Received: 5 June 2024 | Accepted: 5 January 2025

DOI: 10.1002/ame2.12563

REVIEW

# Bird's eye view of natural products for the development of new anti-HIV agents: Understanding from a therapeutic viewpoint

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## Abstract

Acquired immune deficiency syndrome (AIDS) is the name used to describe several potentially life-threatening infections and disorders that happen when HIV has severely compromised the immune system. The primary effect of HIV is to decrease host immunity, exposing the host to external pathogens. The development of pharmaceutical drugs that directly cure the infection is crucial because of the current wide-ranging epidemic of HIV. Most therapeutic anti-HIV drugs are nucleosides. However, their high toxicity and potential for drug resistance restrict their use. Many of the most effective clinical drugs used to inhibit HIV, the activation of latent HIV, and AIDS have been obtained from natural sources. This review focuses on potential natural medicinal products for treating and managing HIV and AIDS. Notwithstanding, further clinical research studies are needed to understand the subject and its dynamics.

Md. Al Amin, Mohamed H. Nafady and Mehrukh Zehravi contributed equally to this work.

KEYWORDS
AIDS, anti-HIV agents, HIV, immune system, marine compounds, natural products, phytoconstituents

## 1 | INTRODUCTION

Human immunodeficiency virus (HIV) infections are responsible for causing acquired immune deficiency syndrome (AIDS). This virus affects many individuals, causing immunosuppression as a secondary effect and can lead to death. According to the Joint United Nations Program on HIV/AIDS (UNAIDS) and World Health Organization (WHO) 2018 factsheet on Global HIV and AIDS statistics, of the 38.4 million people infected with HIV at the end of 2021, 28.7 million were receiving antiretroviral treatment. Seventy-eight million people have been infected with HIV, with the most significant impact being on people living in Sub-Saharan Africa.[1–3] AIDS patients are at high risk of acquiring a broad range of life-threatening diseases and cancers because of the destruction of their immune systems. Life expectancy without treatment after HIV infection is 9–11 years, depending on the HIV subtype.[2,4] Immune cells, particularly CD4+ T cells, dendritic cells, and macrophages, are the primary targets of HIV infection.[5] These immune cells die through various mechanisms following infection, including pyroptosis in T helper cells, apoptosis in uninfected bystander cells,[6] and CD8+ cytotoxic lymphocyte-mediated apoptosis of infected CD4+ T cells. HIV patients are immunocompromised due to an absence of cell-mediated immunity, making them more susceptible to opportunistic infections, eventually leading to AIDS.[7]

Antiretroviral therapy (ART) with anti-HIV medications is now available, enhancing the lifespan and quality of life for individuals living with HIV and AIDS. Lipodystrophy is a potential consequence of ART, indicated by fringe fat loss and focal fat accumulation, causing slim face cushions, thin legs and arms, and abdominal protuberance. Antiretroviral drugs have various disadvantages, including restricted or obstructed access, toxicity, and poor performance. Moreover, limitations of the ART program have posed challenges to the development of new anti-HIV drugs. Herbal therapeutics are highly effective in AIDS treatment, and medicinal herbs have shown considerable antiviral potential. In Australia, 44.3% of HIV patients use a marijuana component for therapeutic purposes.[8] Patients have reported feeling more peaceful, less pain, less stress, and a better sense of well-being after using medicinal herbs and it was found that ~9% of outpatients thought herbal remedies might be used to cure HIV and that others thought they might help them regain vitality. According to research conducted in the United States,[9,10] anxiety, depression, fear, pain, and nervousness are among the most common illnesses treated with herbal therapies. While descriptions of traditional medicinal plants used to treat specific diseases globally, particularly in the Middle East, are sometimes available, herbal remedies for treating HIV and AIDS remain largely unknown and poorly documented.[11] New anti-HIV compounds have been discovered in medicinal plants. For example, the alkaloids, flavonoids, phenolics, glycosides, tannins, and saponins in medicinal plants increase immune responses and reduce HIV transmission. Identifying novel antiviral compounds that can replace or supplement the current pharmacological options for HIV and AIDS is critical.[2,12,13]

Despite slight increases in HIV prevalence and frequency in parts of Eastern Europe and Central Asia, there has been a general global decline over the last 10 years because of the development of highly active antiretroviral therapy (HAART) and other preventive measures.[14–18] While HAART results in long-term viral suppression, it is not without side effects, particularly for long-term users. Therefore, new drugs and drug targets are urgently needed to overcome multidrug resistance, treat HIV infections, and prevent viral accumulation in parts of the body, such as the cerebrum and lymph nodes, and accomplish the final objectives of preventing and curing HIV and AIDS.[19–21] This review highlights therapeutically promising natural medicinal products for HIV and AIDS treatment.

## 2 | METHODOLOGY

Following an extensive literature search, we discovered current and pertinent publications in multiple databases, such as Scopus, Science Direct, Elsevier, PubMed, and Web of Science. In our search, we utilized the keywords "natural products," "HIV," "AIDS," antiretroviral therapy, and "anti-HIV agents." The selection and evaluation process involved choosing and assessing research papers, review articles, and original publications written in English and published up to 2024.

## 3 | HIV PRIMARY INFECTION AND DISEASE PROGRESSION

Several viral and host variables affect HIV-1 infection outcomes and disease progression (Figure 1). In HIV pathogenesis, cellular tropism affects viral phenotypic, and co-receptors control viral entry into certain cell types. Despite almost a quarter-century of research, the mechanism by which these variables cause significant CD4+ T cell depletion and R5 and X4 strain maintenance during AIDS is unknown.[22] The results of HIV-1 infection and the speeds at which the disease progresses are affected by many viral and host variables (Figure 1). Cellular tropism and co-receptors are two important factors in HIV pathogenesis. Cellular tropism determines the viral phenotype, while co-receptors control the entry of the virus into specific types of cells. The specific mechanism via which these factors contribute to the significant depletion of CD4+ T cells and the persistence of R5 and X4 strains during AIDS

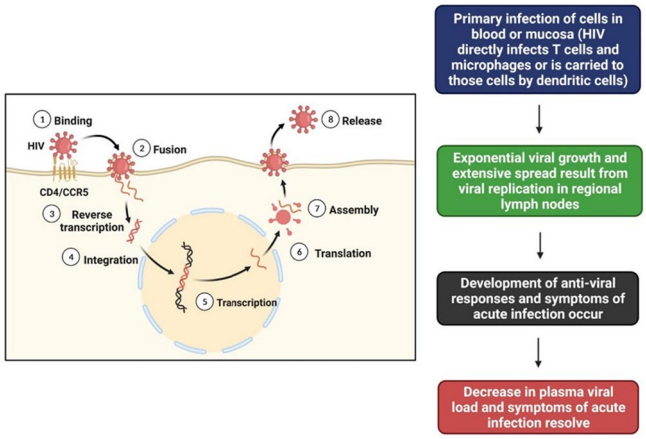


FIGURE 1 Development and progression of HIV infection. The figure was designed by Biorender.com program (https://biorender.com/, accessed on 2 January 2024).

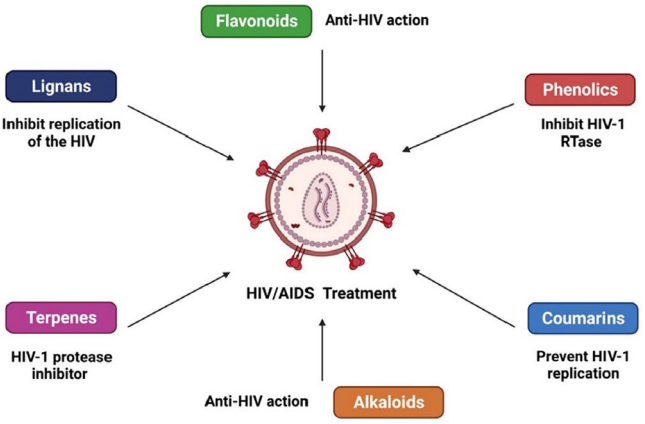


FIGURE 2 Natural products used for treating HIV and AIDS. The figure was designed by Biorender.com program (https://biorender.com/, accessed on 4 January 2024).

is still not understood after over 25 years of research.[23] While individuals might look well at the outset, the virus propagates effectively in infected individuals' lymph nodes and impacting their immunity because of their viral burden.[24] For example, opportunistic infections (OIs) by pathogens such as *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Pneumocystis carinii*, cytomegalovirus (CMV), toxoplasmosis, and candidiasis can emerge during the later phases of HIV infection, indicating AIDS development.[24]

Intervention is required when an infected individual's plasma HIV load is high, and their CD4+ count exceeds 200 cells/mm$^3$.[25] Because of the current availability of HAART, whether every individual who seroconverts to HIV will acquire AIDS remains to be determined. HIV weakens the immune system by infecting and destroying CD4+ T cells, causing immunodeficiency later in infection.[24] HIV attaches to the CD4+ protein located on the surface of many cells, leading to infection. However, the lack of CD4+ protein in other cell types, including monocytes and dendritic cells, hinders their infection due to the absence of a suitable entrance site. Consequently, the chemokine receptor was identified as a critical HIV-1 coreceptor. HIV may use different coreceptors to infect different cell types. The two most common chemokine receptors are C-C chemokine receptor type 5 (CCR5) and C-X-C chemokine receptor type 4 (CXCR4), also known as Fusin.[26]

## 4 | NATURALLY DERIVED ANTI-HIV AGENTS

### 4.1 | Flavonoids

Flavonoids and other polyphenols have demonstrated anti-HIV properties, as depicted in Figure 2. They possess cancer-preventive properties and exhibit antiviral action in some groups of cells.[27] Baicalin, an anti-HIV flavonoid from *Scutellaria baicalensis*, inhibits HIV replication in peripheral blood mononuclear cells (PBMCs).[28,29] In addition, the prenylated flavonoids 6,8-diprenylaromadendrin and 6,8-diprenylkaempferol obtained from the extract of *Monotes africanus* were also found to inhibit HIV infection in cell screens with 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT).[30] Moreover, gallate ester and quercetin-3-O-(2-galloyl) a-L-arabinopyranose from the Aceraceae family member *Acer okamotoanum* have been found to inhibit HIV-1 integrase activity.[31] Furthermore, hinokiflavone, robustaflavone, and biflavonoids in methanolic preparations of the leaves of Anacardiaceae family member *Rhus succedanea* were shown to inhibit HIV-1 reverse transcriptase (RT) activity.[32,33] The roots of Thymelaeaceae member *Wikstroemia indica* can be used to extract the anti-HIV biflavonoid Wikstrol B.[34] Finally, the prenylchalcone xanthohumol isolated from the hops *Humulus lupulus* has been found to inhibit HIV activity.[21,35]

### 4.2 | Coumarins

Calanolides are a sort of coumarin that may be found in some tropical tree species belonging to the Calophyllum class. They are an example of a viral non-nucleoside reverse transcriptase inhibitor (NNRTI) from the Clusiaceae family.[36] Calanolide A and B,[37] and their derivative 7,8-dihydrocalanolide B from *Calophyllum lanigerum* have a structure similar to cardenolides. They can reduce the cytopathogenic effects of HIV-1 on cells and prevent its replication (Figure 1). *Calophyllum cordato-oblongum*[38] is used to extract the pyrocoumarin derivative suksdorfin[39] from *Angelica morii* and *Lomatium suksdorfii* fruits of the Apiaceae family,[40] which have inhibitory effects on viral replication in T-cell lines.

### 4.3 | Alkaloids

Anti-HIV activity has been observed with many alkaloids (Figure 2). The sweet-smelling alkaloid polycitone A from the marine ascidian

*Polycitor* spp. has critical RT activity, inhibiting RNA-dependent DNA polymerase (RDDP).[41,42] Papaverine is an alkaloid derived from *Papaver sominiferum*, a Papaveraceae family plant that prevents HIV replication. Buchapine is a quinolone derived from *Eodia roxburghiana* and has been shown preventing the cytopathogenic effects of HIV-1.[43] Nitidine is derived from the roots of *Toddalia asiatica*, a Rutaceae family plant with anti-HIV activity.[44] The alkaloid O-demethylbuchenavianine, discovered in the Combretaceae family member *Buchenavia capitata*, reduces HIV activity.[45] Harmine from *Symplocos setchuensis* has been shown to limit HIV replication in H9 cells.[46] 1-Methoxycanthionone is an anti-HIV compound produced by the plant *Leitneria floridana*.[47] Troponine A and B and hypoglaumine B are anti-HIV sesquiterpene pyridine alkaloids from *Tripterygium wilfordii* and *Tripterygium hypoglaucum*, respectively.[48]

### 4.4 | Terpenes

Some triterpenoids show antiretroviral activity through several mechanisms. Platanic acid, betulinic acid, and oleanolic acid made from the leaves of *Syzygium claviflorum* have been shown to suppress HIV in H9 lymphocyte cells (Figure 2).[49,50] In addition, oleanolic acid prepared from a methanolic extract of the Sapindaceae tree *Xanthoceras sorbifolia* inhibits HIV-1 replication in these cells.[51] Maslinic acid from *Geum japonicum* is a proficient HIV-1 protease inhibitor.[52] Celasdin B from the Celastraceae family member *Celastrus hindsii* has anti-HIV replication activity in H9 cells.[53] Garcisaterpenes A and C prepared from an ethyl acetic acid derivation concentrate of *Garcinia speciosa* stems and bark have been shown to inhibit HIV-1 RT activity.[54] The suberosol lanostane-type triterpene prepared from an ethanolic extract of the leaves and stems of Annonaceae family member *Polyalthia suberosa* has also been found to inhibit HIV replication in H9 cells.[55] Lancilactone C, a triterpene lactone derived from the roots and stems of *Kadsura lancilimba*, effectively suppresses HIV replication in these cells. The phorbol diester 12-O-tetradecanoylphorbol-13-acetic acid, derived from a methanolic extract of *Croton tiglium*, a plant belonging to the Euphorbiaceae family, can decrease the harmful effects caused by HIV-1 infection. Prostratin, a phorbol ester derived from the plant *Homalanthus nutans* of the Euphorbiaceae family, has been found to reduce the effects of HIV.[56,57]

### 4.5 | Phenolics

Because of enhanced phytohaemagglutinin-induced lymphocyte proliferation, the long-term effects of polyphenol-rich natural products on HIV+ individuals are beneficial (Figure 2). Tannins and similar phenolic substances have demonstrated virucidal action in several viral frameworks. The synthesis of lithospermic acid from *Salvia miltiorrhiza* affects the activity of HIV in H9 cells.[58] The chebulagic acid punicalagin and punicalin are anti-HIV hydrolyzable tannins identified in *Terminalia chebula*.[59] Repandusinic acid from *Phyllanthus niruri*, a Euphorbiaceae plant, has been shown to inhibit HIV-1 RTase.[60,61] HIV replication is inhibited by the monopotassium and monosodium salts of an isomeric caffeic acid tetramer derived from the acetone extract of *Arnebia euchroma*, a member of the Boraginaceae family.[62]

### 4.6 | Lignans

Antiviral properties have been found for several lignans.[63,64] Phyllamyricin B and its lactone retrojusticidin B prepared from chloroform extracts of the Euphorbiaceae plants *Phyllanthus myrtifolius* and *P. urinaria* were found to reduce HIV-RTase activity (Figure 2).[65] Anolignan B, anolignan A, and dibenzyl butadiene lignans from *Anogeissus acuminata* have been found to repress HIV-1 RTase.[66] Notably, gomisin from the genus *Kadsura* is perhaps the most potent HIV replication inhibitor.[21,67]

## 5 | MEDICINAL PLANTS AGAINST HIV AND AIDS

Medicinal plants are a preferred treatment option for treatable and non-treatable maladies. There is much evidence that medicinal herbs can treat HIV and AIDS with few adverse effects. Because of the ease of delivery of cancer prevention agents and nutraceutical compounds found in medicinal plants, many plants with anti-HIV activity have been identified (Table 1).

### 5.1 | *Rheum* species

Phytochemical compounds found in *Rheum palmatum* L. and *Rheum officinale baill* have been found to inhibit HIV replication. In biochemical experiments, Esposito et al.[104] observed the anti-HIV activity of anthraquinone derivatives on the activities of HIV-1 RT-related RDDP and Ribonuclease H. (RNase H). To ascertain their potential therapeutic advantages, their impact on HIV components such as HIV-1 reverse transcriptases (RTs), integrase (IN), and viral replication was investigated. *R. palmatum* L. and *R. officinale* baill extracts inhibit HIV-1 reverse transcriptase-related RNase H activity by binding to two locations on the reverse transcriptase enzyme. Sennoside A influenced the reproduction of HIV-1 in trials conducted on cells. Additionally, laboratory investigations demonstrated that this phytochemical affected the function of HIV-1 integrase.[104]

### 5.2 | *Vernonia amygdalina*

*Vernonia amygdalina* is a plant recently used to treat HIV and AIDS. It is commonly known as a bitter leaf because of its flavor and

**TABLE 1** Anti-HIV medicinal plants, phytoconstituents, and mechanisms of action.

| Family & species | Active constituents | Mechanism of action | References |
|---|---|---|---|
| Amaryllidaceae<br>*Glanthus nivalis* | Phytolectins, *Glanthus nivalis* agglutinin | It suppresses HIV infection in lymphocytes by inhibiting HIV infection by targeting the gp120 envelope. | [68,69] |
| Anacardeaceae<br>*Rhus succedanea* | Robustaflavone, hinokiflavone and bioflavonoids | It suppresses the polymerase of HIV-1 reverse transcriptase. | [32] |
| Ancistrocladaceae<br>*Ancistrocladus korupensis* | Michellamines a and b | Because it works at both the early and late stages of HIV infection, it possesses anti-HIV-1 and HIV-2 activity. | [70] |
| Apocyanaceae<br>*Rauwolfia serpentine* | Papaverine | HIV reverse transcriptase and HIV cell proliferation are both inhibited by it. | [71,72] |
| Boraginaceae<br>*Arnebia euchroma* Jonst | Monopotassium and monosodium salt of isomeric caffeic acid | It has anti-HIV replication properties. | [73] |
| Cannabaceae<br>*Humulus lupulus* | Xanthohumol | It possesses anti-HIV properties and exerts cytopathic effect. | [74] |
| Clusiaceae<br>*Callophyllummarila laxiflora* | Cardatolide B and a Laxofloranone | It suppresses HIV as well as the virus's cytopathic effect. | [75] |
| Fabaceae<br>*Peltophorum africanum* | Gallotannin | HIV-1 reverse transcriptase polymerase activity is inhibited. | [76] |
| Hypericeae<br>*Hypericum perforatum* | Pseudohypericin and hypericin | The act of interfering with a viral infection restricts the propagation of the virus. | [54] |
| Lamiaceae<br>*Melissa officinalis* | Rosmarinic acid | It prevents viral particles from fusing in cells | [77] |
| Gentianaceae<br>*Swertia franchetiana* | Glucosside, Xanthone, Flavanone | It prevents the functioning of HIV-1 reverse transcriptase. | [78] |
| Leguminoseae<br>*Dillenia indica* Linn | Epicatechin, Catechin and Epicatechin 3-gallate | Inhibition of HIV protease | [79] |
| Arecaceae<br>*Areca catechu* | B1 arecatannin, procyanidins | It has a protease-inhibitory effect | [80] |
| Physalacriaceae<br>*Flammulina velutipes* | Velutin | It also prevents the functioning of HIV-1 reverse transcriptase. | [81] |
| Rosaceae<br>*Crataegus pinnatifida* | Ursolic acid and uvaol | The anti-protease activity of HIV-1 is inhibited by it. | [82] |
| Theaceae<br>*Clonorchis sinensis*<br>*Camellia japonica* | Epigallocatechin-3-gallate | It exhibits anti-HIV-1 protease action and prevents the formation of viral semen. | [83] |
| Aceraceae<br>*Acer okamotoanum* | F-Gallate ester | It possesses anti-HIV properties. | [30] |
| Asteraceae<br>*Achyrocline satureioides* | Dicaffeoylquinic acid, 1-methoxyoxalyl-3, five dicaffeoylquinic acid | It has an irreversible inhibitory effect on HIV integrase. | [84] |
| Asteraceae<br>*Arctium lappa* | Wedelolactone, coumarin derivative; Orobol | It prevents HIV-1 infection from spreading from cell to cell and also prevents HIV-1 replication. | [85] |
| Leguminosae<br>*Acacia mellifera* | Pentacyclic Triterpenes | HIV-1 reverse transcriptase inhibition. | [86] |
| Liliacea<br>*Aloe barbadensis* | Acemannan Polymanoacetate | It helped to alleviate HIV-related symptoms. | [87] |
| Boraginaceae<br>*Arnebia euchroma* | Monopotassium and monosodium salts of isomeric acid | It prevents HIV from replicating. | [88] |
| Dipterocarpaceae<br>*Vatica cinerea* | Vaticinone | Replication is stopped. | [89] |
| Violaceae<br>*Viola yedoensis* | Sulfonated polysaccharides | It has anti-HIV inhibitory effect. | [84,90,91] |
| Betulaceae<br>*Betula pendula* | Triterpene, pentacyclic betulinic acid | It inhibited the maturation of the HIV gag precursor. | [74,92,93] |
| Dipterocarpaceae<br>*Vatica astrotricha* | Dipterocarpaceae, 6 8-diprenylkaempferol | It prevents the virus from entering the body and replicating. | [94] |

(Continues)

TABLE 1 (Continued)

| Family & species | Active constituents | Mechanism of action | References |
|---|---|---|---|
| Combrataceae *Terminalia bellerica* | Punicalin, punicalagin, punicacortin and chebulagic acid | It prevents viral adsorption and HIV replication | [90] |
| Acanthaceae *Andrographis paniculata* | Diterpene lactones (andrographolide) Andrograpanin, Bis- andrographolide ether | Reverse transcription and HIV protease are both inhibited by it. In HIV-infected cells, it prevents syncytia formation, viral replication, and cell-to-cell transmission | [91,92] |
| Zingiberaceae *Alpinia galangal* | 1′ S-1′-acetoxychavicol acetate | Anti-HIV effect | [93] |
| Lamiaceae *Anisomeles indica* | Ovatodiolide | Anti-HIV effect | [93] |
| Euphorbiaceae *Bridelia micrantha* | Inhibit RDDP & RNase H | Inhibition of HIV-1 reverse transcriptase inhibits the polymerase and ribonuclease activities. | [90] |
| Zingiberaceae *Boesenbergia pandurata* | Panduratin C, Uvangoletin | Anti-HIV effect | [95] |
| Combreataceae *Combretum molle* | Gallotannin, Punicalagin | HIV-1 reverse transcriptase is inhibited. HIV antiviral action | [76] |
| Clusiaceae *Calophyllum inophyllum* | Inophyllum B, P | Anti-HIV effect | [96] |
| Labiateae *Coleus forskohlii* | Forskolin, 1-deoxyforskolin | Anti-HIV effect | [97] |
| Asteraceae *Erigeron breviscapus* | Scutellarin | Inhibited HIV-1 replication. | [98] |
| Fabaceae *Erythrina senegalensis* | Auriculatin, Erysenegalensein | Inhibitors of HIV-1 protease. | [99] |
| Ginkgoaceae *Gingko biloba* | Cardanols, Bilobals | In the reverse transcriptase (RT) assay, anti-HIV-1 activity was detected | [100] |
| Amaryllidaceae *Galanthus nivalis* | *G. nivalis* agglutinin-GNA | InhibitedHIV from spreading among lymphocytes. | [101] |
| Clusiaceae *Hypericum perforatum* | Hypericin, 3-hydroxy lauric acid | HIV-1 replication is inhibited. | [102,103] |

belongs to the Asteraceae family. *V. amygdalina* is a nutrient-dense plant that is also beneficial to health. In HIV+ patients undergoing ART, the impact of *V. amygdalina* leaf extract has been studied. Over time, ART and aqueous extracts of young *V. amygdalina* leaves were employed to investigate their effects on CD4+ cell count. The study found higher CD4 cell counts in individuals using leaf extract and supplements compared to the control group, prompting the study to include non-users. *V. amygdalina* leaves are utilized in HIV treatment because they boost immunity. Fresh bitter leaves benefit AIDS patients with extended fever, headache, or joint pain. *V. amygdalina* supplements are available commercially.[105]

### 5.3 | *Trigonostem xyphophylloides* and *Vatica astrotricha*

The inhibitory effects of medicinal plants on HIV-1 have been evaluated by applying extracts of two Traditional Chinese Medicine (TCM) therapeutic spices, *Trigonostem xyphophylloides* (TXE) and *Vatica astrotricha* (VAD). It was also discovered that the two extracts modulated cell proliferation, and their effects on CD4+ Jurkat cells demonstrated a reduction in HIV-1 replication. The removal of TXE and VAD not only inhibited HIV-1 RT activity, it also reduced HIV replication and cell entry, which is an indication of potential anti-HIV efficacy. Studies at the molecular level have shown that phytochemical substances reduce the amount of contact HIV-1. For instance, they inhibit HIV-1 from interacting with glycoprotein gp120 and CCR5 or CXCR4 by interfering with their interactions with these proteins.[106]

### 5.4 | *Pelargonium sidoides*

*Pelargonium sidoides* (PS) is a Geraniaceae plant commonly known as African geranium, and its extract prevents virus reproduction. Bioactive compounds in PS root extract attack virus particles, preventing their replication and infection of the blood and immune cells. Polyphenols mediate the antiviral impact of PS extract. The polyphenol combination derived from PS extract is a medication that targets HIV-1.[107] After several clinical studies, the root extract of PS was approved for human use in Germany. Various cell culture-based studies have shown PS extracts to have appreciable anti-HIV potential. Helfer et al.[107] showed that PS extracts could prevent HIV infection into periphery macrophages and blood

mononuclear cells and proposed an original mechanism for the phytochemical compounds in PS extracts. The EAST-HIT procedure evaluated the anti-HIV-1 activity of PS root extract. It showed that it inhibited viral replication in step 1 at a dosage of 8.13 g/mL and step 2 at a concentration of 8.00 g/mL. These findings suggest that the plant extracts elicited a reaction during the early stages of HIV-1 replication and inhibited the attachment of HIV particles to the host cell, preventing HIV entry. Numerous polyphenolic compounds have been shown to affect HIV activity. PS extract may represent the current best home-grown HIV treatment.[2,107]

### 5.5 | *Calendula officinalis*

Calendula is a therapeutic spice from the group Asteraceae. *Calendula officinalis* blossoms and the sprouts of other *Calendula* species are used to treat skin lesions, ulcers, frostbite, wounds, and herpes. A botanical dichloromethane-methanol extract of *C. officinalis* (1:1) showed anti-HIV activity in an in vitro tetrazolium-based assay, reducing HIV-induced fusion at a 500 g/mL concentration and inhibiting HIV1-RT at a concentration of 1000 g/mL.[108] In an in vitro MTT tetrazolium-based assay, the regular extract of *C. officinalis* blooms inhibited HIV development, but the liquid concentrate did not. It was also shown that a natural extract of *C. officinalis* blossoms repressed HIV-1 in a time-dependent manner. These discoveries show that the natural *C. officinalis* blossom extract possesses anti-HIV activity, which might be invaluable in HIV treatment.[109,110]

### 5.6 | *Combretum molle*

In Ethiopia's traditional medical system, the plant known as *Combretum molle*, which belongs to the family Combretaceae, is frequently employed to treat liver problems, tuberculosis, and malaria. To determine the in vitro anti-HIV activity of a few extracts derived from the stem bark of *C. molle*, the Soxhlet apparatus was utilized in conjunction with various solvents, including methanol, acetone, chloroform, and oil ether. To assess whether or not the extracts selectively inhibited the growth of the virus, the cytotoxicity of the extracts against MT-4 cells was tested in vitro. The preparation made using acetone was the one that most effectively inhibited the propagation of HIV-1 infection.[111]

### 5.7 | *Cassia abbreviata*

*Cassia abbreviata* is a Fabaceae deciduous bush used by traditional healers to treat HIV and AIDS patients. By assessing the amounts of viral p24 antigen in infected PBMCs, the HIV replication inhibition potential of *C. abbreviata* was evaluated against the HIV-1c clone. It was found to drastically reduce HIV-1c replication at a concentration of 102.8 g/mL, indicating that its root concentrate possesses anti-HIV activity.[112]

### 5.8 | *Hyssopus officinalis*

*Hyssopus officinalis* is a member of the Lamiaceae family that has been used as a natural medication because of the presence of polysaccharides. Its extract has been shown to have anti-HIV-1 activity. HIV-infected MT-2 cells were used to examine the ability of a hydroalcoholic extract of *H. officinalis* to reduce HIV replication as a potential method for delivering new antiviral drugs, especially those against AIDS. This extract reduced HIV-1 infection of MT-2 cells at 50–100 g/mL.[113]

### 5.9 | *Terminalia paniculata*

*Terminalia paniculata* is a member of the Combretaceae group of plants whose natural product extracts in methanol and acetone were assessed in vitro for anti-HIV-1 activity. Their half maximal effective concentration ($EC_{50}$) was found to be 10.3 g/mL with both solvents. Enzymatic tests determined that their anti-HIV-1 activity was through protease inhibition (69.9%) and RT inhibition (77.7%).[109,114]

### 5.10 | *Smilax corbularia*

*Smilax corbularia* is a Smilaceae plant whose anti-HIV-1 IN activity was assessed with ethanolic and aqueous extracts. It was found that the *S. corbularia* ethanolic extract had anti-HIV-1 IN action with an half maximal inhibitory concentration ($IC_{50}$) of 1.0 g/mL compared to 3.4 g/mL for suramin, which acted as a positive control. The $IC_{50}$ of the *S. corbularia* aqueous extract was 5.4 g/mL. In this experiment, the *S. corbularia* ethanolic extract had a twofold lower $IC_{50}$ estimation.[115]

### 5.11 | *Tuberaria lignosa*

The Asteraceae plant family includes *Tuberaria lignosa*, a herb commonly used in traditional medicine to treat viral infections. Its ethanolic and aqueous extracts possess anti-HIV properties, decreasing HIV replication. The *T. lignosa* aqueous extract partially protected human lymphocytic MT-2 cells in the 12.5–50 g/mL range with apparent anti-HIV activity. However, the toxicity of the ethanolic extract meant that its antiviral activity could not be evaluated at higher concentrations.[116]

## 6 | POTENTIAL MARINE-DERIVED ANTI-HIV AGENTS AND THEIR ANTI-HIV ACTIVITY

### 6.1 | Lectins

Lectins are proteins that bind reversibly to glycosylated particles on the cell surface, regulating cell–cell interactions, protecting against infections, and facilitating cell–cell adhesion.[117] Although there have only

been a few studies that have demonstrated the anti-HIV capabilities of lectins, they have recently acquired recognition as potentially useful antiretroviral medicines. A shift in the interaction between HIV gp120 or gp41 and their linked receptors was observed to be the mechanism by which their antiviral activity was seen,[118] inhibiting HIV infectivity and ultimately reducing the syncytium.[119] Several review studies have described the antiretroviral activity of previously discovered marine lectins.[120,121] Gogineni et al.[121] described the galactose-specific lectins CVL, CGL, DTL, DTL-A, SVL-1, and SVL-2. *Boodlea coacta*, griffithsin, and oscillatoria agardhii agglutinin are some of the new algal lectins. Additionally, cyanobacterial lectins such as cyanovirin-N, microvirin, mi-crocystis viridis, and scytovirin were included in the list of lectins reported. There has been a recent surge in the popularity of anti-HIV lectins produced from marine sources. A unique high-mannose lectin and its anti-HIV recombinants were initially reported by Hirayama et al.,[122] who were the pioneers in documenting this discovery, showing two KAA mannose-binding lectin isomers, KAA-1 and KAA-2, from the red alga *Kappaphycus alvarezii* to be powerful anti-HIV drugs. The mechanism of action of these two anti-HIV compounds involves binding to the viral envelope glycoprotein gp120, inhibiting HIV entry into host cells with an $IC_{50}$ of 7.3–12.9 nM in Jurkat cells. The authors concluded that these KAAs are promising retroviral medicines for use in therapies against viruses rich in mannose glycans on their envelope and can substantially inhibit HIV entry into cells.[123]

## 6.2 | Phlorotannins

Phlorotannins are components of phloroglucinol (1,3,5-trihydroxybenzene) monomer units that are polymerized and biosynthesized via the acetate-malonate pathway.[124,125] Phlorotannins are highly hydrophilic, with molecular loads from 126 Da to 650 kDa.[126] Low, middle, and high molecular weight phlorotannins containing phenyl and phenoxy units are present as phloroglucinol-based polyphenols in the earthy-colored green seaweed of various marine taxa on beaches,[127,128] including brown and red algae.[127,129] They are phloroglucinol units joined differently. Based on their interface, phlorotannins are divided into four subclasses: fuhalols and phlorethols (ether-linked), fucols (phenyl-linked), fucophloroethols (ether and phenyl-linked), and eckols. Brown algae with high phlorotannin levels are anti-HIV. 8,8′-bieckol and 8,4‴-dieckol in *Ecklonia cava* inhibited HIV-1 protease and RT.[130,131] In a study of two eckol dimers, 8,8′-bieckol with a biaryl linkage ($IC_{50}$, 0.5 μM) inhibited RT 10-fold more than 8,4‴-dieckol with a diphenyl ether linkage ($IC_{50}$, 5.3 μM). The authors concluded that the steric hindrance of the hydroxyl and aryl groups around the biaryl link gave 8,8′-bieckol RT inhibitory activity. Additionally, 8,8′-beckon inhibited RT but not protease, with an $IC_{50}$ of 0.28 μM, identical to the positive control nevirapine. The inhibitory action of 8,8′-bieckol was higher than 8,4‴. This study revealed that 8,8′-bieckol inhibits HIV-1 RT's RNA-dependent DNA synthesis against dUTP/dTTP, and also non-competitively inhibits the homopolymer (rA)n(dT)15. This chemical inhibits RT, like the non-nucleoside RT inhibitors like pyridinones[132] and trovirdine.[133] Therefore, 8,8′-bieckol is a potential new and effective inhibitor of HIV-1 RT that is not derived from nucleosides. Another study demonstrated that diphlorethohydroxycarmalol (DPHC) obtained from Ishige okamurae yendo[134] effectively hinders the activity of HIV-1, particularly its reverse transcriptase (RT) and integrase enzymes, with an $IC_{50}$ ranging from 9.1 to 25.2 μM, but does not hinder the activity of the HIV-1 protease. However, 6,6′-bieckol, a notable derivative of phloroglucinol found in *E.cava*, effectively hinders the formation of HIV-1-related syncytia, suppresses lytic effects, and reduces the levels of viral p24 antigen.[135] Moreover, it reduced HIV-1 RT activity and HIV-1 cell entry with an $IC_{50}$ of 1.07 μM. Furthermore, it displayed negligible cytotoxicity even at doses almost completely inhibiting HIV-1 replication. Therefore, 6,6′-bieckol could form the basis of novel HIV therapeutics.[136]

## 6.3 | Chitin, chitosan, and chitooligosaccharide derivatives

Chitin is a polymer composed of long chains of N-acetylglucosamine and can be found in a wide variety of living species, such as insects, seaweeds, crabs, and invertebrates.[137] It is quite possibly the most common polysaccharide obtained from the shells of crabs and shrimp.[138] Chitosan is a mostly deacetylated polymer of N-acetylglucosamine made by the deacetylation of chitin.[139] Chitin and chitosan are chemically modified to provide new biofunctional materials with favorable biological and physicochemical properties.[140–144] The antiviral properties of sulfated chitin and chitosan against HIV-1 are anticipated to include antioxidant, antibacterial, anticoagulant, and hemagglutination inhibition, among other potential applications. Further applications include the delivery of drugs, the adsorption of metal ions, the prevention of cancer metastasis, and the production of late blight resistance elicitors in potatoes.[145–148] Sosa et al.[149] showed that N-carboxymethylchitosan-N-O-sulfate (NCMCS), a polysaccharide synthesized through a random sulfation process from N-carboxymethylchitosan, can restrict the replication of HIV-1 in human CD4+ cells. The study concluded that this was due to the suppression of the interaction of the viral coat glycoprotein receptor with lymphocyte target proteins and HIV-1 red blood cell transcription. As a result, NCMCS is being explored as a possible medicine for the treatment of HIV infection. It works by inhibiting viral attachment to the CD4 receptor as well as the reverse transcription of the viral genome, which in turn prevents HIV-1 illness from occurring. However, the anti-HIV-1 activity of chitin sulfates is highly dependent on the sulfation sites.[150] Chitin with C-2 (C-2S) or C-3 (C-3S) regioselective sulfation slowed AIDS infection in vitro better than 6-O-sulfonated (C-6S) derivatives. In addition, chitin-containing sulfation at positions 2 and 3 (C-2,3S) prevented HIV infection in T cells without causing significant cytotoxicity at 0.28 g/mL.[150] These findings indicate that changing the positions of sulfate groups in sulfated chitin changes its biological function.

The development of amino-derivatized chitosans against oxidants, antihypertensive drugs, protein inhibitors, and antibacterial agents has been the subject of many investigations.[151] Aminoethyl-chitosan produced from half-deacetylated chitosan has an $IC_{50}$ of 17 g/mL against HIV-1.[152] Consequently, aminoethyl-chitosan is

a potential candidate for the next generation of HIV treatments. Chitosan can be changed into chitooligosaccharides (COSs) by chemical or enzymatic hydrolysis to facilitate its dissolvability in water and natural development.[153–155] COSs and their derivatives are not water dissolvable[156] and have higher assimilation profiles.[157] However, they have many natural benefits, including ACE chemical restraint,[158] antioxidant,[159] antimicrobial,[160] antidisease,[161,162] immunostimulant,[163] antidiabetic,[164] hypocholesterolemic,[165] and hypoglycemic actions,[166] Alzheimer's prevention,[167] anticoagulant activity,[168] and adipogenesis inhibition.[169] Moreover, a sulfated chitooligosaccharide (SCOS), created by a random sulfation system, with a low molecular weight (3–5 kDa), has shown anti-HIV activity.[170] SCOS independently reduced HIV-1-mediated syncytia and lytic activity at nontoxic concentrations, with an $EC_{50}$ of 2.19 g/mL and 1.43 g/mL. HIV-1 strain RF has an $EC_{50}$ of 4.33 g/mL, and HIV-1 strain Ba-L has an $EC_{50}$ of 7.76 g/mL, an improvement over the p24 antigen. In addition, by restricting HIV-1 gp120 to the CD4 cell surface receptor, SCOS reduced viral entry and infection. These findings indicate that SCOS is a viable candidate for development as an anti-HIV-1 medication.[136]

### 6.4 | Chitosan and its derivatives

Chitosan, an essential marine product, is a poly-cationic linear polysaccharide produced from chitin by deacetylation. Shrimp and crab exoskeletons contain chitin, a vital component primarily comprising (1–4)-associated d-glucosamine and N-acetyl-d-glucosamine. This compound shows a broad scope of bioactivities and may be used as a transporter for HIV medications.[171,172] Chitosan contains saquinavir, a protease-inhibitory anti-HIV drug, and is more effective than saquinavir alone for cell targeting.[173,174] Trimethyl chitosan enhances the anti-HIV-1 activity of Atripla, a drug cocktail containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate at lower dosages.[175] The cationic effect of chitosan enables it to make electrostatic complexes or multilayered structures with other alternatively charged polymers with antiviral properties.[175] Karagozlu et al. identified new anti-HIV WMQ-COS and QMW-COS oligomers. These oligomers are chitosan-Gln-Met-Trp peptide conjugates developed as a follow-up to the authors' previous investigation, demonstrating that synthetically manufactured chitosan oligomers exhibited high anti-HIV therapeutic effectiveness. These oligomers reduce syncytium formation induced by HIV, which occurs when infected cells join with nearby cells, in a dose-dependent manner. However, the authors observed that syncytia increased with time, suggesting that the cells must be re-treated with QMW-COS and WMQ-COS oligomers to preserve their primary therapeutically significant effect. In their cell viability experiment, QMW-COS had an $IC_{50}$ of 48.14 g/mL, and WMQ-COS had an $IC_{50}$ of 48.01 g/mL for reducing HIV-1-induced lysis. These oligomers lowered HIV load in vitro but did not affect HIV-1 RT or protease activity. Higher dosages were also required to reduce HIV-1IIIB p24 antigen production and HIV-1RTMDR p24 antigen production, based on ELISA. The $IC_{50}$ values reported by the authors on infection-induced luciferase activity in infected cells showed that QMW-COS performs better than WMQ-COS. Finally, they used CD4-gp41 ELISA to assess how oligomers affect the interaction between gp41 and CD4, and both were quite effective. These oligomers showed they were most effective when administered soon after cells were infected with HIV-1, demonstrating that they could be used as a standard treatment during the early stages of HIV infection, possibly at the passage stage.[123,171]

## 7 | NATURAL PRODUCTS AND HIV

### 7.1 | HIV suppression

A key focus of natural product-based HIV research is viral suppression. Several promising plant-based HIV medications were studied early on and continue to be studied today. For HIV infections resistant to current treatments, these novel inhibitory compounds may lead to new cost-effective ART with improved inhibitory activities (Figure 3). Calanolides produced by the mangosteen tree *C. lanigerum* in Malaysian tropical rainforests is one of the principal plant-based compounds with anti-HIV activity.[176,177] Its therapeutic properties were discovered following a 1992 sample collection field study financed by the US National Institute of Health (NIH). Calanolides A and B are isolated from the leaves of *C. lanigerum* and inhibit nonnucleoside RT.[178] However, deforestation has led to a shortage of *C. lanigerum*, leading to Calanolide A and B being

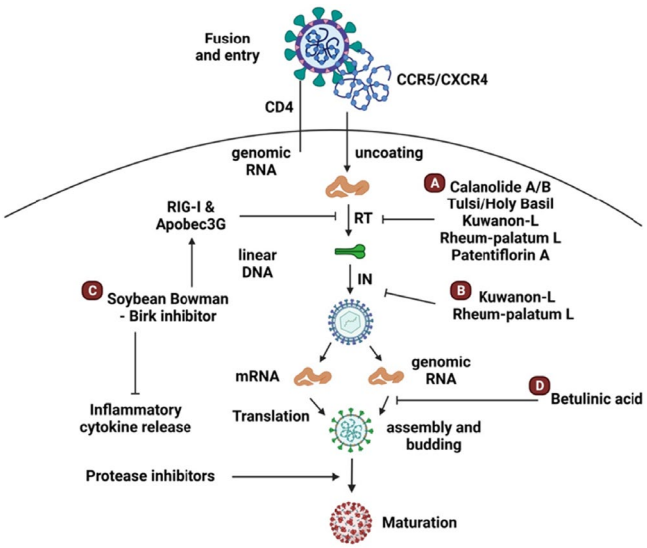


FIGURE 3 Natural HIV inhibitors. Natural product-derived medicines reduce HIV proliferation at multiple stages. (A) HIV RT inhibition by Calanolide A/B, Tulsi/Holy Basil, Kuwanon-L, *Rheum palmatum* L, and Patentiflorin A prevents HIV RNA genome reverse-transcribing into proviral DNA. (B) In addition to their anti-RT action, Kuwanon-L and *R. palmatum* L. inhibit HIV-proviral DNA from entering the host genome. (C) Soybean-derived Bowman-Birk protease inhibitor increases HIV-inhibiting factor RIG-I and Apobec3G and inflammatory cytokine expression during RT. (D) Betulinic acid prevents HIV Gag processing and viral particle release. The figure was designed by Biorender.com program (https://biorender.com/, accessed on 10 January 2024).

artificially synthesized.[179] Both compounds have been thoroughly studied and determined to be safe.[180]

## 7.2 | HIV reactivation

A promising area of HIV research is the search for natural agents that promote HIV transcription to achieve a functional cure[181,182] (Figure 3). Activation is essential to target latently infected cells and facilitate their death and removal through immunological clearance and targeted ART.[183] However, the scarcity of key initiating factors, including nuclear factor kappa B (NF-κB), positive transcription elongation factor b (P-TEFb), and cyclin-dependent kinase 11 (CDK11),[184,185] that are essential for the high expression and successful transcription of HIV significantly limits HIV reactivation in infected cells. Multiple signaling pathways activate NF-κB, controlling transcriptional initiation.[186] The P-TEFb exists in two forms in the cell: an inactive complex containing 7SK-RNA and hexamethylene bisacetamide inducible 1 (Hexim1) and an active complex containing only P-TEFb.[187,188] Reactivation treatments enabling P-TEFb to form the active complex will fail if cyclin-dependent kinase 9 (CDK9) and cyclin T1 (CycT1) are not expressed as expected.[184] CDK11 is required for HIV mRNA 3′-end processing, and HIV mRNA is destroyed if they are not adequately cleaved and polyadenylated.[185] To completely reactivate latent HIV, increased cellular production of these components is required.[183] Since cell transcriptional factor initiation is not HIV-specific, care must be taken to prevent widespread T cell initiation and inflammatory cytokine release while providing a sufficient activation signal to start dormant HIV transcription. Several organizations are studying combined treatments that may reduce nonspecific inflammatory activation by lowering the effective dose of each medicine.[189–191]

The *Euphorbia kansui* plant from the genus *Euphorbia* has been used in TCM for generations to treat fluid retention,[192] cancer,[193] and ascites,[194] with very mild side effects, particularly loose stools.[195] Twelve ingenols, such as triterpenoids, sesquiterpenoids, and euphols, are found in *E. kansui* . The anti-inflammatory effects of euphols may help reduce inflammatory damage caused by ingenol's PKC agonist activity.[196] Euphorbia reactivates latent HIV by increasing cellular levels of P-TEFb and CDK11, similar to refined ingenol (Figure 4).[190] Kansui is currently being studied as a potential clinical LRA in a restricted clinical trial with Nottingham Health Profile (NHP) patients.[177]

Grape, apple, cinnamon, and chocolate contain procyanidins and flavonoids in various plant sources.[197–200] Procyanidin is a supplement produced from plants with antioxidant properties. Procyanidin C1 from the cocoa plant *Theobroma cacao* reactivates latent HIV through the mitogen-activated protein kinase (MAPK) pathway that, together with PKC agonist phorbol 12-myristate 13-acidic acid, shows synergistic activation.[201] Health benefits have been associated with cocoa, including metabolic and cardiovascular improvement, calming, and malignant growth fighting abilities.[202,203] Procyanidin C-13,3′3′′-tri-O-gallate was prepared from the Japanese knotweed *Polygonum cuspidatum* Sieb. Et Zucc.[204] Knotweed promotes P-TEFb, reactivating latent HIV in cell lines, and is used in TCM to maintain heart health.[177]

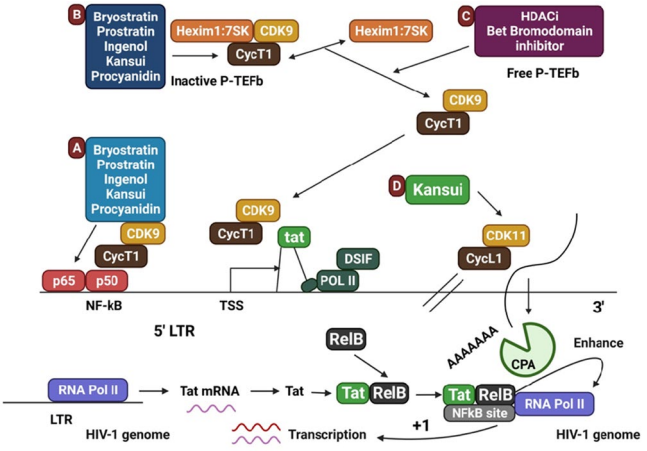


FIGURE 4 Activators of HIV transcription from nature. (A) Natural substances have been examined for their ability to reawaken latent HIV by reactivating HIV transcription. Bryostatin, prostratin, ingenol, and a crude kansui and procyanidin extract stimulate cellular NF-κB, initiating transcription. (B) PKC agonists bryostatin, prostratin, ingenol, a crude kansui extract, and procyanidin increase the cellular synthesis of CycT1, an inactive P-TEFb complex component. (C) CycT1 increases HDACi and BET-bromodomain inhibitor activation and P-TEFb release. Increased expression and free P-TEFb can recruit NF-κB and POLII, leading to transcription elongation. (D) A crude kansui extract increases cellular CDK11 production, which forms a complex with CycL to recruit CPA and correct mRNA end processing. The figure was designed by Biorender.com program (https://biorender.com/, accessed on 10 January 2024).

## 8 | MARINE INVERTEBRATE NATURAL PRODUCTS FOR HIV/AIDS

Different processes have been invented to investigate synthetics that may be therapeutic medicines for HIV. Complementary and alternative medicine (CAM) are characterized as any treatment used as an alternative to traditional clinical therapy.[205,206] However, further research is needed to understand the potential adverse and observed outcomes of using CAM concurrently in HIV and AIDS treatment. In addition, they may have another clinical application in HIV and AIDS treatment. For example, marine-derived compounds may have potential application in the treatment of HIV. The peptides tachyplesin and polyphemusin found in the hemocyte debris of *Tachypleus tridentatus* and *Limulus polyphemus*, and the sponge metabolites avarol, avarone, ilimaquinone, and other phloroglucinols have been found to have anti-HIV activity.[207,208] Avarol represses HIV by preventing the regular UAG silencer glutamine tRNA step from being completed. After viral infection, the uses for this tRNA expand, and it is essential for viral protease activity, which is required for viral proliferation.[209]

## 9 | CLINICAL STUDIES

The clinical importance of herbs and combined tonics in TCM for treating HIV and AIDS have been explored. Many plants have strong anti-HIV properties, blocking virus growth and disrupting its life cycle. TCM can be used as an adjuvant therapy alongside modern antiretroviral medications, improving patients' quality of life.[210] A 12-week clinical trial was conducted to assess the short-term safety and efficacy of a Chinese herbal preparation for alleviating symptoms of HIV infection in 30 adults. The primary outcome indicators included alterations in life satisfaction, subjective health, and the quantity and severity of symptoms. The study found that herb-treated individuals had increased life satisfaction and a reduction in symptoms, with the belief in using herbs being significantly correlated with treatment efficacy.[211] A study involving ten randomized controlled trials found that CHM may enhance liver function indices and effective rates in HIV patients with drug-induced liver damage. The CHM group showed lower levels of aspartate aminotransferase, alanine aminotransferase, total bilirubin, and bilirubin when directly compared to routine treatment. However, the quality of the trials could have been better, and more extensive trials are needed.[212] Another study evaluated herbal remedies for AIDS and HIV patients. Ten trials with 571 participants found some herbs helpful in alleviating symptoms but no noticeable effects on immunity-boosting or antiviral properties. Combining CHM, SH, and antiretroviral drugs showed greater antiviral effects.[213] A trial at Thailand's Sanpatong Hospital is testing a combination of medication extracts from five CHM (SH) for treating HIV infection in individuals living with HIV/AIDS. The open-label trial involved 28 patients with CD4 cell counts greater than 200 cells/$mm^3$ and HIV-1 RNA counts greater than 20 000 copies/mL. This study found that 4–10 patients had positive responses with decreased plasma HIV-1 RNA, while 2–4 had negative responses. SH is safe when prescribed, but more comprehensive scientific evidence is needed to establish its clinical value.[214] Additionally, a randomized trial in northern Thailand assessed the safety and effectiveness of mixed herbs (SH) combined with zidovudine (ZDV) and zalcitabine (ddC) for HIV treatment in adult Thai patients. This study involved 60 participants aged 70+, randomized to receive either a combination of ZDV, ddC, and SH or a placebo. Results showed no significant differences in baseline characteristics, but the SH group experienced a greater drop in HIV RNA and increased CD4 cells. It is suggested that SH herbs could be a substitute for antiretroviral medication in low-resource countries.[215] Furthermore, 9 randomized placebo-controlled trials with 499 HIV-positive and AIDS-positive participants found that a CHM called IGM-1 significantly improved health-related quality of life in 30 symptomatic HIV-positive patients. However, 35 Chinese herbs combined into a herbal formulation did not affect the quality of life, psychosocial measures, AIDS events, viral loads, CD4 cell counts, or symptoms. Combining Chinese herbal components with antiretroviral drugs had a greater antiviral effect. Qiankunning, Curcumin, and capsaicin did not affect HIV-1 RNA levels, CD4 cell counts, or viral load reduction.[216]

## 10 | CONCLUSION AND FUTURE PERSPECTIVES

Studies have endeavored to find treatment solutions for AIDS ever since its discovery in the 1980s. In the 1990s, ARTs revolutionized AIDS treatment research. However, concerns about its side effects have reinvigorated the search for new treatments that reduce infection and replication and protect cells susceptible to disease, particularly CD4+ T-lymphocytes. This review has highlighted many herbal plants that hold the potential for producing novel anti-HIV therapeutics with potent antiviral activities. Furthermore, it highlights discoveries where natural products contain several compounds that could be used to treat HIV+ individuals and reduce their symptoms. Medicinal plants include anti-HIV drugs, immunomodulators, immunostimulants, antioxidants, and nutraceuticals, which help to inhibit viral replication and improve the immune system of infected individuals.

Consequently, this literature review advances our understanding of natural products that can be used to develop novel HIV and AIDS treatments. However, further studies are required to isolate compounds with anti-HIV properties, and undertake clinical trials to explore the cytotoxicity of phytochemical compounds relative to their beneficial outcomes. The anti-HIV activity of medicinal plants should be studied in-depth in the future. Natural compounds offer the potential for producing chemotherapeutic drugs, particularly anti-HIV drugs, despite their toxicity being a significant limiting factor in AIDS treatment.

### AUTHOR CONTRIBUTIONS

**Md. Al Amin:** Conceptualization; data curation; formal analysis; resources; validation; visualization; writing – original draft; writing – review and editing. **Mohamed H. Nafady:** Data curation; resources; validation; visualization; writing – original draft; writing – review and editing. **Mehrukh Zehravi:** Data curation; resources; supervision; validation; visualization; writing – original draft; writing – review and editing. **Sherouk Hussein Sweilam:** Formal analysis; investigation; validation; visualization; writing – review and editing. **Kusuma Praveen Kumar:** Formal analysis; investigation; validation; visualization; writing – review and editing. **M. Akiful Haque:** Investigation; validation; visualization; writing – review and editing. **Aziz Unnisa:** Investigation; validation; visualization; writing – review and editing. **Laliteshwar Pratap Singh:** Formal analysis; investigation; validation; visualization; writing – review and editing. **Mohammed Sayeed:** Data curation; formal analysis; investigation; resources; writing – review and editing. **Mohammed Ali Alshehri:** Investigation; validation; visualization; writing – review and editing. **Irfan Ahmad:** Funding acquisition; investigation; validation; visualization; writing – review and editing. **Talha Bin Emran:** Project administration; supervision; validation; visualization; writing – review and editing. **Md. Zia Uddin:** Formal analysis; investigation; supervision; visualization; writing – review and editing.

### ACKNOWLEDGMENTS

The authors express their gratitude to their own institutions and to the Deanship of Scientific Research at King Khalid University for

funding this work through the Large Research Group Project under grant number RGP.02/513/45.

## FUNDING INFORMATION

Not applicable.

## CONFLICT OF INTEREST STATEMENT

No potential conflict of interest was reported by the author(s).

## ETHICS STATEMENT

Not applicable.

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**How to cite this article:** Al Amin M, Nafady MH, Zehravi M, et al. Bird's eye view of natural products for the development of new anti-HIV agents: Understanding from a therapeutic viewpoint. *Anim Models Exp Med*. 2025;8:441-457. doi:10.1002/ame2.12563