Review

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

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Abstract: Acquired Immunodeficiency Syndrome (AIDS) which is chiefly originated by a retrovirus named Human Immunodeficiency Virus (HIV), has influenced about 70 million populations worldwide. Even though several advancements have been invented in the field of antiretroviral combination therapy, still HIV has become the dominant reason for death in South Africa, for example. The current antiretroviral therapies have achieved success in providing instant HIV suppression but with countless undesirable adverse effects. In the present day, 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 the drugs obtained from natural plants as well as the synthetic derivatives that have been derived from the natural compounds by various chemical reactions. Several plants such as *Andrographis paniculata*, *Dioscorea bulbifera*, *Aegle marmelos*, *Wistaria floribunda*, *Lindera chunii*, *Xanthoceras sorbifolia* and others have displayed significant anti-HIV activity showing more potent anti-HIV activity along with their structures, SARs & important key findings.

Keywords: AIDS; anti-HIV; natural products; SARs.

1. Introduction

The acquired immunodeficiency syndrome (AIDS) is a disease of cell-mediated immune system or T-lymphocytes of the human body. In AIDS, the count of helper T cells gets reduced which directly stimulates the production of antibodies from B cells. As a result, the body's natural defense system against AIDS infection gets destroyed [1]. According to the World Health Organization, about 75

million individuals have been infected from the human immunodeficiency virus (HIV), and about 37 million people are still fighting with this life-threatening infection. HIV is going to be increased day by day due to illiteracy, unhygienic living pattern, unsafe sexual relationships and lack of awareness [2]. In 1981, AIDS was first observed among homosexuals. The first human retrovirus was founded at the National Cancer Institute, in the USA by Robert Gallo and his colleagues. In 1983, Professor Luc Montagnier along with his co-workers had discovered the AIDS virus at the Institute Pasteur, in Paris [3]. In 1986, the International Committee on Viral Nomenclature firstly named the AIDS virus officially as Human Immunodeficiency Virus (HIV) [4]. It is considered that during the 1960s, the virus of AIDS has come from a monkey host cell into human host cells in Africa. South Africa is also known as “world AIDS capital”. In practice, Africans worldwide are additionally stricken by this unwellness than any other race [5].

1.1. Pathogenesis

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's 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 enzyme. The 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 that is called 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. Reverse transcriptase is an enzyme that causes the conversion of the viral RNA into viral DNA. Integrase is an enzyme that allows the entry of viral DNA into the host nucleus [10,11].

Figure 1. Structure of HIV Virus [8]

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 the individual, the virus enters into the body cells through various binding receptors that are depicting on the top of the macrophages, T lymphocytes, dendritic cells and monocytes [6, 7]. To

enter into the host cell, the virus binds with certain chemokine receptors along with interaction with cell membrane proteins. Inside the host cell, the HIV releases and utilizes its reverse transcriptase enzyme for the synthesis of viral DNA from its viral genome that is HIV RNA. The conversion of viral RNA into DNA allows the virus to enter into the host cell nucleus [10, 11]. Inside the nucleus, the HIV releases an enzyme Integrase that helps it to integrate its viral DNA into the host cell's DNA [8- 10]. Newly formed HIV protein and viral RNA shift towards the cell membrane and reunite into immature HIV. The new immature virus (non-infectious) budded off from the host cell. Then, the protease enzyme is released from the viruses that cause the breakdown of long-chain polypeptides of immature virus and 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: HIV Replication Cycle [6]

1.3. Diagnosis

The HIV infection is generally diagnosed from the blood plasma. The diagnosis of the viral infection into the blood of the host is normally estimated from the viral RNA mass. The infection is linked with the period of acute symptoms which include lymphadenopathy, fever, weight loss, lethargy, general malaise, pharyngitis, rashes, nausea, headache, myalgias, anyhow severe consequences like meningitis may also occur [2,6]. While the duration of acute HIV infection, the viral RNA is at the highest levels in the blood plasma and also the symptoms as well as the severity of infection is dependent on the viral mass in the plasma. It is estimated that the amount and characteristics of the virus indicate its pathogenesis as well as the replication. Hence, the clinical details and infection progression are relying on the host characteristics along with the viral genotype [14-16]. ELISA and Western Blotting were the two 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]. The western blotting test 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 the tests is 99% accurate. At the time, various alternatives are available in place of Western Blotting test which is less time consuming [18].

1.4. *Present Therapy for HIV/AIDS*

Despite the fact, HIV was known within the past 1980s, however, there's no efficacious therapy or vaccine for the entire destruction of HIV [2]. The present therapy for AIDS is quite complex, tedious, requires expertise, solid motivation and patient's commitment, suitable means and is costly. Antiretroviral therapy (ART) is only about twenty years old, and further approaches are still progressing. Many patients are still suffering from this untreated infection. The use of certain medicines can recover the disease quality but cannot promise the life of a patient. However, with the development of new entities and immune modulators, it is possible to fight with this disease [19-21]. The drugs provide a meaningful advancement in mitigation, control, cure and prevention. With the establishment of HAART (highly active antiretroviral therapy) and anti-retroviral agents in 1996 necessarily decreased the mortality and morbidity of AIDS. Antiretroviral therapy is presently prescribed for all adult patients with HIV [2]. A combination of various drugs is given to achieve an efficacious treatment like; nucleoside reverse transcriptase inhibitors, fusion inhibitors, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, protease inhibitors along with immunomodulators. Because none of the presently accessible regimens can abolish HIV from the body of the patient, the objective of therapy is to durably and maximally prohibit viral replication so that the individual can achieve and maintain adequate immune response against the potential viral pathogens. Higher the abolition of viral replication, lower is the incidence of development of 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 of their count of CD4 cells, should be dealt with anti-retroviral therapy (ART) quickly after diagnosis, so as to avoid infection progression, promote clinical outcomes in addition to minimizing AIDS-associated incidents, non-AIDS regarding incidents etc [20].

1.5. *Drawbacks of Present 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 dangerous side effects of anti-HIV drugs, their toxicity and destructive effect of anti-HIV drugs on quality of life, principally lipid abnormalities, possibility of drug resistance restricting future treatment opportunities, drug interactions, limited capability of available regimens, failure of treatment, risk of distribution of resistance virus and big cost [23-25]. The right time to start anti-HIV therapy stays uncertain. The antiviral drugs that act on the HIV virus, also affect the host cells; they may harm the host cell's nuclear material also 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 [24-26].

2. Natural Plants as Anti-HIV Agents

The present treatments are restricted by the evolution of multidrug resistance. That's why novel targets and new more effective drugs are required for achieving the goal of an entire eradication of AIDS. Also, infected cells stay persisted and put a basic barrier to the elimination of HIV-1. From the past 10 years the mechanism by which the virus persists put forward the way for the invention and discovery of new drug compounds that worked efficaciously against HIV without activating the T cells of the immune system [27, 28]. Since more effective and new drug compounds were still required for the manipulation and control of HIV, it has been recommended by the World Health Organization (WHO) that ethnomedicines and various other natural constituents should be orderly tested in contrast to HIV while they may produce more affordable and durable therapeutic agents [29, 30]. Interestingly, in the 1990s, a lot of tasks were performed in this field, specific inventions of natural products with their mechanisms against HIV-1 enzymes like reverse transcriptase, integrase, protease and some fusion inhibitors. The natural drugs have chemical diversity with higher hit rates in High throughput screening and high capability to approach the target site [31]. A number of alkaloids, flavonoids, coumarins, terpenoids, and polyphenolic compounds are investigated to exert anti-HIV activity extracted from various plants [32,33]. From this inspiration Chaniad *et al.* studied anti-HIV activity from *Dioscorea bulbifera* [34], Jiang *et al.* again evaluated *Euphorbia sikkimensis* for anti-HIV properties [35], Kalvatchev *et al.* reported that the extracts of *Culendula officinalis* also shows significant effects against HIV [36], Kapewwangolo *et al.* described anti-HIV action of *Sceletium tortuosum* [37], similarly *Brazilian propolis*, *Kadsura lancilimba*, *Lithocarpus litseifolius*, and *Ocimum labiatum* have also been studied for their anti-HIV properties [38-41].

Keeping in the view that numerous plants having significant anti-HIV properties, therefore, this review highlights the discovery of plant-based compounds/molecules during the last decades that have been used in the treatment/management of HIV. A detailed account of plants according to the mechanism of action and activity of secondary metabolites has been discussed. In addition to the design strategies, structure-activity relationships, mechanistic insights revealed during the biological evaluation, IC_{50} values and important key findings have also been presented diagrammatically. This assemblage will be of great help for the researchers/academicians working in the area of anti-HIV drugs. The article presents medicinal plants that have been classified into various categories. The classification is given below.

In this review, the natural medicinal plants are described into 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 derived from medicinal plants may be an encouraging alternative for a number of disorders and conditions [42-48]. Antiviral research, attention is chiefly paid on the 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 virus, i.e., protease, integrase, reverse transcriptase, etc [49]. Anti-HIV drugs can be categorized into several classes according to their action on the life cycle of HIV [50]. Hence, different drugs act on these different steps of replication and inhibit the further expansion of virus into the body. A group of researchers reported

the activities of HIV-PR inhibitors from different plants [51-60]. Primarily, all the anti-HIV drugs are divided into the following categories:

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

1.5.1. 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 [61]. Infection is chiefly started by 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 a conformational change which further stimulates the interaction of secondary gp120 with co-receptor CCR5 [62]. Fusion inhibitors prevent the entry of virus into the host cell by inhibiting the fusion of virus particle with the membrane of host cell which is the early first step of virus replication [63].

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 [64,65]. Matsuda *et al.* in 2014 reported an alkaloid Cepharanthine (**1**) isolated from *Stephania cepharantha* having anti-HIV and anti tumor activities without exerting any serious side effects. It modifies the plasma membrane fluidity and prevents the viral cell fusion [66]. A diterpene lactone named Andrographolide (**2**) shown in Figure 3 is obtained from the herb *Andrographis paniculata* possesses HIV-1 fusion inhibition properties [67-71]. Several derivatives of this compound have been produced synthetically to exert more potent anti-HIV properties [72, 73].

Figure 3. Structure of fusion inhibitors.

1.5.2. Natural plants as Reverse Transcriptase Inhibitors

The HIV virus utilizes reverse transcriptase enzyme for conversion of its viral RNA into DNA. RT inhibitors mainly act upon this enzyme and prohibit the very important step of viral replication [74]. A number of natural products have been isolated from natural plants have been derived for their activity against RT [55]. The plants used as reverse transcriptase inhibitors viz; *Culendula officinalis*, *Acacia mellifera*, *Uvaria angolensis*, *Hypericum scruglii*, *Spaganium stoloniferum*, *Calophyllum brasiliense*, *Maytenus buechanani*, *Prunus Africana*, *Vernonia jugalis*, *Maytenus senegalensis*, *Melia azedarach*, *Calophyllum inophyllum*, *Lomatium suksdorfii*, *Coriandrum sativum*, *Chrysanthemum morifolium* and *Swertia franchetiana* [36, 55-82]. Capryl aldehyde and methyl-n-nonyl ketone obtained from *Houttuynia cordata* directly inhibit the RT enzyme [55]. Calanolides A (3) and B (4) [78] have been obtained from the plant *Calophyllum inophyllum*. Some naphthoquinones such as michellamines A, B and C, were extracted from the plant *Ancistrocladus korupensis*, exhibited inhibitory activity on the HIV-RT enzyme [83]. From lichen named as *Cetraria islandica*, a RT inhibitory compound acetogenin protolichensterinic acid is obtained [84]. The compounds mallotochromene (5) and mallotojaponin (6) have been given in Figure 4 and separated from *Mallotus japonicas* have shown strong inhibition of HIV-RT [85]. Another compound nigranoic acid has been extracted from *Schisandra lancifolia*, acted effectively on the reverse transcriptase replicative enzyme of HIV [86]. Some other plants showing HIV RT inhibitory property are given in the Table 1.

Table 1. Plant Based Reverse Transcriptase inhibitors

Category	Plant Species	Chemical Constituents	Reference
Terpenoid	<i>Excoecaria agallocha</i>	Phorbol	[87]
Terpenoid	<i>Trypterygium wilfordii</i>	Salaspermic acid	[88]
Terpenoid	<i>Euphorbia myrsinites</i>	15-O-acetyl-3-O-butanoyl-5-O-propionyl-7-O-nicotinoylmyrsinol	[89]
Terpenoid	<i>Polyalthia suberosa</i>	Suberosol	[90]
Terpenoid	<i>Andrographis paniculata</i>	Dehydroandrographolide succinic acid monoester	[91]
Terpenoid	<i>Glycyrrhiza radix</i>	Glycyrrhizin	[92]
Terpenoid	<i>Cowania Mexicana</i>	Cucurbitacin F	[93]
Terpenoid	<i>Trypterygium wilfordii</i>	Tripterifordin	[94]
Terpenoid	<i>Maprounea Africana</i>	1 β -hydroxymaprounic acid 3-p-hydroxybenzoate	[95]
Terpenoid	<i>Szigium claviform</i>	Betulinic acid, platonic acid	[96]
Terpenoid	<i>Houttuynia cordata</i>	Lauryl aldehyde, capryl aldehyde	[97]
Flavonoid	<i>Chrysanthemum morifolium</i>	Acacetin-7-O- β -galactopyranoside	[81]
Flavonoid	<i>Scutellaria baicalensis</i>	Baicalin	[98]
Flavonoid	<i>Buchenavia capitata</i>	Buchenavianine	[99]
Flavonoid	<i>Kummerowia striata</i>	Apigenin-7-O- β -D-glucopyranoside	[100]
Coumarin	<i>Calophyllum inophyllum</i>	Inophyllums	[101]
Coumarin	<i>Coriandrum sativum</i>	Coriandrin	[80]
Coumarin	<i>Lomatium suksdorfii</i>	Suksdorfin	[79]
Coumarin	<i>Aegle marmelous</i>	Imperatorin, xanthotoxol, xanthotoxin	[102,103]

Tannin	<i>Euphorbia jolkini</i>	Putranjivain A	[104]
Tannin	<i>Cornus officinalis</i>	Cornusin A	[105]
Tannin	<i>Mallotus repandus</i>	Repandusinic acid	[106]
Tannin	<i>Hyssop officinalis</i>	Caffeic acid	[107]
Polysaccharide	<i>Thuja occidentalis</i>	Thujone	[108]
Polysaccharide	<i>Prunella vulgar</i>	Sulfated polysaccharide	[109]
Polysaccharide	<i>Viola yedoensis</i>	Sulfonated polysaccharide	[110]
Xanthone	<i>Tripterospermum</i>	1,3,5,6-tetrahydroxyxanthone,	[111]
	<i>lenceolaum</i>	3,4,5,6-tetrahydroxyxanthone	
Lignan	<i>Haplophyllum ptilostylum</i>	Ptilostin	[112]
Lignan	<i>Schisandra chinensis</i>	Gomisin J	[113]
Lignan	<i>Ipomoea cairica</i>	Arctigenin, trachelogenin	[114]
Marine origin	<i>Hyatella intestinalis</i>	Hyatellaquinone	[115]
Marine origin	<i>Fascaplysinopsis reticulate</i>	Fascaplysin, isodehydroluffariellolide,	[116]
		Homofascaplysin C	
-	<i>Toxiclona toxius</i>	Toxiusol	[117]
-	<i>Plakortis sp.</i>	Plakinidine A	[118]
-	<i>Kelletia kelletii</i>	Kelletinin 1	[119]
-	<i>Buccinulum corneum</i>	Kelletinin A	[120]
-	<i>Maprounea Africana</i>	1 β -hydroxyaleuritolic acid	[121]
		3-p-hydroxybenzoate	

The therapeutic compounds obtained from different plants, showing anti-HIV reverse transcriptase activity are named as suksdorfin (**7**) [79], salaspermic acid (**8**) [88], cucurbitacin F (**9**) [93], batulinic acid (**10**) [96], baicalin (**11**) [98], buchenavianine (**12**) [99], thujone (**13**) [106], hyatellaquinone (**14**) [115], isodehydroluffariellolide (**15**) [116], homofascaplysin C (**16**) [116], toxiusol (**17**) [117] represented in Figure 4.

Figure 4. Structure of some potent Reverse Transcriptase Inhibitors.

1.5.3. Natural plants as Integrase Inhibitors

The insertion of HIV DNA into the DNA of host cell is generally catalyzed by the integrase enzyme of HIV virus. The reaction is preceded in two phases; the first phase is 3'-processing phase and second phase includes the transfer of strand [122]. Various therapeutic active components have been

separated from the plant *Dioscorea bulbifera*. The plant extract has exhibited several therapeutic properties such as; anticancer, antibacterial, analgesic, and antidiabetic [123-127]. Chaniad *et al.* isolated seven different components have been recognized from the *D. bulbifera* extract with anti-IT property. Structure of allantoin (**18**), 5,7,4'- trihydroxy- 2- styrylchromone, 2,4,3',5'- tetrahydroxybibenzyl, quercetin 3-O- β -D -galactopyranoside, 2,4,6,7- tetrahydroxy- 9,10-dihydrophenanthrene, quercetin- 3-O- β -D- glucopyranoside (**19**) and myricetin (**20**) shown in Figure 5 [34]. In another study Panthong *et al.* revealed that *Albizia procera* is a medicinal plant that has been used in the antiretroviral therapy [128,129]. Catechin (**21**), suramin and protocatechuic acid (**22**) are the components identified from the plant extract and are considered to act on the integrase enzyme of HIV virus, hence prohibiting the viral replication [128]. Some ribosome inactivating proteins are considered to act on the integrase enzyme [130]. Currently, a ribosome inactivating protein (RIP) named MAP30, has been extracted from *Momordica charantia*, has reported to act against the HIV as well as cancer [131,132]. Zhao *et al.* discovered another RIP trichosanthin, is obtained from the roots of *Trichosanthes kirilowii*, shown inhibitory activity against integrase enzyme [133]. A number of plant RIPs involving agrostin, saporin, R-momorcharin, gelonin, α -momorchain, trichosanthin and luffin have also exhibited an inhibitory effect on the HIV replication [134].

Figure 5. Natural Integrase Inhibitors.

1.5.4. Natural plants as Protease Inhibitors

Protease is a viral enzyme that acts at the last step of virus replication. It causes the breakdown of long polypeptides and proteins into the small functional proteins that are generally infectious [135,138]. 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

[136,138,139]. From *Camellia japonica* pericarp, plant components camelliatannin A, F and H have been reported that exhibit potent anti-HIV PR inhibitory property [137]. Several Korean therapeutic plants like *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 activity against protease [60]. From the plant stems of *Stauntonia obovatifoliola*, various components that act on the HIV protease have been extracted such as lupenone (23) [140], 3-O-acetyloleanolic acid (24) [141], resinone (25) [142], lupeol (26) [143] and mesenbryanthemoidgenic acid (27) presented in Figure 6 [144]. In another invention the therapeutic compounds like oleanolic acid (28), dihydromyricetin, epigallocatechin gallate, myricetin [145, 146] and epiafzelechin [147] have been extracted from the wood of plant *Xanthoceras sorbifolia* has been proved for the treatment of AIDS [57, 145].

Figure 6. Compounds having Protease inhibitory activity

1.5.5. Natural plants as Immunomodulators

Immunomodulators are the agents that stimulate the cellular and humoral immune system against any pathogenic infection [148-150]. The dendritic cells of the immune system act as antigen representing cells and move alongwith antigen into the lymph nodes from the tissues. They represent the antigen to the T cells and the T cells then initiate 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 also which attack on the pathogen [151]. There are several classes of natural compounds that exhibit immunomodulatory properties such as; alkaloids, tannins, terpenoids, coumarins, glycosides, flavonoids, polysaccharides and lignans etc [152,153]. Among alkaloids, berberine **(29)** [148] is obtained from *Hydrasti Canadensis* [154], sinomenine **(30)** [148] is isolated from *Sinomenium acutum* [155], piperine **(31)** [148] is obtained from *Piper longum* [156], and tetrandrine is obtained from *Stephania tetrandra* [157] have shown immunomodulatory property in HIV infection. Among glycosides, aucubin is obtained from *Plantago major* [158], isorhamnetin-3-O-glucoside is extracted from *Urtica dioica* [159], and mangiferin is obtained from *Mangifera indica* [160] have exhibited immune stimulatory properties in HIV. Among phenols, ellagic acid **(32)** from *Punica granatum* [161], curcumin from *Curcuma longa* [162] and ferulic acid **(33)**, vanillic acid **(34)** shown in Figure 7 [148] and chlorogenic acid are obtained from *Plantago major* [158], have been expressed effective immunomodulatory potential in AIDS. Within tannins, chebulagic acid and corilagin from *Terminalia chebula* [163] and punicalagin [164] act as immunomodulatory agents. Among flavonoids, centaurein from *Bidens pilosa* [165] and apigenin 7-O- β -D-neohesperidoside, orientin, vitexin and apigenin 7-O- β -D-galactoside obtained from *Jatropha curcas* [166], have exhibited the effective immunomodulatory action against HIV. From saponins, asiaticoside obtained from *Centella asiatica* [167] and glycyrrhizin is extracted from the roots of *Glycyrrhiza glabra* [168], have shown significant immunomodulatory activity.

Figure 7. Plants based Immunomodulators

1.5.6. Natural plants as Antioxidants

In AIDS, many reactive oxygen species have been produced due to the alteration in the levels of antioxidant enzymes [169]. This further leads to the damage of DNA and lipid peroxidation [170]. Reactive oxygen species can also stimulate a NF- κ B factor which helps in the transcription of HIV virus and thus promote its replication [171]. Antioxidants are the agents that reduce the levels of reactive oxygen species and protect the cellular DNA. N-Acetylcysteine is an agent that acts as antioxidant and used in the treatment of HIV infection [172]. Various other antioxidants like Selenium, lipoic acid, vitamin C, β -carotene and vitamin E are used in the HIV infection [173,174]. Cyanidin-3-glucoside (**35**) is an antioxidant obtained from the blackberry, have been used in HIV infection and Peonidin (**36**) given in Figure 8 is another antioxidant obtained from blackberry which is used in this infection [148,175].

Figure 8. Plant based antioxidants used in AIDS.

1.6. Plants according to their Secondary Metabolites

Secondary metabolites are plant components that have some therapeutic activity. They are generally obtained from the primary metabolites such as carbohydrates, proteins, amino acids, phenolics etc [176-179]. Secondary metabolites mainly include alkaloids, glycosides, coumarins, terpenoids, lignans, tannins, pectins, flavonoids, phenols, lectins, proteins etc [180-182].

1.6.1. Alkaloids

Alkaloids are the basic nitrogen containing secondary metabolites of the plants, active against many diseases including HIV. Buchapine is a quinolone alkaloid obtained from *Eodia roxburghiana*, has shown an effective activity towards HIV infection [183]. From the roots of *Tripterygium hypoglaucum*, various alkaloid compounds have been extracted like hypoglaumine B and triptonine A (**37**) and B exhibiting anti-HIV activity and are used in the antiretroviral therapy [184]. Nitidine is another alkaloid that is isolated from plant roots of *Toddalia asiatica*, have shown a strong potential against HIV [185]. From the plant *Symplocos setchuensis*, an alkaloid harman (**38**) and another compound matairesinoside (**39**) is separated and is used in antiretroviral therapy for its anti-HIV potential. It acts on the viral replicative enzymes and inhibits the HIV replication [186]. Another aromatic alkaloid polycitorone A that is obtained from marine source *Polycitor sp.*, exhibited potential activity against the reverse transcriptase of HIV. Hence, it efficiently prohibits the HIV replication. Several other marine sponges have been used which act against the viral diseases as well as the bacterial ones [187]. From *Leitneria floridana*, an alkaloid 1-methoxy canthionone is isolated for its anti-HIV property [188]. Papaverine is obtained from *Papaver somniferum*, inhibits the HIV replication [33].

Norisoboldine and corydine are the two alkaloids obtained from the leaves of *Croton echinocarpus*, showing anti-HIV activity [189]. Table 2 depicts the plant based alkaloids possessing anti-HIV activity.

Table 2: Alkaloidal based compounds as Anti-HIV agents

Plant Species	Parts used	Chemical Constituents	References
<i>Ancistrocladus korupensis</i>	Leaves	Michellamine A, B and C	[190]
<i>Stephania cepharantha</i>	Roots	Cepharantine	[191]
<i>Murraya siamensis</i>	Roots, leaves	Siamenol	[192]
<i>Clausena excavate</i>	Leaves	O-Methylmukonal, clauszoline and 3-formyl-2,7-dimethoxy-carbazole	[193]
<i>Drymaria diandra</i>	Leaves	Canthin-4-one drymaritin	[194]
<i>Glycosmis Montana</i>	Twigs, leaves	(E)-3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl)-1H-indole	[195]
<i>Aniba species</i>	Stems	Anibamine	[196]
<i>Zanthoxylum ailanthoides</i>	Root bark	Decarine, γ -fagarine and tembamide	[197]
<i>Nelumbo nucifera</i>	Leaves	Coclaurine, norcoclaurine, reticuline	[198]
<i>Pericampylus glaucus</i>	Leaves	Norruffscine, 8-oxotetrahydro-palmatine	[199]
<i>Begonia nantoensis</i>	Rhizomes	Indole-3-carboxylic acid	[200]
<i>Leucojum vernum</i>	Bulbs	Lycorine, homolycorine	[201]
<i>Epinetrum villosum</i>	Root	Cycleanine	[202]
<i>Argemone mexicana</i>	bark	6-Acetyl-dihydrochelerythrine, nuciferine	[203]
<i>Monanchora sp.</i>	Roots	Crambescidin 826, fromiamycalin and crambescidin 800	[204]
	Stems	Manadomanzamines A and B	
<i>Acanthostromgylophora sp.</i>	-	Hernandonine, lindechunine, 7-oxohernangerine and laurolistene	[205]
<i>Lindera chunii</i>	Roots		[206]
<i>Artemisia caruifolia</i>	Stems		[207]

Several alkaloid compounds such as, michellamine A (**40**) [190], siamenol (**41**) [192], decarine (**42**) [197], reticuline (**43**), norcoclaurine (**44**) [198], indole-3-carboxylic acid (**45**) [200], lycorine (**46**) [201], homolycorine (**47**) [201], cycleanine (**48**), 6-Acetyl-dihydrochelerythrine (**49**) [203] and hernandonine (**50**) [206] have shown significant HIV inhibitory potential in Figure 9.

Figure 9. Alkaloidal compounds possessing anti-HIV activity. (Continue)

Figure 9. Alkaloidal compounds possessing anti-HIV activity.

1.6.2. Terpenoids

Terpenoids are the secondary metabolites that are derived from the isoprene unit (C₅H₈) [208]. Many plant terpenoids have been used for their therapeutic potential [209]. Plant terpenoids betulinic acid, oleanolic acid and platanic acid are isolated from *Syzygium claviflorum* leaves and have exhibited efficient inhibition of HIV replication [210]. Celastrol B (51) is a triterpene that is isolated from *Celastrus hindsii* belonging to the family Celastraceae, has reported to inhibit the HIV replication [211]. Prostratin has been expressed significant anti-HIV activities and is separated from *Homalanthus nutans* belonging to the family Euphorbiaceae [212]. From the stem bark of plant *Garcinia speciosa*, some anti-HIV therapeutic components have been isolated that are garcisaterpenes A, C and theprotostanes. They inhibit the activity of HIV reverse transcriptase and thus stop the HIV life cycle [213]. Maslinic acid (52) is a terpenoid compound that acts against the HIV protease enzyme and is obtained from *Geum japonicum* [214]. From the stems and roots of plant *Kadsura*

lancilimba, another triterpene lancilactone C (**53**) has been derived that restricts the viral replication [215]. Oleanolic acid is chief terpenoid isolated from many plant species including *Xanthoceras sorbifolia* belonging to the family Sapindaceae. It effectively inhibits the HIV replication and plays an important role in the treatment of AIDS [216]. Suberosol (**54**) is a lanostane type triterpenoid and is extracted from the leaves of *Polyalthia suberosa*, belonging to family Annonaceae has shown effective inhibition of HIV replication [217]. An another phorbol diester known as 12-O-tetradecanoylphorbol-13-acetate, has been exhibited anti-HIV activity and was obtained from *Croton tiglium* belonging to family Euphorbiaceae [212]. A Brazilian alga isolated from *Dictyota pfaffii*, from which an active diterpene component 8,10,18-trihydroxy-2,6-dolabelladiene has been extracted and has shown inhibitory activity of HIV reverse transcriptase [218,219]. A butenolide triterpene known as 3-epi-litsenolide D₂ has been expressed significant anti-HIV activity and was extracted from *Litsea verticilla* [220]. Alga *Dictyota menstrualis* is an important source for various diterpenes that exhibit HIV reverse transcriptase inhibition potential [221]. From the roots and rhizomes of plant *Clausena excavate*, a limonoid terpene named as clausenolide-1-ethyl ether has been obtained and has used in the antiretroviral therapy [222]. Glycyrrhizin is another saponin terpenoid that consists of significant anti-HIV activity and prohibits the viral life cycle, has extracted from the *Glycyrrhiza glabra* roots [223]. Oleanolic acid is a potent anti-HIV component and is widely distributed in various plants involving leaves of *Rosa woodsii*, leaves of *Syzygium claviflorum*, aerial parts of *Ternstroemia gymnanthera*, plant of *Hyptis capitata* and plant of *Phoradendron juniperinum* [216]. 12-Deoxyphorbol-13-phenylacetate is a phorbol ester and is obtained from the plant *Euphorbia poissonii*, has been reported for possessing anti-tumor activity and recently, it has been used in the antiretroviral therapy for its anti-HIV activity [224]. Pedilstatin [13-O-acetyl-12-O-(2'Z,4'Eoctadienoyl)-4 α -deoxyphorbol] is another phorbol ester obtained from *Pedilanthus sp.*, possessing anticancer and anti-HIV properties [225]. Some other plant species containing terpenoid compounds with efficient anti-HIV activity have been represented in the Table 3.

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	[226-228]
<i>Propolis</i>	Roots	Melliferone, moronic acid, betulonic acid	[38, 229]
<i>Homalanthus nutans</i>	Leaves	Prostratin	[230, 231]
<i>Cassine xylocarpa</i>	Stem	Germanicol, nivadiol	[232]
<i>Glycyrrhiza uralensis</i>	Roots	Galacturonic acid, xylose, uralsaponin C	[233]
<i>Daphne gnidium</i>	Aerial parts	Daphnetoxin, gniditrin, gnidicin	[234]
<i>Euphorbia micractina</i>	Roots	Lanthyrane diterpenoids	[235]
<i>Kaempferia pulchra</i>	Rhizomes	Kaempulchraol A, C, E	[236]
<i>Picrasama javanica</i>	Bark	Picrajavanicin A, javanicin B, picrasin A	[237]
<i>Schisandra lancifolia</i>	Leaves, stem	Lancifodilactone F	[238]
<i>Stellera chamaejasme</i>	Roots	Stelleralide D, gnidimacrin	[239]
<i>Lindera strychnifolia</i>	Roots	Lindenanolides E, G and F	[240]
<i>Daphne acutiloba</i>	Roots	Wikstroelide M	[241]

<i>Annona squamosa</i>	Leaves	16 β ,17-dihydroxy-entkauran-19-oic acid	[242]
<i>Cimicifuga racemosa</i>	Rhizomes	Actein	[243]
<i>Schisandra sphaerandra</i>	Leaves	Nigranoic acid	[244]
<i>Allanthus altissima</i>	Roots	Shinjulactone B	[245]
<i>Panax ginseng</i>	Roots	Isodehydroprotopanaxatriol	[246]
<i>Garcinia hanburyi</i>	Stem, roots	3-acetoxyalphitolic acid, 2-acetoxyalphitolic acid	[247]
<i>Euphorbia officinarum</i>		8-methoxyingol-7,12-diacetate-3-phenylacetate	[248]
	Leaves	Dihydrocucurbitacin F	
<i>Hemsleya jinfushanensis</i>		Forskolin, 1-deoxyforskolin	[249]
<i>Coleus forskohlii</i>	Tubers	28-hydroxy-3-oxo-lup-20(29)-en-3-O-al	[250]
<i>Microtropis fokienensis</i>	Roots	Betulonic acid	[251]
<i>Betula platyphylla</i>	Stem	25-hydroxy-3-oxoolean-12-en-28-oic acid	[252]
<i>Amoora rohituka</i>	Roots	Capilliposide B	[253]
	Stem bark	Ganoderic acid D	
<i>Lysimachia capillipes</i>		Ganoderiol F	[254]
<i>Ganoderma lucidum</i>	Roots	Impatienside A, bivittoside D	[255]
<i>Ganoderma amboinense</i>	Stem,	25-methoxyhispidol A	[256]
<i>Holothuria impatiens</i>	Leaves	23,24-dihydrocucurbitacin B	[257]
<i>Poncirus trifoliata</i>	Stem	Dichapetalin A	[258]
<i>Trichosanthes kirilowii</i>	-	Acutissimatriterpene A, B , E	[259]
<i>Dichapetalum gelonioides</i>	Fruits	Celastrol	[260]
<i>Phyllanthus acutissima</i>	Roots	3 α ,7 α -dideacetylkhivarin	[261]
<i>Celastrus orbiculatus</i>	Stem bark	Nimbolide	[262]
<i>Khaya senegalensis</i>	Aerial	Gedunin, 1 α -hydroxy1,2-dihydrogedunin	[263]
<i>Azadirachta indica</i>	parts	6 α -tigloyloxychaparrinone	[264]
<i>Xylocarpus granatum</i>	Bark		[265]
	Roots		
<i>Ailanthus integrifolia</i>	Flowers		[266]
	-		
	Roots		

Many of the terpenoid compounds with their chemical structures have been represented in Figure 10, melliferone (**55**) [38], moronic acid (**56**) [38], ribenone (**57**) [226], germanicol (**58**) [232], nivadiol (**59**) [232], wikstroelide M (**60**) [241], shinjulactone B (**61**) [245], ganoderic acid D (**62**) [255], ganoderiol F (**63**) [256] gedunin (**64**) [265] and 1 α -hydroxy1,2-dihydrogedunin (**65**) [265] exhibiting anti-HIV activity.

Figure 10. Potent Terpenoids in HIV. (Continue)

Figure 10. Potent Terpenoids in HIV.

1.6.3. Flavonoids

Flavonoids are the plant components and have shown several antiviral and antioxidant properties. Thus these are used in various viral diseases [267]. Flavonoids like quercetin 3-O-(2-galloyl) a *L*-arbinopyranose and gallate ester have been separated from *Acer okamotoanum* belonging to family Aceraceae, exhibited significant activity against integrase of HIV [268]. Xanthohumol (66) is an important flavonoid that is isolated from *Humulus lupulus*, has shown anti-HIV activity [269]. Two flavonoids 6,8-diprenylkaempferol and 6,8-diprenylaromadendrin have expressed a potential activity against the AIDS virus and were isolated from plant *Monotes africanus* [270]. From *Wikstroemia indica* plant roots belonging to the Thymelaeaceae, a biflavonoid named wikstrol B (67) has been extracted and is used for its anti-HIV activity [271]. Baicalin is a flavonoid compound that prohibits HIV replication and is derived from the plant *Scutellaria baicalensis* [272]. From twigs and

leaves of medicinal plant *Rhus succedanea*, various anti-HIV flavonoids have been separated that act on the polymerase of the reverse transcriptase of HIV-1. The flavonoids robustaflavone, biflavonoids and hinokiflavone are the potent inhibitors of HIV replication [273]. 2-methoxy-3-methyl-4,6-dihydroxy-5-(3'-hydroxy)-cinnamoylbenzaldehyde is a chalcone flavonoid that has been extracted from *Desmos spp.* roots and exhibited strong activity against HIV-1 [274]. Hydroxypanduratin A is a chalcone that acts on the HIV protease enzyme and is obtained from the rhizomes of *Boesenbergia pandurata* [275].

Figure 11. Flavanoid based compounds used as Anti-HIV agents.

Several flavonoids like chrysin, epigallocatechin gallate (68) and quercetin (69) have been isolated from a number of plants and are reported to show potent inhibitory activity on the replication of HIV virus [276,277]. Thalassiolins A, B and C are flavonoid compounds that act on the HIV integrase and prohibit the life cycle of HIV-1 and are obtained from the grass *Thalassia testudinum*. Thalassiolin A is the most potent compound which prohibits the terminal cleavage [278]. Some biflavonoids such as 2'',3''-dihydrochonaflavone 7''-O-methylether and ochnaflavone 7''-O-methyl ether are isolated from *Ochna integerrima*, have shown moderate to weak anti-HIV activity [280]. Another flavonoid taxifolin (70) which is also known as dihydroquercetin is chiefly

extracted from the stems of *Juglans mandshurica*, expressed strong inhibitory activity on the reverse transcriptase enzyme of HIV and thus plays a role in the prevention of HIV replication [281]. From *Chrysanthemum morifolium* flowers, two important flavonoids apigenin 7-O β -D-(4'caffeoyl)glucuronide and glucuronide have been extracted that exhibited a significant activity on the integrase of HIV-1 [282]. *Mentha longifolia* is another plant whose methanolic extracts are used for the isolation of several therapeutic flavonoids and are considered to act on the HIV reverse transcriptase [283]. Several other flavonoids such as flemiphyllin, formosanatin C (**71**), euchretin I (**72**) and quercetin are reported to inhibit the HIV replication and are obtained from the alcoholic extracts of *Euchresta formosana* [284]. Many important flavonoids such as epicatechin-3-O-gallate and epicatechin have extracted from *Detarium microcarpum*, shown anti-HIV potential [285]. 4'-methylepigallocatechin-3'-O β -glucopyranoside, and 4'-methylepigallocatechin-5-O β -glucopyranoside are two medicinal flavonoids that are separated from *Maytenus senegalensis* and exhibit anti-HIV activity [286]. Kaempferol (**73**) presented in Figure 11, a tetrahydroxyflavonol shown inhibitory activity on the protease enzyme and is isolated from *Rosa damascene* [287, 288].

1.6.4. Coumarins

Calanolides are a group of coumarins that act as non-nucleoside reverse transcriptase inhibitors and are derived from the genus *Calophyllum* belonging to family Clusiaceae [289]. Calanolide A [290] and Calanolide B along with its derivative known as 7,8-dihydrocalanolide B are obtained from the plant *Calophyllum lanigerum*, have shown inhibition of the cytopathogenic results of HIV on the cells of host [289]. Another coumarin named suksdorfii (**74**) [292] is isolated from the fruits of *Lomatium suksdorfii* belonging to the family Apiaceae, which has expressed inhibitory property on the HIV replication [291]. Cordatolide A and B are the coumarin compounds obtained from *Calophyllum cordato-oblongum*, inhibit the replication of the HIV virus and are very identical in structures with the Calanolides [289]. Other coumarins like heraclenol (**75**), heraclenin (**76**) and imperatorin (**77**) also inhibit HIV replication and are extracted from *Ferula sumbul* roots [293]. Several furanocoumarins such as bergapten (**78**) and psolaren are extracted from the roots of *Prangos tschimganica*, have exhibited significant activity against the HIV virus [294]. Mesuol (**79**) is another coumarin compound from the category 4-phenylcoumarin, also reported inhibiting the replication of HIV-1. It prohibits the reverse transcription and phosphorylation of HIV [295]. A semisynthetic derivative of calanolide known as oxocalanolide acts efficiently against HIV [296]. Various furanocoumarins like imperatorin, xanthotoxin and xanthotoxol have been extracted from the *Aegle marmelos* fruits [110,111]. The stem, roots, fruits, leaves, seeds and bark of the *A. marmelous* are used for their significant therapeutic properties and have an important role in the Ayurvedic medication. The component imperatorin is reported to exhibit about 60% inhibition of HIV-RT. Other furanocoumarins xanthotoxin (**80**) and xanthotoxol (**81**) do not have a prenyl group, thus they exhibit weak activity shown in Figure 12 [297,298].

Figure 12. Coumarins based molecule with significant Anti-HIV potential.

1.6.5. Proteins

Proteins are the amino acid-containing plant components that usually contain ribosome-inactivating proteins as well as lectins [299]. A plant protein called MAP30 possessed anticancer potential along with anti-HIV properties and is obtained from *Momordica charantia* [300]. Trichosanthin is a ribosome-inactivating protein that exhibit anti-HIV activity and is isolated from *Trichosanthes kirilowii* [301]. Various plant ribosome-inactivating proteins have been identified for their anti-HIV activity. *Momordica balsamina* is a plant from which an anti-HIV ribosome-inactivating protein balsamin has been extracted [302]. Pf-gp6 is another protein that is extracted from *Perilla frutescens* has exhibited an inhibitory action on the HIV replication [303]. Some ribosome-inactivating proteins known as Pokeweed antiviral proteins have been separated from a pokeweed plant called *Phytolacca americana*, expressed efficient anti-HIV activity [304]. Some plant proteins along with their botanical sources have been given in Table 4.

Table 4: Proteins containing plants used in HIV

Plant Species	Parts used	Proteins	References
<i>Allium ascalonicum</i>	Bulbs	Ascalin	[305]
<i>Chrysanthemum coronarium</i>	Seeds	Chrysancorin	[306]
<i>Ginkgo biloba</i>	Seeds	Ginkbilobin	[307]
<i>Arachis hypogaea</i>	Seeds	Hypogin	[308]
<i>Lyophyllum shimeji</i>	Fruit bodies	Lyophyllin	[309]
<i>Panax quinquefolium</i>	Roots	Quinqueginsin	[310]

<i>Flammulina velutipes</i>	Fruit bodies	Velutin	[311]
<i>Tricholoma giganteum</i>	Fruit bodies	Laccase protein	[312]
<i>Castanea mollissima</i>	Seeds	Mollisin	[313]
<i>Treculia obovoidea</i>	Bark	Treculavirin	[314]
<i>Vigna sesquipedalis</i>	Seeds	Ground bean lectin	[315]
<i>Delandia unbellata</i>	Seeds	Delandin	[316]
<i>Dorstenia contrajerva</i>	Leaves	Contrajervin	[314]
<i>Vigna angularis</i>	Seeds	Angularin	[317]
<i>Castanopsis chinensis</i>	Seeds	Castanopsis thaumatin protein	[318]
<i>Vigna unguiculata</i>	Seeds	Cowpea α protein	[319]
<i>Phaseolus vulgaris</i>	Seeds	A homodimeric lectin	[320]
<i>Actinidia chinensis</i>	Fruits	Kiwi fruit thaumatin	[321]
<i>Lentinus edodes</i>	Fruit bodies	protein	[322]
<i>Allium tuberosum</i>	Shoots	Lentin	[323]
<i>Phaseolus vulgaris</i>	Seeds	A mannose-binding lectin	[324]
<i>Lilium brownie</i>	Bulbs	Phasein A	[325]
<i>Vicia faba</i>	Seeds	Lilin	[326]
		A trypsin-chymotrypsin	
<i>Vigna unguiculata</i>	Seeds	Inhibitor peptide	[327]
<i>Panax notoginseng</i>	Roots	Unguulin	[328]
<i>Phaseolus vulgaris</i>	Seeds	A xylanase	[329]
<i>Cicer arietinum</i>	Seeds	Vulgin	[330]
		Chickpea cyclophilin-like	
<i>Basella rubra</i>	Seeds	protein	[331]
<i>Delandia unbellata</i>	Seeds	α -Basrubrin	[332]
		Rice bean peptide	

1.6.6. Tannins

Tannins are mainly categorized into hydrolyzable and non-hydrolyzable, also called condensed tannins [333]. The hydrolyzable tannins include gallic acid polyesters (gallotannins) and hexahydroxydiphenic acids that is ellagitannins. The non-hydrolyzable or condensed tannins consist of flavan-3-ol moieties which are generally known as proanthocyanidins [334]. Corilagin (**82**) and geraniin (**83**) represented in Figure 13 are the two ellagitannins that possessed anti-HIV activity and have extracted from *Phyllanthus amarus* roots [335]. From the plant *Cupressus sempervirens*, a proanthocyanidin compound is obtained containing anti-HIV property [336]. Catechins are the polyphenols that are obtained from the green tea and theaflavins (**84**) are obtained from black tea, possessing antiviral activity. Theaflavins and their derivatives are the potent inhibitors of HIV replication [337].

Figure 13. Tannins containing compounds used in HIV.

1.6.7. Lignans

Lignans are the secondary metabolites of the plants and many of them have shown strong activities against viral diseases including AIDS [338]. Several lignans like anolignan A (85) and B along with dibenzylbutadiene lignans have been isolated from *Anogeissus acuminata* and have exhibited significant activity against HIV virus [339]. From the plant *Phyllanthus myrtifolius* belonging to the family Euphorbiaceae, phyllamycin D (86) and phyllamycin F shown in Figure 14 (87) are isolated and possess inhibitory activity against the HIV-RT enzyme [340]. Gomisins are another lignan isolated from *Kadsura interior*, shown potent inhibitory activity against reverse transcriptase enzyme of HIV [341]. From the plant *Arnebia euchroma*, some caffeic acid isomers have been evaluated and have expressed weak activity against the HIV replication [342]. 2-hydroxy-2-(3',4'-dihydroxyphenyl)-methyl-3-(3'',4''-dimethoxyphenyl)-methyl-γ-butyrolactone is a dibenzylbutyrolactone type lignin that is extracted from *Phenax angustifolius*, has been expressed anti-HIV activity [343]. From *Schisandra rubriflora* fruits other dibenzocyclooctadiene type lignans have been isolated having anti-HIV activity known as rubrisandrin A and rubrisandrin B [344].

Figure 14. Lignans possessing anti HIV actions.

1.6.8. Miscellaneous plants used as anti-HIV agents

A number of plants have been evaluated for their anti-HIV activity and are being used in antiretroviral therapy for AIDS [1, 2]. Various phenolic compounds such as *Quercus pedunculata*, *Terminalia horrida*, *Phyllanthus emblica* and *Rumex cyprius* have been identified for their anti-HIV activity [345,346]. From the plant *Strychnos vanprukii* leaves and twigs, various betulinic acid derivatives have been extracted that exhibit strong potential anti-HIV activity. These are 3 β -O-*cis*-feruloylbetulinic acid, 3 β -O-*trans*-feruloylbetulinic acid (88), ursolic acid and 3 β -O-*trans*-coumaroylbetulinic acid (89) [347]. Various therapeutic components have been extracted from the bark of *Cinnamomum zylanicum* by suitable extraction [348]. The constituents have shown anti-inflammatory [349], anti-cancer, antiviral, antioxidant and immunomodulatory properties [350]. The ingenol compound extracted from the plant *Euphorbia ingens* has exhibited anti-HIV activity [351]. It also represents many anti-inflammatory and immunomodulatory potentials [352,353]. *Oldenlandia affinis* is a medicinal plant from which various cyclotides have been isolated for their anti-HIV activity [354,355]. Another plant *Plectranthus barbatus* have shown various antiviral, antibacterial and antifungal properties along with antioxidant and anti-inflammatory effects [356,357]. From the plant *Clausena excavate* some therapeutic constituents like O-methylmukonal (90), 3-formyl-2,7-dimethoxycarbazole, limonoid, and clausenidin have been isolated for their anti-HIV property [358, 359]. Several antiviral components like tectorigenin, cytosine (91), formononetin, trifolirhizin (92), matrine (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 activity [360-363].

Extracts from the plant *Alepidea amatymbica*, have shown efficient anti-HIV activity and inhibit the HIV replication [364]. Artemisinin is obtained from the plant *Artemisia annua*, have exhibited antimalarial and anti-HIV activities [365]. Rosmarinic acid is a polyphenolic compound that is isolated from the plant *Prunella vulgaris*, is used for the anti-HIV potential [366]. From the plant *Polygonum glabrum*, various medicinal constituents with antiretroviral activity have been obtained such as (2)-2-methoxy-2-butenolide-3-cinnamate, pinocembrin (96), 3-hydroxy-5-methoxystilbene (97), sitosterol-3-O- β -D-glucopyranoside and pinocembrin-5-methyl

ether [367]. Actein (**98**) is extracted from the rhizomes of plant *Cimicifuga racemosa*, has possessed significant activity against the HIV virus [368]. Chrysoeriol is separated from *Eurya ciliate*, has used for anti-HIV activity [369]. Several constituents have been isolated for anti-HIV potential from the stems of plant *Aristolochia manshuriensis*. Some of them are demethylaristofolin E (**99**), aristofolin, denitroaristolochic acid, aristolochic acid, aristomanoside (**100**), N-p-coumaroyltyramine, p-hydroxybenzoic acid etc. [370-374]. Malaferin A, is isolated from *Malania oleifera* for its antiviral property [375]. Diptoindonesin D, Acuminatol (**101**), Shoreaphenol, Hopeahainol and Vaticanol B have separated from the plant *Vatica mangachapoi* and are used in the antiretroviral therapy [376-379]. Cararosinol C and D, maackin and scirpusin B (**102**) are extracted from the plant *Caragana rosea* for their anti-HIV effects [380]. Structures of some important constituents obtained from plants effective in HIV therapy are represented in Figure 15.

Figure 15. Plant-based compounds having anti-HIV activity.

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

Plant Species	Family	Parts used	References
<i>Khaya grandifoliola</i>	Meliaceae	Leaves	[381]
<i>Diospyros mespiliformis</i>	Ebenaceae	Bark	[382]
<i>Alternanthera brasiliana</i>	Amaranthaceae	Roots	[383]
<i>Ricinus communis</i>	Euphorbiaceae	Leaves	[384]
<i>Butea monosperma</i>	Fabaceae	Roots	[385]
<i>Prosopis glandulosa</i>	Fabaceae	Leaves	[386]
<i>Sophora tonkinensis</i>	Fabaceae	Roots	[387]
<i>Gunnera magellanica</i>	Gunneraceae	Stem	[388]
<i>Swertia franchetiana</i>	Gentianaceae	Roots	[389]
<i>Curcuma longa</i>	Zingiberaceae	Rhizomes	[390]
<i>Stewartia koreana</i>	Theaceae	Leaves	[391]
<i>Cissus quadrangularis</i>	Vitaceae	Stems	[392]
<i>Withania somnifera</i>	Solanaceae	Roots	[393]
<i>Ailanthus altissima</i>	Simaroubaceae	Stem bark	[394]
<i>Toddalia asiatica</i>	Rutaceae	Roots	[395]
<i>Oldenlandia herbacea</i>	Rubiaceae	Roots	[396]
<i>Aloe vera</i>	Xanthorrhoeaceae	Leaves	[397]
<i>Urtica dioica</i>	Urticaceae	Rhizomes	[398]
<i>Rheum tanguticum</i>	Polygonaceae	Leaves	[399]
<i>Saccharum officinarum</i>	Poaceae	Stems	[400]
<i>Ochna integerrima</i>	Ochnaceae	Leaves	[401]
<i>Nelumbo nucifera</i>	Nelumbonaceae	Leaves	[402]
<i>Aglaia lawii</i>	Meliaceae	Leaves	[403]
<i>Fritillaria cirrhosa</i>	Liliaceae	Rhizomes	[404]
<i>Magnolia biondii</i>	Magnoliaceae	Flower buds	[405]
<i>Lythrum salicaria</i>	Lythraceae	Leaves	[406]
<i>Reseda lutea</i>	Resedaceae	Whole plant	[407]
<i>Hypericum perforatum</i>	Hypericaceae	Leaves	[408]
<i>Trigonostemon thyrsoideus</i>	Euphorbiaceae	Stems	[409]
<i>Hemsleya endecaphylla</i>	Cucurbitaceae	Tubers	[410]
<i>Garcinia kingaensis</i>	Clusiaceae	Stem bark	[411]
<i>Woodwardia unigemmata</i>	Blechnaceae	Rhizomes	[412]
<i>Berberis holstii</i>	Berberidaceae	Roots, leaves	[413]
<i>Foeniculum vulgare</i>	Apiaceae	Fruits	[394]
<i>Alepidea amatymbica</i>	Apiaceae	Roots	[414]
<i>Stachytarpheta jamaicensis</i>	Verbenaceae	Whole plant	[415]
<i>Schisandra sphaerandra</i>	Schisandraceae	Stems	[416]
<i>Alpinia galangal</i>	Zingiberaceae	Roots	[417]
<i>Zanthoxylum chalybeum</i>	Rutaceae	Root bark	[418]
<i>Berchemia berchemiifolia</i>	Rhamnaceae	Bark	[419]
<i>Scoparia dulcis</i>	Plantaginaceae	Leaves	[420]
<i>Phyllanthus myrtifolius</i>	Phyllanthaceae	Fruits	[421]

<i>Arundina graminifolia</i>	Orchidaceae	Whole plant	[422]
<i>Ximenia Americana</i>	Olacaceae	Stem bark	[423]

3. Conclusions

A significant number of reports on capable nascent natural and synthetic therapeutic compounds as anti- HIV agents discussed in 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 fields of HIV chemotherapy, still there is a great demand for novel anti-HIV drug development and drug discovery. A number of plant species have been evaluated for their inhibitory activity on the essential HIV enzymes such as reverse transcriptase, protease and integrase which play an important role in the HIV replication. Several secondary metabolites have been extracted from the various plants that act as potent anti-HIV agents via different mechanisms of action. Therapeutically active compounds from natural 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 on the basis of naturally occurring compound Ingenol and a variety of synthetic derivatives have been evolved from the naturally occurring compound Artemisinin, exhibiting a significant anti-HIV activity of potential scaffolds from them for the complete eradication of HIV/AIDS.

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