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- Review -

Plant-derived Anti-HIV Natural Products: A Review of Recent Research

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Currently, around 40 million people worldwide are living with human immunodeficiency virus (HIV) infection making HIV a critical global health risk. Present therapies for HIV infection consist of drug cocktails that target different steps of the HIV life cycle to prevent infection, replication, and release of the virus. Due to its mutating nature, drug resistance coupled with side-effects of long-term drug use, novel strategies, and pharmaceuticals to treat and manage HIV infection are constant needs and continuously being studied. Plants allocate a major repertoire of chemical diversity and are therefore regarded as an important source of new bioactive agents that can be utilized against HIV. Since the early 1990s, upon recommendations of the World Health Organization, numerous studies reported phytochemicals from different structural classes such as flavonoids, coumarins, tannins and terpenes with strong inhibitory effects against HIV infection. The present review gathered and presented recent research (2021-present) on plant extracts and phytochemicals that exhibit anti-HIV properties with the aim of providing insights into future studies where ethnomedical and underutilized plant sources may yield important natural products against HIV. Considering the relation and importance of HIV treatment with current viral infection risks such as SARS-CoV-2, screening plants for anti-HIV agents is an important step towards the discovery of novel antivirals.

Key words : HIV, integrase, phytochemical, protease, reverse transcriptase

Introduction

The human immunodeficiency virus (HIV) is the cause of one of the most serious pandemics, acquired immunodeficiency syndrome (AIDS). As of today, approximately 40 million people are living with HIV infection and slightly over half of them have been subjected to a drug cocktail therapy called highly active antiretroviral therapy (HAART) [15]. Despite the success of HAART in increasing life expectancy and quality in HIV-infected patients, until now total eradication of HIV could be achieved with drug therapies which means that HIV-infected patients continue using drug cocktails long-term. Long-term drug use comes with critical complications of side effects and drug-resistant viruses [2, 7]. Therefore, the need to discover, develop and apply new therapies, drugs, or pharmacophores to treat AIDS and/or complement the current treatments is constant. In this context, last years witnessed an increasing number of studies focused on finding anti-HIV bioactive agents from natural sources [22]. The consensus is that natural compound-based treatments have the potential to surpass current therapies in effectiveness and side effects. Different types of compounds from different types of organisms such as plants, microbes and marine organisms have been reported to possess anti-HIV properties with varying efficacies [1, 3, 10]. Some of the natural products even reached clinical trials while some others have only been reported to be effective *in vitro* [1]. This review aims to gather the bioactive agents and natural products from plants reported during the last few years and summarize their possible action mechanisms. Structure-activity relationships (if reported) and provide insights towards better utilization of phytochemicals as novel anti-HIV pharmaceuticals.

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The HIV structure and drug targets

HIV is a spherical retrovirus of the genus *Lentivirus*. It contains two copies of single-stranded RNA that upon host entry reverse transcribed into viral DNA which is subsequently integrated into host DNA to produce viral proteins.

HIV targets cells that produce high amounts of Nf-κB (a necessary transcription factor for viral gene expression). The cells that HIV infects in the human body are crucial parts of the human immune system: helper T cells, macrophages, and dendritic cells. Following the replication and production of new viral proteins, the HIV life cycle continues with an assembly of protein into viral buds and releasing of these buds as mature viruses via the help of an enzyme called protease.

Current HIV drug therapies target three crucial steps in the HIV life cycle to limit the entry, production, and release of the virus (Fig. 1). All these three steps are regulated and progressed by the activation of enzymes called integrase, reverse transcriptase, and protease, respectively [15, 26]. Reverse transcriptase turns the viral single-stranded RNA into DNA which is then spliced and integrated into the host chromosome via integrase enzyme. At this stage, the viral DNA can lie dormant without producing any viral proteins, a period which is called the latent stage. After the host expresses the viral proteins the new HIV virions are produced at the host cell membrane. The HIV protease enzyme then cleaves the virions causing mature viral loads to be released into the bloodstream. Drugs aim to inhibit these three enzymes to prevent the production of new viruses and hence, halting the damaging effects of HIV infection and keeping the host to be infectious to some extent.

Plants with anti-HIV potential

Present drug therapies, especially HAART, continuously fight against multidrug resistance along with HIV infection [15]. This is one of the main reasons that novel drug candidates are a necessity to achieve a successful AIDS treatment, and even for complete removal of HIV from hosts. However, this is not a novel approach. Since the early 1990s, the World Health Organization (WHO) recommends and supports the systematical screening of traditional medicines and other natural sources with the goal of discovering novel anti-HIV constituents [31]. Since then, natural sources provided numerous natural products that combat HIV via inhibition of reverse transcriptase, protease, integrase, and even viral-host cell fusion in some cases. Natural resources have significant chemical diversity like flavonoids, coumarins, terpenes, polyphenols, and alkaloids to name a few [12]. All these classes of compounds have therapeutic potential against tumors, inflammation, metabolic syndromes, skin complications, viral and bacterial infections and so on. Therefore, it's natural to assume that natural products possess real potential to yield effective anti-HIV agents. In this context, the reported anti-HIV properties of plant extracts from the last few years

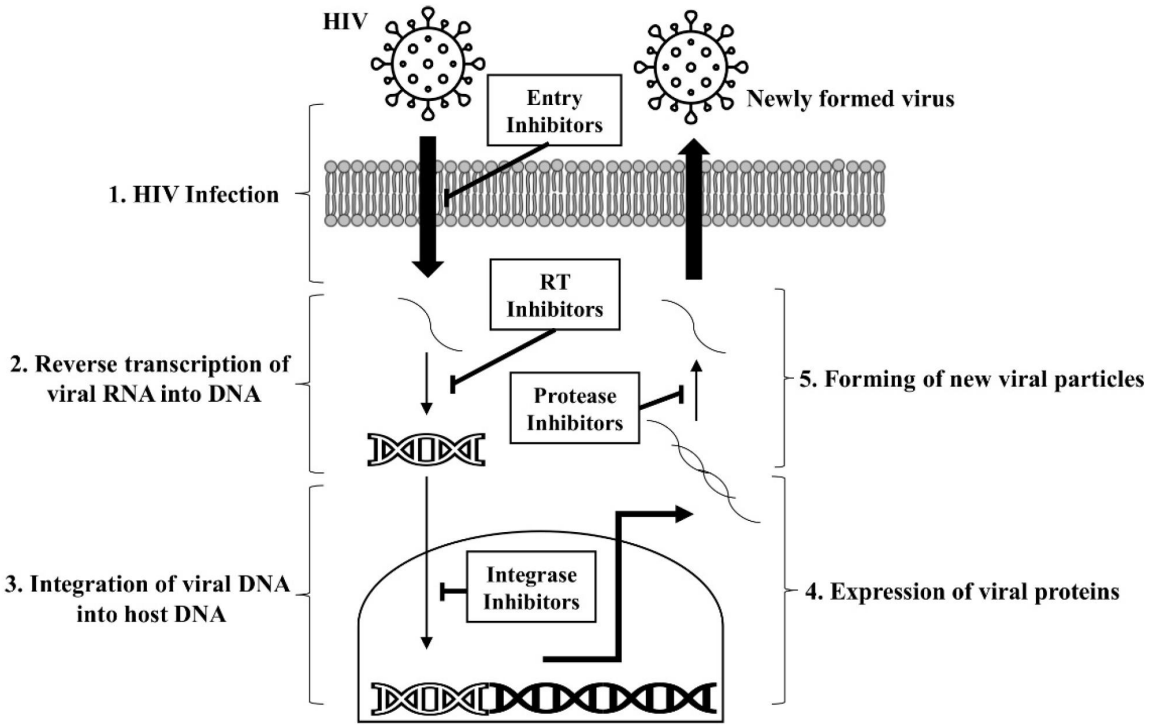

Fig. 1. Human immunodeficiency virus (HIV) life cycle and most common drug targets. RT: HIV reverse transcriptase.

were gathered around in this review and grouped by their action mechanism target.

Plant-derived HIV reverse transcriptase (RT) inhibitors

Upon infection, HIV releases its viral RNA into the host cell cytoplasm. The virus then employs its reverse transcriptase (RT) enzyme to convert viral RNA into DNA. RT inhibitors halt the activity of this enzyme and stop the virus from integrating its genetic material into the host genome [14]. The literature contains numerous reports of the natural sources that have been screened for their inhibitory effects against HIV RT [14, 22].

Researchers often screen their traditional medicinal herbs and plants for anti-HIV properties. Discovering HIV RT inhibitors are one of the common goals of anti-HIV studies (Table 1). A recent screening revealed that *Vitex negundo* (Chinese chaste tree) methanolic extracts inhibited HIV-1 RT by 74.76% of untreated control [23]. The same study also reported that *Datura metel* (Indian thornapple) methanolic extract was able to inhibit HIV RT activity by 71.96%. In a similar fashion, Panvilai et al. [21] screened aqueous extracts of some Thai medicinal plants for their anti-HIV-1 activity where they used extracts from the stems of *Euphorbia antiquorum* (Antique spurge) which is an ingredient of traditional medicine for the treatment of skin infection. Results showed that the *E. antiquorum* extracts inhibited the HIV-1 RT by 57.23% being the only active inhibitor among all other tested plants. In order to utilize waste biomass, Harb and Chow [9] screened fifteen macroalgae from Brazilian shores which are beach-cast for their anti-HIV activity. Previously, the polysaccharide extracts of *Fucus vesiculosus* ($IC_{50:}$ 0.5-1.0 μg/ml) and *Adenocystis utricularis* ($IC_{50:}$ 0.6-7.0 μg/ml) were reported to exhibit significant anti-HIV RT activities along with diterpenes from *Dictyota menstrualis* which exerted a similar inhibitory effect with IC_{50} of 1.0 μg/ml. The study by Harb and Chow [9] also added the aqueous extracts of *Zonaria tournefortii* ($IC_{50:}$ 5.0 μg/ml) and *Alsidium seaforthii* ($IC_{50:}$ 18.93 μg/ml), and methanolic extract of *Dictyopteris jolyana* ($IC_{50:}$ <50.0 μg/ml) as significant potential sources for HIV-RT inhibitors.

In several reports, following the confirmation of HIV RT inhibitory effect, the phytochemical profile is analyzed and further, the active ingredients are isolated to be utilized. Sillapachaiyaporn et al. [27] reported that the *Curcuma aeruginosa* Roxb., a plant from the ginger family, inhibited HIV RT moderately: 64.97% for hexane extract and 76.93% for methanol extract. The phytochemical analysis followed by docking analysis on critical target sites of HIV RT revealed dihydroergocornine, 3β,6α,7α-trihydroxy-5β-cholan-24-oic acid, and 6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione-16,17-acetonide were three compounds with possible anti-HIV properties, showing significant binding affinity at the active site of HIV RT. In the same vein, Sanna et al. [25] showed that extracts from *Punica granatum* (pomegranate) leaves, barks and peels inhibited HIV RT with IC_{50} values of 0.61, 0.22 and 0.85 μg/ml, respectively. Analysis of major components of *P. granatum* extracts yielded ellagic acid, luteolin, apigenin, punicalins, and punicalagins as the active ingredients which showed notable inhibitory activities against HIV-1 group M subtype B heterodimeric RT. Among them, punicalins and punicalagins exhibited IC_{50} values of 0.18 and 0.12 μM, respectively and quantitative analysis of these compounds reported that punicalins and punicalagins present in both bark and peel extracts of *P. granatum* with the following concentrations: punicalin 15.80 mg per gram of bark extract and 2.51 mg per gram of peel extracts; punicalagin 76.06 mg/g for bark and 29.51 mg/g for peel extract. Fois et al.

Table 1. Plant-derived HIV reverse transcriptase inhibitors

Source	Active ingredient	Ref. no
Vitex negundo	Methanolic extract	[23]
Datura metel	Methanolic extract	[23]
Euphorbia antiquorum	Stem water extract	[21]
Zonaria tournefortii	Water extract	[9]
Alsidium seaforthii	Water extract	[9]
Dictyopteris jolyana	Methanolic extract	[9]
Curcuma aeruginosa	Methanolic extract, Dihydroergocornine, 3β,6α,7α-trihydroxy-5β-cholan-24-oic acid*, 6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione-16,17-acetonide*	[27]
Punica granatum	Ellagic Acid, Luteolin, Apigenin, Punicalagins	[25]
Teucrim flavum	Salvigenin, Cirsimaritin, Cirsiliol	[5]

*Compounds tested with computational methods instead of *in vitro*.

[5] subjected the ethyl acetate extract of *Teucrim flavum* subsp. *glaucum* to bioassay-guided fractionation which yielded salvigenin, cirsimaritin and cirsiliol. They reported that although all compounds showed some effect against the HIV-1 group M subtype B heterodimeric RT-associated RNase H by binding to its active site, cirsiliol was the most active. The reported IC_{50} values were 100 μM for salvigenin, 89 μM for cirsimaritin and 8.2 μM for cirsiliol.

Plant-derived HIV integrase inhibitors

After the viral RNA is converted to DNA, the insertion of HIV DNA into the host gel genome is mainly catalyzed by the activity of the integrase enzyme of HIV. The bioactive agents targeting the activity of integrase aim to prevent the virus from copying itself and therefore, inhibiting the virus replication. Therefore, studying plant-derived materials for integrase inhibitors yielded promising results towards finding anti-HIV agents (Table 2). Several herbal remedies are being touted to be effective against HIV-1 infection without scientific evidence [28]. To alter this, Rotich et al. [24] screened an herbal remedy called CareVid^{TM} for any anti-HIV constituents. They reported that ellagic acid, pellitorine, lupeol, and betulin showed *in vitro* integrase inhibitory effects with 21.1%, 19.0%, 18.5%, and 16.8% inhibitory rates, respectively, when administered at the 25 μg/ml dose compared with sodium azide (positive control). On the other hand, docking studies promoted oleuropein as the best candidate for integrase binding whereas ellagic acid exerted a moderate inhibition prediction. A study on torch ginger (*Etlingera elatior*) also showed that it contains a steroid compound 5α,8α-Epidioxyergosta-6,22-dien-3β-ol with integrase inhibitory potential as a result of a docking simulation [35]. Messi et al. [17] isolated two novel biflavonoids from *Ochna rhizomatosa*: (R)-rhizomatobiflavonoid A (RA) and (R)-rhizomatobiflavonoid B. Among them, RA showed a very significant HIV-1 subtype C integrase activity with IC_{50} values of 0.047 μM. Docking simulation also confirmed the suggestion by showing the binding score of −121.8 Kcal/mol for RA. Guzzo et al. [8] showed that the crude extract of *Scrophularia trifoliata* showed a HIV-1 recombinant 6xHis tagged integrase inhibitory effect with the IC_{50} value of 2.5 μg/ml. Further analysis of the extract led to isolation of 11 flavonoids as active ingredients and among them kaempferol-3-*O*-glucopyranoside showed strong inhibition of HIV-1 integrase activity *in vitro* with 0.024 μM IC_{50} value, overall suggesting the potential of flavonoids as promising integrase inhibitors. This was also evidenced by comprehensive screening of flavonoid library for HIV-1 integrase inhibition [33]. They concluded that flavonoids with specific chemical features such as hydroxyl group in C3-, C4-, C5- and C7-position, might be more active against integrase activity through competitive inhibition. The representative bioflavonoids they have chosen which are continuously being isolated from plants, showed affinity for HIV-1 integrase with K_d values ranging from 1.0 to 3.6 μM.

Plant-derived HIV protease inhibitors

Protease is a crucial viral enzyme that regulates the last step of HIV viral cycle. It cleaves the long viral polypeptides and proteins to yield mature viral peptides and proteins to be released. The products of protease enzyme are infectious viral loads. Therefore, protease is also an important target for anti-HIV agents as the inhibition of this enzyme's activities results in halted viral replication and subsequent diminishing of infectivity (Table 3). Like other enzymes mentioned earlier, up to date numerous plant-based extracts, remedies and isolated compounds were reported to possess anti-HIV-1 protease effects among others [22]. With the help of computational advances, *in vitro* screening of plant extracts followed by compound isolation can successfully predict potential inhibitors. In a recent report, *C. aeruginosa* hexane, ethyl acetate and methanol extracts were screened for their HIV-1 protease inhibitor potential and consequently subjected to phytochemical analysis [27]. Isolated compounds were then investigated via in silico molecular docking analysis to predict the possibility of binding to the active site of HIV-1 protease. Their study concluded that among 67 compounds isolated from *C. aeruginosa* extracts, 4 presented notably

Table 2. Plant-derived HIV integrase inhibitors

Source	Active ingredient	Ref. no
CareVid^{TM}	Ellagic acid, Pellitorine, Lupeol, Betulin	[28]
Etlingera elatior	α,8α-Epidioxyergosta-6,22-dien-3β-ol*	[35]
Ochna rhizomatosa	Rhizomatobiflavonoid A, Rhizomatobiflavonoid B	[17]
Scrophularia trifoliata	Methanolic extract, kaempferol-3-*O*-glucopyranoside	[8]

*Compounds tested with computational methods instead of *in vitro*.

Table 3. Plant-derived HIV protease inhibitors

Source	Active ingredient	Ref. no
Curcuma aeruginosa	Dihydroergocornine*, 27-nor-5β-cholestane-3α,7α,12α,24,25-pentol*, 3β,6α,7α-trihydroxy-5β-cholan-24-oic acid*	[27]
Croton megalocarpus	1β-acetoxy-3β-chloro-5α,6α-dihydroxycrotocascarin L	[29]
Pangium edule	(5β) pregnane-3,20β-diol, 14α,18α-[4-methyl-3-oxo-(1-oxa-4-azabutane-1,4-diyl)]-diacetate*, phthalic acid butyl undecyl ester*, bis(3,5,5-trimethylhexyl) phthalate*,	[6]
Morus alba	Mulberroside C	[30]
Sarcandra glabra	Chlorogenic acid	[20]
Camellia sinensis	(-)-epicatechingallate	[11]

*Compounds tested with computational methods instead of *in vitro*.

lower binding energies to HIV-1 protease than that of Amprenavir, a HIV-1 drug targeting the protease. These compounds dihydroergocornine, 27-nor-5β-cholestane-3α,7α,12α, 24,25-pentol, 3β,6α,7α-trihydroxy-5β-cholan-24-oic acid, and 6β,11β,16α,17α,21-pentahydroxypregna-1,4-diene-3,20-dione-16,17-acetonide recorded binding energies of −12.65, −11.53, −10.92, and −10.71 kcal/mol, respectively where Amprenavir binding energy was −9.73 kcal/mol. Authors suggested that these four compounds hold potential to be protease inhibitors both due to docking studies and their chemical structure as three of the compounds were triterpenoids, a phytochemical class known to contain reported protease inhibitors [32]. Likewise, Terefe et al. [29] isolated a rare crotofolane diterpenoid from the bark of *Croton megalocarpus*, an oil producing tree found in Africa. This diterpenoid, 1β-acetoxy-3β-chloro-5α,6α-dihydroxycrotocascarin L, was found to inhibit HIV-1 replication with an IC_{50} value of 28 nM. They also reported that its inhibitory effect on HIV-1 replication might stem from its inhibition of protease, which was recorded at the rate of 63% compared to the untreated control.

Another study by Tumilaar et al. [6] subjected the isolated compounds from *Pangium edule* to computational analysis for binding energy and docking ability to the active site of HIV-1 protease. Study concluded that (5β)pregnane-3,20β-diol, 14α,18α-[4-methyl-3-oxo-(1-oxa-4-azabutane-1,4-diyl)]-diacetate, phthalic acid butyl undecyl ester, bis(3,5,5-trimethylhexyl) phthalate, ψ,ψ-carotene, 1,1′,2,2′-tetrahydro-1,1′-dimethoxy-, ethyl cholate, and octadecane, 3-ethyl-5-(2-ethylbutyl)- showed very strong binding affinity and have potential to be developed into HIV-1 protease inhibitors. Other studies also reported mulberroside C from *Morus alba* [30], chlorogenic acid from *Sarcandra glabra* [20], and (-)-epicatechingallate from *Camellia sinensis* [11] were also reported to inhibit HIV-1 protease activity with varying rates.

Other mechanisms targeted by phytochemicals

Although the majority of drugs and drug candidates target the aforementioned three enzymes in the HIV-1 life cycle to exert anti-HIV properties, there are some other reported mechanisms that studies aim to tackle. One of the main mechanisms apart from RT, integrase and protease inhibition is to prevent cell-cell fusion. Agents that prevent virus-host fusion are also called fusion inhibitors and their main effect is to prevent virus to enter the host cell. Maia et al. [16] presented that *Anandenanthera colubrina* Brenan extracts were able to inhibit 70% of cell-cell fusion using TZM-bl and HIV-infected HL2/3 cells. On a side note, they reported *A. colubrina* extracts to be rich in flavonoids, phenolic acids, and fatty acids. In another study Zheng et al. [34] isolated oleanolic acid, palmitic acid, taxifolin, piceatannol, guibourtinidol-(4α→8)-epiafzelechin, and cassiabrevone, the latter being a novel compound, from the bark and root of *Cassia abbreviate*. This study showed that guibourtinidol-(4α→8)-epiafzelechin and cassiabrevone significantly inhibited HIV-1 entry into target cells. The recorded IC_{50} values were 42.5 μM and 31.0 μM, respectively. Another way to prevent HIV-1 replication is to prevent the expression of critical proteins to injure the viral life cycle. Studies showed that the HIV-1 mutants without a gene that codes for protein Vpu exhibit remarkedly diminished pathogenicity [13]. Therefore, more and more studies are focusing on Vpu protein as a pharmaceutical target to combat HIV-1 infection. As reviewed by Langarizadeh et al. [13], phlorotannins, a phenolic tannin derivative phytochemical class, are showing promise as HIV Vpu inhibitors. Apart from directly targeting HIV-1 life cycle, some natural products were screened for their immunomodulatory effects to regulate the immune system to fight HIV-1 infection. Olwenyi et al. [19] reported that extracts from neem tree (*Azadirachta indica*) showed *in vitro* immunomodulatory activities against HIV-induced T-cell ex-

haustion without causing any harm to T-cell functions.

Conclusions

Plants have been the major source of natural origin pharmaceuticals through a vast supply of bioactive constituents. Up to date phytochemicals have been the leading bioactive agents targeting almost all type of diseases and complications. Although poor biocompatibility, difficulties in mass production, possible toxicities and non-specific bindings might propose certain drawbacks for natural products, diversification through chemical modifications can yield safer options. Recent reports indicated that antiviral phytochemicals previously reported to inhibit numerous viral infections such as HIV are producing promising results against the recent SARS-CoV-2 [4, 18]. Studies showed that some antivirals that are effective against HIV-infection also show promising results against new viral infections that cause global scares such as COVID-19. Therefore, screening medicinal, dietary, underutilized or ignored plants for any bioactive ingredient that can act against viral infections might provide useful data to be used for further studies targeting different types of complications. In this context, the current review gathered around recent reports from 2021 onwards that exhibited anti-HIV-1 properties of plant extracts and isolated compounds with the hope that it will provide valuable insights to further studies to tackle HIV-1 infection via natural sources.

The Conflict of Interest Statement

The authors declare that they have no conflicts of interest with the contents of this article.

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초록 : 천연물의 항 HIV 효능에 대한 최신 연구동향

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전세계적으로 약 4천만 명의 사람들이 인체면역결핍증바이러스(HIV) 감염이 되어 있으며, HIV에 감염된 세포의 수가 치명적인 수준에 다르면 후천성면역결핍증후군을 일으키게 된다. HIV에 감염이 되면 완치 치료가 어려우며 현재 알려진 치료방법으로는 감염, 복제 및 바이러스 방출 억제를 위해 항레트로바이러스 치료법이 병용되고 있다. 하지만 HIV 바이러스는 지속적인 돌연변이 유발 및 약물에 대한 내성을 갖게 하므로 장기간 약물복용 시 심각한 부작용을 초래한다. 이에 새로운 치료방법과 효능약물에 대한 연구가 필요한 실정이다. 식물유래 천연물은 수많은 생리활성물질들이 보고되어 있으며, 이는 항HIV 효능 지닌 잠재성을 가진 후보 물질이 될 수 있다. 1990년 세계보건기구에서는 플라보노이드, 쿠마린, 탄닌 및 테르펜의 항 HIV 효능을 보고하였으며, 이러한 물질은 SARS-CoV-2와 같은 바이러스 감염을 또한 억제하는 것으로 밝혀졌다. 따라서, 본 연구에서는 항 HIV 효능을 나타내는 식물 추출물 및 파이토케미컬에 대한 최신 연구동향(2021-현재)을 검토하였으며, 이를 통해 항HIV 효능을 지닌 새로운 천연물 발굴의 기초자료로 활용될 것으로 사료된다.