany

* Correspondence: fidele.ntie-kang@ubuea.cm (F.N.-K.); dineshpharma.rsh@gndu.ac.in (D.K.)

† These authors contributed equally to this work.

Academic Editor: Kyoko Nakagawa-Goto

Received: 26 March 2020; Accepted: 22 April 2020; Published: 29 April 2020



Abstract: Acquired Immunodeficiency Syndrome (AIDS), which chiefly originates from a retrovirus named Human Immunodeficiency Virus (HIV), has impacted about 70 million people worldwide. Even though several advances have been made in the field of antiretroviral combination therapy, HIV is still responsible for a considerable number of deaths in Africa. The current antiretroviral therapies have achieved success in providing instant HIV suppression but with countless undesirable adverse effects. Presently, the biodiversity of the plant kingdom is being explored by several researchers for the discovery of potent anti-HIV drugs with different mechanisms of action. The primary challenge is to afford a treatment that is free from any sort of risk of drug resistance and serious side effects. Hence, there is a strong demand to evaluate drugs derived from plants as well as their derivatives. Several plants, such as *Andrographis paniculata*, *Dioscorea bulbifera*, *Aegle marmelos*, *Wistaria floribunda*, *Lindera chunii*, *Xanthoceras sorbifolia* and others have displayed significant anti-HIV activity. Here, we attempt to summarize the main results, which focus on the structures of most potent plant-based natural products having anti-HIV activity along with their mechanisms of action and IC₅₀ values, structure-activity-relationships and important key findings.

Keywords: AIDS; anti-HIV; natural products; MOAs

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a disease of the cell-mediated immune system or T-lymphocytes of the human body. In AIDS, the count of helper T cells is reduced, which directly stimulates the production of antibodies from B-cells. Consequently, the body's natural defense system against AIDS infection is destroyed [1]. According to the World Health Organization (WHO), it is estimated that about 75 million individuals have been infected from the human immunodeficiency virus (HIV), and about 37 million people are still under the fighting stage. The prevalence of HIV is expected to increase significantly due to illiteracy, non-hygienic living conditions, unsafe sexual relationships and lack of awareness [2]. Initially, the first human retrovirus was founded at the National Cancer Institute, in the USA by Robert Gallo and his colleagues, after being first discovered in 1981

among homosexuals. In 1983, Professor Luc Montagnier and co-workers later discovered the AIDS virus at the Institute Pasteur, in Paris [3]. In 1986, the International Committee on Viral Nomenclature were the first to officially name the AIDS virus the human immunodeficiency virus (HIV) [4]. Currently, Africans worldwide are stricken by this illness more than any other race [5].

1.1. The HIV Structure

The motor agent for AIDS is an animal retrovirus named HIV that is ready to replicate and integrate its infectious DNA into the host cell's healthy DNA. It is an animal virus that chiefly attacks the body's helper T cells [6,7]. The virus is spherically shaped, having a diameter of around 90–120 nm. Its genetic material generally contains a single standard RNA fiber metameric into two similar fibers and is connected with an enzyme called reverse transcriptase (RT). The viral coating contains a lipid bilayer that is derived from the membrane of the host cells and spikes of glycoprotein that are like projecting knob. It consists of two protein coats, as depicted in Figure 1 [8,9]. Internally, the virus contains a protein layer (the matrix), which consists of the necessary proteins and nuclear material. The virus also contains an enzyme known as a protease that disintegrates the viral polyproteins to form new functional proteins. The role of reverse transcriptase is to catalyse the conversion of the viral RNA into viral DNA and integrase, which allows the entry of viral DNA into the host nucleus [10,11].

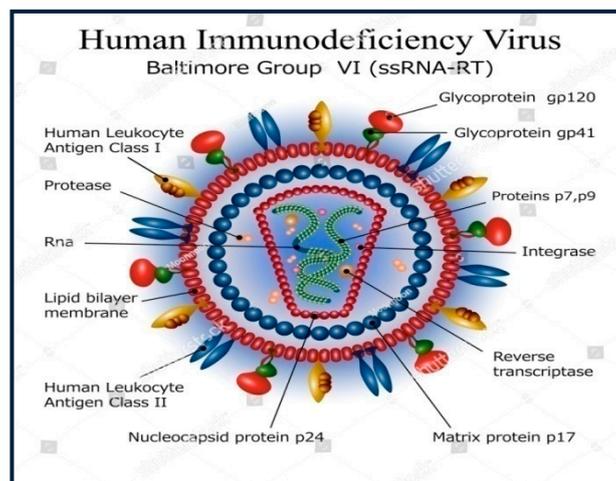


Figure 1. Structure of human immunodeficiency virus (HIV) virus [10]. Image was originally published within Open Access license.

1.2. Replication Cycle of HIV

The complete HIV replication cycle is represented in Figure 2. After the entrance of the virus into the body of an individual, the virus invades the body cells through CCR5 or CXCR4 receptors shown on the top of the macrophages, known as T-lymphocytes, dendritic cells and monocytes [6,7]. After entering the host cell, the virus binds with chemokine receptors and interacts with cell membrane proteins. The virus then releases and utilizes its reverse transcriptase (RT) enzyme for the synthesis of viral DNA from its viral genome i.e., HIV RNA. This conversion allows the virus to enter into the host cell nucleus, where the enzyme integrase releases and perform integration of its viral DNA into the host cell's DNA [8–11]. Newly formed HIV proteins and viral RNA shifts towards the cell membrane and reunites with immature HIV. The new immature (non-infectious) virus then buds off from the host cells, which in turn initiates the release of the protease enzyme from the viruses that cause the breakdown of long-chain polypeptides of immature viruses. The newly formed small protein particles make the new mature viruses that enter into the new host cells for spreading the infection [12,13].

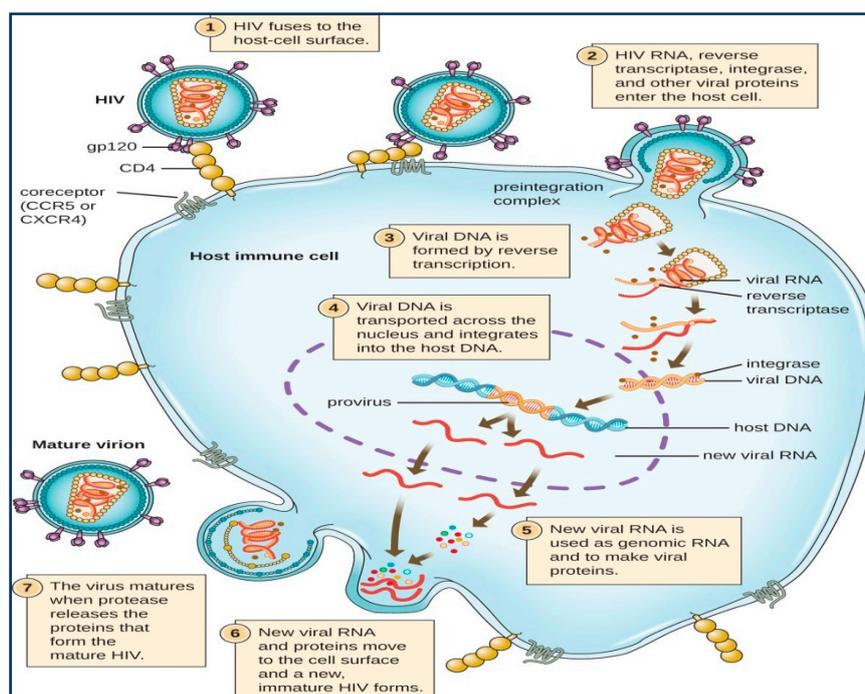


Figure 2. The HIV replication cycle [13]. Image was originally published within Open Access license.

1.3. Diagnosis

The level of HIV infection is diagnosed from the blood plasma of the host through their viral RNA mass estimation. The infection has been associated with the period of acute symptoms viz; lymphadenopathy, fever, weight loss, lethargy, general malaise, pharyngitis, rashes, nausea, headache, myalgias and meningitis, etc. [2,6]. During acute HIV infection, the viral RNA is at the highest levels in the blood plasma. It is estimated that the amount and characteristics of the virus indicate its pathogenesis and replication. Hence, the clinical details and infection progression depend on the host characteristics, along with the viral genotype [14–16]. ELISA and Western Blotting were the two main tests employed for the diagnosis of AIDS in the past. ELISA is used for the detection and measurement of the antibodies that are produced against a specific pathogen [17], while Western Blotting was employed for confirmation of ELISA positive tests. It is used to check the specific proteins in the blood sample. The samples go through the protein denaturation and then gel electrophoresis. The combined effect of both tests is found to be 99% accurate. Nowadays, various advantageous alternatives are available in place of Western Blotting. Among the advantages associated with such alternatives is less time-consuming testing [18].

1.4. Present Therapy for HIV/AIDS

The knowledge of HIV has been made public since the 1980s. However, there is currently no availability of efficacious therapy or vaccine for the entire destruction of the virus [2]. Current AIDS treatments have many drawbacks, e.g., complex and tedious treatment protocols, requiring expertise from medical practitioners, solid motivation and patient's commitment. Antiretroviral therapy (ART) is only about twenty years old, meaning that further approaches are still in progress. The usage of certain medications can slow the progress of the disease without the patient necessarily being promised total recovery. However, with the development of new entities and immune modulators, it is now feasible to fight this deadly disease [19–21]. The drugs provide a meaningful advancement in mitigation, control, cure, and prevention. With the establishment of highly active antiretroviral therapy (HAART) and anti-retroviral agents in 1996 decreased the mortality and morbidity of AIDS has been observed. Antiretroviral therapy is presently prescribed for all adult patients living with HIV [2]. Many types of

combination approaches such as the use of nucleoside reverse transcriptase inhibitors, fusion inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors, together with immunomodulators have been prescribed to achieve a proficient therapeutic response [3,6,9–11]. Due to the lack of non-accessible effective regimens, it has been noted that the objective of therapy is to sturdily and maximally prohibit viral replication so that the individual can achieve and maintain an adequate immune response against the potential viral pathogens. The higher the abolition of viral replication, the lower the incidence of development of the drug-resistant virus. The minimization in the mortality and morbidity of the disorder has turned it from a lethal syndrome to a chronic and controllable situation [5,19,21]. It is now advised that all HIV positive individuals with the perceptible virus, disregarding their count of CD4 cells, should be recommended with ART quickly after diagnosis, to avoid further progression [20].

1.5. Drawbacks of Current Anti-Retroviral Therapy

Even though it is impressive to deal with all the symptomatic and asymptomatic HIV infected persons, no long-lasting clinical outcomes have been illustrated in asymptomatic patients with acceptable immune competency [22]. Arguments in contrast to early remedies in asymptomatic patients involve the dangerous side effects of anti-HIV drugs, their toxicity and destructive effect of anti-HIV drugs on quality of life, the possibility of drug resistance restricting future treatment opportunities, big cost, drug interactions, the limited capability of available regimens, failure of treatment [23–25]. The right time to start anti-HIV therapy remains uncertain. The antiviral drugs that act on the HIV also affect the host cells; they may harm the host cell's nuclear material along with the HIV genome. With nucleoside reverse transcriptase inhibitors, toxicity is primarily due to the partial provision of cellular DNA polymerase. Neutropenia and Anaemia are extremely critical and dose-dependent adverse effects. Moreover, to date, there is no vaccine or cure for HIV infection, and the efficacy of antiretroviral therapy consist of a combination of two or three antiviral agents, targeting different steps of the virus replication cycle, can be compromised by the selection of strains resistant to one or multiple drug classes and current treatment-associated toxicity. However, these drugs have only limited or transient clinical benefit due to their noxious side effects and the emergence of viral variants resistant to HIV-1 inhibitors. Unfortunately, their use is limited due to the speedy emergence of resistant viral strains and to the severe toxic side effects. Hence, new natural products can be considered as novel leads for the development of new effective and selective anti-AIDS agents [24–26].

2. Plants with Anti-HIV Potential

Presently, strategies available to combat AIDS are restricted by the evolution of multidrug resistance. That is why novel targets and new efficacious drugs are required for achieving the goal of an entire eradication of AIDS. Also, infected cells persist and constitute a basic barrier to the elimination of HIV-1. For the past 10 years, the mechanism by which the virus persists has necessitated a novel pathway in the discovery of new drug compounds that work efficaciously against HIV without activating the T cells of the immune system [27,28]. To attain this goal, it has been recommended by the WHO that ethnomedicines and various other natural constituents should be systematically tested to combat HIV [29,30]. Interestingly, in the 1990s, natural products with their mechanisms against HIV-1 enzymes like reverse transcriptase, integrase, protease and some fusion inhibitors were discovered. The natural drugs have chemical diversity with higher hit rates in high throughput screening and high capability to reach the target site [31–33]. Several alkaloids, flavonoids, coumarins, terpenoids, and polyphenolic compounds, as well as known therapeutic agents having an array of biological activities like anticancer, analgesics, anti-inflammatory and exert anti-HIV activity extracted from various plants, were found [34–44]. These became the sources of inspiration for many research activities, e.g., the anti-HIV potential of components of *Dioscorea bulbifera* [45], *Euphorbia sikkimensis* [46], *Culendula officinalis* [47], *Sceletium tortuosum* [48], *Brazilian propolis*, *Kadsura lancilimba*, *Lithocarpus litseifolius*, and *Ocimum labiatum* [49–52].

Taken together, the present review highlights the discovery of plant-based molecules during the last few decades that have been used in the management of HIV. A detailed account of plants according to their mechanism of action and activity of secondary metabolites has been discussed. In addition to the structures of most potent phytochemicals, mechanistic insights revealed during the biological evaluation, IC_{50} values and important key findings have also been presented. The detailed mechanisms of this action and structure-activity-relationships of some of the compound classes remain to be further investigated. This assemblage will be of great help for the scientific community working towards the development of anti-HIV drugs. In this review, the natural medicinal plants are described in two categories:

1. Plants according to their mechanism of action.
2. Plants according to the activity of secondary metabolites.

2.1. Natural Plants According to Their Mechanism of Action

Therapeutic agents of natural origin may be an encouraging alternative solution for the treatment of several disorders and conditions [53–59]. In anti-HIV research, attention is chiefly paid to compounds which interfere with several steps involved in the HIV replication process. For example, almost all the anti-HIV drugs act against the viral proteins represented by the viral protease, integrase, and reverse transcriptase [60]. Anti-HIV drugs can be classified into several groups according to their action on the life cycle of HIV [61]. Hence, different drugs act on these different steps of replication and inhibit the further expansion of the virus into the body. A group of researchers reported the activities of HIV-PR inhibitors from different plants primarily divided into the following categories [62–71]:

- (a) Fusion inhibitors (FI)
- (b) Reverse transcriptase inhibitors (RTI)
- (c) Integrase inhibitors (ITI)
- (d) Protease inhibitors (PRI)
- (e) Immunomodulators
- (f) Antioxidants

2.1.1. Fusion Inhibitors

Fusion inhibitors are also known as Entry inhibitors. These are mainly CCR5 co-receptor antagonists which inhibit the binding of HIV surface glycoproteins with the host cell's receptor [72]. Infection primarily starts with the binding of the viral gp120 to the CD4 cell receptor expressed on the surface of T cells, macrophages, and some monocytes. This results in the conformational change which further stimulates the interaction of secondary gp120 with co-receptor CCR5 [73]. FIs prevent the entry of the virus into the host cell by inhibiting the fusion of virus particles with the membrane of the host cell, which is the early first step of virus replication [74].

Phytoconstituents from some plants, like *Listeria ovate*, *Cymbidium hybrid*, *Hippeastrum hybrid*, *Epipactis helleborine* and *Urtica dioica* possessing the activities of fusion inhibitors and act against the HIV-1 and HIV-2 [75,76]. Matsuda et al. reported an alkaloid Cepharanthine (**1**) isolated from *Stephania cepharantha* having anti-HIV and anti-tumour potential without exerting any type of serious toxic effects. This compound modifies the plasma membrane fluidity and prevents viral cell fusion [77]. A diterpene lactone named Andrographolide (**2**) shown in Figure 3 was obtained from the herb *Andrographis paniculata* and possesses HIV-1 fusion inhibition properties evaluated in vitro using AZT (Zidovudine) as a positive control [78–82]. Several other derivatives have been derived synthetically to exert more potent anti-HIV properties [83,84].

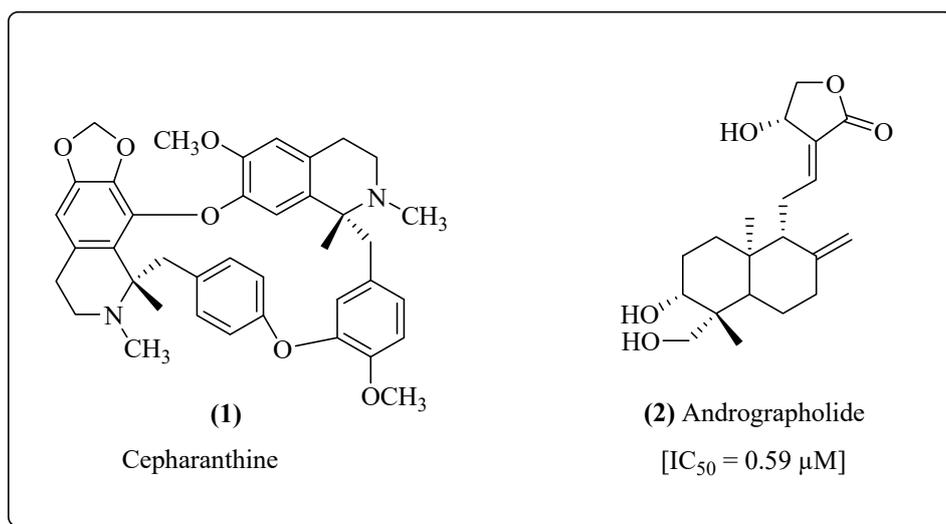


Figure 3. Structures of fusion inhibitors.

2.1.2. Plant Extracts as Reverse Transcriptase Inhibitors

The HIV virus utilizes the reverse transcriptase enzyme for the conversion of its viral RNA into DNA. RT inhibitors mainly act upon this enzyme and prohibit one of the essential steps of viral replication [85,86]. Several natural products have been isolated from plants are available in the literature, which have been screened for their activity against RT [66]. The plants which tested positively for reverse transcriptase inhibition include; *Culendula officinalis*, *Acacia mellifera*, *Uvaria angolensis*, *Hypericum scruglii*, *Spaganium stoloniferum*, *Calophyllum brasiliense*, *Maytenus buchanani*, *Prunus Africana*, *Vernonia jugalis*, *Maytenus senegalensis*, *Melia azedarach*, *Calophyllum inophyllum*, *Lomatium suksdorfii*, *Coriandrum sativum*, *Chrysanthemum morifolium* and *Swertia franchetiana* [47,66–93]. Capryl aldehyde and methyl-*n*-nonyl ketone obtained from *Houttuyniu cordata* directly inhibit the RT enzyme [66]. Calanolides A (3) and B (4) [89] have been obtained from the plant *Calophyllum inophyllum*. The introduction of bulky groups has been shown to be essential at the C-4 position to enhance anti-HIV activity. The stereochemistry of the C-12 hydroxyl (*R* or *S* configured) is not, however, as critical for activity. Methyl groups at the C-10 and C-11 positions were also shown to be required for activity. Hydrogen bond acceptors at C-12 were also shown to be responsible for the activity, both in calanolides and inophyllums. In vitro assay results revealed that (+)-Calanolide-A inhibits RT in two diverse template primer systems. The action of (+)-Calanolide-A is possible due to the bi-bi prearranged mechanism of RT. Calanolide is at least partially competitive about dNTP binding. Structure-activity-relationships and important key findings of Calanolides are shown in Figure 4.

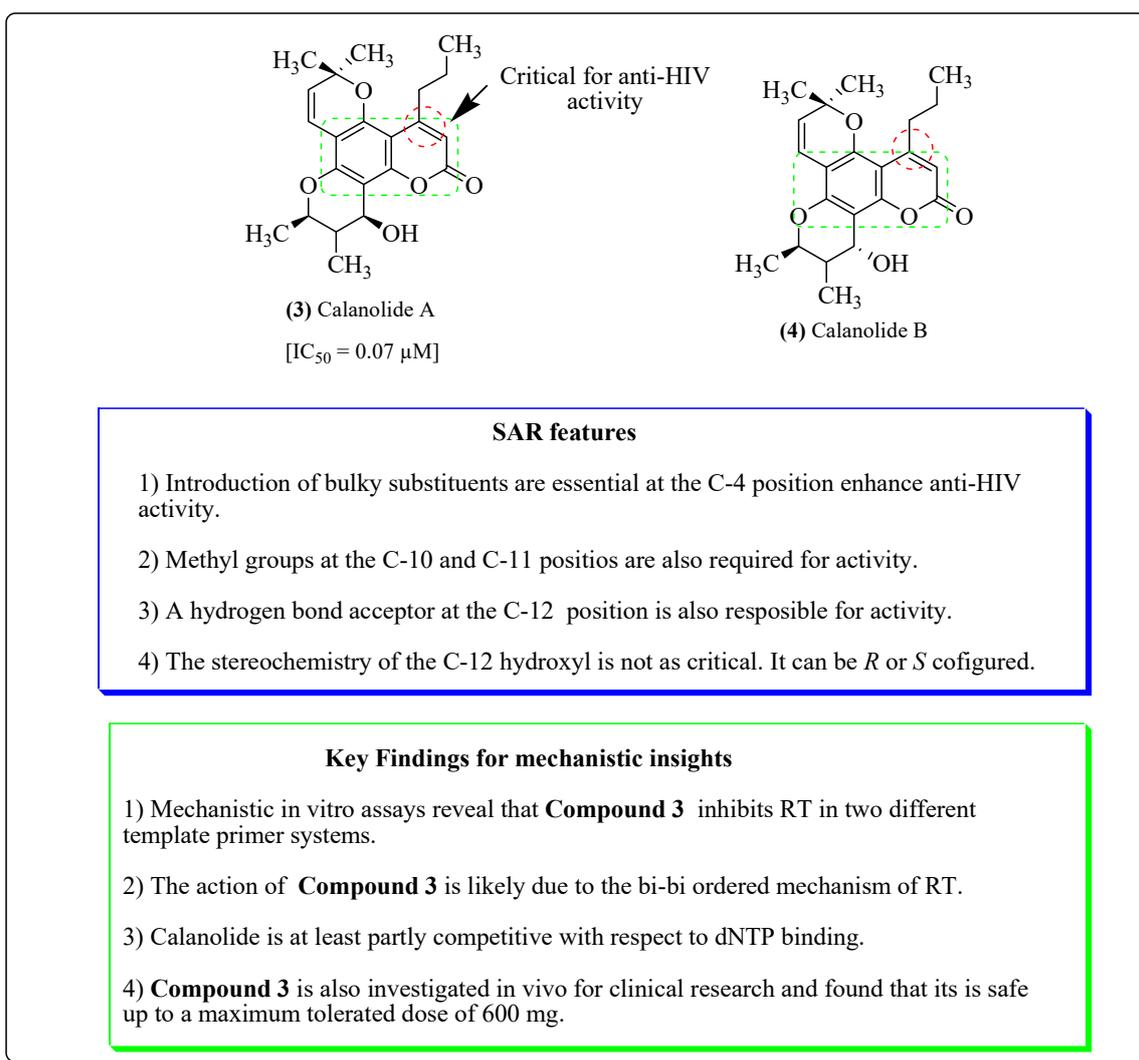


Figure 4. Structure-activity-relationships and important key findings of some potent reverse transcriptase (RT) inhibitors.

Some naphthoquinones, e.g., Michellamines A, B and C, isolated from the plant *Ancistrocladus korupensis*, exhibited inhibitory activity against the HIV-RT enzyme [94]. The compound Acetogenin protolichensterinic acid is a RT inhibitory agent, obtained from *Cetraria islandica* [95]. The compounds Mallotochromene (5) and Mallotojaponin (6) (Figure 5) from *Mallotus japonicas* have shown strong inhibition against HIV-RT [96]. Nigranoic acid, from *Schisandra lancifolia*, acted effectively on the RT of HIV [97]. A few more examples of plants showing HIV-RT inhibitory properties are given in Table 1.

Table 1. Plant-based reverse transcriptase inhibitors.

Compound Class	Plant Species	Chemical Constituents	Reference
Terpenoid	<i>Excoecaria agallocha</i>	Phorbol	[98]
Terpenoid	<i>Tripterygium wilfordii</i>	Salaspermic acid	[99]
Terpenoid	<i>Euphorbia myrsinites</i>	15-O-acetyl-3-O-butanoyl-5-O-propionyl-7-O-nicotinoylmyrsinol	[100]
Terpenoid	<i>Polyalthia suberosa</i>	Suberosol	[101]
Terpenoid	<i>Andrographis paniculata</i>	Dehydroandrographolide succinic acid monoester	[102]
Terpenoid	<i>Glycyrrhiza radix</i>	Glycyrrhizin	[103]
Terpenoid	<i>Cowania Mexicana</i>	Cucurbitacin F	[104]
Terpenoid	<i>Tripterygium wilfordii</i>	Tripterifordin	[105]
Terpenoid	<i>Maprounea Africana</i>	1 β -hydroxymaprounic acid 3- <i>p</i> -hydroxybenzoate	[106]
Terpenoid	<i>Szigium claviform</i>	Betulinic acid, platonin acid	[107]
Terpenoid	<i>Houttuynia cordata</i>	Lauryl aldehyde, capryl aldehyde	[108]
Flavonoid	<i>Chrysanthemum morifolium</i>	Acacetin-7-O- β -galactopyranoside	[92]
Flavonoid	<i>Scutellaria baicalensis</i>	Baicalin	[109]
Flavonoid	<i>Buchenavia capitata</i>	Buchenavianine	[110]
Flavonoid	<i>Kummerovia striata</i>	Apigenin-7-O- β -D-glucopyranoside	[111]
Coumarin	<i>Calophyllum inophyllum</i>	Inophyllums	[112]
Coumarin	<i>Coriandrum sativum</i>	Coriandrin	[91]
Coumarin	<i>Lomatium suksdorfii</i>	Suksdorfirin	[90]
Coumarin	<i>Aegle marmelous</i>	Imperatorin, xanthotoxol, xanthotoxin	[113,114]
Tannin	<i>Euphorbia jolkini</i>	Putranjivain A	[115]
Tannin	<i>Cornus officinalis</i>	Cornusin A	[116]
Tannin	<i>Mallotus repandus</i>	Repandusinic acid	[117]
Tannin	<i>Hyssop officinalis</i>	Caffeic acid	[118]
Polysaccharide	<i>Thuja occidentalis</i>	Thujone	[119]
Polysaccharide	<i>Prunella vulgar</i>	Sulfated polysaccharide	[120]
Polysaccharide	<i>Viola yedoensis</i>	Sulfonated polysaccharide	[121]
Xanthone	<i>Tripterospermum lenceolaum</i>	1,3,5,6-tetrahydroxyxanthone, 3,4,5,6-tetrahydroxyxanthone	[122]
Lignan	<i>Haplophyllum ptilostylum</i>	Ptilostin	[123]
Lignan	<i>Schisandra chinensis</i>	Gomisin J	[124]
Lignan	<i>Ipomoea cairica</i>	Arctigenin, trachelogenin	[125]
Marine origin	<i>Hyatella intestinalis</i>	Hyatellaquinone	[126]
Marine origin	<i>Fascaplysinopsis reticulata</i>	Fascaplysin, isodehydroloffariellolide, Homofascaplysin C	[127]
-	<i>Toxiclona toxius</i>	Toxiusol	[128]
-	<i>Plakortis</i> sp.	Plakinidine A	[129]
-	<i>Kelletia kelletii</i>	Kelletinin 1	[130]
-	<i>Buccinulum corneum</i>	Kelletinin A	[131]
-	<i>Maprounea Africana</i>	1 β -hydroxyaleuritic acid 3- <i>p</i> -hydroxybenzoate	[132]

The compounds obtained from different plants, showing anti-HIV RT activity show the presence of certain pharmacophores which are essential for the therapeutic activity. These pharmacophores include; coumarin, chromone, indole moiety and steroidal nucleus in the compounds, e.g., suksdorfirin (7) [90], salaspermic acid (8) [99], cucurbitacin F (9) [104], batulinic acid (10) [107], baicalin (11) [109], buchenavianine (12) [110], thujone (13) [117], hyatellaquinone (14) [126], isodehydroloffariellolide (15) [127], homofascaplysin-C (16) [127], toxiusol (17) [128] represented in Figure 5.

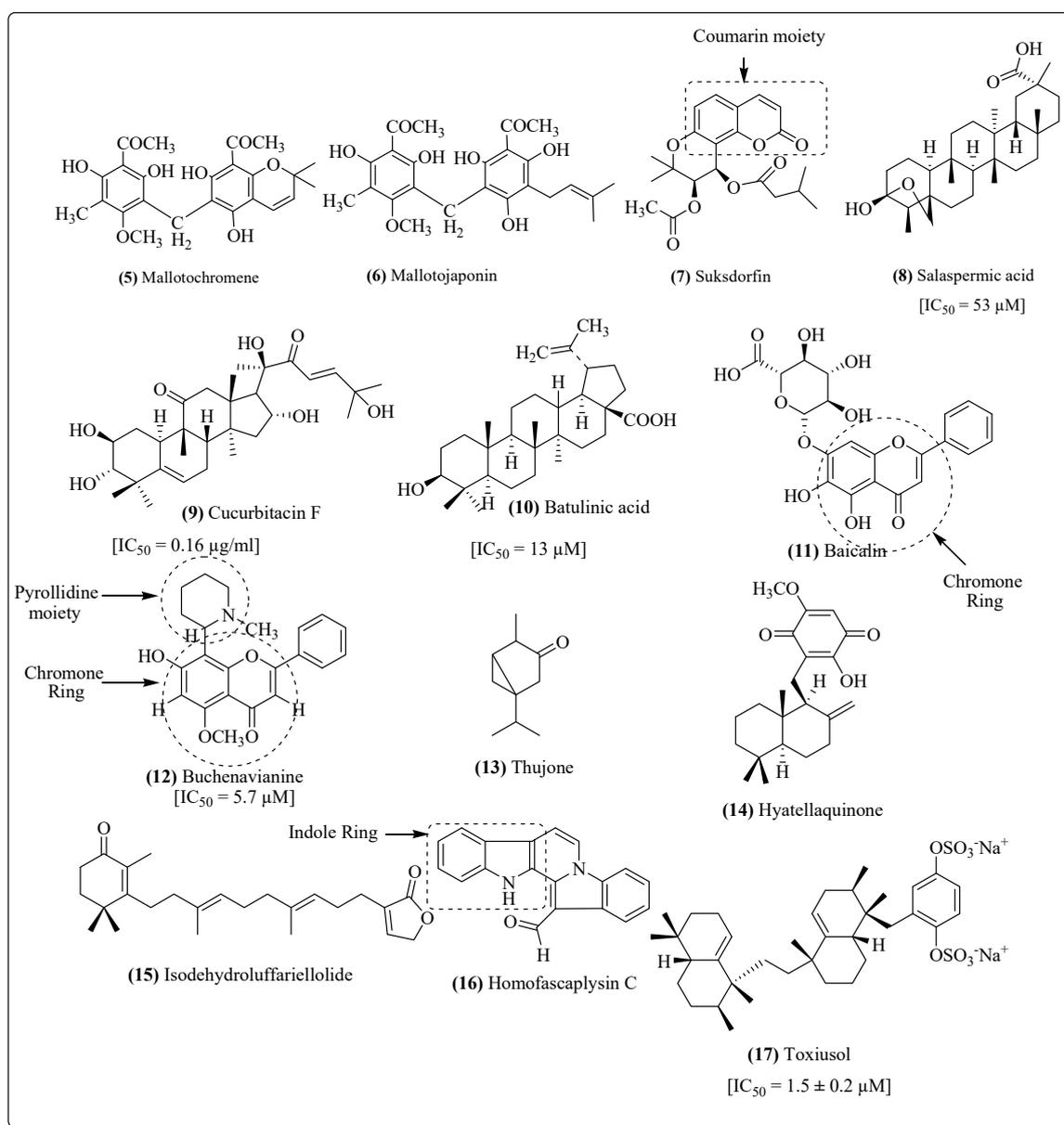


Figure 5. Structure of some potent reverse transcriptase inhibitors.

2.1.3. Plants Exhibiting Integrase Inhibition

The insertion of HIV DNA into the DNA of the host cell is generally catalyzed by the integrase enzyme of HIV. The reaction proceeds in two phases; the first phase is the processing phase and the second phase includes strand transfer [133]. Various active components have been separated from the plant *Dioscorea bulbifera* and exhibited several therapeutic properties such as: anticancer, antibacterial, analgesic, and antidiabetic [134–138]. Chaniad et al. isolated seven different compounds from *D. bulbifera* which showed anti-HIV properties [45]. These include; allantoin (18), 5,7,4'-trihydroxy-2-styrylchromone, 2,4,3',5'-tetrahydroxybibenzyl, quercetin-3-O- β -D-galacto-pyranoside, 2,4,6,7-tetrahydroxy-9,10-dihydrophenanthrene, quercetin-3-O- β -D-glucopyranoside (19), and myricetin (20) (Figure 6). The results indicate that compound 20 had the best binding affinity within the active site of the integrase enzyme, forming strong interactions with amino acids. Moreover, significant activity is due to the presence of the galloyl, catechol, and sugar moieties which are responsible for the potential actions. In another study, Panthong et al. revealed that *Albizia procera* is a medicinal plant that has been used in antiretroviral therapy [139,140].

Catechin (**21**), suramin and protocatechuic acid (**22**) were shown to be the components identified from the plant extract and were considered to act on the integrase enzyme of HIV, thus prohibiting viral replication [139]. Compound **21** interacted with Thr66, Gly148, and Glu152 in the core domain of the enzyme, whereas compound **22** interacted with Thr66, His67, Glu152, Asn155, and Lys159. Some ribosome-inactivating proteins are considered to act on the integrase enzyme [141]. It was observed that compound **20**, having a galloyl moiety, possessed the most potent activity due to its strong binding with amino acids of the integrase enzyme. In compound **19**, the catechol group was partly responsible for the activity. Since compound **19** contains sugar moiety as well, which increases the solubility of the molecule, this enhances its activity. A ribosome-inactivating protein (RIP) named MAP30, which has been extracted from *Momordica charantia*, has been reported to act against HIV and cancer [142,143]. Zhao et al. discovered another RIP trichosanthin, from the roots of *Trichosanthes kirilowii*, which showed inhibitory activity against the integrase enzyme [144]. A variety of plant RIPs including agrostin, saporin, *R*-momorcharin, gelonin, α -momorcharin, trichosanthin and luffin have also exhibited an inhibitory effect on HIV replication [145].

2.1.4. Plants Containing Protease Inhibitors

Protease is a viral enzyme that acts at the last step of replication of the virus. It causes the breakdown of long polypeptides and proteins into the small functional proteins that are generally infectious [146–149]. Hence, protease is another target for the antiretroviral therapy and by inhibiting this enzyme the viral replication can be prohibited. Mostly, drugs act on this enzyme preferentially [147,149,150]. From the *Camellia japonica* pericarp, the plant components camelliatannins A, F and H have been reported that exhibited potent anti-HIV PR inhibitory properties [148]. Several Korean therapeutic plants, e.g., *Viburnum furcatum*, *Ilex cornuta*, *Berberis amurensis*, *Lonicera japonica*, *Chloranthus glaber*, *Geranium nepalense*, *Lindera sericea*, *Wistaria floribunda*, *Smilax china*, *Hibiscus hamabo*, *Lingustrum lucidum*, *Zanthoxylum piperitum*, *Styrax obassia*, *Viola mandshurica*, *Schisandra nigra*, and *Cocculus trilobus* have also been reported potent activities against protease [71]. From the plant stems of *Stauntonia obovatifoliola*, various components that act against HIV protease have been identified, e.g., lupenone (**23**) [151], 3-*O*-acetyloleanolic acid (**24**) [152], resinone (**25**) [153], lupeol (**26**) [154] and mesembryanthemoidgenic acid (**27**) (Figure 7) [155]. Moreover, the therapeutic compounds like oleanolic acid (**28**), dihydromyricetin, epigallocatechin gallate, myricetin [156,157] and epiafzelechin [158] have been extracted from the wood of *Xanthoceras sorbifolia* and have the potential for the treatment of AIDS [68,156].

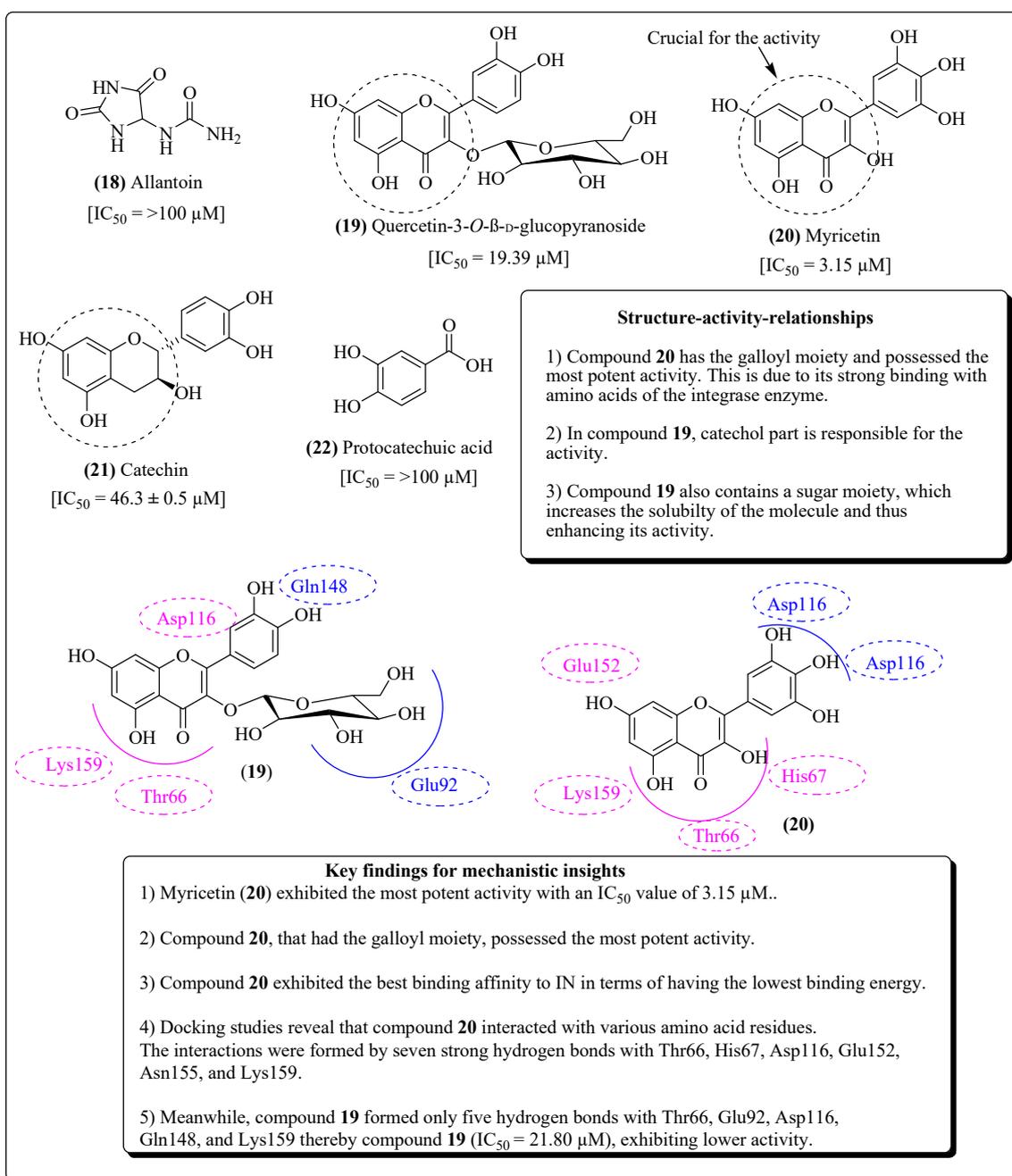


Figure 6. Structure-activity-relationships of naturally occurring integrase inhibitors.

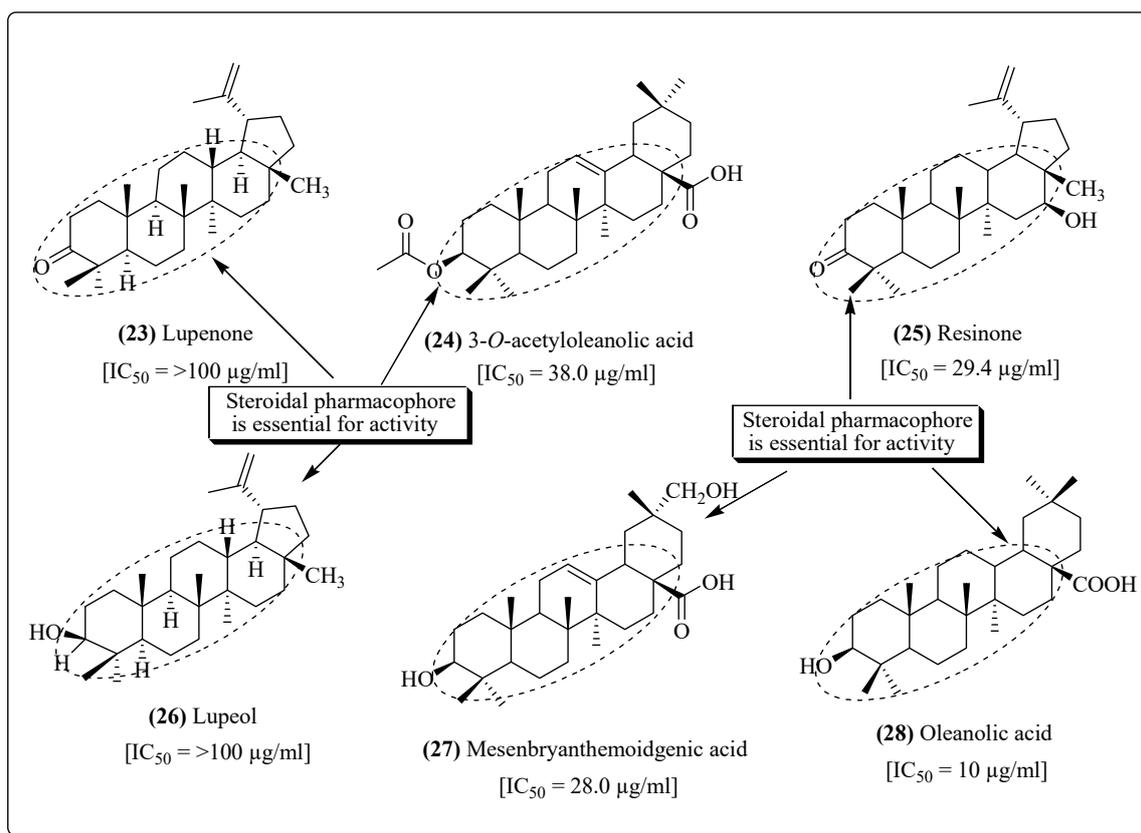


Figure 7. Compounds exhibiting protease inhibitory activity.

2.1.5. Plants Containing Immunomodulators

Immunomodulators are the agents that stimulate the cellular and humoral immune system against any pathogenic infection [159–161]. The dendritic cells of the immune system act as antigen presenting cells and move along with antigens into the lymph nodes from the tissues. They represent the antigen to the T cells and the T cells then initiate an immune response. T cells stimulate the B cells for the production of antibodies that bind with the antigen and the T cells activate killer T cells which attack the pathogens [162]. There are several classes of naturally occurring compounds that exhibit immunomodulatory properties, e.g., alkaloids, tannins, terpenoids, coumarins, glycosides, flavonoids, polysaccharides, lignans, etc [163,164]. Among alkaloids, berberine (29) from *Hydrasti Canadensis* [159,165], sinomenine (30) from *Sinomenium acutum* [159,166], piperine (31) from *Piper longum* [159,167], and tetrandrine from *Stephania tetrandra* [168] have shown immunomodulatory properties in HIV. Among glycosides, aucubin from *Plantago major* [169], isorhamnetin-3-O-glucoside from *Urtica dioica* [170], and mangiferin from *Mangifera indica* [171] have exhibited immune-stimulatory properties in HIV. Among phenols, ellagic acid (32) from *Punica granatum* [172], curcumin from *Curcuma longa* [173], ferulic acid (33), vanilic acid (34) (Figure 8) [159] were shown to be immunostimulators in HIV. Chlorogenic acid from *Plantago major* [169], also expressed effective immunomodulatory potential in AIDS [159]. Within tannins, chebulagic acid and corilagin from *Terminalia chebula* [174] and punicalagin [175] acted as immunomodulatory agents. Among flavonoids, centaurein from *Bidens pilosa* [176] and apigenin 7-O-β-D-neohesperidoside, orientin, vitexin and apigenin 7-O-β-D-galactoside from *Jatropha curcas* [177] have exhibited the effective immunomodulatory action against HIV. From saponins, asiaticoside obtained from *Centella asiatica* [178] and glycyrrhizin from the roots of *Glycyrrhiza glabra* [179] have shown significant immunomodulatory activities.

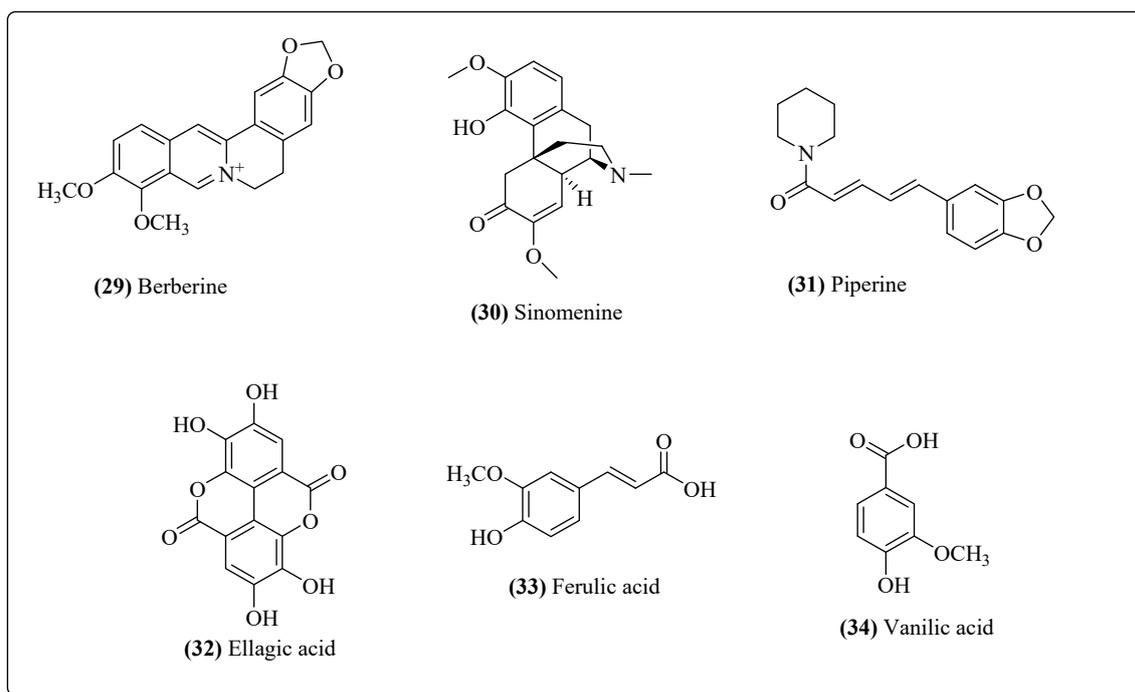


Figure 8. Plant-based Immunomodulators.

2.1.6. Plants with Antioxidant Potential

In AIDS, many reactive oxygen species (ROS) have been produced due to the alteration in the levels of antioxidant enzymes [180]. This further leads to the damage of DNA and lipid peroxidation [181]. ROS can also stimulate the nuclear factor kappa B (NF- κ B factor) which helps in the transcription of HIV and thus promote its replication [182]. Antioxidants are agents that reduce the levels of ROS and protect cellular DNA. *N*-Acetylcysteine is reported to act as an antioxidant and is often used in the management of HIV infection [183]. Various other antioxidants like selenium, lipoic acid, vitamin C, β -carotene and vitamin E have been utilized for the same purpose [184,185]. The antioxidants Cyanidin-3-glucoside (35) and peonidin (36), which are obtained from blackberries, have also been shown to slow down AIDS infection (Figure 9) [159,186].

2.2. Classification of Plants According to Their Secondary Metabolites

Secondary metabolites are the main active compounds in plants that are mainly responsible for therapeutic effects. They are generally obtained from the primary metabolites such as carbohydrates, proteins, amino acids, etc. [187–190]. Plant-based secondary metabolites mainly include alkaloids, glycosides, coumarins, terpenoids, lignans, tannins and flavonoids, etc. [191–193].

2.2.1. Alkaloids

Alkaloids are the basic nitrogen-containing secondary metabolites in plants, active against many pathogens, including HIV. Buchapine is a quinolone alkaloid obtained from *Eodia roxburghiana*, which has shown activity against HIV [194]. From the roots of *Tripterygium hypoglaucum*, various alkaloidal compounds have been isolated, e.g., hypoglaumine B, triptonine A (37) and B [159], which exhibited anti-HIV potential and have potential for antiretroviral therapy [195]. Nitidine is another alkaloid that was isolated from plant roots of *Toddalia asiatica*, and has shown efficacy against HIV [196]. From the plant *Symplocos setchuensis*, the alkaloid harman (38) and another compound matairesinoside (39) were isolated and showed potential for antiretroviral therapy due to their anti-HIV potential. Compound 39 acts on the viral replication enzymes, thus inhibiting HIV replication [197]. Another aromatic alkaloid polycitron A, from marine source *Polycitor* sp., exhibited potential activity

against the reverse transcriptase of HIV. Hence, it efficiently inhibits HIV replication. Several other marine sponges have acted against the virus as well as other bacterial diseases [198]. The alkaloid 1-methoxy canthionone was reported from *Leitneria floridana*, and exhibited anti-HIV property [199]. Papaverine was obtained from *Papaver somniferum*, and inhibited HIV replication [39]. Norisoboldine and corydine are two alkaloids obtained from the leaves of *Croton echinocarpus*, showing anti-HIV activity [200]. Table 2 summarizes plant-based alkaloids possessing anti-HIV activity.

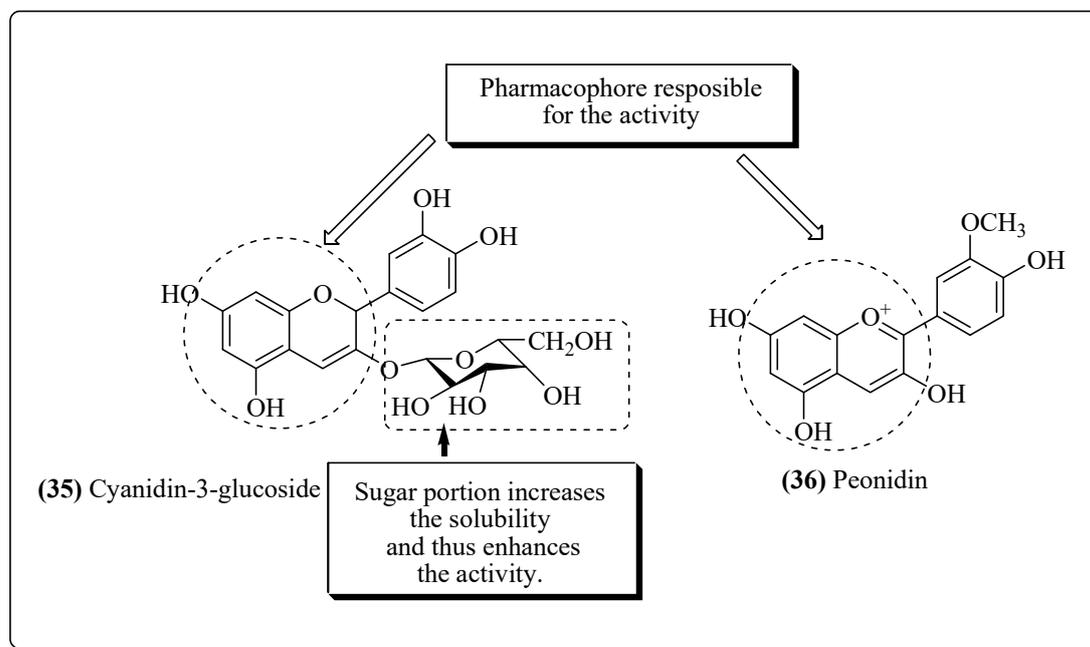


Figure 9. Plant-based antioxidants compounds possessing anti-HIV potential.

Table 2. Alkaloidal compounds as anti-HIV agents.

Plant Species	Parts Used	Chemical Constituents	References
<i>Ancistrocladus korupensis</i>	Leaves	Michellamine A, B and C	[201]
<i>Stephania cepharantha</i>	Roots	Cepharantine	[202]
<i>Murraya siamensis</i>	Roots, leaves	Siamenol	[203]
<i>Clausena excavate</i>	Leaves	O-Methylmukonal, clauszoline and 3-formyl-2,7-dimethoxy-carbazole	[204]
<i>Drymaria diandra</i>	Leaves	Canthin-4-one drymaritin	[205]
<i>Glycosmis montana</i>	Twigs, leaves	(E)-3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl)-1H-indole	[206]
<i>Aniba</i> sp.	Stems	Anibamine	[207]
<i>Zanthoxylum ailanthoides</i>	Root bark	Decarine, γ -fagarine and tembamide	[208]
<i>Nelumbo nucifera</i>	Leaves	Coclaurine, norcoclaurine, reticuline	[209]
<i>Pericampylus glaucus</i>	Leaves	Norruffscine, 8-oxotetrahydro-palmatine	[210]
<i>Begonia nantoensis</i>	Rhizomes	Indole-3-carboxylic acid	[211]
<i>Leucojum vernum</i>	Bulbs	Lycorine, homolycorine	[212]
<i>Epinetrum villosum</i>	Root bark	Cycleanine	[213]
<i>Argemone mexicana</i>	Roots	6-acetyldihydrochelerythrine, nuciferine	[214]
<i>Monanchora</i> sp.	Stems	Crambescidin 826, fromiamycalin and crambescidin 800	[215]
		Manadomanzamines A and B	[216]
<i>Acanthostrongylophora</i> sp.	-	Hernandonine, lindechunine, 7-oxohernangerine and laurolistine	[217]
	Roots		
<i>Lindera chunii</i>			
<i>Artemisia caruifolia</i>	Stems		[218]

Several alkaloidal compounds, e.g., michellamine A (40) [201], siamenol (41) [203], decarine (42) [208], reticuline (43), norcoclaurine (44) [209], indole-3-carboxylic acid (45) [211], lycorine (46) [212], homolycorine (47) [212], cycleanine (48), 6-acetyldihydrochelerythrine (49) [214] and hernandonine (50) [217] have revealed significant HIV inhibitory potential (Figures 10 and 11).

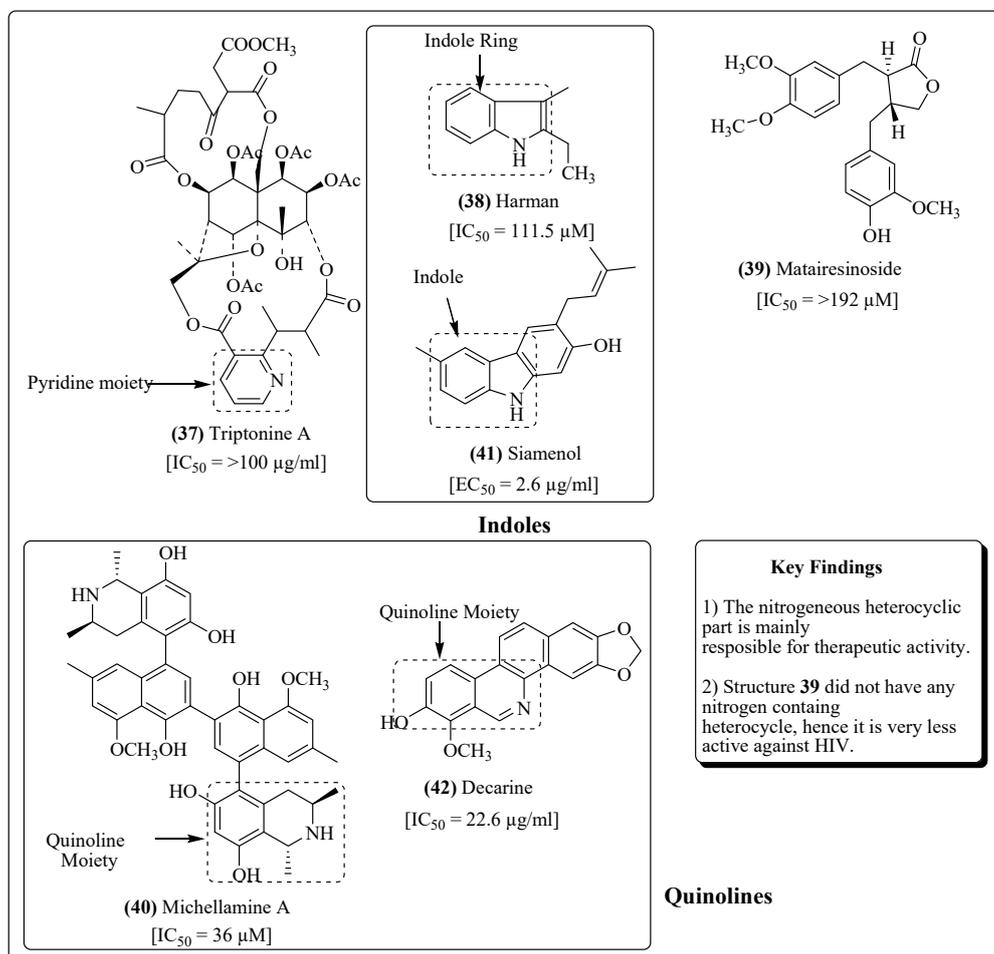


Figure 10. Alkaloidal compounds possessing anti-HIV activity.

2.2.2. Terpenoids

Terpenoids are the secondary metabolites that are derived from the isoprene unit (C₅H₈). Terpenoids are the most abundant plant-based secondary metabolites and several compounds from this class have been derived from plants and found useful for their therapeutic potential [210,219,220]. Examples of terpenoids that have exhibited inhibition of HIV replication include betulinic acid, oleanolic acid, and platanic acid from *Syzygium claviflorum* leaves [221]. Celasdin B (51), is a triterpene from *Celastrus hindsii* (Celastraceae), reported inhibiting the HIV replication [222]. Prostratin from *Homalanthus nutans* (Euphorbiaceae) has also expressed significant anti-HIV activities [223]. From the stem bark of *Garcinia speciosa*, some anti-HIV therapeutic constituents have been isolated viz; garcisaterpenes A and C and theprotostanes. These compounds have been found to inhibit the activity of HIV reverse transcriptase and thus stop the HIV life cycle [224]. Maslinic acid (52), a terpenoid compound obtained from *Geum japonicum* also acts against the HIV protease enzyme [225]. From the stems and roots of plant *Kadsura lancilimba*, another triterpene lancilactone C (53) has been isolated which is used to restrict the viral replication [226]. Oleanolic acid is the main terpenoid isolated from many plant species including *Xanthoceras sorbifolia* (Sapindaceae). The compound is known to inhibit HIV replication and play an important role in the treatment of AIDS [227]. Suberosol (54) is a lanostane type triterpenoid

from the leaves of *Polyalthia suberosa* (Annonaceae) known to act through the same mechanism [228]. Another phorbol diester from *Croton tiglium* (Euphorbiaceae), 12-*O*-tetradecanoylphorbol-13-acetate, exhibited anti-HIV activity [223]. A Brazilian alga isolated from *Dictyota pfaflii*, from which an active diterpene component 8,10,18-trihydroxy-2,6-dolabelladiene has been isolated and has shown inhibitory activity of HIV reverse transcriptase [229,230]. A butenolide triterpene known as 3-*epi*-litsenolide has been articulated significant anti-HIV activity and was extracted from *Litsea verticilla* [231]. The alga *Dictyota menstrualis* is an important source for various diterpenes that exhibit HIV reverse transcriptase inhibition potential [232]. From the roots and rhizomes of plant *Clausena excavate*, a limonoid terpene named clausenolide-1-ethyl ether has shown potential for antiretroviral therapy [233]. Glycyrrhizin from the *Glycyrrhiza glabra* roots is another saponin terpenoid that showed anti-HIV activity by inhibiting the viral life cycle [234]. Oleanolic acid is a potent anti-HIV compound and is widely distributed in various plants including the leaves of *Rosa woodsii*, the leaves of *Syzygium claviflorum*, the aerial parts of *Ternstroemia gymnanthera*, and the whole plants *Hyptis capitata* and *Phoradendron juniperinum* [227]. 12-Deoxyphorbol-13-phenylacetate, a phorbol ester from *Euphorbia poissonii*, has been reported for possessing anti-tumour activity and recently, it has potential for antiretroviral therapy because of its anti-HIV activity [235]. Pedilstatin [13-*O*-acetyl-12-*O*-(2'-*Z*-4'-Eoctadienoyl)-4- α -deoxyphorbol] is another phorbol ester from *Pedilanthus* sp., possessing anticancer and anti-HIV properties [236]. Some other plant species containing terpenoid based compounds with efficient anti-HIV activity have been summarized in Table 3.

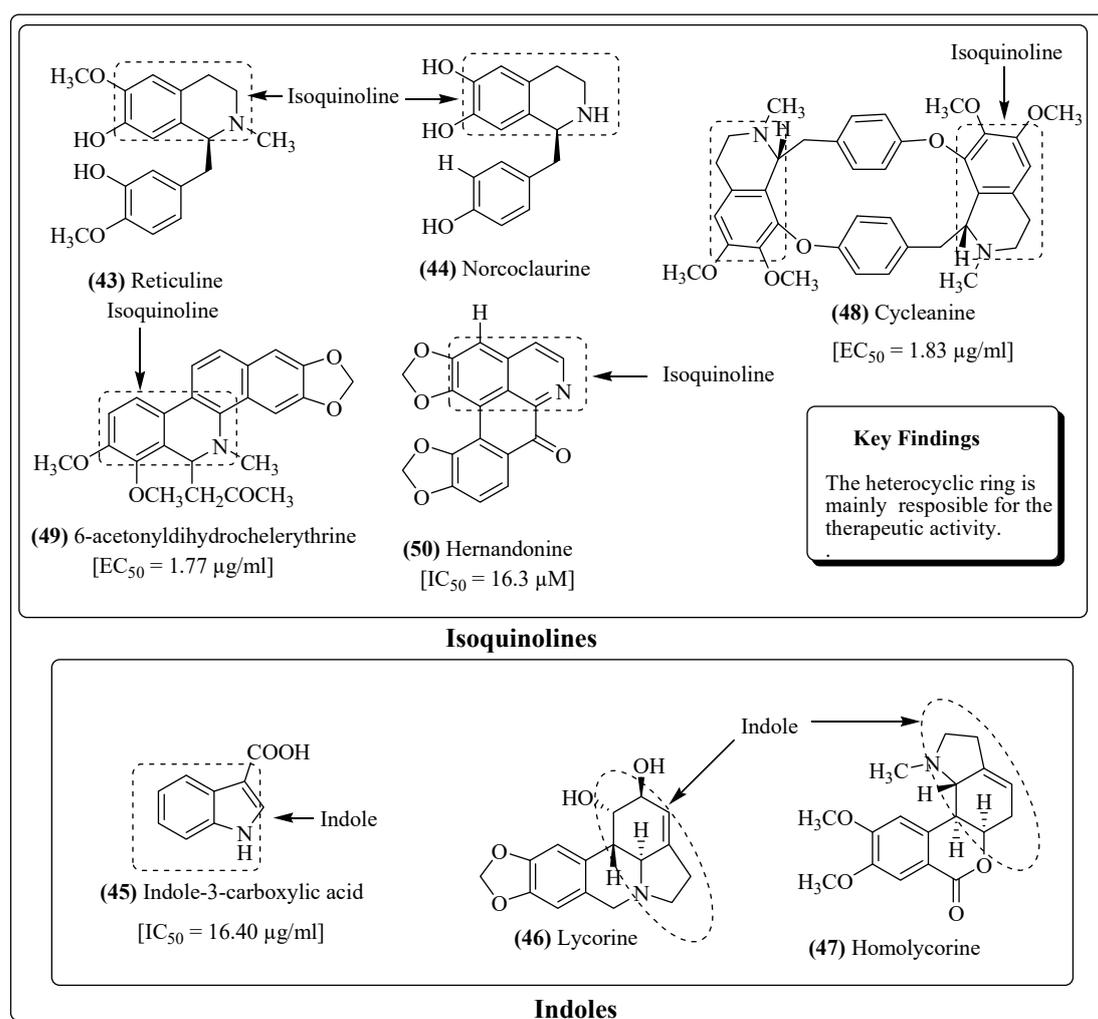


Figure 11. More alkaloidal compounds possessing anti-HIV activity.

Table 3. Terpenoids act as Anti-HIV agents.

Plant Species	Parts Used	Chemical Constituents	References
<i>Excoecaria acerifolia</i>	Roots	Agallochin J, ribenone, angustanoic acid B	[237–239]
<i>Propolis</i>	Roots	Melliferone, moronic acid, betulonic acid	[49,240]
<i>Homalanthus nutans</i>	Leaves	Prostratin	[241,242]
<i>Cassine xylocarpa</i>	Stem	Germanicol, nivadiol	[243]
<i>Glycyrrhiza uralensis</i>	Roots	Galacturonic acid, xylose, uralsaponin C	[244]
<i>Daphne gnidium</i>	Aerial parts	Daphnetoxin, gniditrin, gnidicin	[245]
<i>Euphorbia micractina</i>	Roots	Lanthyrane diterpenoids	[246]
<i>Kaempferia javanica</i>	Rhizomes	Kaempulchraol A, C, E	[247]
<i>Picrasama javanica</i>	Bark	Picrajavanicin A, javanicin B, picrasin A	[248]
<i>Schisandra lancifolia</i>	Leaves, stem	Lancifodilactone F	[249]
<i>Stellera chamaejasme</i>	Roots	Stelleralide D, gnidimacrin	[250]
<i>Lindera strychnifolia</i>	Roots	Lindenanolides E, G and F	[251]
<i>Daphne acutiloba</i>	Roots	Wikstroelide M	[252]
<i>Annona squamosa</i>	Leaves	16- β ,17-dihydroxy-entkauran-19-oic acid	[253]
<i>Cimicifuga racemosa</i>	Rhizomes	Actein	[254]
<i>Schisandra sphaerandra</i>	Leaves	Nigranoic acid	[255]
<i>Allanthus altissima</i>	Roots	Shinjulactone B	[256]
<i>Panax ginseng</i>	Roots	Isodehydroprotopanaxatriol	[257]
<i>Garcinia hanburyi</i>	Stem, roots	3-acetoxyaliphitolic acid, 2-acetoxyaliphitolic acid 8-methoxyingol-7,12-diacetate-3-phenylacetate	[258]
<i>Euphorbia officinarum</i>	Leaves	Dihydrocucurbitacin F Forskolin, 1-deoxyforskolin	[259]
<i>Hemsleya jinfushanensis</i>	Tubers	28-hydroxy-3-oxo-lup-20(29)-en-3-O-al	[260]
<i>Coleus forskohlii</i>	Roots	Betulonic acid	[261]
<i>Microtropis fokiensis</i>	Stem	25-hydroxy-3-oxoolean-12-en-28-oic acid	[262]
<i>Betula platyphylla</i>	Roots	Capilliposide B	[263]
<i>Amoora rohituka</i>	Stem bark	Ganoderic acid D Ganoderiol F	[264]
<i>Lysimachia capillipes</i>	Roots	Impatienside A, bivittoside D	[265]
<i>Ganoderma lucidum</i>	Stem, Leaves	25-methoxyhispidol A	[266]
<i>Ganoderma amboinense</i>	Stem	23,24-dihydrocucurbitacin B	[267]
<i>Holothuria impatiens</i>	-	Dichapetalin A	[268]
<i>Poncirus trifoliata</i>	Fruits	Acutissimatriterpene A, B, E	[269]
<i>Trichosanthes kirilowii</i>	Roots	Celastrol	[270]
<i>Dichapetalum gelonioides</i>	Stem bark	3 α ,7 α -dideacetylkhivorin	[271]
<i>Phyllanthus acutissima</i>	Aerial parts	Nimbolide	[272]
<i>Celastrus orbiculatus</i>	Bark	Gedunin, 1 α -hydroxy-1,2-dihydrogedunin	[273]
<i>Khaya senegalensis</i>	Roots	6 α -tigloyloxychaparrinone	[274]
<i>Azadirachta indica</i>	Flowers		[275]
<i>Xylocarpus granatum</i>	Roots		[276]
<i>Ailanthus integrifolia</i>			[277]

Many of the terpenoid compounds, e.g., melliferone (55), whose anti-HIV potential has been evaluated in anti-HIV assays towards T cell line H9, and compared with the positive control AZT has been shown in Figures 12 and 13. Melliferone exhibited an IC₅₀ value of 0.205 μ g/mL [49], moronic acid (56), [49], ribenone (57) [237], germanicol (58) [243], nivadiol (59) [243], wikstroelide M (60) [252], shinjulactone B (61) [256], ganoderic acid D (62) [266], ganoderiol F (63) [267] gedunin (64) [276] and 1- α -hydroxy-1,2-dihydrogedunin (65) [276] also exhibited anti-HIV activities.

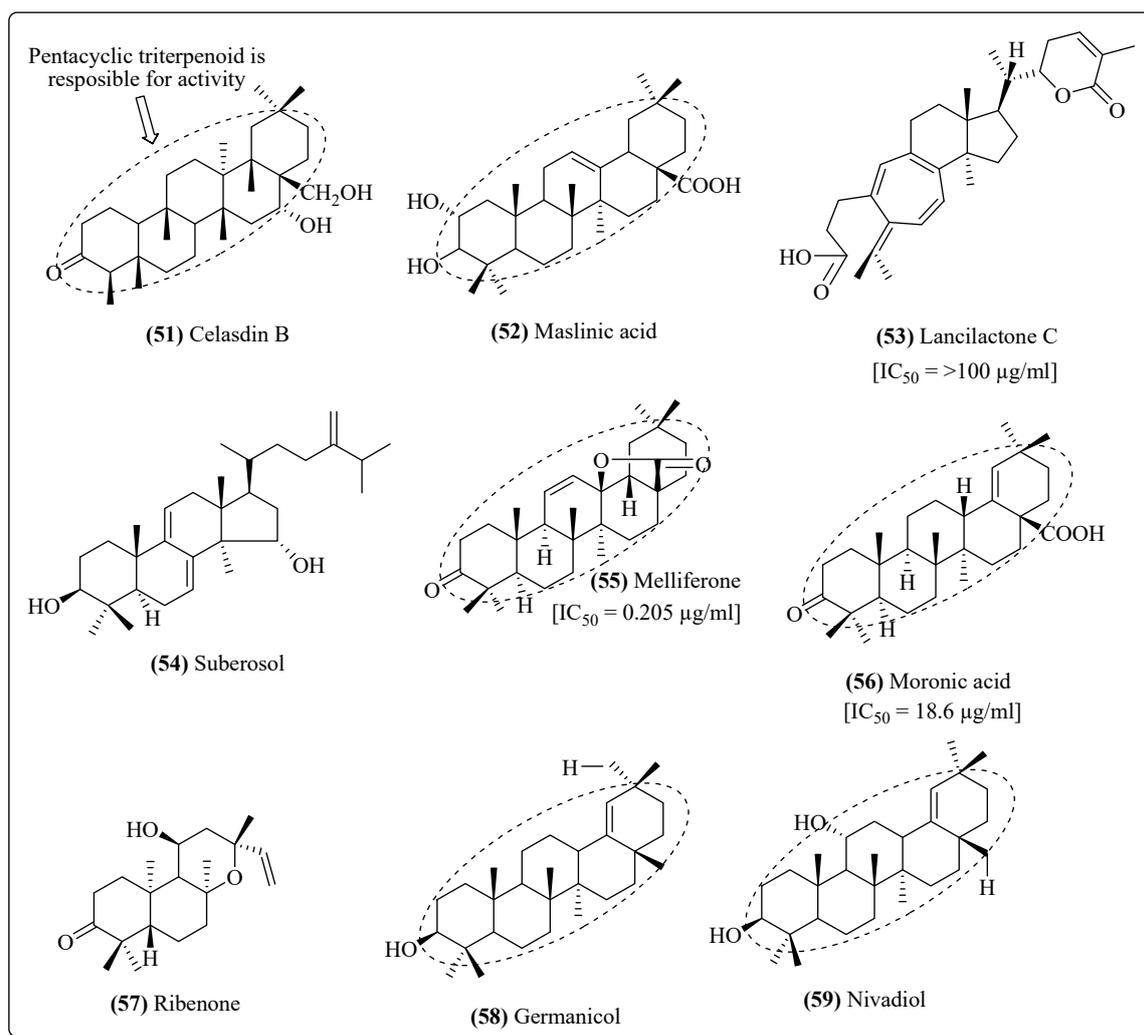


Figure 12. Potent terpenoids against HIV.

2.2.3. Flavonoids

Flavonoids are well-known phytoconstituents reported to exhibit several antiviral and antioxidant properties [278]. Flavonoids like quercetin 3-*O*-(2-galloyl)-*L*-arbinopyranose and gallate ester from *Acer okamotoanum* (Aceraceae), exhibited significant activity against integrase of HIV [279]. Xanthohumol (66), an important flavonoid from *Humulus lupulus*, has shown anti-HIV activity [280]. The flavonoid moiety (4*H*-chromen-4-one) is known to be mainly responsible for the therapeutic activity, while glycosidic portion attached to the flavonoid enhances the solubility of the compounds and thus boosts its therapeutic activity. Two flavonoids 6,8-diprenylkaempferol and 6,8-diprenylaromadendrin isolated from *Monotes africanus* have expressed potential activity against the AIDS virus [281]. Another anti-HIV biflavonoid named wikstrol B (67) (Figure 14) has been isolated from *Wikstroemia indica* (Thymelaeaceae) roots [282]. Baicalin is a flavonoid compound that inhibits HIV replication and is derived from *Scutellaria baicalensis* [282]. From the twigs and leaves of the medicinal plant *Rhus succedanea*, various anti-HIV flavonoids (robustflavone, biflavonoids, and hinokiflavone) have been reported to act on the polymerase of the reverse transcriptase of HIV-1 [283,284]. 2-methoxy-3-methyl-4,6-dihydroxy-5-(3'-hydroxy)-cinnamoylbenzaldehyde, a chalcone flavonoid that has been extracted from *Desmos* sp. roots and exhibited strong activity against HIV-1 [285]. Another chalcone, Hydroxy panduratin A, from the rhizomes of *Boesenbergia pandurata* depicted its action on the HIV protease enzyme [286].

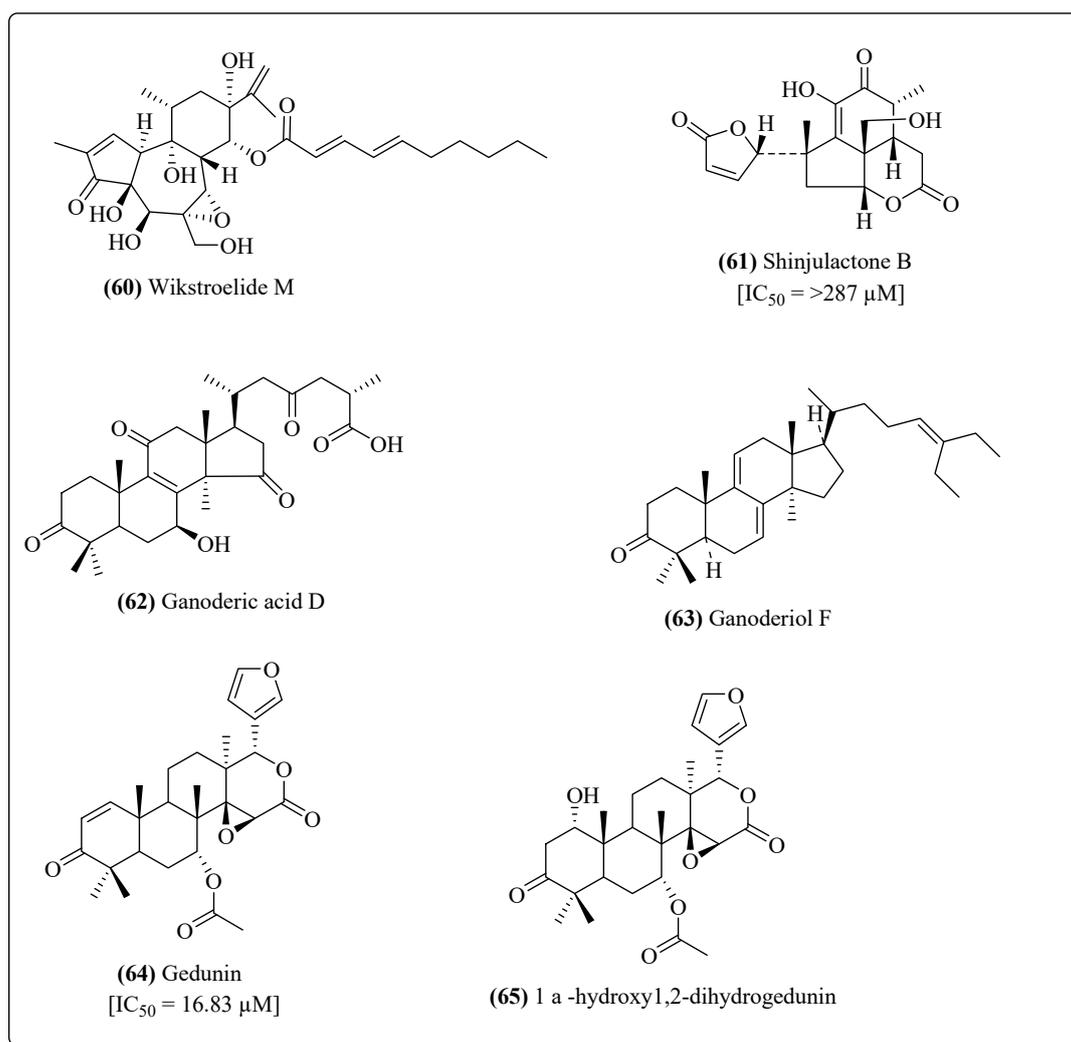


Figure 13. More potent terpenoids against HIV.

Several naturally obtained flavonoids, e.g., chrysin, epigallocatechin gallate (68) and quercetin (69) have been reported to show potent inhibitory activities against the replication of HIV [276,277]. The flavonoids Thalassiolin A, B and C from the grass *Thalassia testudinum* acted against HIV integrase, which in turn inhibited the life cycle of HIV-1. Thalassiolin A was found to be the most potent compound which inhibits the terminal cleavage [287–289]. Some biflavonoids, e.g., 2'',3''-dihydroochnaflavone 7''-O-methylether and ochnaflavone 7''-O-methyl ether from *Ochna integerrima*, have shown moderate to weak anti-HIV activities [290,291]. Taxifolin (70), also known as dihydroquercetin, is mostly found in the stems of *Juglans mandshurica*, and expressed strong inhibitory activity on the reverse transcriptase enzyme of HIV and thus plays a role in the prevention of HIV replication [292]. From *Chrysanthemum morifolium* flowers, two important flavonoids apigenin-7-O-β-D-(4'-caffeoyl)glucuronide and glucuronide have been isolated, which exhibited significant activity against the integrase of HIV-1 [293]. *Mentha longifolia* is another plant whose methanolic extracts are used for the isolation of several therapeutic flavonoids those were found to be active through the same mechanism [294]. Compound 70 was demonstrated to inhibit the activity of HIV-1 replication. Several other flavonoids such as flemiphyllin, formosanatin C (71), euchretin I (72) and quercetin are reported to inhibit the HIV replication and obtained from the alcoholic extracts of *Euchresta formosana* [295]. Many important flavonoids such as epicatechin-3-O-gallate and epicatechin have been extracted from *Detarium microcarpum*, have shown anti-HIV potential [296]. 4'-methylepigallocatechin-3'-O-β-glucopyranoside, and 4'-methylepigallocatechin-5-O-β-glucopyranoside from *Maytenus senegalensis* shown anti-HIV

potential [297]. Kaempferol (73) (Figure 14), a tetrahydroxyflavonol was isolated from *Rosa damascene* and showed inhibitory activity on the protease enzyme [298,299].

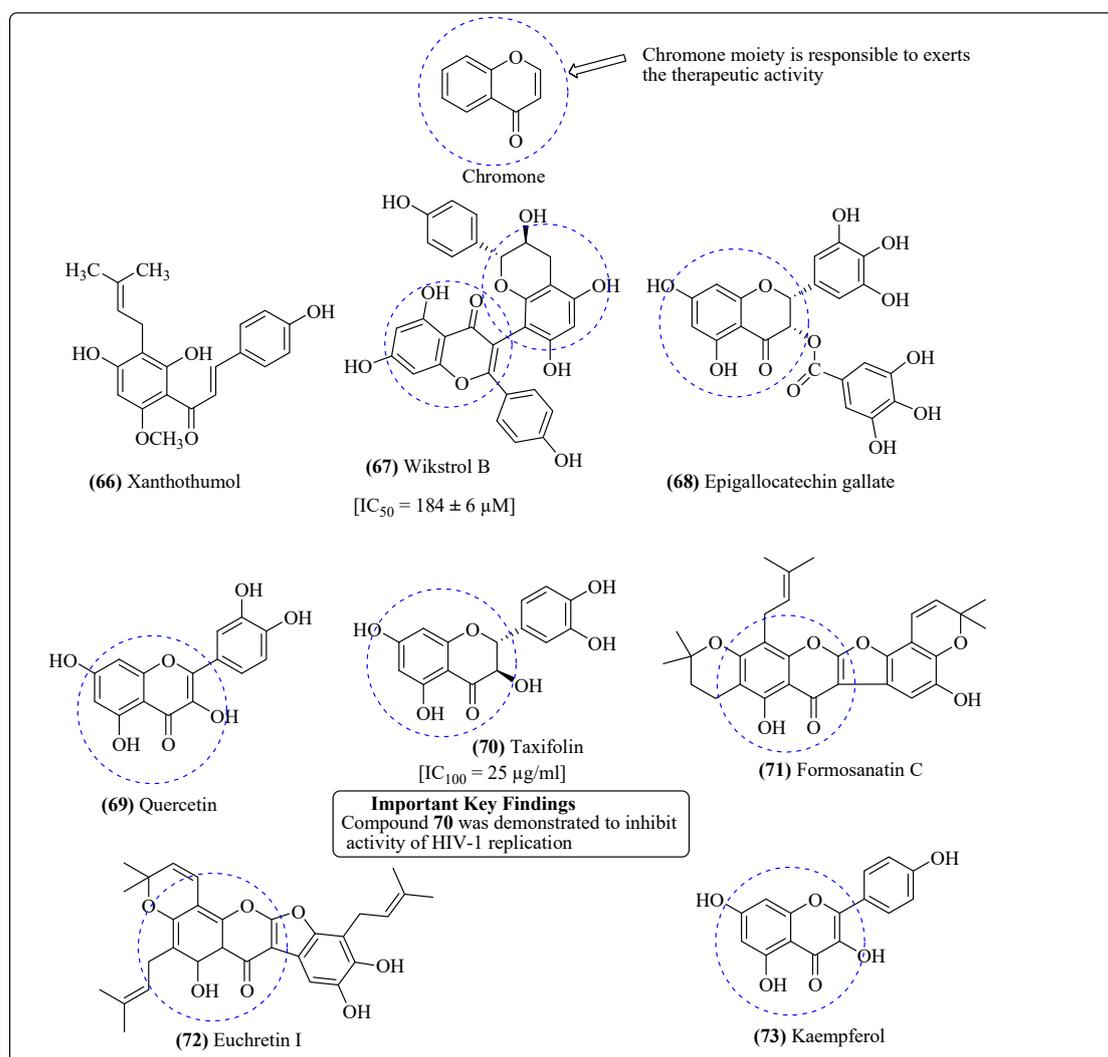


Figure 14. Flavanoids with anti-HIV properties.

2.2.4. Coumarins

Calanolides are a group of coumarins that act as non-nucleoside reverse transcriptase inhibitors and are derived from plants of the genus *Calophyllum* (Clusiaceae) [300]. The coumarin (+)-Calanolide A has already been subjected to in vivo studies and up to phase II clinical trials in healthy, HIV-negative subjects. These studies reveal that (+)-calanolide A has a favourable safety profile in humans as well as in animals [301,302], while calanolide B along with its derivative known as 7,8-dihydrocalanolide B from the plant *Calophyllum lanigerum*, showed significant anti-HIV potential based on cytopathogenic results of HIV on the cells of the host [300]. Another coumarin named suksdorfii (74) [303,304] isolated from the fruits of *Lomatium suksdorfii* belonging to the family Apiaceae, which has expressed inhibitory property on the HIV replication [303]. The compounds Cordatolides A and B from *Calophyllum cordato-oblongum*, were similar in structure to the Calanolides and were found to inhibit the replication of the HIV [300]. The coumarin skeleton is essential for anti-HIV activity (Figure 15). Other coumarins like heraclenol (75) and heraclenin (76) exhibit IC₅₀ value of 20.1 µg/mL against H9 lymphocytes, while imperatorin (77) from the roots of *Ferula sumbul* falls under the same therapeutic category [305]. Bulky groups at the C-4 are also required to retain the anti-HIV activity, which is present in the prototype of a molecule like

(+)-Calanolide-A. (+)-Calanolide-A is the most potent compound when compared with Cordatolide A (less active and devoid of the bulky group at the C-4 position). Several furanocoumarins (e.g., bergapten (78) and psolaren) from the roots of *Prangos tschimganica*, have exhibited significant activities against the HIV virus [306]. Mesuol (79) is another coumarin (from the category 4-phenylcoumarin) reported to inhibit the replication of HIV-1 through the prohibition of the reverse transcription and phosphorylation of HIV [307]. A semisynthetic derivative of calanolide (known as oxocalanolide) was also reported to act efficiently against HIV [308]. Various furanocoumarins (e.g., imperatorin, xanthotoxin and xanthotoxol) have been extracted from the *Aegle marmelos* fruits [121,122]. The stem, roots, fruits, leaves, seeds and bark of the *A. marmelos* showed variable antiviral effects and have played an important role in Ayurvedic medicine. Imperatorin (77) is reported to exhibit about 60% inhibition of HIV-RT. The absence of a prenyl group resulted in the observed weak activity. This is exemplified in the cases of other furanocoumarins xanthotoxin (80) and xanthotoxol (81), shown in Figure 15 [309,310].

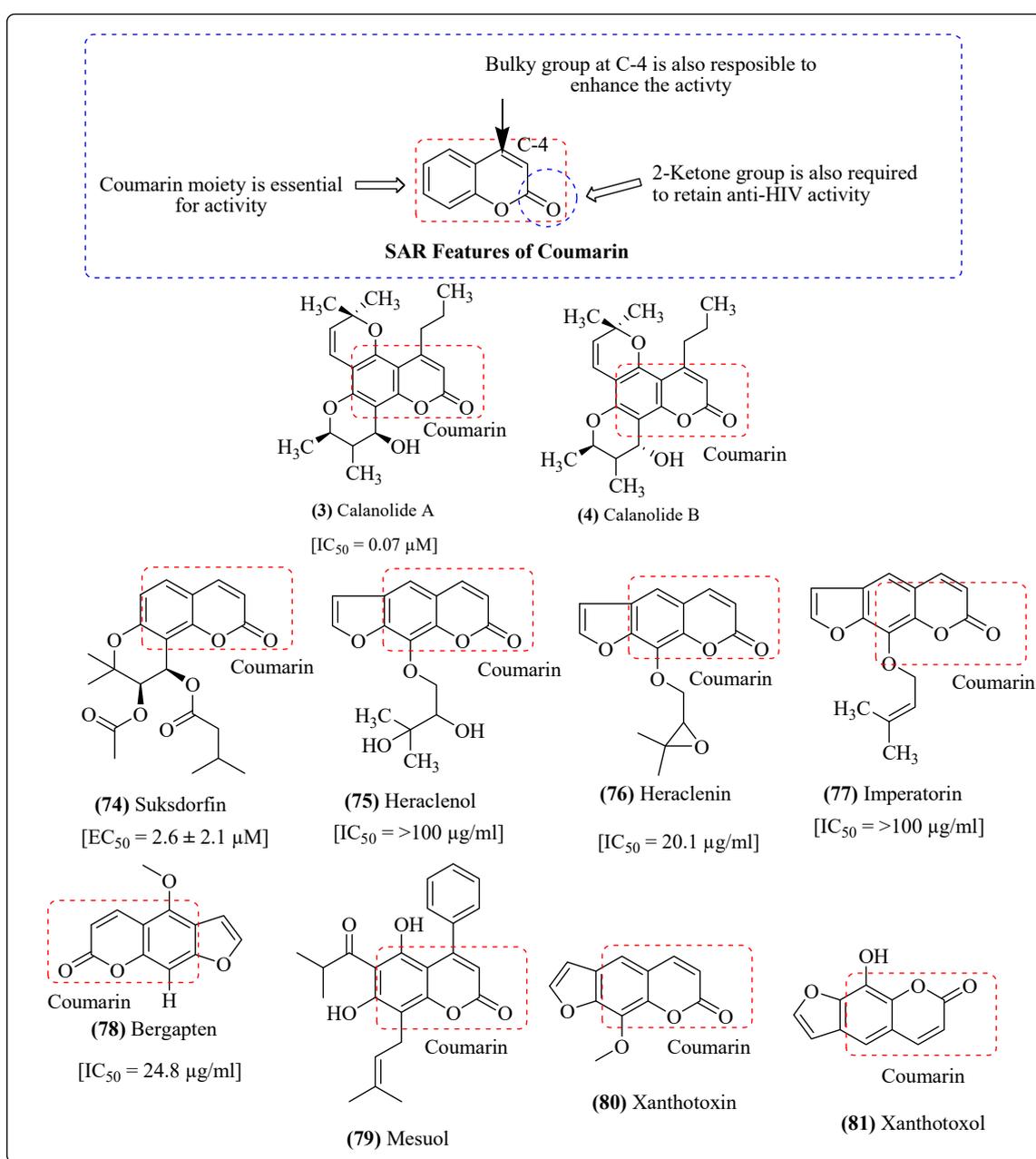


Figure 15. Coumarins with significant Anti-HIV potential.

2.2.5. Proteins

Proteins are the amino acid-containing plant components that usually contain ribosome-inactivating proteins as well as lectins [311]. A plant protein called MAP30 from *Momordica charantia* is known to possess anticancer potential along with anti-HIV properties [312]. Various plant ribosome-inactivating proteins have been identified for their anti-HIV activities. Trichosanthin is a ribosome-inactivating protein isolated from *Trichosanthes kirilowii* that has shown anti-HIV activity [313]. Various plant ribosome-inactivating proteins have been identified for their anti-HIV activities, e.g., an anti-HIV ribosome-inactivating protein balsamin has been extracted from *Momordica balsamina* [314]. Pf-gp6 is another protein reported from *Perilla frutescens* which has exhibited an inhibitory action on HIV replication [315]. Some ribosome-inactivating proteins known as Pokeweed antiviral proteins have been separated from a pokeweed plant (*Phytolacca americana*) and have expressed efficient anti-HIV activities [316]. A list of plant proteins has been given in Table 4, along with their botanical sources.

Table 4. Proteins containing plants used in HIV.

Plant Species	Parts Used	Proteins	References
<i>Allium ascalonicum</i>	Bulbs	Ascalin	[317]
<i>Chrysanthemum coronarium</i>	Seeds	Chrysancorin	[318]
<i>Ginkgo biloba</i>	Seeds	Ginkbilobin	[319]
<i>Arachis hypogaea</i>	Seeds	Hypogin	[320]
<i>Lyophyllum shimeji</i>	Fruit bodies	Lyophyllin	[321]
<i>Panax quinquefolium</i>	Roots	Quinqueginsin	[322]
<i>Flammulina velutipes</i>	Fruit bodies	Velutin	[323]
<i>Tricholoma giganteum</i>	Fruit bodies	Laccase protein	[324]
<i>Castanea mollissima</i>	Seeds	Mollisin	[325]
<i>Treculia obovoidea</i>	Bark	Treculavirin	[326]
<i>Vigna sesquipedalis</i>	Seeds	Ground bean lectin	[327]
<i>Delandia unbellata</i>	Seeds	Delandin	[328]
<i>Dorstenia contrajerva</i>	Leaves	Contrajervin	[326]
<i>Vigna angularis</i>	Seeds	Angularin	[329]
<i>Castanopsis chinensis</i>	Seeds	Castanopsis thaumatin protein	[330]
<i>Vigna unguiculata</i>	Seeds	Cowpea α protein	[331]
<i>Phaseolus vulgaris</i>	Seeds	A homodimeric lectin	[332]
<i>Actinidia chinensis</i>	Fruits	Kiwi fruit thaumatin protein	[333]
<i>Lentinus edodes</i>	Fruit bodies	Lentin	[334]
<i>Allium tuberosum</i>	Shoots	A mannose-binding lectin	[335]
<i>Phaseolus vulgaris</i>	Seeds	Phasein A	[336]
<i>Lilium brownie</i>	Bulbs	Lilin	[337]
<i>Vicia faba</i>	Seeds	A trypsin-chymotrypsin Inhibitor peptide	[338]
<i>Vigna unguiculata</i>	Seeds	Unguulin	[339]
<i>Panax notoginseng</i>	Roots	A xylanase	[340]
<i>Phaseolus vulgaris</i>	Seeds	Vulgin	[341]
<i>Cicer arietinum</i>	Seeds	Chickpea cyclophilin-like protein α -Basrubrin	[342]
<i>Basella rubra</i>	Seeds	Rice bean peptide	[343]
<i>Delandia unbellata</i>	Seeds		[344]

2.2.6. Tannins

Tannins are mainly categorized into gallotannins and ellagitannins. While gallotannins are hydrolysable and contain gallic acid polyesters ellagitannins are non-hydrolyzable, so-called condensed tannins containing hexahydroxydiphenic acids, i.e., flavan-3-ol (proanthocyanidins) moieties [345,346]. Corilagin (82) and Geraniin (83) (Figure 16), from roots of *Phyllanthus amarus*, are two ellagitannins that possess anti-HIV activities [347]. Besides, a proanthocyanidin compound from the plant *Cupressus sempervirens*, exerted anti-HIV properties [348]. Catechins, the polyphenols that are obtained from green

tea, and theaflavins (e.g., compound **84**) isolated from black tea, possess antiviral activity. Theaflavins and their derivatives are potent inhibitors of HIV replication [349]. Compounds **82** and **83** blocked the interaction of HIV-1 gp120 with its primary cellular receptor CD4. Besides, the observed results showed that compound **83** exhibited inhibitory effects on HIV, not only *in vitro* but also *in vivo*. Compound **84** inhibited HIV-1 entry into target cells by blocking the HIV-1 envelope glycoprotein-mediated membrane fusion. The ability of this compound to block the formation of the gp41 six-helix bundle was determined using Fluorescence native polyacrylamide gel electrophoresis, while detection of the binding of gp120 to CD4 was done by ELISA. Molecular docking analyses suggested that compound **84** may bind with to the highly conserved hydrophobic pocket on the surface of the central trimeric coiled-coil of gp41.

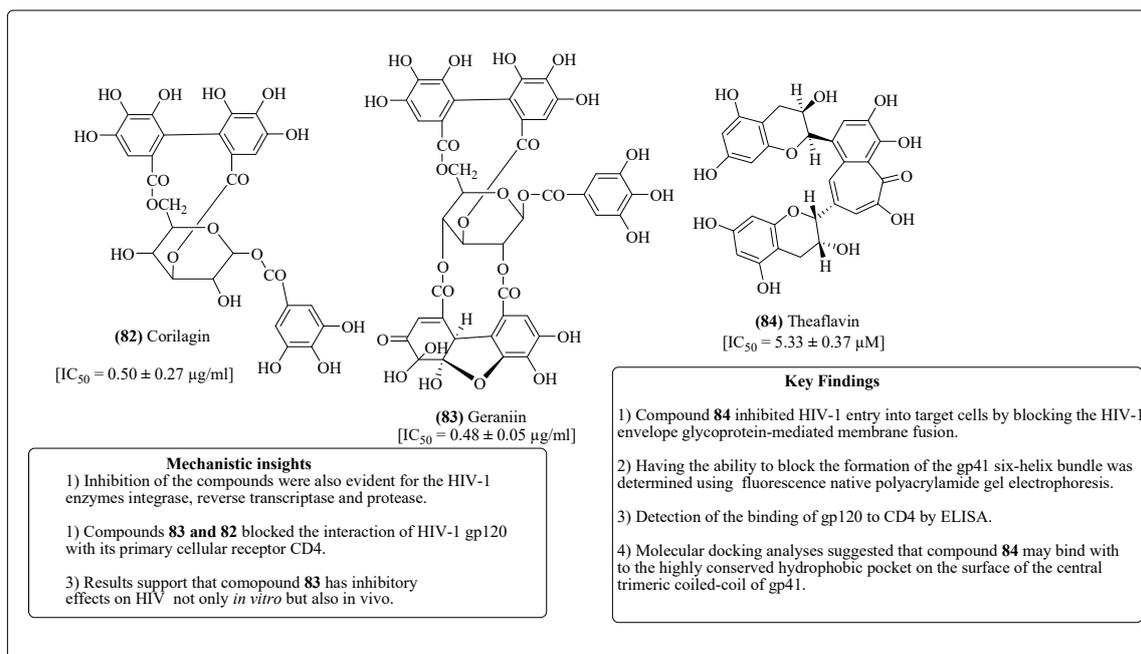


Figure 16. Tannins with anti-HIV properties.

2.2.7. Lignans

Several extensive reports on plant-based lignans which have shown strong activities against viral diseases, including AIDS, exist [350]. Several lignans like anolignan A (**85**) and anolignan B, alongwith dibenzylbutadiene lignans have been isolated from *Anogeissus acuminata* and have exhibited significant activity against HIV [351]. From *Phyllanthus myrtifolius* (Euphorbiaceae), phyllamyricin D (**86**) and phyllamyricin F (**87**) (Figure 17) were isolated and shown to possess inhibitory activity against the HIV-RT enzyme [352]. The benzoaryl moiety was proven to be essential for the anti-HIV activity of lignans. This group is responsible for inhibiting HIV replication. Gomisin is another example of lignan isolated from *Kadsura interior* and showed potent inhibitory activity against the RT enzyme of HIV [353]. From *Arnebia euchroma*, some caffeic acid isomers have been evaluated but have only expressed weak activities against HIV replication [354]. The compound 2-hydroxy-2-(3',4'-dihydroxyphenyl)-methyl-3-(3'',4''-dimethoxyphenyl) methyl γ -butyrolactone is a dibenzylbutyrolactone type lignan from *Phenax angustifolius* with established anti-HIV activity [355]. From *Schisandra rubriflora* fruits, other dibenzocyclooctadiene type lignans (rubrisandrin A and rubrisandrin B) have been isolated having anti-HIV activities [356].

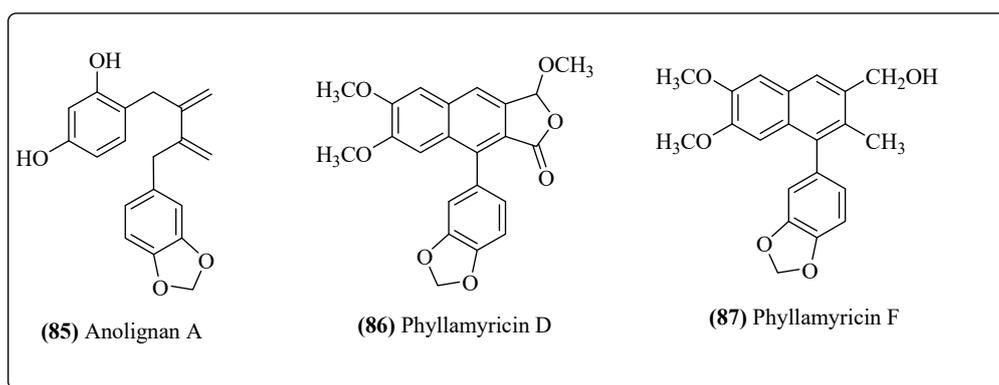


Figure 17. Lignans possessing anti-HIV activities.

2.2.8. Miscellaneous Plant-Based Anti-HIV Agents

Numerous plants have been evaluated for their anti-HIV activities and are being used in antiretroviral therapy for AIDS [1,2]. Various phenolic compounds isolated from plants such as *Quercus pedunculata*, *Terminalia horrida*, *Phyllanthus emblica* and *Rumex cyprius* have been identified for their anti-HIV activities [357,358]. From the leaves and twigs of plant *Strychnos vanprukii*, various betulinic acid derivatives, such as 3- β -*O*-*cis*-feruloylbetulinic acid (**88-B**), 3- β -*O*-*trans*-feruloylbetulinic acid (**88-A**), ursolic acid and 3- β -*O*-*trans*-coumaroylbetulinic acid (**89**) have exhibited potential against HIV [359]. Compounds **88-A**, **88-B** and **89** have been evaluated for anti-HIV activities against HOG.R5 cells in the anti-HIV assay. Compound **88-A** showed significant inhibition against HIV-1 replication. The *trans*-isomer (**88-A**) showed a more favourable activity when compared with the *cis*-isomer (**88-B**) (Figure 18). The compounds shown in Figure 18 exhibited significant potential against HIV due to the presence of the pharmacophore/heterocyclic moieties, such as chromone, indole, steroidal nucleus, benzodioxole, quinolizine, etc. These compounds also demonstrated various therapeutic properties, e.g., anti-inflammatory, anti-cancer, antiviral, antioxidant and immunomodulatory properties [360]. The constituents of *Cinnamomum zylanicum* bark have shown anti-inflammatory [361], anti-cancer, antiviral, antioxidant and immunomodulatory properties [362]. The ingenol compounds from *Euphorbia ingens* have exhibited anti-HIV activities [363], apart from their anti-inflammatory and immunomodulatory potentials [364,365]. *Oldenlandia affinis* is a medicinal plant from which various cyclotides have been isolated and tested for their activities against HIV [366,367]. *Plectranthus barbatus* has also shown diverse antiviral, antibacterial and antifungal properties along with antioxidant and anti-inflammatory effects [368,369]. From *Clausena excavate* some therapeutic constituents like *O*-methylmukonal (**90**), 3-formyl-2,7-dimethoxycarbazole, limonoids, and clausenidin have been reported for their anti-HIV properties [370,371]. Several antiviral components like tectorigenin, cytisine (**91**), formononetin, trifolirhizin (**92**), mattrine (**93**), blumenol A (**94**), pterocarpin (**95**), 30,40,5-trihydroxyisoflavone, euchretin and 5,7-dihydroxy-3-(2-hydroxy-4-methoxy-phenyl)-chromen-4-one have been isolated from *Euchresta formosana* and exhibited anti-HIV activities [372–375].

Extracts from *Alepidea amatymbica*, have shown efficient anti-HIV activities, as well as inhibitory effect on HIV replication [376]. Artemisinin from the plant *Artemisia annua*, has established antimalarial and anti-HIV activities [377]. Rosmarinic acid is a polyphenolic compound from the plant *Prunella vulgaris*, used for the treatment of isolated HIV [378]. From *Polygonum glabrum*, various bioactive constituents with antiretroviral activities have been reported, e.g., (-)-2-methoxy-2-butenolide-3-cinnamate, pinocembrin (**96**), 3-hydroxy-5-methoxystilbene (**97**), sitosterol-3-*O*- β -D-glucopyranoside, and pinocembrin-5-methyl ether [379]. Actein (**98**) from the rhizomes of *Cimicifuga racemosa*, possessed a significant activity against HIV [380]. Chrysoeriol from *Eurya ciliate* is known for its anti-HIV activity [381]. Several constituents such as demethylaristofolin E (**99**), aristofolin, denitroaristolochic acid, aristolochic acid, aristomanoside

(100), *N*-*p*-coumaroyltyramine, *p*-hydroxybenzoic acid, etc. have been isolated for their anti-HIV potential from the stem bark of *Aristolochia manshuriensis* [382–386]. Malaferin A, from *Malania oleifera*, was also tested for its antiviral property [387]. Diptoinonesin D, Acuminatol (101), Shoreaphenol, Hopeahainol, and Vaticanol B from *Vatica mangachapoi* have shown positive effects in the management of antiretroviral therapy [388–391]. Cararosinol C and D, maackin and scirpusin B (102) from *Caragana rosea* have been evaluated for their anti-HIV effects [392]. Structures of some important constituents obtained from plants effective in HIV therapy are represented in Figure 18. A list of other plants having anti-HIV potential has been listed in Table 5.

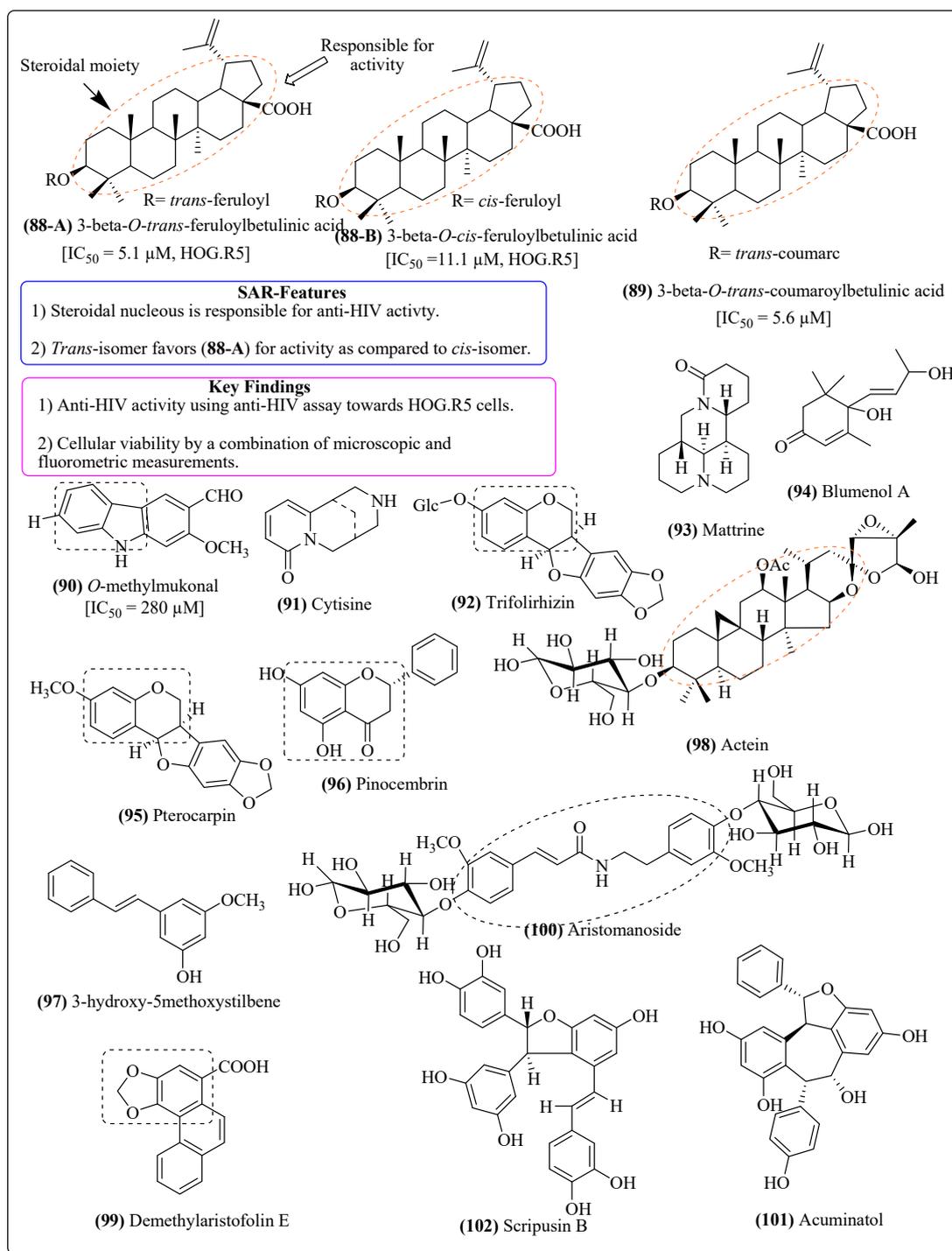


Figure 18. Other plant-based compounds with anti-HIV activities.

Table 5. Assortments of other plant species have been given in Table 5.

Plant Species	Family	Parts Used	References
<i>Khaya grandifoliola</i>	Meliaceae	Leaves	[393]
<i>Diospyros mespiliformis</i>	Ebenaceae	Bark	[394]
<i>Alternanthera brasiliana</i>	Amaranthaceae	Roots	[395]
<i>Ricinus communis</i>	Euphorbiaceae	Leaves	[396]
<i>Butea monosperma</i>	Fabaceae	Roots	[397]
<i>Prosopis glandulosa</i>	Fabaceae	Leaves	[398]
<i>Sophora tonkinensis</i>	Fabaceae	Roots	[399]
<i>Gunnera magellanica</i>	Gunneraceae	Stem	[400]
<i>Swertia franchetiana</i>	Gentianaceae	Roots	[401]
<i>Curcuma longa</i>	Zingiberaceae	Rhizomes	[402]
<i>Stewartia koreana</i>	Theaceae	Leaves	[403]
<i>Cissus quadrangularis</i>	Vitaceae	Stems	[404]
<i>Withania somnifera</i>	Solanaceae	Roots	[405]
<i>Ailanthus altissima</i>	Simaroubaceae	Stem bark	[406]
<i>Toddalia asiatica</i>	Rutaceae	Roots	[407]
<i>Oldenlandia herbacea</i>	Rubiaceae	Roots	[408]
<i>Aloe vera</i>	Xanthorrhoeaceae	Leaves	[409]
<i>Urtica dioica</i>	Urticaceae	Rhizomes	[410]
<i>Rheum tanguticum</i>	Polygonaceae	Leaves	[411]
<i>Saccharum officinarum</i>	Poaceae	Stems	[412]
<i>Ochna integerrima</i>	Ochnaceae	Leaves	[413]
<i>Nelumbo nucifera</i>	Nelumbonaceae	Leaves	[414]
<i>Aglaiia lawii</i>	Meliaceae	Leaves	[415]
<i>Fritillaria cirrhosa</i>	Liliaceae	Rhizomes	[416]
<i>Magnolia biondii</i>	Magnoliaceae	Flower buds	[417]
<i>Lythrum salicaria</i>	Lythraceae	Leaves	[418]
<i>Reseda lutea</i>	Resedaceae	Whole plant	[419]
<i>Hypericum perforatum</i>	Hypericaceae	Leaves	[420]
<i>Trigonostemon thyrsoideus</i>	Euphorbiaceae	Stems	[421]
<i>Hemsleya endecaphylla</i>	Cucurbitaceae	Tubers	[422]
<i>Garcinia kingaensis</i>	Clusiaceae	Stem bark	[423]
<i>Woodwardia unigemmata</i>	Blechnaceae	Rhizomes	[424]
<i>Berberis holstii</i>	Berberidaceae	Roots, leaves	[425]
<i>Foeniculum vulgare</i>	Apiaceae	Fruits	[406]
<i>Alepidea amatymbica</i>	Apiaceae	Roots	[426]
<i>Stachytarpheta jamaicensis</i>	Verbenaceae	Whole plant	[427]
<i>Schisandra sphaerandra</i>	Schisandraceae	Stems	[428]
<i>Alpinia galangal</i>	Zingiberaceae	Roots	[429]
<i>Zanthoxylum chalybeum</i>	Rutaceae	Root bark	[430]
<i>Berchemia berchemiifolia</i>	Rhamnaceae	Bark	[431]
<i>Scoparia dulcis</i>	Plantaginaceae	Leaves	[432]
<i>Phyllanthus myrtifolius</i>	Phyllanthaceae	Fruits	[433]
<i>Arundina graminifolia</i>	Orchidaceae	Whole plant	[434]
<i>Ximenia Americana</i>	Olacaceae	Stem bark	[435]

3. Conclusions

Plants are known to exhibit a huge repertoire of bioactive metabolites [436]. A significant number of reports on the capability of natural compounds with potential as anti-HIV agents have appeared during the last few decades. This review article presents the rational approaches for the design of therapeutic potential candidates as anti-HIV agents. Even though there have been many extensive achievements in the field of HIV chemotherapy, there remains a great demand for novel lead compounds for anti-HIV drug discovery and drug development. Numerous plant species have been evaluated for their inhibitory activities on the essential HIV enzymes such as RT, protease, and integrase, which play an important role in HIV replication. Several secondary metabolites have been extracted from the various parts of plants that act as potent anti-HIV agents via different mechanisms of action.

Therapeutically active compounds from plants can also aid as necessary leads for the discovery and development of novel and more potent compounds that can be derived synthetically. For instance, synthetic ingenol compounds have been derived based on naturally occurring compound Ingenol and a variety of synthetic derivatives have been evolved from the naturally occurring compound Artemisinin, which exhibits significant anti-HIV activities of potential scaffolds from them for the complete eradication of HIV/AIDS. A recent review has attempted to show the most successful medical therapeutics derived from natural products, including those studied in the field of HIV/AIDS [437]. Besides, computer-aided (virtual) [438] and large-scale in vitro screening [439] approaches have recently been carried out on natural compound libraries to identify natural products with anti-HIV properties. Novel therapeutic approaches have been attempted, including searching for new HIV-1 latency-reversing agents, i.e., compounds not only capable of HIV suppression but also eliminating HIV reservoirs [440,441].

Author Contributions: Conceptualization, G.K.G., F.N.-K. and D.K.; methodology, R.K., P.S. and D.K.; software, data curation, R.K., P.S., F.N.-K. and D.K.; writing—original draft preparation, R.K., P.S., and D.K., writing—review and editing, R.K., P.S., G.K.G., F.N.-K., and D.K.; visualization, X.X.; supervision, F.N.-K., and D.K.; project administration, F.N.-K., G.K.G., and D.K.; funding acquisition, F.N.-K. All authors have read and agreed to the published version of the manuscript.

Funding: F.N.-K. would also like to acknowledge an equipment subsidy and return fellowship from the Alexander von Humboldt Foundation, Germany.

Acknowledgments: Authors are thankful to B. S. Guman, Vice-chancellor of Punjabi University Patiala for their encouragement. The authors are also thankful to Er. S. K. Punj, Chairman, Sri Sai Group of Institutes and Smt. Tripta Punj, Managing Director, Sri Sai Group of Institutes for their constant moral support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sabde, S.; Bodiwala, H.S.; Karmase, A.; Deshpande, P.J.; Kaur, A.; Ahmed, N.; Chauthe, S.K.; Brahmabhatt, K.G.; Phadke, R.U.; Mitra, D.; et al. Anti-HIV activity of Indian medicinal plants. *J. Nat. Med.* **2011**, *65*, 662–669. [[CrossRef](#)]
2. Salehi, B.; Kumar, N.V.A.; Sener, B.; Sharifi-Rad, M.; Kılıç, M.; Mahady, G.B.; Vlasisavljevic, S.; Iriti, M.; Kobarfard, F.; Setzer, W.N.; et al. Medicinal plants used in the treatment of human immunodeficiency virus. *Int. J. Mol. Sci.* **2018**, *19*, 1459. [[CrossRef](#)]
3. Reynolds, C.; de Koning, C.B.; Pelly, S.C.; Otterlo, W.A.L.; Bode, M.L. In search of a treatment for HIV—Current therapies and the role of non-nucleoside reverse transcriptase inhibitors (NNRTIs). *Chem. Soc. Rev.* **2012**, *41*, 4657–4670. [[CrossRef](#)]
4. Prasad, S.; Tyagi, A.K. Curcumin and its analogues: A potential natural compound against HIV 1 infection and AIDS. *Food Funct.* **2015**, *6*, 3412–3419. [[CrossRef](#)]
5. Kharsany, A.B.; Karim, Q.A. HIV infection and AIDS in sub-saharan Africa: Current status, challenges and opportunities. *Open AIDS J.* **2016**, *10*, 34–48. [[CrossRef](#)]
6. Moir, S.; Chun, T.-W.; Fauci, A.S. Pathogenic mechanisms of HIV disease. *Annu. Rev. Pathol. Mech. Dis.* **2011**, *6*, 223–248. [[CrossRef](#)]
7. Deeks, S.G.; Overbaugh, J.; Phillips, A.; Buchbinder, S. HIV infection. *Nat. Rev. Dis. Prim.* **2015**, *1*, 15035. [[CrossRef](#)]
8. Freed, E.O. HIV-1 assembly, release and maturation. *Nat. Rev. Microbiol.* **2015**, *13*, 484–496. [[CrossRef](#)]
9. Engelman, A.; Cherepanov, P. The structural biology of HIV-1: Mechanistic and therapeutic insights. *Nat. Rev. Microbiol.* **2012**, *10*, 279–290. [[CrossRef](#)]
10. Turner, B.G.; Summers, M.F. Structural biology of HIV. *J. Mol. Biol.* **1999**, *285*, 1–32. [[CrossRef](#)]
11. Goodsell, D.S. Illustrations of the HIV life cycle. *Curr. Top. Microbiol. Immunol.* **2015**, *389*, 243–252. [[PubMed](#)]
12. Mailler, E.; Bernacchi, S.; Marquet, R.; Paillart, J.C.; Vivet-Boudou, V.; Smyth, R.P. The life-cycle of the HIV-1 Gag–RNA complex. *Viruses* **2016**, *8*, 248. [[CrossRef](#)] [[PubMed](#)]
13. Sundquist, W.I.; Kräusslich, H.-G. HIV-1 assembly, budding, and maturation. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006924. [[CrossRef](#)] [[PubMed](#)]
14. Harden, V.A.; Fauci, A. *AIDS at 30: A History*; Potomac Books, Inc.: Lincoln, NE, USA, 2012.

15. Lewis, J.M.; Macpherson, P.; Adams, E.R.; Ochodo, E.; Sanda, A.; Taegtmeier, M. Field accuracy of fourth-generation rapid diagnostic tests for acute HIV-1: A systematic review. *AIDS* **2015**, *29*, 2465–2471. [[CrossRef](#)]
16. Alexander, T.S. Human immunodeficiency virus diagnostic testing: 30 years of evolution. *Clin. Vaccine Immunol.* **2016**, *23*, 249–253. [[CrossRef](#)]
17. Colebunders, R.; Francis, H.; Duma, M.-M.; Groen, G.V.D.; Lebughe, I.; Kapita, H.; Quinn, T.C.; Heyward, W.L.; Piot, P. HIV-1 infection in HIV-1 enzyme-linked immunoassay seronegative patients in Kinshasa, Zaire. *Int. J. STD AIDS* **1990**, *1*, 330–334. [[CrossRef](#)]
18. Feng, X.; Wang, J.; Gaod, Z.; Tiana, Y.; Zhanga, L.; Chene, H.; Zhang, T.; Xiaof, L.; Yao, J.; Xing, W.; et al. An alternative strategy to Western Blot as a confirmatory diagnostic test for HIV Infection. *J. Clin. Virol.* **2017**, *88*, 8–11. [[CrossRef](#)]
19. Auvert, B.; Taljaard, D.; Lagarde, E.; Sobngwi-Tambekou, J.; Sitta, R.; Puren, A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. *PLoS Med.* **2005**, *2*, e298. [[CrossRef](#)]
20. Günthard, H.F.; Saag, M.S.; Benson, C.A.; Del Rio, C.; Eron, J.J.; Gallant, J.E.; Hoy, J.F.; Mugavero, M.J.; Sax, P.E.; Thompson, M.A. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2016 recommendations of the International Antiviral Society—USA panel. *JAMA* **2016**, *316*, 191–210. [[CrossRef](#)]
21. Bailey, R.C.; Moses, S.; Parker, C.B.; Agot, K.; Maclean, I.; Krieger, J.N.; Williams, C.F.; Campbell, R.T.; Ndinya-Achola, J.O. Male circumcision for HIV prevention in young men in Kisumu, Kenya: A randomised controlled trial. *Lancet* **2007**, *369*, 643–656. [[CrossRef](#)]
22. Gravatt, L.A.H.; Leibrand, C.R.; Patel, S.; McRae, M. New drugs in the pipeline for the treatment of HIV: A review. *Curr. Infect. Dis. Rep.* **2017**, *19*, 42. [[CrossRef](#)] [[PubMed](#)]
23. Sendagire, H.; Easterbrook, P.J.; Nankya, I.; Arts, E.; Thomas, D.; Reynolds, S.J. The challenge of HIV-1 antiretroviral resistance in Africa in the era of HAART. *AIDS Rev.* **2009**, *11*, 59–70. [[PubMed](#)]
24. Ramana, L.N.; Anand, A.R.; Sethuraman, S.; Krishnan, U.M. Targeting strategies for delivery of anti-HIV drugs. *J. Control. Release* **2014**, *192*, 271–283. [[CrossRef](#)] [[PubMed](#)]
25. Lu, D.-Y.; Wu, H.Y.; Yarla, N.S.; Xu, B.; Ding, J.; Lu, T.R. HAART in HIV/AIDS treatments: Future trends. *Infect. Disord. Drug Targ.* **2018**, *18*, 15–22. [[CrossRef](#)]
26. Li, X.; Chan, W.K. Transport, metabolism and elimination mechanisms of anti-HIV agents. *Adv. Drug Deliv. Rev.* **1999**, *39*, 81–103. [[CrossRef](#)]
27. Cohen, M.S.; Chen, Y.Q.; McCauley, M.; Gamble, T.; Hosseinipour, M.C.; Kumarasamy, N.; Hakim, J.G.; Kumwenda, J.; Grinsztejn, B.; Pilotto, J.H. Prevention of HIV-1 infection with early antiretroviral therapy. *N. Engl. J. Med.* **2011**, *365*, 493–505. [[CrossRef](#)]
28. Sharifi-Rad, J. Herbal antibiotics: Moving back into the mainstream as an alternative for “superbugs”. *Cell. Mol. Biol.* **2016**, *62*, 1–2.
29. WHO. In vitro screening of traditional medicines for anti-HIV activity: Memorandum from a WHO meeting. *Bull. World Health Organ.* **1989**, *87*, 613–618.
30. WHO. *Report of a Who Informal Consultation on Traditional Medicine and AIDS: In Vitro Screening for Anti-HIV Activity*; WHO: Geneva, Switzerland, 1989.
31. Cos, P.; Maes, L.; Berghe, D.V.; Hermans, N.; Pieters, L.; Vlietinck, A. Plant substances as anti-HIV agents selected according to their putative mechanism of action. *J. Nat. Prod.* **2004**, *67*, 284–293. [[CrossRef](#)]
32. Kumar, D.; Sharma, P.; Singh, H.; Nepali, K.; Gupta, G.K.; Jain, S.K.; Ntie-Kang, F. The value of pyrans as anticancer scaffolds in medicinal chemistry. *RSC Adv.* **2017**, *7*, 36977–36999. [[CrossRef](#)]
33. Kumar, D.; Jain, S.K. A comprehensive review of N-heterocycles as cytotoxic agents. *Curr. Med. Chem.* **2016**, *23*, 4338–4394. [[CrossRef](#)] [[PubMed](#)]
34. Cos, P.; Maes, L.; Vlietinck, A.; Pieters, L. Plant-derived leading compounds for chemotherapy of human immunodeficiency virus (HIV) infection—An Update (1998–2007). *Planta Med.* **2008**, *74*, 1323–1337. [[CrossRef](#)] [[PubMed](#)]
35. Nepali, K.; Sharma, S.; Kumar, D.; Budiraja, A.; Dhar, K.L. Anticancer hybrids—a patent survey. *Recent Pat. Anticancer Drug Discov.* **2014**, *9*, 303–339. [[CrossRef](#)] [[PubMed](#)]
36. Kumar, D.; Bedi, P.M.S. Anti-Inflammatory Agents: Some recent advances. *Indian Drug.* **2009**, *46*, 675–681.
37. Sharma, P.; Sharma, R.; Rao, H.S.; Kumar, D. Phytochemistry and medicinal attributes of *Alstonia scholaris*: A review. *Int. J. Pharm. Sci. Res.* **2015**, *6*, 505–513.

38. Kumar, D.; Nepali, K.; Bedi, P.M.S.; Kumar, S.; Malik, F.; Jain, S. 4,6-diaryl pyrimidones as constrained chalcone analogues: Design, synthesis and evaluation as anti-proliferative agents. *Anticancer Agents Med. Chem.* **2015**, *15*, 793–803. [[CrossRef](#)]
39. Kurapati, K.R.V.; Atluri, V.S.; Samikkannu, T.; Garcia, G.; Nair, M.P.N. Natural products as anti-HIV agents and role in HIV-associated neurocognitive disorders (HAND): A brief overview. *Front. Microbiol.* **2016**, *6*, 1444. [[CrossRef](#)]
40. Kumar, D.; Singh, O.; Nepali, K.; Bedi, P.M.S.; Qayum, A.; Singh, S.; Jain, S.K. Naphthoflavones as anti-proliferative agents: Design, synthesis and biological evaluation. *Anticancer Agents Med. Chem.* **2016**, *16*, 881–890. [[CrossRef](#)]
41. Kumar, D.; Malik, F.; Bedi, P.M.S.; Jain, S. 2,4-diarylpyrano[3,2-c]chromen-5(4H)-ones as coumarin-chalcone conjugates: Design, synthesis and biological evaluation as apoptosis inducing agents. *Chem. Pharm. Bull.* **2016**, *64*, 399–409. [[CrossRef](#)]
42. Kumar, D.; Singh, G.; Sharma, P.; Qayum, A.; Mahajan, G.; Minto, M.J. 4-aryl/heteroaryl-4H-fused pyrans as anti-proliferative agents: Design, synthesis and biological evaluation. *Anticancer Agents Med. Chem.* **2018**, *18*, 57–73. [[CrossRef](#)]
43. Kumar, D.; Sharma, P.; Nepali, K.; Mahajan, G.; Minto, M.J.; Singh, A.; Singh, G.; Mondhe, D.M.; Singh, G.; Jain, S.K.; et al. Antitumour, acute toxicity and molecular modeling studies of 4-(pyridin-4-yl)-6-(thiophen-2-yl) pyrimidin-2(1H)-one against Ehrlich ascites carcinoma and sarcoma-180. *Heliyon* **2018**, *4*, e00661. [[CrossRef](#)] [[PubMed](#)]
44. Guzman, J.D.; Gupta, A.; Bucar, F.; Gibbons, S.; Bhakta, S. Anti-mycobacterials from natural sources: Ancient times, antibiotic era and novel scaffolds. *Front. Biosci.* **2012**, *17*, 1861–1881. [[CrossRef](#)] [[PubMed](#)]
45. Chaniad, P.; Wattanapiromsakul, C.; Pianwanit, S.; Tewtrakul, S. Anti-HIV-1 integrase compounds from *Dioscorea bulbifera* and molecular docking study. *Pharmaceut. Biol.* **2016**, *54*, 1077–1085. [[CrossRef](#)] [[PubMed](#)]
46. Jiang, C.; Luo, P.; Zhao, Y.; Hong, J.; Morris-Natschke, S.L.; Xu, J.; Chen, C.H.; Lee, K.H.; Gu, Q. Carolignans from the aerial parts of *Euphorbia sikkimensis* and their anti-HIV activity. *J. Nat. Prod.* **2016**, *79*, 578–583. [[CrossRef](#)] [[PubMed](#)]
47. Kalvatchev, Z.; Walder, R.; Garzaro, D. Anti-HIV activity of extracts from *Culendula officinalis* flowers. *Biomed. Pharmacother.* **1997**, *51*, 176–180. [[CrossRef](#)]
48. Kapewangolo, P.; Tawha, T.; Nawinda, T.; Knott, M.; Hans, R. *Sceletium tortuosum* demonstrates in vitro anti-HIV and free radical scavenging activity. *S. Afr. J. Bot.* **2016**, *106*, 140–143. [[CrossRef](#)]
49. Ito, J.; Chang, F.R.; Wang, H.K.; Park, Y.K.; Ikegaki, M.; Kilgore, N.; Lee, K.H. Anti-AIDS agents. 48. Anti-HIV activity of moronic acid derivatives and the new melliferone-related triterpenoid isolated from Brazilian propolis. *J. Nat. Prod.* **2001**, *64*, 1278–1281. [[CrossRef](#)]
50. Cassels, B.K.; Asencio, M. Anti-HIV activity of natural triterpenoids and hemisynthetic derivatives 2004–2009. *Phytochem. Rev.* **2011**, *10*, 545–564. [[CrossRef](#)]
51. Cheng, Y.B.; Liu, F.J.; Wang, C.H.; Hwang, T.L.; Tsai, Y.F.; Yen, C.H.; Wang, H.C.; Tseng, Y.H.; Chien, C.T.; Chen, Y.M.A.; et al. bioactive triterpenoids from the leaves and twigs of *Lithocarpus litseifolius* and *L. corneus*. *Planta Med.* **2018**, *84*, 49–58. [[CrossRef](#)]
52. Kapewangolo, P.; Kandawa-Schulz, M.; Meyer, D. Anti-HIV activity of *Ocimum labiatum* extract and isolated pheophytin-A. *Molecules* **2017**, *22*, 1763. [[CrossRef](#)]
53. Sharifi-Rad, M.; Varoni, E.M.; Salehi, B.; Sharifi-Rad, J.; Matthews, K.R.; Ayatollahi, S.A.; Kobarfard, F.; Ibrahim, S.A.; Mnayer, D.; Zakaria, Z.A. Plants of the genus *Zingiber* as a source of bioactive phytochemicals: From tradition to pharmacy. *Molecules* **2017**, *22*, 2145. [[CrossRef](#)] [[PubMed](#)]
54. Sharifi-Rad, J.; Salehi, B.; Schnitzler, P.; Ayatollahi, S.; Kobarfard, F.; Fathi, M.; Eisazadeh, M.; Sharifi-Rad, M. Susceptibility of herpes simplex virus type 1 to monoterpenes thymol, carvacrol, *p*-cymene and essential oils of *Sinapis arvensis* L., *Lallemantiaroyleana* Benth. and *Pulicaria vulgaris* Gaertn. *Cell. Mol. Biol.* **2017**, *63*, 42–47. [[CrossRef](#)] [[PubMed](#)]
55. Salehi, B.; Zucca, P.; Sharifi-Rad, M.; Pezzani, R.; Rajabi, S.; Setzer, W.; Varoni, E.; Iriti, M.; Kobarfard, F.; Sharifi-Rad, J. Phytotherapeutics in cancer invasion and metastasis. *Phytother. Res.* **2018**, *32*, 1425–1449. [[CrossRef](#)] [[PubMed](#)]
56. Sharifi-Rad, J.; Hoseini-Alfatemi, S.; Sharifi-Rad, M.; Miri, A. Phytochemical screening and antibacterial activity of different parts of the *Prosopis farcta* extracts against methicillin-resistant *Staphylococcus aureus* (MRSA). *Min. Biotechnol.* **2014**, *26*, 287–293.

57. Sharifi-Rad, M.; Tayeboon, G.; Sharifi-Rad, J.; Iriti, M.; Varoni, E.; Razazi, S. Inhibitory activity on type 2 diabetes and hypertension key-enzymes, and antioxidant capacity of *Veronica persica* phenolic-rich extracts. *Cell. Mol. Biol.* **2016**, *62*, 80–85. [[PubMed](#)]
58. Sharifi-Rad, J.; Mnayer, D.; Tabanelli, G.; Stojanovic'-Radic', Z.; Sharifi-Rad, M.; Yousaf, Z.; Vallone, L.; Setzer, W.; Iriti, M. Plants of the genus *Allium* as antibacterial agents: From tradition to pharmacy. *Cell. Mol. Biol.* **2016**, *62*, 57–68.
59. Bagheri, G.; Mirzaei, M.; Mehrabi, R.; Sharifi-Rad, J. Cytotoxic and antioxidant activities of *Alstonia scholaris*, *Alstonia venenata* and *Moringa oleifera* plants from India. *Jundishapur J. Nat. Pharm. Prod.* **2016**, *11*, e31129. [[CrossRef](#)]
60. Farnsworth, N.R. The role of ethnopharmacology in drug development. In *Bioactive Compounds from Plants*; Chadwick, D.J., Marsh, J., Eds.; John Wiley & Sons: New York, NY, USA, 1990; pp. 2–21.
61. Clercq, E.D. Antiviral therapy for human immunodeficiency virus infections. *Clin. Microbiol. Rev.* **1995**, *8*, 200–239. [[CrossRef](#)]
62. Blanco, J.L.; Whitlock, G.; Milinkovic, A.; Moyle, G. HIV integrase inhibitors: A new era in the treatment of HIV. *Expert Opin. Pharmacother.* **2015**, *16*, 1313–1324. [[CrossRef](#)]
63. Andreola, M.L.; Soultrait, V.R.D.; Fournier, M.; Parissi, V.; Desjobert, C.; Litvak, S. HIV-1 integrase and RNase H activities as therapeutic targets. *Expert Opin. Ther. Targets* **2002**, *6*, 433–446. [[CrossRef](#)]
64. Kanyara, J.N.; Njagi, E.N.M. Anti-HIV-1 activities in extracts from some medicinal plants as assessed in an in vitro biochemical HIV-1 reverse transcriptase assay. *Phytother. Res.* **2005**, *19*, 287–290. [[CrossRef](#)] [[PubMed](#)]
65. Painter, G.; Almond, M.; Mao, S.; Liotta, D. Biochemical and mechanistic basis for the activity of nucleoside analogue inhibitors of HIV reverse transcriptase. *Curr. Top. Med. Chem.* **2004**, *4*, 1035–1044. [[CrossRef](#)] [[PubMed](#)]
66. Ng, T.B.; Huang, B.; Fong, W.P.; Yeung, H.W. Anti-Human Immunodeficiency Virus (Anti-HIV) natural products with special emphasis on hiv reverse transcriptase inhibitors. *Life Sci.* **1997**, *61*, 933–949. [[CrossRef](#)]
67. Deng, X.; Zhang, Y.; Jiang, F.; Chen, R.; Peng, P.; Wen, B.; Liang, J. The Chinese herb-derived Sparstolonin B suppresses HIV-1 transcription. *Viol. J.* **2015**, *12*, 108. [[CrossRef](#)]
68. Ma, C.M.; Nakamura, N.; Hattori, M.; Kakuda, H.; Qiao, J.C.; Yu, H.L. Inhibitory effects on HIV-1 protease of constituents from the wood of *Xanthoceras sorbifolia*. *J. Nat. Prod.* **2000**, *63*, 238–242. [[CrossRef](#)]
69. Konvalinka, J.; Kräusslich, H.-G.; Müller, B. Retroviral proteases and their roles in virion maturation. *Virology* **2015**, *479–480*, 403–417. [[CrossRef](#)]
70. Wei, Y.; Ma, C.-M.; Chen, D.-Y.; Hattori, M. Anti-HIV-1 protease triterpenoids from *Stauntonia obovatifoliola* Hayata subsp. *intermedia*. *Phytochemistry* **2008**, *69*, 1875–1879. [[CrossRef](#)]
71. Park, J.C.; Hur, J.M.; Park, J.G.; Hatano, T.; Yoshida, T.; Miyashiro, H.; Min, B.S.; Hattori, M. Inhibitory effects of korean medicinal plants and camelliatannin H from *Camellia japonica* on human immunodeficiency virus type 1 protease. *Phytother. Res.* **2002**, *16*, 422–426. [[CrossRef](#)]
72. Burke, B.P.; Boyd, M.P.; Impey, H.; Breton, L.R.; Bartlett, J.S.; Symonds, G.P.; Hütter, G. CCR5 as a natural and modulated target for inhibition of HIV. *Viruses* **2014**, *6*, 54–68. [[CrossRef](#)]
73. Jiang, S.; Zhao, Q.; Debnath, A.K. Peptide and Non-peptide HIV Fusion Inhibitors. *Curr. Pharm. Des.* **2002**, *8*, 563–580. [[CrossRef](#)]
74. Quinones-Mateu, M.E.; Schols, D. Virus-inhibitory peptide: A natural HIV entry inhibitor in search for a formal target in the viral genome. *AIDS* **2011**, *25*, 1663–1664. [[CrossRef](#)] [[PubMed](#)]
75. Balzarini, J.; Neyts, J.; Schols, D.; Hosoya, M.; Damme, E.V.; Peumans, W.; Clercq, E.D. The mannose-specific plant lectins from *Cymbidium* hybrid and *Epipactis helleborine* and the (N-acetylglucosamine)n-specific plant lectin from *Urtica dioica* are potent and selective inhibitors of human immunodeficiency virus and cytomegalovirus replication in vitro. *Antivir. Res.* **1992**, *18*, 191–207. [[PubMed](#)]
76. Vlietinck, A.J.; Bruyne, T.D.; Apers, S.; Pieters, L.A. Plant-Derived Leading Compounds for Chemotherapy of Human Immunodeficiency Virus (HIV) Infection. *Planta Med.* **1998**, *64*, 97–109. [[CrossRef](#)] [[PubMed](#)]
77. Matsuda, K.; Hattori, S.; Komizu, Y.; Kariya, R.; Ueoka, R.; Okada, S. Cepharanthine inhibited HIV-1 cell-cell transmission and cell-free infection via modification of cell membrane fluidity. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2115–2117. [[CrossRef](#)] [[PubMed](#)]

78. Uttekar, M.M.; Das, T.; Pawar, R.S.; Bhandari, B.; Menon, V.; Nutan; Gupta, S.K.; Bhat, S.V. Anti-HIV activity of semisynthetic derivatives of andrographolide and computational study of HIV-1 gp120 protein binding. *Eur. J. Med. Chem.* **2012**, *56*, 368–374. [[CrossRef](#)] [[PubMed](#)]
79. Kumar, R.A.; Sridevi, K.; Kumar, N.V.; Nanduri, S.; Rajagopal, S. Anticancer and immunostimulatory compounds from *Andrographis paniculata*. *J. Ethnopharmacol.* **2004**, *92*, 291–295. [[CrossRef](#)]
80. Adams, J.D.; Lien, E.J. *Traditional Chinese Medicine: Scientific Basis for Its Use*; The Royal Society of Chemistry: London, UK, 2013.
81. Chao, W.-W.; Lin, B.-F. Isolation and identification of bioactive compounds in *Andrographis paniculata* (Chuanxinlian). *Chin. Med.* **2010**, *5*, 17. [[CrossRef](#)]
82. Varma, A.; Padh, H.; Shrivastava, N. Andrographolide: A new plant-derived antineoplastic entity on horizon. *Evid. Based Complement. Alternat. Med.* **2011**, *2011*, 815390. [[CrossRef](#)]
83. Jayakumar, T.; Hsieh, T.Y.; Lee, J.J.; Sheu, J.R. Experimental and clinical pharmacology of *Andrographis paniculata* and its major bioactive phytoconstituent andrographolide. *Evid. Based Complement. Alternat. Med.* **2013**, *2013*, 846740. [[CrossRef](#)]
84. Wang, C.K.L.; Clark, R.J.; Harvey, P.J.; Rosengren, K.J.; Cemazar, M.; Craik, D.J. The role of conserved Glu residue on cyclotide stability and activity: A structural and functional study of Kalata B12, a naturally occurring Glu to Asp mutant. *Biochemistry* **2011**, *50*, 4077–4086. [[CrossRef](#)]
85. Mfopa, A.N.; Coron, A.; Elo, K.; Tramontano, E.; Frau, A.; Boyom, F.F.; Caboni, P.; Tocco, G. *Uvaria angolensis* as a promising source of inhibitors of HIV-1 RT-associated RNA-dependent DNA polymerase and RNase H functions. *Nat. Prod. Res.* **2018**, *32*, 640–647. [[CrossRef](#)] [[PubMed](#)]
86. Sanna, C.; Scognamiglio, M.; Fiorentino, A.; Corona, A.; Graziani, V.; Caredda, A.; Cortis, P.; Montisci, M.; Ceresola, E.R.; Canducci, F.; et al. Prenylated phloroglucinols from *Hypericum scruglii*, an endemic species of Sardinia (Italy), as new dual HIV-1 inhibitors effective on HIV-1 replication. *PLoS ONE* **2018**, *13*, e0195168. [[CrossRef](#)]
87. Liang, Q.; Yu, F.; Cui, X.; Duan, J.; Wu, Q.; Nagarkatti, P.; Fan, D. Sparstolonin B suppresses lipopolysaccharide-induced inflammation in human umbilical vein endothelial cells. *Arch. Pharm. Res.* **2013**, *36*, 890–896. [[CrossRef](#)] [[PubMed](#)]
88. Huerta-Reyes, M.; Basualdo, M.D.C.; Abe, F.; Jimenez-Estrada, M.; Soler, C.; Reyes-Chilpa, R. HIV-1 inhibitory compounds from *Calophyllum brasiliense* Leaves. *Biol. Pharm. Bull.* **2004**, *27*, 1471–1475. [[CrossRef](#)] [[PubMed](#)]
89. Matthee, G.; Wright, A.D.; Konig, G.M. HIV reverse transcriptase inhibitors of natural origin. *Planta Med.* **1999**, *65*, 493–506. [[CrossRef](#)] [[PubMed](#)]
90. Lee, T.T.-Y.; Kashiwada, Y.; Huang, L.; Snider, J.; Cosentino, M.; Lee, K.-H. Suksdorfins: An Anti-HIV principle from *Lomatium suksdorfii*, its structure-activity correlation with related coumarins, and synergistic effects with anti-AIDS nucleosides. *Bioorg. Med. Chem.* **1994**, *2*, 1051–1056. [[CrossRef](#)]
91. Hudson, J.B.; Graham, E.A.; Harris, L.; Ashwood-Smith, M.J. The unusual Uva-dependent antiviral properties of the furoisocoumarin, coriandrin. *Photochem. Photobiol.* **1993**, *57*, 491–496. [[CrossRef](#)]
92. Hu, C.Q.; Chen, K.; Shi, Q.; Killuskie, R.E.; Cheng, Y.C.; Lee, K.H. Anti-aids agents, 10. Acacetin-7-O- β -D-galactopyranoside, an anti-HIV principle from *Chrysanthemum morifolium* and a structure-activity correlation with some related flavonoids. *J. Nat. Prod.* **1994**, *57*, 42–51. [[CrossRef](#)]
93. Wang, J.N.; Hou, C.Y.; Liu, Y.L.; Lin, L.Z.; Gil, R.R.; Cordell, G.A. Swertifrancheside, an HIV-reverse transcriptase inhibitor and the first flavone-xanthone dimer from *Swertia francheitiana*. *J. Nat. Prod.* **1994**, *57*, 211–217. [[CrossRef](#)]
94. Boyd, M.R.; Hallock, Y.F.; Cardellina, J.H.; Manfredi, K.P.; Blunt, J.W.; McMahon, J.B.; Buckheit, R.W., Jr.; Bringmann, G.; Schiiffer, J.M.; Cragg, G.M.; et al. Anti-HIV michellamines from *Ancistrocladus korupensis*. *J. Med. Chem.* **1994**, *37*, 1740–1745. [[CrossRef](#)]
95. Ingolfsson, K.; Hjalmarsdottir, M.A.; Sigurdsson, A.; Gudjonsdottir, G.A.; Brynjolfsdottir, A.; Steingrimsdottir, O. In vitro susceptibility of *Helicobacter pylori* to protolichesteric acid from the lichen *Cetraria islandica*. *Antimicrob. Agents Chemother.* **1997**, *41*, 215–217. [[CrossRef](#)] [[PubMed](#)]
96. Nakane, H.; Arisawa, M.; Fujita, A.; Koshimura, S.; Ono, K. Inhibition of HIV reverse transcriptase activity by some phloroglucinol derivatives. *FEBS Lett.* **1991**, *286*, 83–85. [[CrossRef](#)]
97. Xiao, W.L.; Tian, R.R.; Pu, J.X.; Li, X.; Wu, L.; Lu, Y.; Li, S.H.; Li, R.T.; Zheng, Y.T.; Zheng, Q.T.; et al. Triterpenoids from *Schisandra lancifolia* with anti-HIV-1 activity. *J. Nat. Prod.* **2006**, *69*, 277–279. [[CrossRef](#)] [[PubMed](#)]

98. Erickson, K.L.; Beutler, J.A.; Cardellina, J.H.; McMahon, J.B.; Newman, D.J.; Boyd, M.R. A novel phorbol ester from *Excoecaria agallocha*. *J. Nat. Prod.* **1995**, *58*, 769–772. [[CrossRef](#)] [[PubMed](#)]
99. Chen, K.; Shi, Q.; Kashiwada, Y.; Zhang, D.C.; Hu, C.Q.; Jin, J.Q.; Nozaki, H.; Kilkuskie, R.E.; Tramontano, E.; Mcphail, D.R.; et al. Anti-AIDS agents, 6. Salaspermic acid, an anti-HIV principle from *Tripterygium wilfordii*, and the structure activity correlation with its related compounds. *J. Nat. Prod.* **1992**, *55*, 340–346. [[CrossRef](#)]
100. Oksuz, S.; Gurek, F.; Gil, R.R.; Pengsuparp, T.; Pezzuto, J.M.; Cordell, G.A. 4 diterpene esters from *Euphorbia myrsinites*. *Phytochemistry* **1995**, *38*, 1457–1462. [[CrossRef](#)]
101. Chinsebu, K.C.; Hedimbi, M. A survey of plants with anti-HIV active compounds and their modes of action. *Med. J. Zambia* **2009**, *36*, 178–186.
102. Chang, R.S.; Ding, L.; Chen, G.Q.; Pan, Q.C.; Zhao, J.L.; Smith, K.M. Dehydroandrographolide succinic acid monoester as an inhibitor against the human immunodeficiency virus. *Proc. Sot. Exp. Biol. Med.* **1991**, *197*, 59–66. [[CrossRef](#)]
103. Ito, M.; Sato, A.; Hirabayashi, K.; Tanabe, F.; Shigeta, S.; Baba, M.; Clercq, E.D.; Nakashima, H.; Yamamoto, N. Mechanism of inhibitory effect of glycyrrhizin on replication of human immunodeficiency virus (HIV). *Antivir. Res.* **1988**, *10*, 289–298. [[CrossRef](#)]
104. Konoshima, T.; Kashiwada, Y.; Takasaki, M.; Kozuka, M.; Yasuda, I.; Cosentino, L.M.; Lee, K.H. Cucurbitacin F derivatives, anti-HIV principles from *Cowania mexicana*. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1323–1326. [[CrossRef](#)]
105. Chen, K.; Shi, Q.A.; Fujioka, T.; Zhang, D.C.; Hu, C.Q.; Jin, J.Q.; Kilkuskie, R.E.; Lee, K.H. Anti-aids agents, 4. Tripterifordin, a novel anti-HIV principle from *Tripterygium wilfordii*: Isolation and structural elucidation. *J. Nat. Prod.* **1992**, *55*, 88–92. [[CrossRef](#)] [[PubMed](#)]
106. Pengsuparp, T.; Cai, L.; Fong, H.H.; Kinghorn, A.D.; Pezzuto, J.M.; Wani, M.C.; Wall, M.E. Pentacyclic triterpenes derived from *Maprounea africana* are potent inhibitors of HIV-1 reverse transcriptase. *J. Nat. Prod.* **1994**, *57*, 415–418. [[CrossRef](#)] [[PubMed](#)]
107. Fujioka, T.; Kashiwada, Y.; Kilkuskie, R.E.; Cosentino, L.M.; Ballas, L.M.; Jiang, J.B.; Janzen, W.P.; Chen, I.S.; Lee, K.H. Anti-aids agents, 11. Betulinic acid and platanic acid as anti-HIV principles from *Syzgium claviflorum*, and the anti-HIV activity of structurally related triterpenoids. *J. Nat. Prod.* **1994**, *57*, 243–247. [[CrossRef](#)] [[PubMed](#)]
108. Hayashi, K.; Kamiya, M.; Hayashi, T. Virucidal effects of steam distillate from *Houttuynia cordata* and its components on HSV-1, influenza virus, and HIV. *Planta Med.* **1995**, *61*, 237–241. [[CrossRef](#)] [[PubMed](#)]
109. Li, B.Q.; Fu, T.; Yan, Y.D.; Baylor, N.W.; Ruscetti, F.W.; Kung, H.F. Inhibition of HIV infection by baicalin-a flavonoid compound purified from Chinese herbal medicine. *Cell. Mol. Biol. Res.* **1993**, *39*, 119–124. [[PubMed](#)]
110. Beutler, J.A.; Cardellina, J.H.; McMahon, J.B.; Boyd, M.R.; Cragg, G.M. Anti-HIV and cytotoxic alkaloids from *Buchenavia capitata*. *J. Nat. Prod.* **1992**, *55*, 207–213. [[CrossRef](#)] [[PubMed](#)]
111. Tang, X.; Chen, H.; Zhang, X.; Quan, K.; Sun, M. Screening anti-HIV Chinese material medica with HIV and equine infectious anemic virus reverse transcriptase. *J. Trad. Chin. Med.* **1994**, *14*, 10–13.
112. Patil, A.D.; Freyer, A.J.; Eggleston, D.S.; Haltiwanger, R.C.; Bean, M.F.; Taylor, P.B.; Caranfa, M.J.; Breen, A.L.; Bartus, H.R.; Johnson, R.K. The inophyllums, novel inhibitors of HIV-1 reverse transcriptase isolated from Malaysian tree, *Calophyllum inophyllum* Linn. *J. Med. Chem.* **1993**, *36*, 4131–4138. [[CrossRef](#)]
113. Sharma, B.R.; Rattan, R.K.; Sharma, P. Marmeline, an alkaloid, and other components of unripe fruits of *Aegle marmelos*. *Phytochemistry* **1981**, *20*, 2606–2607. [[CrossRef](#)]
114. Harkar, S.; Razdan, T.K.; Waight, E.S. Steroids, chromone and coumarins from *Angelica officinalis*. *Phytochemistry* **1984**, *23*, 419–426. [[CrossRef](#)]
115. Cheng, H.Y.; Lin, T.C.; Yang, C.M.; Wang, K.C.; Lin, L.T.; Lin, C.C. Putranjivain A from *Euphorbia jolkini* inhibits both virus entry and late stage replication of herpes simplex virus type 2 in vitro. *J. Antimicrob. Chemother.* **2004**, *53*, 577–583. [[CrossRef](#)] [[PubMed](#)]
116. Hatano, T.; Ogawa, N.; Kira, R.; Yasuhara, T.; Okuda, T. Tannins of cornaceous plants. I. Cornusins A, B and C, dimeric monomeric and trimeric hydrolysable tannins from *Cornus officinalis*, and orientation of valoneoyl group in related tannins. *Chem. Pharm. Bull. (Tokyo)* **1989**, *37*, 2083–2090. [[CrossRef](#)] [[PubMed](#)]
117. Ogata, T.; Higuchi, H.; Mochida, S.; Matsumoto, H.; Kato, A.; Endo, T.; Kaji, A.; Kaji, H. HIV-1 reverse transcriptase inhibitor from *Phyllanthus niruri*. *AIDS Res. Hum. Retrovir.* **1992**, *8*, 1937–1944. [[CrossRef](#)] [[PubMed](#)]

118. Kreis, W.; Kaplan, M.H.; Freeman, J.; Sun, D.K.; Sarin, P.S. Inhibition of HIV replication by *Hyssop officinalis* extracts. *Antivir. Res.* **1990**, *14*, 323–337. [[CrossRef](#)]
119. Naser, B.; Bodinet, C.; Tegtmeier, M.; Lindequist, U. *Thuja occidentalis* (Arbor vitae): A review of its pharmaceutical, pharmacological and clinical properties. *Evid. Based Complement. Altern. Med.* **2005**, *2*, 69–78. [[CrossRef](#)]
120. Tabbá, H.D.; Chang, R.S.; Smith, K.M. Isolation, purification, and partial characterization of Prunellin, an Anti-HIV component from aqueous extracts of *Prunella vulgaris*. *Antivir. Res.* **1989**, *11*, 263–273. [[CrossRef](#)]
121. Ngan, F.; Chang, R.S.; Tabbá, H.D.; Smith, K.M. Isolation, purification and partial characterization of an active anti-HIV compound from the Chinese medicinal herb *Viola yedoensis*. *Antivir. Res.* **1988**, *10*, 107–116. [[CrossRef](#)]
122. Wang, J.P.; Raung, S.L.; Lin, C.N.; Teng, C.M. Inhibitory effect of norathyriol, a xanthone from *Tripterospermum lanceolatum*, on cutaneous plasma extravasation. *Eur. J. Pharmacol.* **1994**, *251*, 35–42. [[CrossRef](#)]
123. Ulubelen, A.; Gil, R.R.; Cordell, G.A.; Mericli, A.H.; Mericli, F. Prenylated lignans from *Haplophyllum ptilostylum*. *Phytochemistry* **1995**, *39*, 417–422. [[CrossRef](#)]
124. Fujihashi, T.; Hara, H.; Sakata, T.; Mori, K.; Higuchi, H.; Tanaka, A.; Kaji, H.; Kaji, A. Anti-human immunodeficiency virus (HIV) activities of halogenated gomisin J derivatives, new nonnucleoside inhibitors of HIV type 1 reverse transcriptase. *Antimicrob. Agents Chemother.* **1995**, *39*, 2000–2007. [[CrossRef](#)]
125. Schröder, H.C.; Merz, H.; Steffen, R.; Müller, W.E.G. Differential in vitro Anti-HIV Activity of Natural Lignans. *Z. Naturforsch.* **1990**, *45c*, 1215–1221. [[CrossRef](#)] [[PubMed](#)]
126. Talpir, R.; Rudi, A.; Kashman, Y.; Hizi, A. Three new sesquiterpene hydroquinones from marine origin. *Tetrahedron* **1994**, *50*, 4179–4184. [[CrossRef](#)]
127. Jimenez, C.; Quinoa, E.; Adamczeski, M.; Hunter, L.M.; Crews, P. Novel sponge-derived amino acids. 12. Tryptophan-derived pigments and accompanying sesterterpenes from *Fascapilsinopsis reticulata*. *J. Org. Chem.* **1991**, *56*, 3403–3410. [[CrossRef](#)]
128. Loya, S.; Tal, R.; Hizi, A.; Issacs, S.; Kashman, Y.; Loya, Y. Hexprenoid hydroquinones, novel inhibitors of the reverse transcriptase of human immunodeficiency virus type 1. *J. Nat. Prod.* **1993**, *56*, 2120–2125. [[CrossRef](#)]
129. Inman, W.D.; Johnson, M.O.; Crews, P. Novel marine sponge alkaloids. 1. Plakinidine A and B, anthelmintic active alkaloids from a *Plakortis* sponge. *J. Am. Chem. Soc.* **1990**, *112*, 1–4. [[CrossRef](#)]
130. Tymiak, A.A.; Rinehart, K.L., Jr. Structures of kellestinins 1 and 2, antibacterial metabolites of the marine mollusk *Kelletia kelletii*. *J. Am. Chem. Soc.* **1983**, *105*, 7396–7401. [[CrossRef](#)]
131. Silvestri, I.; Albonici, L.; Ciotti, M.; Lombardi, M.P.; Sinibaldi, P.; Manzari, V.; Orlando, P.; Carretta, F.; Strazzullo, G.; Grippo, P. Antimitotic and antiviral activities of Kelletin A in HTLV-1 infected MT2 cells. *Experientia* **1995**, *51*, 1076–1080. [[CrossRef](#)]
132. Chaudhuri, S.K.; Fullas, F.; Brown, D.M.; Wani, M.C.; Wall, M.E.; Cai, L.; Mar, W.; Lee, S.K.; Luo, Y.; Zaw, K.; et al. Isolation and structural elucidation of pentacyclic triterpenoids from *Maprounea africana*. *J. Nat. Prod.* **1995**, *58*, 1–9. [[CrossRef](#)]
133. Pani, A.; Marongiu, M.E. Anti-HIV integrase drugs how far from the shelf. *Curr. Pharm. Des.* **2000**, *6*, 569–584. [[CrossRef](#)]
134. Ghosh, S.; Ahire, M.; Patil, S.; Jabgunde, A.; Dusane, M.B.; Joshi, B.N.; Pardesi, K.; Jachak, S.; Dhavale, D.D.; Chopade, B.A. Antidiabetic activity of *Gnidia glauca* and *Dioscorea bulbifera*: Potent amylase and glucosidase inhibitors. *Evid. Based Complement. Altern. Med.* **2012**, *2012*, 929051. [[CrossRef](#)]
135. Wang, J.M.; Ji, L.L.; Branford-White, C.J.; Wang, Z.Y.; Shen, K.K.; Liu, H.; Wang, Z.T. Antitumor activity of *Dioscorea bulbifera* L. rhizome in vivo. *Fitoterapia* **2012**, *83*, 388–394. [[CrossRef](#)] [[PubMed](#)]
136. Teponno, R.B.; Tapondjou, A.L.; Gatsing, D.; Djoukeng, J.D.; AbouMansour, E.; Tabacchi, R.; Tane, P.; Stoekli-Evans, H.; Lontsi, D. Bafoudiosbulbins A, and B, two anti-salmonella clerodane diterpenoids from *Dioscorea bulbifera* L. var *sativa*. *Phytochemistry* **2006**, *67*, 1957–1963. [[CrossRef](#)] [[PubMed](#)]
137. Mbiantcha, M.; Kamanyi, A.; Teponno, R.B.; Barreca, M.L.; Villa, L.; Monforte, P.; Chimirri, A. Analgesic and anti-inflammatory properties of extracts from the bulbils of *Dioscorea bulbifera* L. var *sativa* (Dioscoreaceae) in mice and rats. *Evid. Based Complement. Alternat. Med.* **2011**, *2011*, 912935. [[CrossRef](#)] [[PubMed](#)]
138. Ahmed, Z.; Chishti, M.Z.; Johri, R.K.; Bhagat, A.; Gupta, K.K.; Ram, G. Antihyperglycemic and antidiabetic activity of aqueous extract of *Dioscorea bulbifera* tubers. *Diabetol. Croat.* **2009**, *38*, 63–72.

139. Panthong, P.; Bunluepuech, K.; Boonnak, N.; Chaniad, P.; Pianwanit, S.; Wattanapiromsakul, C.; Tewtrakul, S. Anti-HIV-1 integrase activity and molecular docking of compounds from *Albizia procera* bark. *Pharm. Biol.* **2015**, *53*, 1861–1866. [[CrossRef](#)]
140. Kokila, K.; Priyadharshini, S.D.; Sujatha, V. Phytopharmacological properties of *Albizia* species: A review. *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 70–73.
141. Yadav, S.K.; Batra, J.K. Mechanism of anti-HIV activity of ribosome inactivating protein, saporin. *Protein Pept. Lett.* **2015**, *22*, 497–503. [[CrossRef](#)]
142. Puri, M.; Kaur, I.; Kanwar, R.K.; Gupta, R.C.; Chauhan, A.; Kanwar, J.R. Ribosome inactivating proteins (RIPs) from *Momordica charantia* for anti viral therapy. *Curr. Mol. Med.* **2009**, *9*, 1080–1094. [[CrossRef](#)]
143. Sun, Y.; Huang, P.L.; Li, J.J.; Huang, Y.Q.; Zhang, L.; Huang, P.L.; Lee-Huang, S. Anti-HIV agent MAP30 modulates the expression profile of viral and cellular genes for proliferation and apoptosis with Kaposi's sarcoma-associated virus. *Biochem. Biophys. Res. Commun.* **2001**, *287*, 983–994. [[CrossRef](#)]
144. Zhao, W.; Feng, D.; Sun, S.; Han, T.; Sui, S. The anti-viral protein of trichosanthin penetrates into human immunodeficiency virus type 1. *Acta. Biochim. Biophys. Sin.* **2010**, 91–97. [[CrossRef](#)]
145. Au, T.K.; Collins, R.A.; Lam, T.L.; Ng, T.B.; Fong, W.P.; Wan, D.C.C. The plant ribosome inactivating proteins luffin and saporin are potent inhibitors of HIV-1 integrase. *FEBS Lett.* **2000**, *471*, 169–172. [[CrossRef](#)]
146. Kohl, N.E.; Emini, E.A.; Schiief, W.A. Active human immunodeficiency virus protease is required for viral infectivity. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 4686–4690. [[CrossRef](#)] [[PubMed](#)]
147. Katoch, I.; Ikawa, Y.; Yoshinaka, Y. Retrovirus protease characterized as a dimeric aspartic proteinase. *J. Virol.* **1989**, *63*, 2226–2232. [[CrossRef](#)]
148. Han, L.; Hatano, T.; Yoshida, T.; Okuda, T. Tannins of Theaceous plants. V. Camelliatannins F, G and H, three new tannins from *Camellia japonica* L. *Chem. Pharm. Bull.* **1994**, *42*, 1399–1409. [[CrossRef](#)] [[PubMed](#)]
149. Mcquade, T.J.; Tomasselli, A.G.; Liu, L. A synthetic HIV-1 protease inhibitor with antiviral activity arrests HIV-like particle maturation. *Science* **1990**, *247*, 454–456. [[CrossRef](#)]
150. Meek, T.D.; Dayton, B.D.; Metcalf, B.W. Human immunodeficiency virus 1 protease expressed in *Escherichia coli* behaves as a dimeric aspartic protease. *Proc. Natl. Acad. Sci. USA.* **1989**, *86*, 1841–1845. [[CrossRef](#)]
151. Dantanarayana, A.P.; Kumar, N.S.; Muthukuda, P.M.; Wazzeer, M.I.M. A lupine derivative and the ¹³C NMR chemical shifts of some lupanols from *Pleurostyliia opposita*. *Phytochemistry* **1982**, *21*, 2065–2068. [[CrossRef](#)]
152. Ikuta, A. The triterpenes from *Stauntonia hexaphylla* callus tissues and their biosynthetic significance. *J. Nat. Prod.* **1989**, *52*, 623–628. [[CrossRef](#)]
153. Pech, G.G.; Brito, W.F.; Mena, G.J.; Quijano, L. Constituents of *Acacia cedilloi* and *Acacia gaumeri*. Revised structure and complete NMR assignments of resinone. *Z. Naturforsch.* **2002**, *57c*, 773–776. [[CrossRef](#)]
154. Wenkert, E.; Baddeley, G.V.; Burfit, I.R.; Moreno, L.N. Carbon-13 nuclear magnetic resonance spectroscopy of naturally –occurring substances. LVII. Triterpenes related to lupine and hopane. *Org. Magn. Reson.* **1978**, *11*, 343–377. [[CrossRef](#)]
155. Ikuta, A.; Itokawa, H. Triterpenoids of *Akebia quinata* callus tissue. *Phytochemistry* **1986**, *25*, 1625–1628. [[CrossRef](#)]
156. Seo, S.; Tomita, Y.; Tori, K. Carbon-13 NMR spectra of urs-12-enes and application to structural assignments of components of *Isodon japonicus* hara tissue cultures. *Tetrahedron Lett.* **1975**, *16*, 7–10. [[CrossRef](#)]
157. Hakkinen, S.H.; Karenlampi, S.O.; Heinonen, I.M.; Mykkanen, H.M.; Torronen, A.R. Content of flavonols quercetin, myricetin, and kaempferol in 25 edible berries. *J. Agric. Food Chem.* **1999**, *47*, 2274–2279. [[CrossRef](#)] [[PubMed](#)]
158. Liang, S.; Tian, J.-M.; Feng, Y.; Liu, X.-H.; Xiong, Z.; Zhang, W.-D. Flavonoids from *Daphne aurantiaca* and their inhibitory activities against nitric oxide production. *Chem. Pharm. Bull.* **2011**, *59*, 653–656. [[CrossRef](#)]
159. Venkatalakshmi, P.; Vadivel, V.; Brindha, P. Role of phytochemicals as immunomodulatory agents: A review. *Int. J. Green Pharm.* **2016**, *10*, 1–18.
160. Sell, S. Immunomodulation. In *Immunology Immunopathology and Immunity*; Elsevier Science Publishing Company, Inc.: New York, NY, USA, 1987; pp. 655–683.
161. Agarwal, S.S.; Singh, V.K. Immunomodulators: A review of studies on Indian medicinal plants and synthetic peptides. Part-I: Medicinal plants. *Proc. Indian Nation Sci. Acad. B* **1999**, *65*, 179–204.
162. Holtmeier, W.; Kabelitz, D. Gammadelta T cells link innate and adaptive immune responses. *Chem. Immunol. Allergy* **2005**, *86*, 151–183.
163. Harborne, J.B. *Phytochemical Methods*; Chapman and Hall, Ltd.: London, UK, 1973; pp. 149–188.

164. Okwu, D.E. Phytochemicals and vitamin content of indigenous spices of South Eastern. *Nig. J. Sust. Agric. Environ.* **2004**, *6*, 30–37.
165. Li, F.; Wang, H.D.; Lu, D.X.; Wang, Y.P.; Qi, R.B.; Fu, Y.M.; Li, C.J. Neutral sulfate berberine modulates cytokine secretion and increases survival in endotoxemic mice. *Acta. Pharmacol. Sin.* **2006**, *27*, 1199–1205. [[CrossRef](#)]
166. Mark, W.; Schneeberger, S.; Seiler, R.; Stroka, D.M.; Amberger, A.; Offner, F.; Candinas, D.; Margreiter, R. Sinomenine blocks tissue remodeling in a rat model of chronic cardiac allograft rejection. *Transplantation* **2003**, *75*, 940–945. [[CrossRef](#)]
167. Sunila, E.S.; Kuttan, G. Immunomodulatory and antitumor activity of *Piper longum* Linn. and piperine. *J. Ethnopharmacol.* **2004**, *90*, 339–346. [[CrossRef](#)] [[PubMed](#)]
168. Lai, J.H.; Ho, L.J.; Kwan, C.Y.; Chang, D.M.; Lee, T.C. Plant alkaloid tetrandrine and its analog block CD28-costimulated activities of human peripheral blood T cells: Potential immunosuppressants in transplantation immunology. *Transplantation* **1999**, *68*, 1383–1392. [[CrossRef](#)] [[PubMed](#)]
169. Chiang, L.C.; Ng, L.T.; Chiang, W.; Chang, M.Y.; Lin, C.C. Immunomodulatory activities of flavonoids, monoterpenoids, triterpenoids, iridoid glycosides and phenolic compounds of *Plantago* species. *Planta Med.* **2003**, *69*, 600–604. [[PubMed](#)]
170. Akbay, P.; Basaran, A.A.; Undeger, U.; Basaran, N. In vitro immunomodulatory activity of flavonoid glycosides from *Urtica dioica* L. *Phytother. Res.* **2003**, *17*, 34–37. [[CrossRef](#)] [[PubMed](#)]
171. Garcia, D.; Leiro, J.; Delgado, R.; Sanmartín, M.L.; Ubeira, F.M. *Mangifera indica* L. extract (Vimang) and mangiferin modulate mouse humoral immune responses. *Phytother. Res.* **2003**, *17*, 1182–1187. [[CrossRef](#)] [[PubMed](#)]
172. Seeram, N.P.; Adams, L.S.; Henning, S.M.; Niu, Y.; Zhang, Y.; Nair, M.G.; Heber, D. In vitro anti-proliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *J. Nutr. Biochem.* **2005**, *16*, 360–367. [[CrossRef](#)]
173. Ranjan, D.; Johnston, T.D.; Wu, G.; Elliott, L.; Bondada, S.; Nagabhushan, M. Curcumin blocks cyclosporine A-resistant CD28 costimulatory pathway of human T-cell proliferation. *J. Surg. Res.* **1998**, *77*, 174–178. [[CrossRef](#)]
174. Reddy, D.B.; Reddanna, P. Chebulagic acid (CA) attenuates LPS-induced inflammation by suppressing NF-kappaB and MAPK activation in RAW 264.7 macrophages. *Biochem. Biophys. Res. Commun.* **2009**, *381*, 112–117. [[CrossRef](#)]
175. Lee, S.I.; Kim, B.S.; Kim, K.S.; Lee, S.; Shin, K.S.; Lim, J.S. Immune-suppressive activity of punicalagin via inhibition of NFAT activation. *Biochem. Biophys. Res. Commun.* **2008**, *371*, 799–803. [[CrossRef](#)]
176. Chang, S.L.; Chiang, Y.M.; Chang, C.L.; Yeh, H.H.; Shyur, L.F.; Kuo, Y.H. Flavonoids, centaurein and centaureidin, from *Bidens pilosa*, stimulate IFN-gamma expression. *J. Ethnopharmacol.* **2007**, *112*, 232–236. [[CrossRef](#)] [[PubMed](#)]
177. Abd-Alla, H.I.; Moharram, F.A.; Gaara, A.H.; El-Safty, M.M. Phytoconstituents of *Jatropha curcas* L. leaves and their immunomodulatory activity on humoral and cell-mediated immune response in chicks. *Z. Naturforsch. C* **2009**, *64*, 495–501. [[CrossRef](#)] [[PubMed](#)]
178. Punturee, K.; Wild, C.P.; Kasinrerk, W.; Vinitketkumnuen, U. Immunomodulatory activities of *Centella asiatica* and *Rhinacanthus nasutus* extracts. *Asian Pac. J. Cancer Prev.* **2005**, *6*, 396–400. [[PubMed](#)]
179. Ablise, M.; Leininger-Muller, B.; Wong, C.D.; Siest, G.; Loppinet, V.; Visvikis, S. Synthesis and in vitro antioxidant activity of glycyrrhetic acid derivatives tested with the cytochrome P450/NADPH system. *Chem. Pharm. Bull. (Tokyo)* **2004**, *52*, 1436–1439. [[CrossRef](#)] [[PubMed](#)]
180. Pace, G.W.; Leaf, C.D. The role of oxidative stress in HIV disease. *Free Radic. Biol. Med.* **1995**, *19*, 523–528. [[CrossRef](#)]
181. Olinski, R.; Gackowski, D.; Foksinski, M.; Rozalski, R.; Roszkowski, K.; Jaruga, P. Oxidative DNA damage: Assessment of the role in carcinogenesis, atherosclerosis, and acquired immunodeficiency syndrome. *Free Radic. Biol. Med.* **2002**, *33*, 192–200. [[CrossRef](#)]
182. Torre, D.; Pugliese, A.; Speranza, F. Role of nitric oxide in HIV-1 infection: Friend or foe? *Lancet Infect. Dis* **2002**, *2*, 273–280. [[CrossRef](#)]

183. Kinscherf, R.; Fischbach, T.; Mihm, S.; Roth, S.; HohenhausSievert, E.; Weiss, C.; Edler, L.; Bartsch, P.; Droge, W. Effect of glutathione depletion and oral *N*-acetyl-cysteine treatment on CD4+ and CD8+ cells. *FASEB J.* **1994**, *8*, 448–451. [[CrossRef](#)]
184. Sappey, C.; Legrand-Poels, S.; Best-Belpomme, M.; Favier, A.; Rentier, B.; Piette, J. Stimulation of glutathione peroxidase activity decreases HIV type 1 activation after oxidative stress. *AIDS Res. Hum. Retrovir.* **1994**, *10*, 1451–1461. [[CrossRef](#)]
185. Bailly, F.; Cotellet, P. Anti-HIV activities of natural antioxidant caffeic acid derivatives: Toward an antiviral supplementation Diet. *Curr. Med. Chem.* **2005**, *12*, 1811–1818. [[CrossRef](#)]
186. Rechner, A.R.; Kroner, C. Anthocyanins and colonic metabolites of dietary polyphenols inhibit platelet function. *Thromb. Res.* **2005**, *116*, 327–334. [[CrossRef](#)]
187. Tanahashi, T. Diversity of secondary metabolites from some medicinal plants and cultivated lichen mycobionts. *Yakugaku Zasshi* **2017**, *137*, 1443–1482. [[CrossRef](#)] [[PubMed](#)]
188. Shitan, N. Secondary metabolites in plants: Transport and self-tolerance mechanisms. *Biosci. Biotechnol. Biochem.* **2016**, *80*, 1283–1293. [[CrossRef](#)] [[PubMed](#)]
189. Connor, S.E.O. Engineering of secondary metabolism. *Annu. Rev. Genet.* **2015**, *49*, 5.1–5.2. [[CrossRef](#)] [[PubMed](#)]
190. Musilova, L.; Ridl, J.; Polivkova, M.; Macek, T.; Uhlik, O. Effects of secondary plant metabolites on microbial populations: Changes in community structure and metabolic activity in contaminated environments. *Int. J. Mol. Sci.* **2016**, *17*, 1205. [[CrossRef](#)]
191. Singh, I.P.; Bodiwala, H.S. Recent advances in anti-HIV natural products. *Nat. Prod. Rep.* **2010**, *27*, 1781–1800. [[CrossRef](#)]
192. Yu, D.; Morris-Natschke, S.L.; Lee, K.-H. New developments in natural products-based anti-AIDS research. *Med. Res. Rev.* **2007**, *27*, 108–132. [[CrossRef](#)] [[PubMed](#)]
193. Asres, K.; Seyoum, A.; Veeresham, C.; Bucar, F.; Gibbons, S. Naturally derived anti-HIV agents. *Phytother. Res.* **2005**, *19*, 557–581. [[CrossRef](#)]
194. McCormick, J.L.; Mckee, T.C.; Cardellina, J.H.; Boyd, M.R. HIV inhibitory natural products. 26. Quinoline alkaloids from *Euodia roxburghiana*. *J. Nat. Prod.* **1996**, *59*, 469–471.
195. Duan, H.; Takaishi, Y.; Imakura, Y.; Jia, Y.; Li, D.; Cosentino, L.M. Sesquiterpene alkaloids from *Tripterygium hypoglaucum* and *Tripterygium wilfordii*: A new class of potent Anti-HIV agents. *J. Nat. Prod.* **2000**, *63*, 357–361. [[CrossRef](#)]
196. Tan, G.T.; Pezzuto, J.M.; Kinghorn, A.D.; Hughes, S.H. Evaluation of natural products as inhibitors of human immunodeficiency virus type1 (HIV-1) reverse transcriptase. *J. Nat. Prod.* **1991**, *54*, 143–154. [[CrossRef](#)]
197. Ishida, J.; Wang, H.-K.; Oyama, M.; Cosentino, M.L.; Hu, C.-Q.; Lee, K.H. Anti-AIDS agents. 46.1 anti-HIV activity of harman, an anti-HIV principle from *Symplocos setchuensis*, and its Derivatives. *J. Nat. Prod.* **2001**, *64*, 958–960. [[CrossRef](#)]
198. Loya, S.; Rudi, A.; Kashman, Y.; Hizi, A. Polycitone A, a novel and potent general inhibitor of retroviral reverse transcriptases and cellular DNA polymerases. *Biochem. J.* **1999**, *344*, 85–92. [[CrossRef](#)]
199. Xu, H.X.; Wan, M.; Dong, H.; But, P.P.; Foo, L.Y. Inhibitory activity of flavonoids and tannins against HIV-1 protease. *Biol. Pharm. Bull.* **2000**, *23*, 1072–1076. [[CrossRef](#)]
200. Ravanelli, N.; Santos, K.P.; Motta, L.B.; Lago, J.H.G.; Furlan, C.M. Alkaloids from *Croton echinocarpus* Baill: Anti-HIV potential. *S. Afr. J. Bot.* **2015**, *102*, 153–156. [[CrossRef](#)]
201. White, E.L.; Chao, W.R.; Ross, L.J.; Borhani, D.W.; Hobbs, P.D.; Upender, V.; Dawson, M.I. Michellamine alkaloids inhibit protein kinase C. *Arch. Biochem. Biophys.* **1999**, *365*, 25–30. [[CrossRef](#)]
202. Kondo, Y.; Imai, Y.; Hojo, H.; Hashimoto, Y.; Nozoe, S. Selective inhibition of T cell dependent immune responses by bisbenzylisoquinoline alkaloids in vivo. *Int. J. Immunopharmacol.* **1992**, *14*, 1181–1186. [[CrossRef](#)]
203. Meragelman, K.M.; McKee, T.C.; Boyd, M.R. Siamenol, a new carbazole alkaloid from *Murraya siamensis*. *J. Nat. Prod.* **2000**, *63*, 427–428. [[CrossRef](#)]
204. Kongkathip, B.; Kongkathip, N.; Sunthitikawinsakul, A.; Napaswat, C.; Yoosook, C. Anti-HIV-1 constituents from *Clausena excavata*: Part II. Carbazoles and a pyranocoumarin. *Phytother. Res.* **2005**, *19*, 728–731. [[CrossRef](#)]
205. Hsieh, P.W.; Chang, F.R.; Lee, K.H.; Hwang, T.L.; Chang, S.M.; Wu, Y.C. A new anti-HIV alkaloid, drymaritin, and a new C-glycoside flavonoid, diandroflavone, from *Drymaria diandra*. *J. Nat. Prod.* **2004**, *67*, 1175–1177. [[CrossRef](#)]

206. Wang, J.; Zheng, Y.; Efferth, T.; Wang, R.; Shen, Y.; Hao, X. Indole and carbazole alkaloids from *Glycosmis montana* with weak anti-HIV and cytotoxic activities. *Phytochemistry* **2005**, *66*, 697–701. [[CrossRef](#)]
207. Jayasuriya, H.; Herath, K.B.; Ondeyka, J.G.; Polishook, J.D.; Bills, G.F.; Dombrowski, A.W.; Springer, M.S.; Siciliano, S.; Malkowitz, L.; Sanchez, M.; et al. Isolation and structure of antagonists of chemokine receptor (CCR5). *J. Nat. Prod.* **2004**, *67*, 1036–1038. [[CrossRef](#)]
208. Cheng, M.J.; Lee, K.H.; Tsai, I.L.; Chen, I.S. Two new sesquiterpenoids and anti-HIV principles from the root bark of *Zanthoxylum ailantoides*. *Bioorg. Med. Chem.* **2005**, *13*, 5915–5920. [[CrossRef](#)]
209. Stadler, R.; Kutchan, T.M.; Zenk, M.H. (S)-norcoclaurine is the central intermediate in benzylisoquinoline alkaloid biosynthesis. *Phytochemistry* **1989**, *28*, 1083–1086. [[CrossRef](#)]
210. Yan, M.H.; Cheng, P.; Jiang, Z.Y.; Ma, Y.B.; Zhang, X.M.; Zhang, F.X.; Yang, L.M.; Zheng, Y.T.; Chen, J.J. Periglaucines A–D, Anti-HBV and HIV-1 alkaloid from *Pericampylus glaucus*. *J. Nat. Prod.* **2008**, *71*, 760–763. [[CrossRef](#)]
211. Wu, P.L.; Lin, F.W.; Wu, T.S.; Kuoh, C.S.; Lee, K.H.; Lee, S.J. Cytotoxic and anti-HIV principles from the rhizomes of *Begonia nantoensis*. *Chem. Pharm. Bull.* **2004**, *52*, 345–349. [[CrossRef](#)]
212. Szlavik, L.; Gyuris, A.; Minarovits, J.; Forgo, P.; Molnarand, J.; Hohmann, J. Alkaloids from *Leucojum vernum* and antiretroviral activity of amaryllidaceae alkaloids. *Planta Med.* **2004**, *70*, 871–873. [[CrossRef](#)]
213. Otshudi, A.L.; Apers, S.; Pieters, L.; Claeys, M.; Pannecouque, C.; Clercq, E.D.; Zeebroeck, A.V.; Lauwers, S.; Frederich, M.; Foriers, A. Biologically active bisbenzylisoquinoline alkaloids from the root bark of *Epinetrum villosum*. *J. Ethnopharmacol.* **2005**, *31*, 89–94. [[CrossRef](#)]
214. Chang, Y.C.; Hsieh, P.W.; Chang, F.R.; Wu, R.R.; Liaw, C.C.; Lee, K.H.; Wu, Y.C. Two new protopines argemexicaines A and B and the anti-HIV alkaloid 6-acetyl-dihydrochelerythrine from formosan *Argemone mexicana*. *Planta Med.* **2003**, *69*, 148–152. [[CrossRef](#)]
215. Hua, H.M.; Peng, J.; Dunbar, D.C.; Schinazi, R.F.; de Andrews, A.G.C.; Cuevas, C.; Garcia-Fernandez, L.F.; Kelly, M.; Hamanna, M.T. Batzelladine alkaloids from the caribbean sponge *Monanchora unguifera* and the significant activities against HIV-1 and AIDS opportunistic infectious pathogens. *Tetrahedron* **2007**, *63*, 11179–11188. [[CrossRef](#)]
216. Peng, J.; Hu, J.F.; Kazi, A.B. Manadomanzamines A and B: A novel alkaloid ring system with potent activity against mycobacteria and HIV-1. *J. Am. Chem. Soc.* **2003**, *125*, 13382–13386. [[CrossRef](#)]
217. Zhang, C.F.; Nakamura, N.; Tewtrakul, S. Sesquiterpenes and alkaloids from *Lindera chunii* and their inhibitory activities against HIV-1 integrase. *Chem. Pharm. Bull.* **2002**, *50*, 1195–1200. [[CrossRef](#)] [[PubMed](#)]
218. Ma, C.M.; Nakamura, N.; Hattori, M. Inhibitory effects on HIV-1 protease of tri-*p*-coumaroylspermidine from *Artemisia caruifolia* and related amides. *Chem. Pharm. Bull.* **2001**, *49*, 915–917. [[CrossRef](#)] [[PubMed](#)]
219. Kiyama, R. Estrogenic terpenes and terpenoids: Pathways, functions and applications. *Eur. J. Pharmacol.* **2017**, *815*, 405–415. [[CrossRef](#)]
220. Kuo, R.Y.; Qian, K.; Susan, L.; Natschke, M.; Lee, K.H. Plant-derived triterpenoids and analogues as antitumor and anti-HIV agents. *Nat. Prod. Rep.* **2009**, *26*, 1321–1344. [[CrossRef](#)]
221. Min, B.S.; Jung, H.J.; Lee, J.S.; Kim, Y.H.; Bok, S.H.; Ma, C.M. Inhibitory effect of triterpenes from *Crataegus pinatifida* on HIV-1 protease. *Planta Med.* **1999**, *65*, 374–375. [[CrossRef](#)]
222. Yao-Haur, K.; Li-Ming, Y.K. Antitumor and anti-AIDS triterpenes from *Celastrus hindsii*. *Phytochemistry* **1997**, *44*, 1275–1281. [[CrossRef](#)]
223. El-Mekkawy, S.; Meselhy, M.R.; Nakamura, N.; Hattori, M.; Kawahata, T.; Otake, T. Anti-HIV-1 phorbol esters from the seeds of *Croton tiglium*. *Phytochemistry* **2000**, *53*, 457–464. [[CrossRef](#)]
224. Rukachaisirikul, V.; Pailee, P.; Hiranrat, A.; Tuchinda, P.; Yoosook, C.; Kasisit, J. Anti-HIV-1 protostane triterpenes and digeranylbenzophenone from trunk bark and stems of *Garcinia speciosa*. *Planta Med.* **2003**, *69*, 1141–1146.
225. Xu, H.-X.; Zeng, F.-Q.; Wan, M.; Sim, K.-Y. Anti-HIV triterpene acids from *Geum japonicum*. *J. Nat. Prod.* **1996**, *59*, 643–645. [[CrossRef](#)]
226. Chen, D.-F.; Zhang, S.-X.; Wang, H.-K.; Zhang, S.-Y.; Sun, Q.-Z.; Cosentino, L.M. Novel anti-HIV lanclactone C and related triterpenes from *Kadsura lancilimba*. *J. Nat. Prod.* **1999**, *62*, 94–97. [[CrossRef](#)]
227. Nakamura, N. Inhibitory effects of some traditional medicines on proliferation of HIV-1 and its protease. *Yakugaku Zasshi.* **2004**, *124*, 519–529. [[CrossRef](#)] [[PubMed](#)]

228. Li, H.-Y.; Sun, N.-J.; Kashiwada, Y.; Sun, L.; Snider, J.V.; Cosentino, L.M. Anti-AIDS agents, 9. Suberosol, a new C-31 lanostane-type triterpene and Anti-HIV principle from *Polyalthia suberosa*. *J. Nat. Prod.* **1993**, *56*, 1130–1133.
229. Barbosa, J.P.; Pereira, R.C.; Abrantes, J.L.; DosSantos, C.C.C.; Rebello, M.A.; Frugulhetti, I.C.P.P. In vitro antiviral diterpenes from the Brazil brown alga *Dictyota pfaeffii*. *Planta Med.* **2004**, *70*, 856–860. [[CrossRef](#)] [[PubMed](#)]
230. Cirne-Santos, C.C.; Teixeira, V.L.; Castello-Branco, L.R.; Frugulhetti, I.C.P.P.; Bou Habid, D.C. Inhibition of HIV-1 replication in human primary cells by a dolabellane diterpene isolated from the marine algae *Dictyota pfaeffii*. *Planta Med.* **2006**, *72*, 295–299. [[CrossRef](#)]
231. Zhang, H.J.; Huang, N.V.; Cuong, N.M.; Soejarto, D.D.; Pezzuto, J.M.; Fong, H.H.S. Sesquiterpenes and butenolides, natural anti-HIV constituents from *Litsea verticillata*. *Planta Med.* **2005**, *71*, 452–457. [[CrossRef](#)]
232. Pereira, H.S.; Leao-Ferreira, L.R.; Moussatché, N.; Teieira, V.L.; da Cavalcanti, D.N.; Costa, L.J. Effects of diterpenes isolated from the Brazilian marine alga *Dictyota menstrualis* on HIV-1 reverse transcriptase. *Planta Med.* **2005**, *71*, 1019–1024. [[CrossRef](#)]
233. Sunthitikawinsakul, A.; Kongkathip, N.; Kongkathip, B. Anti-HIV-1 limonoid: First isolation from *Clausena excavata*. *Phytother. Res.* **2003**, *17*, 1101–1103. [[CrossRef](#)]
234. Ito, M.; Nakashima, H.; Baba, M.; Pauwels, R.; De Clercq, E.; Shigeta, S.; Yamamoto, N. Inhibitory effect of glycyrrhizin on the in vitro infectivity and cytopathic activity of the human immunodeficiency virus [HIV (HTLV-III/LAV)]. *Antivir. Res.* **1987**, *7*, 127–137. [[CrossRef](#)]
235. Bocklandt, S.; Blumberg, P.M.; Hamer, D.H. Activation of latent HIV-1 expression by the potent anti-tumor promoter 12-deoxyphorbol 13-phenylacetate. *Antivir. Res.* **2003**, *59*, 89–98. [[CrossRef](#)]
236. Pettit, G.R.; Ducki, S.; Tan, R. Isolation and structure of pedilstatin from a republic of Maldives *Pedilanthus* sp. *J. Nat. Prod.* **2002**, *65*, 1262–1265. [[CrossRef](#)]
237. Huang, S.Z.; Zhang, X.; Ma, Q.Y.; Zheng, Y.T.; Xu, F.Q.; Peng, H.; Dai, H.F.; Zhou, J.; Zhao, Y.X. Terpenoids and their anti-HIV activities from *Excoecaria acerifolia*. *Fitoterapia* **2013**, *91*, 224–230. [[CrossRef](#)] [[PubMed](#)]
238. Anjaneyulu, A.S.R.; Rao, V.L.; Sreedhar, K. Agallochins, New isopimarane diterpenoids from *Excoecaria agallocha*. *J. Nat. Prod. Res.* **2003**, *17*, 27–32. [[CrossRef](#)] [[PubMed](#)]
239. Konishi, T.; Azuma, M.; Itoga, R.; Kiyosawa, S.; Fujiwara, Y.; Shimada, Y. Three new labdane-type diterpenes from wood, *Excoecaria agallocha*. *Chem. Pharm. Bull.* **1996**, *44*, 229–231. [[CrossRef](#)]
240. Gangloff, A.R.; Judge, T.M.; Helquist, P. Light-induced, iodine-catalyzed aerobic oxidation of unsaturated tertiary amines. *J. Org. Chem.* **1990**, *55*, 3679–3682. [[CrossRef](#)]
241. Sun, I.-C.; Kashiwada, Y.; Morris-Natschke, S.L.; Lee, K.-H. Plant-derived terpenoids and analogues as anti-HIV Agents. *Curr. Top. Med. Chem.* **2003**, *3*, 155–169.
242. Gustafson, K.R.; Cardellina, J.H.; McMahon, J.B.; Gulakowski, R.J.; Ishitoya, J.; Szallasi, Z.; Lewin, N.E.; Blumberg, P.M.; Weislow, O.S.; Beutler, J.A.; et al. A Nonpromoting phorbol from the Samoan medicinal plant *Homalanthus nutans* inhibits cell killing by HIV1. *J. Med. Chem.* **1992**, *35*, 1978–1986. [[CrossRef](#)]
243. Osorio, A.A.; Munoz, A.; Romero, D.T.; Bedoya, L.M.; Perestelo, N.R.; Jimenez, I.A.; Alcamí, J.; Bazzocchi, I.L. Olean-18-ene triterpenoids from Celastraceae species inhibit HIV replication targeting NF-Kb and Sp1 dependent transcription. *Eur. J. Med. Chem.* **2012**, *52*, 295–303. [[CrossRef](#)]
244. Song, W.; Si, L.; Ji, S.; Wang, H.; Fang, X.-M.; Yu, L.-Y.; Li, R.-Y.; Liang, L.-N.; Zhou, D.; Ye, M. Uralsaponins M–Y, Antiviral triterpenoid saponins from the roots of *Glycyrrhiza uralensis*. *J. Nat. Prod.* **2014**, *77*, 1632–1643. [[CrossRef](#)]
245. Vidal, V.; Potterat, O.; Louvel, S.; Hamy, F.; Mojarrab, M.; Sanglier, J.-J.; Klimkait, T.; Hamburger, M. Library-based discovery and characterization of daphnane diterpenes as potent and selective HIV inhibitors in *Daphne gnidium*. *J. Nat. Prod.* **2012**, *75*, 414–419. [[CrossRef](#)]
246. Tian, Y.; Xu, W.; Zhu, C.; Lin, S.; Li, Y.; Xiong, L.; Wang, S.; Wang, L.; Yang, Y.; Guo, Y.; et al. Lathyrane diterpenoids from the roots of *Euphorbia micractina* and their biological activities. *J. Nat. Prod.* **2011**, *74*, 1221–1229. [[CrossRef](#)]
247. Win, N.N.; Ito, T.; Matsui, T.; Aimaiti, S.; Kodama, T.; Ngwe, H.; Okamoto, Y.; Tanaka, M.; Asakawa, Y.; Abe, I.; et al. Isopimarane diterpenoids from *Kaempferia pulchra* rhizomes collected in Myanmar and their Vpr inhibitory activity. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1789–1793. [[CrossRef](#)]
248. Win, N.N.; Ngwe, H.; Abe, I.; Morita, H. Naturally occurring Vpr inhibitors from medicinal plants of Myanmar. *J. Nat. Med.* **2017**, *71*, 579–589. [[CrossRef](#)]

249. Xiao, W.-L.; Li, R.-T.; Li, S.-H.; Li, X.-L.; Sun, H.-D.; Zheng, Y.T.; Wang, R.R.; Lu, Y.; Wang, C.; Zheng, Q.T. Lancifodilactone F: A novel nortriterpenoid possessing a unique skeleton from *Schisandra lancifolia* and its anti-HIV activity. *Org. Lett.* **2005**, *7*, 1263–1266. [[CrossRef](#)]
250. Yan, M.; Lu, Y.; Chen, C.H.; Zhao, Y.; Lee, K.H.; Chen, D.F. Stelleralides D–J and anti-HIV daphnane diterpenes from *Stellera chamaejasme*. *J. Nat. Prod.* **2015**, *78*, 2712–2718. [[CrossRef](#)]
251. Takeda, K.; Horibe, I.; Minato, H. Components of the root of *Lindera strychnifolia* vill. Part XIV. Sesquiterpene lactones from the root of *Lindera strychnifolia* vill. *J. Chem. Soc. C* **1968**, *1*, 569–572. [[CrossRef](#)]
252. Zhang, X.; Huang, S.Z.; Gu, W.G.; Yang, L.M.; Chen, H.; Zheng, C.B.; Zhao, Y.X.; Wan, D.C.C.; Zheng, Y.T. Wikstroelide M potently inhibits HIV replication by targeting reverse transcriptase and integrase nuclear translocation. *Chin. J. Nat. Med.* **2014**, *12*, 0186–0193. [[CrossRef](#)]
253. Wu, Y.C.; Hung, Y.C.; Chang, F.R.; Cosentino, M.; Wang, H.K.; Lee, K.H. Identification of ent-16 β , 17 dihydroxykauran-19-oic acid as an anti-HIV principle and isolation of the new diterpenoids annosquamosins A and B from *Annona squamosa*. *J. Nat. Prod.* **1996**, *59*, 635–637. [[CrossRef](#)]
254. Singh, I.P.; Bharate, S.B.; Bhutani, K.K. Anti-HIV natural products. *Curr. Sci.* **2005**, *89*, 269–290.
255. Sun, H.D.; Qiu, S.X.; Lin, L.Z.; Wang, Z.Y.; Lin, Z.W.; Pengsuparp, T.; Pezzuto, J.M.; Fong, H.H.; Cordell, G.A.; Farnsworth, N.R. Nigranoic acid, a triterpenoid from *Schisandra sphaerandra* that inhibits HIV-1 reverse transcriptase. *J. Nat. Prod.* **1996**, *59*, 525–527. [[CrossRef](#)]
256. Okano, M.; Fukamiya, N.; Tagahara, K.; Cosentino, M.; Lee, T.T.-Y.; Morris-Natschke, S.; Lee, K.-H. Anti-AIDS agents 25. Anti-HIV activity of quassinoids. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 701–706. [[CrossRef](#)]
257. Wei, Y.; Ma, C.M.; Hattori, M. Anti-HIV protease triterpenoids from the acid hydrolysate of *Panax ginseng*. *Phytochem. Lett.* **2009**, *2*, 63–66. [[CrossRef](#)]
258. Reutrakul, V.; Anantachoke, N.; Pohmakotr, M.; Jaipetch, T.; Yoosook, C.; Kasisit, J.; Napaswa, C.; Panthong, A.; Santisuk, T.; Prabpai, S.; et al. Anti-HIV-1 and anti-inflammatory lupanes from the leaves, twigs and resin of *Garcinia hanburyi*. *Planta Med.* **2010**, *76*, 368–371. [[CrossRef](#)]
259. Daoubi, M.; Marquez, N.; Mazoir, N.; Benharref, A.; Hernandez-Galan, R.; Munoz, E.; Collado, I.E. Isolation of new phenylacetylglucosyl derivatives that reactivate HIV-1 latency and a novel spirotriterpenoid from *Euphorbia officinarum* latex. *Bioorg. Med. Chem.* **2007**, *15*, 4577–4584. [[CrossRef](#)]
260. Tian, R.R.; Chen, J.C.; Zhang, G.H.; Qiu, M.H.; Wang, Y.H.; Du, L.; Shen, X.; Liu, N.F.; Zheng, Y.T. Cucurbitane triterpenoids from *Hemsleya penxianensis*. *Chin. J. Nat. Med.* **2008**, *6*, 214–218. [[CrossRef](#)]
261. Bodiwala, H.S.; Sabde, S.; Mitra, D.; Bhutani, K.K.; Singh, I.P. Anti-HIV diterpenes from *Coleus forskohlii*. *Nat. Prod. Commun.* **2009**, *4*, 1173–1175. [[CrossRef](#)]
262. Chen, I.H.; Du, Y.-C.; Lu, M.C.; Lin, A.S.; Hsieh, P.W.; Wu, C.C.; Chen, S.L.; Yen, H.F.; Chang, F.R.; Wu, Y.C. Lupane-type triterpenoids from *Microtropis fokiensis* and *Perrottetia arisanensis* and the apoptotic effect of 28-hydroxy-3-oxo-lup-20(29)-en-30-al. *J. Nat. Prod.* **2008**, *71*, 1352–1357. [[CrossRef](#)]
263. Kashiwada, Y.; Sekiya, M.; Yamazaki, K.; Ikeshiro, Y.; Fujioka, T.; Yamagishi, T.; Kitagawa, S.; Takaishi, Y. Triterpenoids from the floral spikes of *Betula platyphylla* var. *japonica* and their reversing activity against multidrug-resistant cancer cells. *J. Nat. Prod.* **2007**, *70*, 623–627. [[CrossRef](#)]
264. Ramachandran, C.; Nair, P.K.; Alamo, A.; Cochrane, C.B.; Escalon, E.; Melnick, S.J. Anticancer effects of amooranin in human colon carcinoma cell line in vitro and in nude mice xenografts. *Int. J. Cancer.* **2006**, *119*, 2443–2454. [[CrossRef](#)]
265. Tian, J.-K.; Xu, L.Z.; Zou, Z.M.; Yang, S.L. Three Novel Triterpenoid Saponins from *Lysimachia capillipes* and Their Cytotoxic Activities. *Chem. Pharm. Bull.* **2006**, *54*, 567–569. [[CrossRef](#)]
266. Yue, Q.X.; Cao, Z.W.; Guan, S.H.; Liu, X.H.; Tao, L.; Wu, W.Y.; Li, Y.X.; Yang, P.Y.; Liu, X.; Guo, D.A. Proteomics characterization of the cytotoxicity mechanism of ganodeic acid D and computer-automated estimation of the possible drug target network. *Mol. Cell Proteom.* **2008**, *7*, 949–961. [[CrossRef](#)]
267. Chang, U.M.; Li, C.H.; Lin, L.I.; Huang, C.P.; Kan, L.S.; Lin, S.B. Ganoderiol F, a ganoderma triterpene, induces senescence in hepatoma HepG2 cells. *Life Sci.* **2006**, *79*, 1129–1139. [[CrossRef](#)]
268. Sun, P.; Liu, B.S.; Yi, Y.H.; Li, L.; Gui, M.; Tang, H.F.; Zhang, D.Z.; Zhang, S.L. A new cytotoxic lansotane-type triterpene glycoside from the sea cucumber *Holothuria impatiens*. *Chem. Biodivers.* **2007**, *4*, 450–457. [[CrossRef](#)] [[PubMed](#)]
269. Feng, T.; Wang, R.R.; Cai, X.H.; Zheng, Y.T.; Luo, X.D. Anti-human immunodeficiency virus-1 constituents of the bark of *Poncirus trifoliata*. *Chem. Pharm. Bull. (Tokyo)* **2010**, *58*, 971–975. [[CrossRef](#)]

270. Yang, L.; Wu, S.; Zhang, Q.; Liuand, F.; Wu, P. 23, 24-Dihydrocucurbitacin B induces G2/M cell-cycle arrest and mitochondria dependent apoptosis in human breast cancer cells (Bcap37). *Cancer Lett.* **2007**, *256*, 267–278. [[CrossRef](#)]
271. Fang, L.; Ito, A.; Chai, H.B.; Mi, Q.; Jones, W.P.; Madulid, D.R.; Oliveros, M.B.; Gao, Q.; Orjala, J.; Farnsworth, N.R.; et al. Cytotoxic constituents from the stem bark of *Dichapetalum gelonioides* collected in the Philippines. *J. Nat. Prod.* **2006**, *69*, 332–337. [[CrossRef](#)]
272. Tuchinda, P.; Kornsakulkarn, J.; Pohmakotr, M.; Kongsaree, P.; Prabpai, S.; Yoosook, C.; Kasisit, J.; Napaswad, C.; Sophasan, S.; Reutrakul, V. Dichapetalin-type triterpenoids and lignans from the aerial parts of *Phyllanthus acutissima*. *J. Nat. Prod.* **2008**, *71*, 655–663. [[CrossRef](#)]
273. Lee, J.H.; Koo, T.H.; Yoon, H.; Jung, H.S.; Jin, H.Z.; Lee, K.; Hong, Y.S.; Lee, J.J. Inhibition of NF-kappa B activation through targeting I kappa B kinase by celastrol, a quinine methide triterpenoid. *Biochem. Pharmacol.* **2006**, *72*, 1311–1321. [[CrossRef](#)]
274. Zhang, H.; Wang, X.; Chen, F.; Androulakis, X.M.; Wargovich, M.J. Anticancer activity of limonoid from *Khaya senegalensis*. *Phytother. Res.* **2007**, *21*, 731–734. [[CrossRef](#)]
275. Awah, F.M.; Uzoegwu, P.N.; Ifeonu, P. In vitro anti-HIV and immunomodulatory potentials of *Azadirachta indica* (Meliaceae) leaf extract. *Afr. J. Pharm. Pharmacol.* **2011**, *5*, 1353–1359. [[CrossRef](#)]
276. Uddin, S.J.; Nahar, L.; Shilpi, J.A.; Shoeb, M.; Borkowski, T.; Gibbons, S.; Middleton, M.; Byres, M.; Sarker, S.D. Gedunin, a limonoid from *Xylocarpus granatum*, inhibits the growth of CaCo-2 colon cancer cell line in vitro. *Phytother Res.* **2007**, *21*, 757–761. [[CrossRef](#)]
277. Seida, A.A.; Kinghorn, A.D.; Cordell, G.A.; Farnsworth, N.R. Potential anticancer agents. IX. Isolation of a new simaroubolide, 6alpha-tigloyloxychaparrinone, from *Ailanthus integrifolia* ssp. *Calyciina* (Simaroubaceae). *Lloydia* **1978**, *41*, 584–587.
278. Orhan, D.D.; Ozcelik, B.; Ozgen, S.; Ergun, F. Antibacterial, antifungal, and antiviral activities of some flavonoids. *Microbiol. Res.* **2010**, *165*, 496–504. [[CrossRef](#)]
279. Kim, H.J.; Woo, E.-R.; Shin, C.-G.; Park, H. A new flavonol glycoside gallate ester from *Acer okamotoanum* and its inhibitory activity against human immunodeficiency virus-1 (HIV-1) integrase. *J. Nat. Prod.* **1998**, *61*, 145–148. [[CrossRef](#)]
280. Wang, Q.; Ding, Z.-H.; Liu, J.-K.; Zheng, Y.-T. Xanthohumol, a novel anti-HIV-1 agent purified from Hops *Humulus lupulus*. *Antivir. Res.* **2004**, *64*, 189–194. [[CrossRef](#)]
281. Meragelman, K.M.; Mckee, T.C.; Boyd, M.R. Anti-HIV prenylated flavonoids from *Monotes africanus* 1. *J. Nat. Prod.* **2001**, *64*, 546–548. [[CrossRef](#)]
282. Hu, K.; Kobayashi, H.; Dong, A.; Iwasaki, S.; Yao, X. Antifungal, antimitotic and anti-HIV-1 agents from the roots of *Wikstroemia indica*. *Planta Med.* **2000**, *66*, 564–567. [[CrossRef](#)]
283. Ohtake, N.; Nakai, Y.; Yamamoto, M.; Sakakibara, I.; Takeda, S.; Amagaya, S. Separation and isolation methods for analysis of the active principles of Sho-saiko-to (SST) oriental medicine. *J. Chromatogr. B* **2004**, *812*, 135–148. [[CrossRef](#)]
284. Lin, Y.-M.; Anderson, H.; Flavin, M.T.; Pai, Y.-H.S.; Mata-Greenwood, E.; Pengsuparp, T. In vitro anti-HIV activity of biflavonoids isolated from *Rhus succedanea* and *Garcinia multiflora*. *J. Nat. Prod.* **1997**, *60*, 884–888. [[CrossRef](#)]
285. Wu, J.H.; Wang, X.H.; Yi, Y.H.; Lee, K.H. Anti-AIDS agents 54. A potent anti-HIV chalcone and flavonoids from genus *Desmos*. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1813–1815. [[CrossRef](#)]
286. Cheenpracha, S.; Karalai, C.; Ponglimanont, C.; Subhadhirasakul, S.; Tewtrakul, S. Anti-HIV-1 protease activity of compounds from *Boesenbergia pandurata*. *Bioorg. Med. Chem.* **2006**, *14*, 1710–1714. [[CrossRef](#)]
287. Critchfield, J.W.; Coligan, J.E.; Folks, T.M.; Butera, S.T. Casein kinase II is a selective target of HIV-1 transcriptional inhibitors. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 6110–6115. [[CrossRef](#)]
288. Harada, S.; Haneda, E.; Maekawa, T.; Morikawa, Y.; Funayama, S.; Nagata, N. Casein kinase II (CK-II)-mediated stimulation of HIV-1 reverse transcriptase activity and characterization of selective inhibitors in vitro. *Biol. Pharm. Bull.* **1999**, *22*, 1122–1126. [[CrossRef](#)]
289. Rowley, D.C.; Hansen, M.S.T.; Rhodes, D.; Sotriffer, C.A.; Ni, H.; McCammon, J.A. Thalassiolins A-C: New marine-derived inhibitors of HIV cDNA integrase. *Bioorg. Med. Chem.* **2002**, *10*, 3619–3625. [[CrossRef](#)]
290. Alves, C.N.; Pinheiro, J.C.; de Camargo, A.J.; Souza, A.J.; da Carvalho, R.B.; Silva, A.B.F. A quantum chemical and statistical study of flavonoid compounds with anti-HIV activity. *J. Mol. Struct. (Theochem)* **1999**, *491*, 123–131. [[CrossRef](#)]

291. Alves, C.N.; Pinheiro, J.C.; Camargo, A.J.; Ferreira, M.M.C.; da Romero, R.A.F.; Silva, A.B.F. A multiple linear regression and partial least squares study of flavonoid compounds with anti-HIV activity. *J. Mol. Struct. (Theochem)* **2001**, *541*, 81–88. [[CrossRef](#)]
292. Min, B.S.; Lee, H.K.; Lee, S.M. Anti-human immunodeficiency virus-type 1 activity of constituents from *Juglans mandshurica*. *Arch. Pharm. Res.* **2002**, *25*, 441–445. [[CrossRef](#)]
293. Lee-Huang, S.; Zhang, L.; Huang, P.L. Anti-HIV activity of olive leaf extract (OLE) and modulation of host cell gene expression by HIV-1 infection and OLE treatment. *Biochem. Biophys. Res. Commun.* **2003**, *307*, 1029–1037. [[CrossRef](#)]
294. Amzazi, S.; Ghoulemi, S.; Bakri, Y. Human immunodeficiency virus type 1 inhibitory activity of *Mentha longifolia*. *Therapie* **2003**, *58*, 531–534. [[CrossRef](#)]
295. Lo, W.L.; Wu, C.C.; Chang, F.R. Antiplatelet and anti-HIV constituents from *Euchresta formosana*. *Nat. Prod. Res.* **2003**, *17*, 91–97. [[CrossRef](#)]
296. Mahmood, N.; Pizza, C.; Aquino, R. Inhibition of HIV infection by flavonoids. *Antivir. Res.* **1993**, *22*, 189–199. [[CrossRef](#)]
297. Hussein, G.; Miyashiro, H.; Nakamura, N. Inhibitory effects of Sudanese plant extracts on HIV-1 replication and HIV-1 protease. *Phytother Res.* **1999**, *13*, 31–36. [[CrossRef](#)]
298. Mahmood, N.; Piacente, S.; Pizza, C. The anti-HIV activity and mechanisms of action of pure compounds isolated from *Rosa damascena*. *Biochem. Biophys. Res. Commun.* **1996**, *229*, 73–79. [[CrossRef](#)]
299. Boskabad, M.H.; Shafei, M.N.; Saberi, Z.; Amini, S. Pharmacological Effects of *Rosa Damascena*. *Iran. J. Basic Med. Sci.* **2011**, *14*, 295–307.
300. Dharmaratne, H.R.W.; Tan, G.T.; Marasinghe, G.P.K.; Pezzuto, J.M. Inhibition of HIV-1 reverse transcriptase and HIV-1 replication by *Calophyllum* coumarins and xanthenes. *Planta Med.* **2002**, *68*, 86–87. [[CrossRef](#)]
301. Zembower, D.E.; Liao, S.; Flavin, M.T.; Xu, Z.Q.; Stup, T.L.; Buckheit, R.W.; Khilevich, A.; Mar, A.A.; Sheinkman, A.K. Structural analogues of the calanolide anti-HIV agents. Modification of the *trans*-10,11-dimethylidihydropyran-12-ol ring (ring C). *J. Med. Chem.* **1997**, *40*, 1005–1017. [[CrossRef](#)]
302. Creagh, T.; Ruckle, J.L.; Tolbert, D.T.; Giltner, J.; Eiznhamer, D.A.; Dutta, B.; Flavin, M.T.; Xu, Z.Q. Safety and pharmacokinetics of single doses of (+)-calanolide A, a novel, naturally occurring nonnucleoside reverse transcriptase inhibitor, in healthy, human immunodeficiency virus-negative human subjects. *Antimicrob. Agents Chemother.* **2001**, *45*, 1379–1386. [[CrossRef](#)]
303. Kostova, I.; Raleva, S.; Genova, P.; Argirova, R. Structure activity relationships of synthetic coumarins as HIV-1 inhibitors. *Bioinorg. Chem. Appl.* **2006**, *2006*, 68274. [[CrossRef](#)]
304. Yu, D.; Suzuki, M.; Xie, L.; Morris-Natschke, S.L.; Lee, K.-H. Recent progress in the development of coumarin derivatives as potent anti-HIV agents. *Med. Res. Rev.* **2003**, *23*, 322–345. [[CrossRef](#)]
305. Zhou, P.; Takaishi, Y.; Duan, H.; Chen, B.; Honda, G.; Itoh, M. Coumarins and bicoumarin from *Ferula sumbul*: Anti-HIV activity and inhibition of cytokine release. *Phytochemistry* **2000**, *53*, 689–697. [[CrossRef](#)]
306. Shikishima, Y.; Takaishi, Y.; Honda, G.; Ito, M.; Takfda, Y.; Kodzhimatov, O.K.; Ashurmetov, O.; Lee, K.H. Chemical constituents of *Prangos tschiniganica*; structure elucidation and absolute configuration of coumarin and furanocoumarin derivatives with anti-HIV activity. *Chem. Pharm. Bull. (Tokyo)* **2001**, *49*, 877–880. [[CrossRef](#)]
307. Marquez, N.; Sancho, R.; Bedoya, L.M.; Alcamí, J.; Lopez-Perez, J.L.; San, F.A. Mesuol, a natural occurring 4-phenylcoumarin, inhibits HIV-1 replication by targeting the NF- κ B pathway. *Antivir. Res.* **2005**, *66*, 137–145. [[CrossRef](#)]
308. Xu, Z.Q.; Kern, E.R.; Westbrook, L.; Allen, L.B.; Buckheit, R.W., Jr.; Tseng, C.K.; Jenta, T.; Flavin, M.T. Plant-derived and semi-synthetic calanolide compounds with in vitro activity against both human immunodeficiency virus type 1 and human cytomegalovirus. *Antivir. Chem. Chemother.* **2000**, *11*, 23–29. [[CrossRef](#)]
309. Mishra, B.B.; Singh, D.D.; Kishore, N.; Tiwari, V.K.; Tripathi, V. Antifungal constituents isolated from the seeds of *Aegle marmelos*. *Phytochemistry* **2010**, *71*, 230–234. [[CrossRef](#)]
310. Maity, P.; Hansda, D.; Bandyopadhyay, U.; Mishra, D.K. Biological activities of crude extracts and chemical constituents of Bael, *Aegle marmelous* (L.) Corr. *Ind. J. Exp. Biol.* **2009**, *47*, 849–861.
311. O’Keefe, B.R. Biologically active proteins from natural product extracts. *J. Nat. Prod.* **2001**, *64*, 1373–1381. [[CrossRef](#)]

312. Lee-Huang, S.; Huang, P.L.; Bourinbaiar, A.S.; Chen, H.C.; Kung, H.F. Inhibition of the integrase of human immunodeficiency virus (HIV) type-1 by anti-HIV plant proteins MAP30 and GAP31. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 8818–8822. [[CrossRef](#)]
313. McGrath, M.S.; Hwang, K.M.; Caldwell, S.E.; Gaston, I.; Luk, K.C.; Wu, P. GLQ223—An inhibitor of human immunodeficiency virus replication in acutely and chronically infected-cells of lymphocyte and mononuclear phagocyte lineage. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 2844–2848. [[CrossRef](#)]
314. Kaur, I.; Puri, M.; Ahmed, Z.; Blanchet, F.P.; Mangeat, B.; Piguët, V. Inhibition of HIV-1 Replication by Balsamin, a Ribosome Inactivating Protein of *Momordica balsamina*. *PLoS ONE* **2013**, *8*, e73780. [[CrossRef](#)]
315. Kawahata, T.; Otake, T.; Mori, H. A novel substance purified from *Perilla frutescens* Britton inhibits an early stage of HIV-1 replication without blocking viral adsorption. *Antivir. Chem. Chemother.* **2002**, *13*, 283–288. [[CrossRef](#)]
316. Irvin, J.D.; Uckun, F.M. Pokeweed antiviral protein: Ribosome inactivation and therapeutic applications. *Pharmacol. Ther.* **1992**, *55*, 279–302. [[CrossRef](#)]
317. Wang, H.X.; Ng, T.B. Ascalin, a new anti-fungal peptide with human immunodeficiency virus type 1 reverse transcriptase-inhibiting activity from shallot bulbs. *Peptides* **2002**, *23*, 1025–1029. [[CrossRef](#)]
318. Wang, H.; Ye, X.Y.; Ng, T.B. Purification of chrysancorin, a novel antifungal protein with mitogenic activity from garland chrysanthemum seeds. *Biol. Chem.* **2001**, *382*, 947–951. [[CrossRef](#)] [[PubMed](#)]
319. Wang, H.; Ng, T.B. Ginkbilobin, a novel antifungal protein from *Ginkgo biloba* seeds with sequence similarity to embryo-abundant protein. *Biochem. Biophys. Res. Commun.* **2002**, *279*, 407–411. [[CrossRef](#)]
320. Ye, X.Y.; Ng, T.B. Hypogin, a novel antifungal peptide from peanuts with sequence similarity to peanut allergen. *J. Pept. Res.* **2001**, *57*, 330–336. [[CrossRef](#)]
321. Lam, S.K.; Ng, T.B. First simultaneous isolation of a ribosome inactivating protein and an antifungal protein from a mushroom (*Lyophyllum shimeji*) together with evidence for synergism of their antifungal effects. *Arch. Biochem. Biophys.* **2001**, *393*, 271–280. [[CrossRef](#)]
322. Wang, H.X.; Ng, T.B. Quinqueginsin, a novel protein with anti-human immunodeficiency virus, antifungal, ribonuclease and cell-free translation-inhibitory activities from American ginseng roots. *Biochem. Biophys. Res. Commun.* **2000**, *269*, 203–208. [[CrossRef](#)]
323. Wang, H.; Ng, T.B. Isolation and characterization of velutin, a novel low-molecular-weight ribosome-inactivating protein from winter mushroom (*Flammulina velutipes*) fruiting bodies. *Life Sci.* **2001**, *68*, 2151–2158. [[CrossRef](#)]
324. Wang, H.X.; Ng, T.B. Purification of a novel low-molecular mass laccase with HIV-1 reverse transcriptase inhibitory activity from the mushroom *Tricholoma giganteum*. *Biochem. Biophys. Res. Commun.* **2004**, *315*, 450–454. [[CrossRef](#)]
325. Chu, K.T.; Ng, T.B. Mollisin, an antifungal protein from the chestnut *Castanea mollissima*. *Planta Med.* **2003**, *69*, 809–813.
326. Bokesch, H.R.; Charan, R.D.; Meragelman, K.M. Isolation and characterization of anti-HIV peptides from *Dorstenia contrajerva* and *Treculia obovoidea*. *FEBS Lett.* **2004**, *567*, 287–290. [[CrossRef](#)]
327. Wong, J.H.; Ng, T.B. Purification of a trypsin-stable lectin with antiproliferative and HIV-1 reverse transcriptase inhibitory activity. *Biochem. Biophys. Res. Commun.* **2003**, *301*, 545–550. [[CrossRef](#)]
328. Ye, X.Y.; Ng, T.B. Delandin, a chitinase-like protein with antifungal, HIV-1 reverse transcriptase inhibitory and mitogenic activities from the rice bean *Delandia umbellata*. *Protein Expr. Purif.* **2002**, *24*, 524–529. [[CrossRef](#)]
329. Ye, X.Y.; Ng, T.B. Purification of angularin, a novel antifungal peptide from adzuki beans. *J. Pept. Sci.* **2002**, *8*, 101–106. [[CrossRef](#)]
330. Chu, K.T.; Ng, T.B. Isolation of a large thaumatin-like antifungal protein from seeds of the Kweilin chestnut *Castanopsis chinensis*. *Biochem. Biophys. Res. Commun.* **2003**, *301*, 364–370. [[CrossRef](#)]
331. Ye, X.Y.; Wang, H.X.; Ng, T.B. Structurally dissimilar proteins with antiviral and antifungal potency from cowpea (*Vigna unguiculata*) seeds. *Life Sci.* **2000**, *67*, 3199–3207. [[CrossRef](#)]
332. Ye, X.Y.; Ng, T.B.; Tsang, P.W.; Wang, J. Isolation of a homodimeric lectin with antifungal and antiviral activities from red kidney bean (*Phaseolus vulgaris*) seeds. *J. Protein Chem.* **2001**, *20*, 367–375. [[CrossRef](#)]
333. Wang, H.; Ng, T.B. Isolation of an antifungal thaumatin-like protein from kiwi fruits. *Phytochemistry* **2002**, *61*, 1–6. [[CrossRef](#)]

334. Ngai, P.H.; Ng, T.B. Lentin, a novel and potent antifungal protein from shitake mushroom with inhibitory effects on activity of human immunodeficiency virus-1 reverse transcriptase and proliferation of leukemia cells. *Life Sci.* **2003**, *73*, 3363–3374. [[CrossRef](#)]
335. Lam, Y.W.; Ng, T.B. A monomeric mannose-binding lectin from inner shoots of the edible chive (*Allium tuberosum*). *J. Protein Chem.* **2001**, *20*, 361–366. [[CrossRef](#)]
336. Ye, X.Y.; Ng, T.B. A new antifungal protein and a chitinase with prominent macrophage-stimulating activity from seeds of *Phaseolus vulgaris* cv. pinto. *Biochem. Biophys. Res. Commun.* **2002**, *290*, 813–819. [[CrossRef](#)]
337. Wang, H.; Ng, T.B. Isolation of lilin, a novel arginine- and glutamate-rich protein with potent antifungal and mitogenic activities from lily bulbs. *Life Sci.* **2002**, *70*, 1075–1084. [[CrossRef](#)]
338. Ye, X.Y.; Ng, T.B. A new peptidic protease inhibitor from *Vicia faba* seeds exhibit antifungal, HIV-1 reverse transcriptase inhibiting and mitogenic activities. *J. Pept. Sci.* **2002**, *8*, 656–662. [[CrossRef](#)]
339. Ye, X.Y.; Ng, T.B. Isolation of unguilin, a cyclophilin-like protein with anti-mitogenic, antiviral, and antifungal activities, from black-eyed pea. *J. Protein Chem.* **2001**, *20*, 353–359. [[CrossRef](#)]
340. Lam, S.K.; Ng, T.B. A xylanase from roots of sanchi ginseng (*Panax notoginseng*) with inhibitory effects on human immunodeficiency virus-1 reverse transcriptase. *Life Sci.* **2002**, *70*, 3049–3058. [[CrossRef](#)]
341. Ye, X.Y.; Ng, T.B. Isolation of vulgin, a new antifungal polypeptide with mitogenic activity from the pinto bean. *J. Pept. Sci.* **2003**, *9*, 114–119. [[CrossRef](#)]
342. Ye, X.Y.; Ng, T.B. Isolation of a new cyclophilin-like protein from chickpeas with mitogenic, antifungal and anti-HIV-1 reverse transcriptase activities. *Life Sci.* **2002**, *70*, 1129–1138. [[CrossRef](#)]
343. Wang, H.; Ng, T.B. Novel antifungal peptides from Ceylon spinach seeds. *Biochem. Biophys. Res. Commun.* **2001**, *288*, 765–770. [[CrossRef](#)]
344. Ye, X.Y.; Ng, T.B. A new antifungal peptide from rice beans. *J. Pept. Res.* **2002**, *60*, 81–87. [[CrossRef](#)]
345. DeBruyne, T.; Pieters, L.; Deelstra, H.; Vlietinck, A. Condensed vegetable tannins: Biodiversity in structure and biological activities. *Biochem. Syst. Ecol.* **1999**, *27*, 445–459.
346. Van Khanbabaee, K.; Ree, T. Tannins: Classification and definition. *Nat. Prod. Rep.* **2001**, *18*, 641–649.
347. Notka, F.; Meier, G.; Wagner, R. Concerted inhibitory activities of *Phyllanthus amarus* on HIV replication in vitro and ex vivo. *Antivir. Res.* **2004**, *64*, 93–102. [[CrossRef](#)]
348. Amouroux, P.; Jean, D.; Lamaison, J.L. Antiviral activity in vitro of *Cupressus sempervirens* on two human retroviruses HIV and HTLV. *Phytother Res.* **1998**, *12*, 367–368. [[CrossRef](#)]
349. Liu, S.; Lu, H.; Zhao, Q.; He, Y.; Niu, J.; Debnath, A.K.; Wu, S.; Jiang, S. Theaflavin derivatives in black tea and catechin derivatives in green tea inhibit HIV-1 entry by targeting gp41. *Biochem. Biophys. Acta.* **2005**, *1723*, 270–281. [[CrossRef](#)]
350. Charlton, J.L. Antiviral activity of lignans. *J. Nat. Prod.* **1998**, *61*, 1447–1451. [[CrossRef](#)]
351. Rimando, A.M.; Pezzuto, J.M.; Farnsworth, N.R.; Santisuk, T.; Reutrakul, V.; Kawanishi, K. New lignans from *Anogeissus acuminata* with HIV1 reverse transcriptase inhibitory activity. *J. Nat. Prod.* **1994**, *57*, 896–904. [[CrossRef](#)]
352. Lee, S.S.; Lin, M.T.; Liu, C.L.; Lin, Y.Y.; Liu, K.C.S.C. Six lignans from *Phyllanthus myrtifolius*. *J. Nat. Prod.* **1996**, *59*, 1061–1065. [[CrossRef](#)]
353. Chen, D.F.; Zhang, S.X.; Xie, L.; Xie, J.X.; Chen, K.; Kashiwada, Y. Anti-AIDS agents–XXVI. Structure-activity correlations of gomisin-G-related anti-HIV lignans from *Kadsura interior* and of related synthetic analogues. *Bioorg. Med. Chem.* **1997**, *5*, 1715–1723. [[CrossRef](#)]
354. Kashiwada, Y.; Nishizawa, M.; Yamagishi, T.; Tanaka, T.; Nonaka, G.; Cosentino, L.M.; Lee, K.-H. Anti-AIDS agents 18. Sodium and potassium salts of caffeic acid tetramers from *Arnebia euchroma* as anti-HIV agents. *J. Nat. Prod.* **1995**, *58*, 392–400. [[CrossRef](#)]
355. Piccinelli, A.L.; Mahmood, N.; Mora, G.; Poveda, L.; De Simone, F.; Rastrelli, L. Anti-HIV activity of dibenzylbutyrolactone-type lignans from *Phenax* species endemic in Costa Rica. *J. Pharm. Pharmacol.* **2005**, *57*, 1109–1115. [[CrossRef](#)]
356. Chen, M.; Kilgore, N.; Lee, K.H.; Chen, D.F. Rubrisandrins A and B, lignans and related anti-HIV compounds from *Schisandra rubriflora*. *J. Nat. Prod.* **2006**, *69*, 1697–1701. [[CrossRef](#)]
357. Khan, M.T.H.; Ather, A. Potentials of phenolic molecules of natural origin and their derivatives as anti-HIV agents. *Biotechnol. Annu. Rev.* **2007**, *13*, 223–264.

358. El-Mekkawy, S.; Meselhy, M.R.; Kusumoto, I.T.; Kadota, S.; Hattori, M.; Namba, T. Inhibitory effects of Egyptian folk medicines on human immunodeficiency virus (HIV) reverse transcriptase. *Chem. Pharm. Bull.* **1995**, *43*, 641–648. [[CrossRef](#)]
359. Chien, N.Q.; Hung, N.V.; Santarsiero, B.D.; Mesecar, A.D.; Cuong, N.M.; Soejarto, D.D.; Pezzuto, J.M.; Fong, H.H.S.; Tan, G.T. New 3-O-acyl betulinic acids from *Strychnos vanprukii* Craib. *J. Nat. Prod.* **2004**, *67*, 994–998. [[CrossRef](#)]
360. Connell, B.J.; Chang, S.-Y.; Prakash, E.; Yousfi, R.; Mohan, V.; Posch, W.; Wilflingseder, D.; Moog, C.; Kodama, E.N.; Clayette, P.; et al. A Cinnamon-derived procyanidin compound displays anti-HIV-1 activity by blocking heparan sulfate- and co-receptor- binding sites on gp120 and reverses T cell exhaustion via impeding Tim-3 and PD-1 upregulation. *PLoS ONE* **2016**, *11*, e0165386. [[CrossRef](#)]
361. Lin, W.L.; Guu, S.Y.; Tsai, C.C.; Prakash, E.; Viswaraman, M.; Chen, H.B.; Chang, C.F. Derivation of cinnamon blocks leukocyte attachment by interacting with sialosides. *PLoS ONE* **2015**, *10*, e0130389. [[CrossRef](#)]
362. Gruenwald, J.; Freder, J.; Armbruster, N. Cinnamon and health. *Crit. Rev. Food Sci. Nutr.* **2010**, *50*, 822–834. [[CrossRef](#)]
363. Hong, K.J.; Lee, H.S.; Kim, Y.S.; Kim, S.S. Ingenol protects human T cells from HIV-1 infection. *Public Health Res. Perspect.* **2011**, *2*, 109–114. [[CrossRef](#)]
364. Hasler, C.M.; Acs, G.; Blumberg, P.M. Specific binding to protein kinase C by ingenol and its induction of biological responses. *Cancer Res.* **1992**, *52*, 202–208.
365. Sorg, B.; Hecker, E.; Zur, C.D.; Ingenols, I.I. On the chemistry of ingenol ii. Esters of ingenol and delta^{7,8}-isogenol. *Z Naturforsch.* **1982**, *37b*, 748–756. [[CrossRef](#)]
366. Ireland, D.C.; Wang, C.K.L.; Wilson, J.A.; Gustafson, K.R.; Craik, D.J. Cyclotides as natural anti-HIV agents. *Biopolymers* **2008**, *90*, 51–60. [[CrossRef](#)]
367. Ireland, D.C.; Clark, R.J.; Daly, N.L.; Craik, D.J. Isolation, Sequencing, and Structure-Activity Relationships of Cyclotides. *J. Nat. Prod.* **2010**, *73*, 1610–1622. [[CrossRef](#)] [[PubMed](#)]
368. Kapewangolo, P.; Hussein, A.A.; Meyer, D. Inhibition of HIV-1 enzymes, antioxidant and anti-inflammatory activities of *Plectranthus barbatus*. *J. Ethnopharmacol.* **2013**, *149*, 184–190. [[CrossRef](#)] [[PubMed](#)]
369. Lukhoba, C.W.; Simmonds, M.S.J.; Paton, A.J. *Plectranthus*: A review of ethnobotanical uses. *J. Ethnopharmacol.* **2006**, *103*, 1–24. [[CrossRef](#)] [[PubMed](#)]
370. Sunthitikawinsakul, A.; Kongkathip, N.; Kongkathip, B.; Phonnakhu, S.; Daly, J.W.; Spande, T.F.; Nimit, Y.; Rochanaruangrai, S. Coumarins and carbazoles from *Clausena excavata* exhibited antimycobacterial and antifungal activities. *Planta Med.* **2003**, *69*, 155–157. [[CrossRef](#)]
371. Ruangrunsi, N.; Ariyaprayoon, J.; Lange, G.L.; Organ, M.G. Three new carbazole alkaloids isolated from *Murraya siamensis*. *J. Nat. Prod.* **1990**, *53*, 946–952. [[CrossRef](#)]
372. Prinsloo, G.; Marokane, C.K.; Street, R.A. Anti-HIV activity of Southern African plants: Current developments, phytochemistry and future research. *J. Ethnopharmacol.* **2018**, *210*, 133–155. [[CrossRef](#)]
373. Lo, W.L.; Chang, F.R.; Liaw, C.C.; Wu, Y.C. Cytotoxic coumaronochromones from the roots of *Euchresta formosana*. *Planta Med.* **2002**, *68*, 146–151. [[CrossRef](#)]
374. Nageswara, R.K.; Srimannarayana, G. Flemiphyllin, an isoflavone from stems of *Flemingia macrophylla*. *Phytochemistry* **1984**, *23*, 927–929.
375. Mizuno, M.; Tamura, K.I.; Tanaka, T.; Iinuma, M. Three prenylflavanones from *Euchresta japonica*. *Phytochemistry* **1988**, *27*, 1831–1834. [[CrossRef](#)]
376. Wintola, O.A.; Afolayan, A.J. *Alepidea amatymbica* Eckl. & Zeyh.: A review of its traditional uses, phytochemistry, pharmacology, and toxicology. *Evid. Based Complement. Alternat. Med.* **2014**, *2014*, 284517.
377. Lubbe, A.; Seibert, I.; Klimkait, T.; Kooy, F.V.D. Ethnopharmacology in overdrive: The remarkable anti-HIV activity of *Artemisia annua*. *J. Ethnopharmacol.* **2012**, *141*, 854–859. [[CrossRef](#)] [[PubMed](#)]
378. Oh, C.S.; Price, J.; Brindley, M.A.; Widrlechner, M.P.; Qu, L.; Coy, J.-A.M.; Murphy, P.; Hauck, C.; Maury, W. Inhibition of HIV-1 infection by aqueous extracts of *Prunella vulgaris* L. *Virol. J.* **2011**, *8*, 188. [[CrossRef](#)] [[PubMed](#)]
379. Said, M.S.; Chinchansurea, A.A.; Nawaleb, L.; Durgec, A.; Wadhwanic, A.; Kulkarnic, S.S.; Sarkarb, D.; Joshia, S.P. A new butenolide cinnamate and other biological active chemical constituents from *Polygonumglabrum*. *Nat. Prod. Res.* **2015**, *29*, 2080–2086. [[CrossRef](#)]

380. Sakurai, N.; Wu, J.H.; Sashida, Y.; Mimaki, Y.; Nikaido, T.; Koike, K.; Itokawa, H.; Lee, K.H. Anti-AIDS agents. Part 57: Actein, an anti-HIV principle from the rhizome of *Cimicifuga racemosa* (black cohosh), and the anti-HIV activity of related saponins. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1329–1332. [[CrossRef](#)]
381. Tai, B.H.; Nhut, N.D.; Nhiem, N.X.; Quang, T.H.; Ngan, N.T.T.; Luyen, B.T.T.; Huong, T.T.; Wilson, J.; Beutler, J.A.; Ban, N.K.; et al. An evaluation of the RNase H inhibitory effects of Vietnamese medicinal plant extracts and natural compounds. *Pharmaceut. Biol.* **2011**, *49*, 1046–1051. [[CrossRef](#)]
382. Wu, P.L.; Su, G.C.; Wu, T.S. Constituents from the stems of *Aristolochia manshuriensis*. *J. Nat. Prod.* **2003**, *66*, 996–998. [[CrossRef](#)]
383. Wu, T.S.; Leu, Y.L.; Chan, Y.Y. Constituents from the stem and root of *Aristolochia kaempferi*. *Biol. Pharm. Bull.* **2000**, *23*, 1216–1219. [[CrossRef](#)]
384. Nakanishi, T.; Iwasak, K.; Nasu, M.; Miura, I.; Yoneda, K. Aristolosite, an aristolochic acid derivative from stems of *Aristolochia manshuriensis*. *Phytochemistry* **1982**, *21*, 1759–1762. [[CrossRef](#)]
385. Wu, T.S.; Kao, M.S.; Wu, P.L.; Lin, F.W.; Shi, L.S.; Teng, C.M. The heartwood constituents of *Tetradium glabrifolium*. *Phytochemistry* **1995**, *40*, 121–124. [[CrossRef](#)]
386. Wu, T.S.; Tsai, Y.L.; Wu, P.L.; Lin, F.W.; Lin, J.K. Constituents from the leaves of *Aristolochia elegans*. *J. Nat. Prod.* **2000**, *63*, 692–693. [[CrossRef](#)]
387. Wu, X.D.; Cheng, J.T.; He, J.; Zhang, X.J.; Dong, L.B.; Gong, X.; Song, L.D.; Zheng, Y.T.; Peng, L.Y.; Zhao, Q.S. Benzophenone glycosides and epicatechin derivatives from *Malania oleifera*. *Fitoterapia* **2012**, *83*, 1068–1071. [[CrossRef](#)] [[PubMed](#)]
388. Wu, S.Y.; Fu, Y.H.; Zhou, Q.; Bai, M.; Chen, G.Y.; Han, C.R.; Song, X.P. Biologically active oligostilbenes from the stems of *Vatica mangachapoi* and chemotaxonomic significance. *Nat. Prod. Res.* **2019**, *33*, 2300–2307. [[CrossRef](#)] [[PubMed](#)]
389. Hakim, E.H.; Juliawaty, L.D.; Syah, Y.M.; Din, L.B.; Ghisalberti, E.L.; Latip, J.; Achmad, S.A. Cytotoxic properties of oligostilbenoids from the tree barks of *Hopea dryobalanoides*. *Z Naturforsch C* **2005**, *60*, 723–727.
390. Patra, A.; Dey, A.K.; Kundu, A.B.; Saraswathy, A.; Purushothaman, K.K. Shoreaphenol, a polyphenol from *Shorea robusta*. *Phytochemistry* **1992**, *31*, 2561–2562. [[CrossRef](#)]
391. Yan, K.X.; Terashima, K.; Takaya, Y.; Niwa, M. Two new stilbenetetramers from the stem of *Vitis vinifera* ‘Kyohou’. *Tetrahedron* **2002**, *58*, 6931–6935. [[CrossRef](#)]
392. Yang, G.X.; Zhou, J.T.; Li, Y.Z.; Hu, C.Q. Anti-HIV bioactive stilbene dimers of *Caragana rosea*. *Planta Med.* **2005**, *71*, 569–571. [[CrossRef](#)]
393. Zofou, D.; Ntie-Kang, F.; Sippl, W.; Efange, S.M.N. Bioactive natural products derived from the central African flora against neglected tropical diseases and HIV. *Nat. Prod. Rep.* **2013**, *30*, 1098–1120. [[CrossRef](#)]
394. Mahwasane, S.T.; Middleton, L.; Boaduo, N. An ethnobotanical survey of indigenous knowledge on medicinal plants used by the traditional healers of the Lwamondo area, Limpopo province, South Africa. *S. Afr. J. Bot.* **2013**, *88*, 69–75. [[CrossRef](#)]
395. Lagrota, M.H.C.; Wigg, M.D.; Santos, M.M.G.; Miranda, M.M.F.S.; Camara, F.P.; Couceiro, J.N.S.S.; Costa, S.S. Inhibitory activity of extracts of *Alternanthera brasiliana* (Amaranthaceae) against the herpes simplex virus. *Phytother. Res.* **1994**, *8*, 358–361. [[CrossRef](#)]
396. Wang, H.X.; Ng, T.B. Examination of lectins, polysaccharopeptide, polysaccharide, alkaloid, coumarin and trypsin inhibitors for inhibitory activity against human immunodeficiency virus reverse transcriptase and glycohydrolases. *Planta Med.* **2001**, *67*, 669–672. [[CrossRef](#)]
397. Thiagarajan, V.R.K.; Shanmugam, P.; Krishnan, U.M.; Muthuraman, A.; Singh, N. Ameliorative potential of *Butea monosperma* on chronic constriction injury of sciatic nerve induced neuropathic pain in rats. *An. Acad. Bras. Cienc.* **2012**, *84*. [[CrossRef](#)] [[PubMed](#)]
398. Kashiwada, Y.; Wang, H.-K.; Nagao, T.; Kitanaka, S.; Yasuda, I.; Fujioka, T.; Yamagishi, T.; Cosentino, L.M.; Kozuka, M.; Okabe, H. Anti-AIDS agents. 30. Anti-HIV activity of oleanolic acid, pomolic acid, and structurally related triterpenoids. *J. Nat. Prod.* **1998**, *61*, 1090–1095. [[CrossRef](#)] [[PubMed](#)]
399. Lam, T.L.; Lam, M.L.; Au, T.K.; Ip, D.T.; Ng, T.B.; Fong, W.P.; Wan, D.C. A comparison of human immunodeficiency virus type-1 protease inhibition activities by the aqueous and methanol extracts of Chinese medicinal herbs. *Life Sci.* **2000**, *67*, 2889–2896. [[CrossRef](#)]
400. Abdel-Malek, S.; Bastien, J.W.; Mahler, W.F.; Jia, Q.; Reinecke, M.G.; Robinson, W.E.; Shu, Y.-H.; Zalles-Asin, J. Drug leads from the Kallawaya herbalists of Bolivia. 1. Background, rationale, protocol and anti-HIV activity. *J. Ethnopharmacol.* **1996**, *50*, 157–166. [[CrossRef](#)]

401. Pengsuparp, T.; Cai, L.; Constant, H.; Fong, H.H.S.; Lin, L.Z.; Kinghorn, A.D.; Pezzuto, J.M.; Cordell, G.A.; Ingoldsdóttir, K.; Wagner, H. Mechanistic evaluation of new plant-derived compounds that inhibit HIV-1 reverse transcriptase. *J. Nat. Prod.* **1995**, *58*, 1024–1031. [[CrossRef](#)]
402. Luthra, P.M.; Singh, R.; Chandra, R. Therapeutic uses of *Curcuma longa* (Turmeric). *Indian J. Clin. Biochem.* **2001**, *16*, 153–160. [[CrossRef](#)]
403. Min, B.S.; Bae, K.H.; Kim, Y.H.; Miyashiro, H.; Hattori, M.; Shimotohno, K. Screening of Korean plants against human immunodeficiency virus type 1 protease. *Phytother. Res.* **1999**, *13*, 680–682. [[CrossRef](#)]
404. Ali, H.; Konig, G.M.; Khalid, S.A.; Wright, A.D.; Kaminsky, R. Evaluation of selected sudanese medicinal plants for their in vitro activity against hemoflagellates, selected bacteria, HIV-1-RT and tyrosine kinase inhibitory, and for cytotoxicity. *J. Ethnopharmacol.* **2002**, *83*, 219–228. [[CrossRef](#)]
405. Wu, N.; Wang, L.; Chzn, Y.K.; Liao, Z.; Yang, G.Y.; Hu, Q.F. Lignans from the stem of *Styrax japonica*. *Asian J. Chem.* **2011**, *23*, 931–932.
406. Chang, Y.S.; Woo, E.R. Korean medicinal plants inhibiting to human immunodeficiency virus type 1 (HIV-1) fusion. *Phytother. Res.* **2003**, *17*, 426–429. [[CrossRef](#)]
407. Rukunga, G.M.; Kofi-Tsekpo, M.W.; Kurokawa, M.; Kageyama, S.; Mungai, G.M.; Muli, J.M.; Tolo, F.M.; Kibaya, R.M.; Muthaura, C.N.; Kanyara, J.N. Evaluation of the HIV-1 reverse transcriptase inhibitory properties of extracts from some medicinal plants in Kenya. *Afr. J. Health Sci.* **2002**, *9*, 81–90. [[CrossRef](#)] [[PubMed](#)]
408. Kusumoto, I.T.; Nakabayashi, T.; Kida, H.; Miyashiro, H.; Hattori, M.; Namba, T.; Shimotohno, K. Screening of various plant-extracts used in ayurvedic medicine for inhibitory effects on human-immunodeficiency-virus type-1 (HIV-1) protease. *Phytother. Res.* **1995**, *9*, 180–184. [[CrossRef](#)]
409. Sookkongwaree, K.; Geitmann, M.; Roengsumran, S.; Petsom, A.; Danielson, U.H. Inhibition of viral proteases by Zingiberaceae extracts and flavones isolated from *Kaempferia parviflora*. *Pharmazie* **2006**, *61*, 717–721. [[PubMed](#)]
410. Mujovo, S.; Hussein, A.; Meyer, J.J.M.; Fourie, B.; MutHIVhi, T.; Lall, N. Bioactive compounds from *Lippia javanica* and *Hoslundia opposita*. *Nat. Prod. Res.* **2008**, *22*, 1047–1054. [[CrossRef](#)] [[PubMed](#)]
411. Piacente, S.; Pizza, C.; De Tommasi, N.; Mahmood, N. Constituents of *Ardisia japonica* and their in vitro anti-HIV activity. *J. Nat. Prod.* **1996**, *59*, 565–569. [[CrossRef](#)]
412. Silprasit, K.; Seetaha, S.; Pongsanarakul, P.; Hannongbua, S.; Choowongkomon, K. Anti-HIV-1 reverse transcriptase activities of hexane extracts from some Asian medicinal plants. *J. Med. Plants Res.* **2011**, *5*, 4194–4201.
413. Maroyi, A. *Ximenia caffra* Sond. (Ximeniaceae) in sub-Saharan Africa: A synthesis and review of its medicinal potential. *J. Ethnopharmacol.* **2016**, *184*, 81–100. [[CrossRef](#)]
414. Thomford, N.E.; Awortwe, C.; Dzobo, K.; Adu, F.; Chopera, D.; Wonkam, A.; Skelton, M.; Blackhurst, D.; Dandara, C. Inhibition of CYP2B6 by medicinal plant extracts: Implication for use of efavirenz and nevirapine based highly active anti-retroviral therapy (HAART) in resource-limited settings. *Molecules* **2016**, *21*, 211. [[CrossRef](#)]
415. Eid, A.M.M.; Elmarzugi, N.A.; El-Enshasy, H.A. A review on the phytopharmacological effect of *Swietenia macrophylla*. *Int. J. Pharm. Pharm. Sci.* **2013**, *5*, 47–53.
416. Hasegawa, H.; Matsumiya, S.; Uchiyama, M.; Kurokawa, T.; Inouye, Y.; Kasai, R.; Ishibashi, S.; Yamasaki, K. Inhibitory effect of some triterpenoid saponins on glucose transport in tumor cells and its application to in vitro cytotoxic and antiviral activities. *Planta Med.* **1994**, *60*, 240–243. [[CrossRef](#)]
417. Xu, H.-X.; Wan, M.; Loh, B.-N.; Kon, O.-L.; Chow, P.-W.; Sim, K.-Y. Screening of traditional medicines for their inhibitory activity against HIV-1 protease. *Phytother. Res.* **1996**, *10*, 207–210. [[CrossRef](#)]
418. Grzybek, J.; Wongpanich, V.; Mata-Greenwood, E.; Angerhofer, C.K.; Pezzuto, J.M.; Cordell, G.A. Biological evaluation of selected plants from Poland. *Pharm. Biol.* **1997**, *35*, 1–5. [[CrossRef](#)]
419. Bedoya, L.M.; Sanchez-Palomino, S.; Abad, M.J.; Bermejo, P.; Alcamí, J. Anti-HIV activity of medicinal plant extracts. *J. Ethnopharmacol.* **2001**, *77*, 113–116. [[CrossRef](#)]
420. Birt, D.F.; Widrlechner, M.P.; Hammer, K.D.P.; Hillwig, M.L.; Wei, J.; Kraus, G.A.; Murphy, P.A.; McCoy, J.A.; Wurtele, E.S.; Neighbors, J.D. *Hypericum* infection: Identification of anti-viral and anti-inflammatory constituents. *Pharm. Biol.* **2009**, *47*, 774–782. [[CrossRef](#)]

421. Zhang, L.; Luo, R.-H.; Wang, F.; Jiang, M.-Y.; Dong, Z.-J.; Yang, L.-M.; Zheng, Y.-T.; Liu, J.-K. Highly functionalized daphnane diterpenoids from *Trigonostemon thyrsoideum*. *Org. Lett.* **2010**, *12*, 152–155. [[CrossRef](#)]
422. Chen, J.C.; Zhang, G.H.; Zhang, Z.Q.; Qiu, M.H.; Zheng, Y.T.; Yang, L.M.; Yu, K.B. Octanorcucurbitane and cucurbitane triterpenoids from the tubers of *Hemsleya endecaphylla* with HIV-1 inhibitory activity. *J. Nat. Prod.* **2008**, *71*, 153–155. [[CrossRef](#)]
423. Magadula, J.J.; Tewtrakul, S. Anti-HIV-1 protease activities of crude extracts of some *Garcinia* species growing in Tanzania. *Afr. J. Biotechnol.* **2010**, *9*, 1848–1852.
424. Au, T.K.; Lam, T.L.; Ng, T.B.; Fong, W.P.; Wan, D.C.C. A Comparison of HIV-1 integrase inhibition by aqueous and methanol extracts of Chinese medicinal herbs. *Life Sci.* **2001**, *68*, 1687–1694. [[CrossRef](#)]
425. Ngwira, K.J.; Maharaj, V.J.; Mgani, Q.A. In vitro antiplasmodial and HIV-1 neutralization activities of root and leaf extracts from *Berberis holstii*. *J. Herb. Med.* **2015**, *5*, 30–35. [[CrossRef](#)]
426. Louvel, S.; Moodley, N.; Seibert, I.; Steenkamp, P.; Nthambeleni, R.; Vidal, V.; Maharaj, V.; Klimkait, T. Identification of compounds from the plant species *Alepidea amatymbica* active against HIV. *S. Afr. J. Bot.* **2013**, *86*, 9–14. [[CrossRef](#)]
427. Woradulayapinij, W.; Soonthornchareonnon, N.; Wiwat, C. In vitro HIV type 1 reverse transcriptase inhibitory activities of Thai medicinal plants and *Canna indica* L. rhizomes. *J. Ethnopharmacol.* **2005**, *101*, 84–89. [[CrossRef](#)] [[PubMed](#)]
428. Xiao, W.L.; Pu, J.X.; Chang, Y.; Li, X.L.; Huang, S.X.; Yang, L.M.; Li, L.M.; Lu, Y.; Zheng, Y.T.; Li, R.T. Sphenadilactones A and B, two novel nortriterpenoids from *Schisandra sphenanthera*. *Org. Lett.* **2006**, *8*, 1475–1478. [[CrossRef](#)] [[PubMed](#)]
429. Voravuthikunchai, S.P.; Phongpaichit, S.; Subhadhirasakul, S. Evaluation of antibacterial activities of medicinal plants widely used among AIDS patients in Thailand. *Pharmaceut. Biol.* **2005**, *43*, 701–706. [[CrossRef](#)]
430. Chinsebu, K.C. Ethnobotanical study of plants used in the management of HIV/AIDS-related diseases in Livingstone, Southern Province, Zambia. *Evid. Based Complement. Alternat. Med.* **2016**, *2016*, 4238625. [[CrossRef](#)]
431. Zhang, H.J.; Tan, G.T.; Hoang, V.D.; Hung, N.V.; Cuong, N.M.; Soejarto, D.D.; Pezzuto, J.M.; Fong, H.H.S. Natural anti-HIV agents. Part 2: Litseaverticillol a, a prototypic litseane sesquiterpene from *Litsea verticillata*. *Tetrahedron Lett.* **2001**, *42*, 8587–8591.
432. Esposito, F.; Carli, I.; Del Vecchio, C.; Xu, L.; Corona, A.; Grandi, N.; Piano, D.; Maccioni, E.; Distinto, S.; Parolin, C. Sennoside a, derived from the traditional Chinese medicine plant *Rheum* L., is a new dual HIV-1 inhibitor effective on HIV-1 replication. *Phytomedicine* **2016**, *23*, 1383–1391. [[CrossRef](#)]
433. Chang, C.W.; Lin, M.T.; Lee, S.S.; Liu, K.C.S.C.; Hsu, F.L.; Lin, J.Y. Differential inhibition of reverse transcriptase and cellular DNA polymerase- α activities by lignans isolated from Chinese herbs, *Phyllanthus myrtifolius* Moon, and tannins from *Lonicera japonica* Thunb and *Castanopsis hystrix*. *Antivir. Res.* **1995**, *27*, 367–374. [[CrossRef](#)]
434. Bessong, P.O.; Rojas, L.B.; Obi, L.C.; Tshisikawe, P.M.; Igunbor, E.O. Further screening of venda medicinal plants for activity against HIV type 1 reverse transcriptase and integrase. *Afr. J. Biotechnol.* **2006**, *5*, 526–528.
435. Asres, K.; Bucar, F.; Kartnig, T.; Witvrouw, M.; Pannecouque, C.; De Clercq, E. Antiviral activity against human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) of ethnobotanically selected Ethiopian medicinal plants. *Phytother. Res.* **2001**, *15*, 62–69. [[CrossRef](#)]
436. Shriwas, P.; Chen, X.; Kinghorn, A.D.; Ren, Y. Plant-derived glucose transport inhibitors with potential antitumor activity. *Phytother. Res.* **2019**. [[CrossRef](#)]
437. Cary, D.C.; Peterlin, B.M. Natural products and HIV/AIDS. *AIDS Res. Hum. Retrovir.* **2018**, *34*, 31–38. [[CrossRef](#)] [[PubMed](#)]
438. Tietjen, I.; Ntie-Kang, F.; Mwimanzi, P.; Onguéné, P.A.; Scull, M.A.; Idowu, T.O.; Ogundaini, A.O.; Meva'a, L.M.; Abegaz, B.M.; Rice, C.M.; et al. Screening of the Pan-African natural product library identifies ixoratanin A-2 and boldine as novel HIV-1 inhibitors. *PLoS ONE* **2015**, *10*, e0121099. [[CrossRef](#)] [[PubMed](#)]
439. Richard, K.; Williams, D.E.; de Silva, E.D.; Brockman, M.A.; Brumme, Z.L.; Andersen, R.J.; Tietjen, I. Identification of novel HIV-1 latency-reversing agents from a library of marine natural products. *Viruses* **2018**, *10*, 348. [[CrossRef](#)] [[PubMed](#)]

440. Margolis, D.M.; Garcia, J.V.; Hazuda, D.J.; Haynes, B.F. Latency reversal and viral clearance to cure HIV-1. *Science* **2016**, *353*, aaf6517. [[CrossRef](#)] [[PubMed](#)]
441. Andersen, R.J.; Ntie-Kang, F.; Tietjen, I. Natural product-derived compounds in HIV suppression, remission, and eradication strategies. *Antiviral. Res.* **2018**, *158*, 63–77. [[CrossRef](#)]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).