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Role of medicinal plants in HIV/AIDS therapy

Umme Laila, Muhammad Akram, Mohammad Ali Shariati, Asif Mehmmod Hashmi ... See all authors

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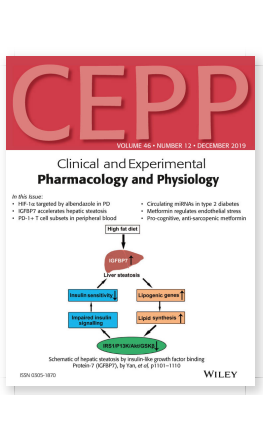

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Abstract

Human immunodeficiency virus (HIV) causes the potentially life-threatening and chronic disease called acquired immune deficiency syndrome (AIDS). The main target of this viral disease is to suppress the immune system and make the body unresponsive to external stimuli. According to global health observatory data since epidemic, more than 78 million people were affected by HIV and 39 million people died globally. Until 2017, 36.5 million people were living with HIV. An estimated 0.8% (0.6%–0.9%) of adults aged 15–49 years worldwide is living with HIV. The World Health Organization (WHO) reported that the African region remains most severely affected, with nearly one in every 25 adults (4.1%) living with HIV and accounting for nearly two-thirds of the people living with HIV worldwide. WHO reported that globally only 21.7 million (19.1 million–22.6 million) people have had access to antiretroviral therapy up to 2017. Currently, antiretroviral therapy (ART) is available for the control of HIV but has serious associated side effects such as lipodystrophy. Because of the limitations, associated with ART, researchers throughout the world are trying to explore and develop more reliable and safe drugs from natural resources to manage HIV infection. A wide range of medicinal plants have been studied and have reported significant potential against HIV. Plants like *Rheum palmatum* L., *Rheum officinale*, *Trigonostem axyphophylloides*, *Vatica astrotricha*, *Vernonia amygdalina*, *Hypoxias pelargonium*, *Sidoides hemerocallidea* and *Sutherlandia frutescens* etc. have high efficacy to cure HIV. The exact mechanism of action is still not known but various phytoconstituents isolated from medicinal plants such as alkaloids, flavonoids, polyphenols, terpenoids, tannins, proteins and coumarins have the potential to interrupt the life cycle of HIV as well as act as immunomodulators to enhance the immune system of infected patients with no well reported side effects. It could be concluded that medicinal plants have potential for the management of HIV/AIDS but more studies are needed to reveal rigorous efficacy and safety concerns by conducting clinical trials at vast level to explore therapeutic impact of medicinal plants.

1 INTRODUCTION

Acquired immune deficiency syndrome (AIDS) occurs due to infection caused by human immune deficiency virus (HIV). This infection causes immunosuppression in the body. It is a serious and life-threatening condition that affects many people. According to UNAIDS and WHO recent report in Global HIV and AIDS Statistics-2018 Fact Sheet, by the end of 2017 worldwide 36.9 Million people were living with HIV and among them only 21.7 Million people were accessing the antiretroviral therapy. Since the start of the HIV epidemic, a total of 78 million people have become infected with this disease.1 Those living in Sub-Saharan Africa are largely affected by this disease. In AIDS, the patients are at significant risk of contracting a wide range of life-threatening opportunistic infections as well as developing cancers due to the destruction of the human immune system and it was estimated that the life span without treatment after the infection of HIV decreased to 9–11 years, depending on the HIV subtype.2 The main targets of HIV infections are the vital immune cells like T helper cells (specifically CD4+ T cells), dendritic and macrophages cells.2 After the infection of these immune cells destruction through a wide range of mechanisms especially of CD4+ T cells occurred like T helper cells become prone to pyroptosis, uninfected bystander cells apoptosis,3 killing of the cells with direct viral infection, and destructive role played by CD8+ cytotoxic lymphocytes on recognizing the infected CD4+ T cells. Due to multiple mechanisms the lower level of CD4+ T cell make immunocompromised due to loss of cell-mediated immunity and make the HIV patient more susceptible towards multiple opportunistic infections, finally to develop AIDS.4 Currently, Anti-HIV therapies (ART) are available which have improved the quality of life as well as life span of HIV/AIDS patients. However, ART is associated with serious side effects like lipodystrophy causing peripheral fat loss and central fat accumulation leading thin facial pads, thin legs and arms, buffalo humps and pot bellies and leaving the patient stigmatized. In addition, antiretroviral drugs have many other disadvantages including the shortage of availability, resistance, toxicity and very low curative effects. Limitations in ART programs continued to find out more potent anti-HIV drugs. It has been reported that medicinal plants have significantly high antiviral potential and herbal medicine proved very effective for the treatment of AIDS. Fogarty et al5 stated that 44.3% of HIV patients in Australia reported the use of a marijuana compound for therapeutic purposes. Patients have been using medicinal plants as they feel more relaxed, less pain, less stress, spiritualism and greater well-being. It was reported that approximately, 9% of outpatients believed that it was possible to treat HIV by taking herbs, while some consider that herbs also improved energy level. However, a study conducted in the US reported the commonly treated conditions using herbal medicine are anxiety, depression, fear, pain and nervousness.6, 7

Although a number of reports are available on folkloric uses of medicinal plants to manage some diseases, knowledge of herbal remedies used to treat HIV/AIDS is limited, impressionistic and not well documented.8 Medicinal plants contain novel anti-HIV compounds. As it has been well reported that medicinal plants contain various types of phytochemical constituents including alkaloids, flavonoids, phenolic compounds, glycosides, tannins, and saponins, so the medicinal plants could be potential sources of boosting immune responses, as well as halting the replication of HIV. Furthermore, it is important to search for novel antiretroviral compounds that can replace or be added to the present arsenal of drugs against HIV/AIDS.9 A literature survey of medicinal plants with anti-HIV property is an important prerequisite to search the novel antiviral agents for the treatment of HIV/AIDS worldwide. Therefore, the effort has been made to review the taxonomic families and species of plants with anti-HIV active compounds and their modes of action. Bioactive compounds from plants which play effective roles in the management of AIDS are also discussed in this review study.

2 THE LIFE CYCLE OF HIV

Human immunodeficiency virus infects on entering into the body, specifically targeting vital immune cells including T helper cells (specifically CD4+ T cells), dendritic and macrophage cells.2 The virus is fused with the targeted cell membrane by viral envelope glycoprotein. Ip120 changes are induced by CD4+ T cells causing the viral entry into the host cell10 where CD4+ and gp120 interaction takes place. Then ternary CD4-co-receptors gp120 complex is formed, and finally, gp41 conformational changes confirm the membrane fusion. Fusion occurred at low pH of endosome compartment after receptors and CD4+ engagement. The targeted cells are composed of lipids which play important role in membrane fusion. In plasma membrane, the fusion of membrane takes place by lipid rafts which are plasma membrane microdomains. These microdomains consist of cholesterol and glycosphingolipid.11 Any disruption from cholesterol particles in the target cell or HIV may disrupt the membrane fusion. In the inhibition of HIV-fusion, amphotericin B methyl esters play an important role. By reverse transcriptase single-stranded HIV RNA is converted into double-stranded HIV DNA.12 The complex of reverse transcription is formed in the cytosol by entry and fusion of ribonuclear protein complex composed of NC, CA, RT, VPr and IN. At 5′ end, DIS (dimerization initiation sequence) is held together by RNA. Retrovirus is called a pseudodiploid because of carrying the two strands of retroviral RNA. DNA synthesis occurs by retrovirus which uses tRNA. The virus enters the target cell then the process of forming RNA into DNA takes place as the retroviral ribonuclease H (retroviral RNase H) is a catalytic domain of the retroviral reverse transcriptase (RT) enzyme. The RT enzyme is used to generate complementary DNA (cDNA) from the retroviral RNA genome. This process is called reverse transcription.13

1. At 3′-OH end of tRNA, the single strand of DNA synthesis occurs. Then DNA synthesis continues towards the 5′ end.
2. A virtue of true repeated region is present at 3′ and 5′ ends, and this minus strand is transferred for hybridization.
3. Moving towards the 5′ end of genome, RNA-DNA hybrid is formed which move along with RNAScH- mediator degradation.
4. Positive-strand is PPT; the residual RNA fragments which are hybridized can also be used in priming plus strand synthesis.
5. After RNase H removed, plus strand synthesizes the tRNA. This allows plus strand to hybridize with homologues region at 3′ end.14

The RT uses one template to synthesize other templates from the two strands of RNA. This can occur 30 times per infection. Intermolecular jumps lead to mutation by deletion, duplication and insertions. If two packages of RNA are not identical, then the intermolecular jumps create recombinants. This recombinant provides a rapid mechanism for HIV to resist drugs. Retroviral gag protein precursors that are synthesized by polyproteins, for example PR55, that are responsible for a non-infectious virus-like particle. The formation of non-infectious particles does not require pol-encoded enzyme, viral genomic RNA and enveloped glycoproteins.15 Retroviral Gag proteins are responsible for targeting the nascent particles which are exported from the cell forming the framework of structural virion.16

2.1 Mode of transmission

The HIV infection is transmitted a number of ways, but most commonly through infected blood or blood components. It is also transmitted through sexual contact with lower risk of infection in heterosexuals as compared to homosexual (male to male). HIV infection is also spread through blood, semen, vaginal secretion, breast milk, use of contaminated needles or syringes and during pregnancy or birth. It also transmits to the mucous membrane through a cut or damaged tissue.15

3 PATHOGENESIS

This virus infects the CD4+ cells and chemokine receptor which is CCR5 or CXCR4. Infection to CD4+ cells indicates that the patient is immune compromised. In 1996, a cohort study reported that HIV infection course could be predicted within 6–12 months based on the viral load in the plasma, and at this stage, CD4+ count confirmed the disease severity. More than half of the CD4+ cells decreased during the early stage of infection. When this cell count decreases, then the disease progresses from acute to chronic phase. During HIV infection, CD4+ T cells are depleted from the gut and the helper cells produce interleukins maintaining the integrity of the mucosal barrier. During acute infections, the loss of CD4+ cells shows two effects on the immune system: it depletes memory CD4 T cells which constitute major portion of the immune system, and allows the microbial translocation.17

4 PHASES OF HIV INFECTION

4.1 Acute HIV phase

This is an early infection stage, which develops within 2–4 weeks after HIV infection. In this stage, HIV multiplies rapidly and spreads into the body. When this virus attacks the body, it destroys the CD4 cells of the immune system. At this stage, the virus levels in the blood are very high and the symptoms appear after 2 weeks of infection. The patient has flu-like symptoms, fever, headache, rash, diarrhoea, nausea and vomiting, fatigue, pharyngitis and arthralgia. Lymphadenopathy also occurs. The common neurologic manifestation is aseptic meningoencephalitis. Symptoms disappear after 3–4 weeks in some patients but in some cases, symptoms persist for 8–12 weeks where CD4+ T-lymphocytes are severely depressed but plasma HIV-1 RNA levels are high, confirming the disease progression. Laboratory investigations show a decrease in CD4+ cell count in primary HIV-1 infection and lymphopenia, and an increase in CD8+ T cell in circulation.16

4.2 Chronic HIV phase

In the chronic phase, HIV continuously multiplies in the body at very low levels. In chronic HIV infection, patients have many HIV related symptoms spreading the virus to other people. During this phase, the patient has fatigue and lymphadenopathy, and some other conditions like oral thrush and vaginal candidiasis. In the acquired immunodeficiency syndrome phase, it severely damages the immune system causing immune suppression. Patients feel tiredness and swelling at the groin and lymph nodes region. Prolonged fever, night sweats, dyspnea, weight loss and prolonged diarrhoea occur.16

5 TREATMENT OPTIONS FOR HIV

5.1 Antiretroviral therapy

The introduction of anti-HIV drugs as monotherapy in the early 1990s was a great achievement in the management of AIDS but due to limited outcomes, more and safer efficient drugs were required. After 1996, the introduction of combination antiretroviral therapy (cART) with different mode of actions (Figure 1) significantly decreased the mortality associated with HIV and improved the life span of AIDS patients who begin treatment early enough, with lifespans now approaching that of the general population. However, adverse side effects and convenience/adherence are the key concerns in the management of long-term control of HIV.18 Although various antiviral drugs are available for the treatment and management of HIV infection (Figure 1) but due to their associated side effects and poor outcomes, more research in drug development for the management of AIDS/HIV is required. Currently, it is recommended to treat all HIV-infected patients with antiretroviral therapy (ART) immediately after the detection of the virus, regardless of CD4 cell count, to prevent disease progression and improve the clinical outcomes including the reduction of AIDS-associated events and to decrease disease transmission. However, repeated dosing of multiple pills predispose the patients to multiple substantial side effects like drug–drug, drug–food interactions, central nervous system symptoms, high risk of virologic failure and development of a drug-resistant virus.19

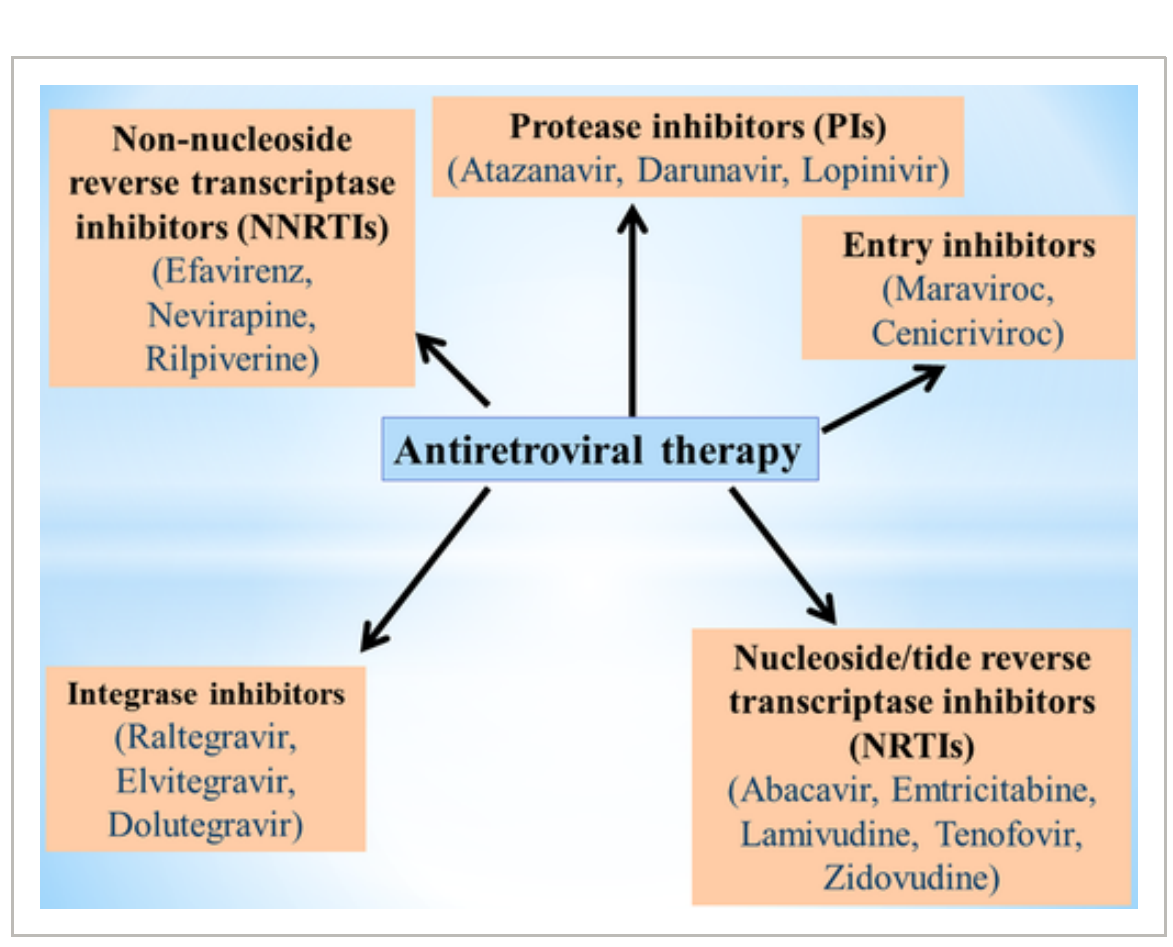
Non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Efavirenz, Nevirapine, Rilpiverine)
Protease inhibitors (PIs) (Atazanavir, Darunavir, Lopinivir)
Entry inhibitors (Maraviroc, Cenicriviroc)
Antiretroviral therapy
Integrase inhibitors (Raltegravir, Elvitegravir, Dolutegravir)
Nucleoside/tide reverse transcriptase inhibitors (NRTIs) (Abacavir, Emtricitabine, Lamivudine, Tenofovir, Zidovudine)

Figure 1 Open in figure viewer | PowerPoint

Different antiretroviral regimens and their mode of actions

5.2 Medicinal plants for HIV/AIDS therapy

Drugs from natural resources like medicinal plants remain a popular choice to treat various infectious as well as non-infectious diseases. It has been well reported that medicinal plants with minimal or no side effects are being used for the treatment of HIV/AIDS. Medicinal herbs not only affect the replication of viral particles but also act as immunomodulators and immune stimulants due to the potential source of antioxidants and nutraceutical compounds. A number of herbs having anti-HIV activity have been reported in the literature. Anti-HIV activity of medicinal plants has been reviewed from the published literature by searching reference materials through various databases/search engines and is listed below.

5.2.1 *Vernonia amygdalina*

Vernonia amygdalina is a shrub used as a traditional herbal medicine for the treatment of HIV/AIDS. It belongs to family Asteraceae and common name of the plant is bitter leaf due to its bitter taste. The studies reported that *Vernonia amygdaline* has antioxidant activity in HIV positive patients when compared with the commercially available tablet Immunace. *V. amygdalina* has nutritional and health improving properties. Studies reported the effect of *V. amygdalina* leaf extract on HIV-infected patients and those taking antiretroviral therapy. Aqueous extracts of fresh leaves of *V. amygdalina* were used along with ART to evaluate the effect of herbs on CD4+ cells count for a period of four months. The study results showed that CD4 count was increased in patients who used the leaf extract or supplements. Those clients who used both supplements and leaf extract had an increase in CD4 count. When compared with the control group, CD4 cell count was found to have increased. Moreover, these patients also recover skin rashes. Leaves of *V. amygdalina* have an immunological effect on HIV-infected patients and are used in HIV management. CD4 count depends on the white blood cell count. CD4 cells reduced to low level in HIV phase, being unable to compete with infections. Leaves of fresh bitter leaf are effective for the treatment of persistent fever, headache and joint pain in AIDS patients. *Vernonia amygdalina* also act as a nutritional supplement.20

5.2.2 *Rheum* species

It has been reported that extracts from *Rheum* species including *Rheum palmatum* L. and *Rheum officinale* Baill contain phytochemical constituents which specifically inhibit the replication of HIV. Esposito et al,21 isolated and investigated the anti-HIV activity of anthraquinone derivatives on both HIV-1 reverse transcriptase (RT)-associated DNA Polymerase (RDDP) and Ribonuclease H (RNase H) activities in biochemical assays. Then HIV-1 mutated RTs, integrase (IN) and viral replication as anti-HIV parameters were also tested to explore the new treatment strategies. Results revealed that HIV-1 RT-associated RNase H function is inhibited by the extracts of both *R. palmatum* L. and *R. officinale* Baill. Further, studies revealed that Sennoside A and B were the phytoconstituents responsible to inhibit both RDDP and RNase H RT-associated functions. When Sennoside A was studied more, it was noted that there are two RT binding sites for its antiviral activity. Moreover, cell-based analysis revealed that Sennoside A affects the HIV-1 replication as well as in vitro studies revealed the phytochemical effects on HIV-1 IN activity. Viral transcription process is the major target for Sennoside A reported at the time of Viral DNA production.21

5.2.3 *Trigonostem xyphophylloides* and *Vatica astrotricha*

To explore the inhibitory effects of medicinal plants on HIV-1, extracts from two traditional Chinese medicinal plants, *Trigonostem xyphophylloides* (TXE) and *Vatica astrotricha* (VAD), were investigated. Results revealed that both extracts had few side effects on the multiplication of host immune cells and their survival significantly halted the replication of HIV-1 and syncytia formation in CD4+ Jurkat cells. Further, research revealed that TXE and VAD extract have no HIV-1 RT enzyme inhibitory effects. Treatment with both extracts demonstrated that TXE and VAD extract have anti-HIV potential by inhibiting the HIV multiplication and the entry of this virus into target cells. Molecular studies revealed that phytochemical constituents block the HIV-1 interaction with target cells, i.e., the interaction between gp120 and CD4/CCR5 or gp120 and CD4/CXCR4 and point to the potential of developing these two extracts to be HIV-1 entry inhibitors.69

5.2.4 *Hypoxis hemerocallidea*

Hypoxis hemerocallidea is also known as the African potato and belongs to the family Hypoxidaceae. African potato is commonly used as an immune booster. Active ingredients of plants which have anti-HIV activity include phytosterols, hypoxide, aglycone and rooperol. African primary health care communities used the root of *H. hemerocallidea* as an immunostimulant in HIV/AIDS patients and have significant potential to enhance immunity.22

5.2.5 *Sutherlandia frutescens*

The flowering shrub of *Sutherlandia frutescens*, also called insiswa, belongs to family Fabaceae. L-canavanine is one of the chemical constituent of *S. frutescens* which has antiviral activity. 95% of HIV-infected lymphocytes were selectively destroyed in vitro. It has been reported that a daily dose of 9 mg/kg/d is effective to stimulate the immune system in infective persons but further investigations are needed to explore the mechanism of actions of phytochemicals present this medicinal plant.23

5.2.6 *Pelargonium sidoides*

Pelargonium sidoides (PS) is a herb which belongs to family Geraniaceae. Its common name is African geranium. The extract of this plant inactivates the virus. *Pelargonium sidoides* root extract has bioactive compounds which attack virus particles, inhibiting the viral replication. Extract of *P. sidoides* protects blood and immune cells from infection by HIV-1. The antiviral effect of *P. sidoides* extract is mediated by polyphenols, and the polyphenol mixture obtained from the extract of *P. sidoides* attacks HIV-1 and their action is different from all anti-HIV-1 drugs which were clinically used.24 In Germany, the root extract of PS has been licensed after various clinical trials and reported a safe drug for human use. Helfer et al,24 found that extract of PS has significant anti-HIV potential evidenced from numerous cell culture-based experiments and reported that HIV entry into peripheral blood mononuclear cells and macrophages could be prevented by using PS extract and described a novel mode of action of the phytochemical constituents from PS extracts. EAST-HIT testing performed on root extract of *P. sidoides* confirmed its Anti-HIV-1 activity. The extract of this plant at 8.13 μg/mL concentration inhibited the step 1 of viral replication while at 8.00 μg/mL concentration inhibited the step 2 of viral replication. The study concluded that the plant extracts showed the response at early steps of HIV-1 replication. The extract of this plant targets initial and final binding of HIV to stop its activity and also prevent the attachment of virus particle to the host, hence prevent the entry of HIV. Multiple polyphenolic compounds show anti-HIV activity after the chemical analysis, which could be separated from the extract by adsorption to polyvinylpyrrolidone to reduce the toxicity of drugs. *P. sidoides* extract could serve as one of herbal medicine which has greater efficacy against HIV infection.24

5.2.7 *Artemisia annua* L

Artemisia annua L. is an annual herb found native to China and belongs to the plant family Asteraceae. The tea infusion prepared from this plant has been identified as having anti-HIV activity with IC50 values as low as 2.0 μg/mL. Additionally, artemisinin was found as inactive at 25 μg/mL has also shown similar activities.18, 25

5.2.8 *Calendula officinalis* L

Calendula species are medicinal herbs that belong to Asteraceae plant family. Among calendula species, *Calendula officinalis* flowers are used in ointments for the treatment of skin damage, ulcers, herpes, wounds and frostbite. The extract of *C. officinalis* flowers prepared in dichloromethane-methanol (1:1) exhibited potential anti-HIV activity in in vitro tetrazolium-based assay. Anti-HIV activity of this plant was attributed to inhibit HIV1-RT at extract concentration of 1000 μg/mL as well as suppressing the HIV mediated fusion at 500 μg/mL concentration.26 The ability of both organic and aqueous extracts of *C. officinalis* flowers to inhibit HIV-1 replication were examined and it was found that the organic extract exhibited anti-HIV activity in an in vitro MTT tetrazolium-based assay. It was also found that the *C. officinalis* flowers organic extract caused a significant reduction of HIV-1 reverse transcription activity in a dose and time-dependent manner. The study results suggested that the organic extract of *C. officinalis* flowers possess anti-HIV properties which are of therapeutic interest.18, 27

5.2.9 *Cassia abbreviata*

Cassia abbreviata is a deciduous shrub and belongs to the Fabaceae plant family. It has been used by the traditional healers for the management of HIV/AIDS. HIV replication inhibition activity of this plant was tested against a clone of HIV-1c by measuring the levels of viral p24 antigen in infected PBMCs and the cytopathic effect protection. Significant inhibition of HIV-1c replication was shown by *C. abbreviata* extracts. Anti-HIV activity of root extract of this plant occurred with an effective concentration (EC 50) of 102.8 μg/mL.28

5.2.10 *Combretum molle*

Combretum molle belongs to Combretaceae plant family. It is widely used in traditional medicinal system of Ethopia in treating liver diseases, tuberculosis and malaria. Various extracts were prepared from the stem bark of *C. molle* using different solvents including methanol, acetone, chloroform and petroleum ether through Soxhlet apparatus for the assessment of in vitro anti-HIV activity against HIV-1 and HIV-2. Selective inhibition of viral growth was evaluated by simultaneously determining the in vitro cytotoxicity of prepared extracts against MT-4 cells. Highest selective inhibition of HIV-1 replication was shown by acetone fraction.29

5.2.11 *Garcinia edulis* Exell

Garcinia edulis belongs to the plant family Clusiaceae. The bioactive compound isoprenylated xanthone derivative isolated from the root bark of *G. edulis* in ethanolic solvent. In vitro anti-HIV-1 protease activity of ethanolic extract of this plant was exhibited at an IC50 value of 11.3 μg/mL while using acetyl pepstatin as positive control which possess anti-HIV-1 PR activity at an IC50 value of 2.2 μg/mL.18, 30

5.2.12 *Hyssopus officinalis* L

Hyssopus officinalis belongs to Lamiaceae family. It has been used as herbal medicine and the extracts of this plant showed strong anti-HIV-1 activity due to the presence of polysaccharides. HIV replication inhibition activity of hydroalcoholic extract of *H. officinalis* was determined using HIV infection of MT-2 cells as a rapid and sensitive test system for the detection of potent antiviral drugs particularly those effective against AIDS. The extract of this plant at concentrations ranging from 50 to 100 μg/mL has shown HIV-1 induced infection inhibition effects in MT-2 cells.31

5.2.13 *Hypericum perforatum* L

Also known as St. John's Wort, *Hypericum perforatum* belongs to the plant family Hypericaceae. It has been used for medicinal purposes in traditional medicinal system particularly for wound healing and also for the treatment of AIDS. The antiretroviral activity of phytoconstituents like hypericin and pseudohypericin isolated from *H. perforatum* in HIV-infected patients have been observed during a clinical trial.32, 33

5.2.14 *Pachymahoelen* Rumph

This plant belongs to the Polyporaceae family. The hexane extract of this plant used in Korean folk medicine has shown anti-HIV-1 activity. The plant extract also showed the protective effect on infected MT-4 cells and the highest protection was observed at 58.2%. The 50% cytotoxic concentration (CC_{50}) of *Pachymahoelen* hexane extract was found 100.6 μg/mL.34

5.2.15 *Terminalia paniculata*

Terminalia paniculata belongs to Combretaceae plant family. The in vitro anti-HIV-1 activity of *T. paniculata* fruits extract prepared in methanol and acetone solvent was tested and the EC50 values of this plant extracts in acetone and methanol were ≤10.3 μg/mL. The mechanism of action was determined through enzymatic assays which indicated the anti-HIV-1 activity due to the inhibition of protease (≥69.9% inhibition) and reverse transcriptase (≥77.7% inhibition) enzymes.18, 35

5.2.16 *Smilax corbularia* Kunth

Smilax corbularia belongs to the plant family Smilaceae. The inhibitory effects of ethanolic and aqueous extracts of *S. corbularia* against HIV-1 protease (HIV-PR) and HIV-1 integrase (HIV-1 IN) was tested and found that *S. corbularia* ethanolic extract exhibited anti-HIV-1 IN activity with an IC_{50} value of 1.0 μg/mL and the suramin was used as positive control having IC_{50} of 3.4 μg/mL. The IC_{50} value determined for the water extract of this plant was 5.4 μg/mL. The study finding showed a two-fold lower IC_{50} value of ethanolic extract of *S. corbularia*.36

5.2.17 *Tuberaria lignose* Sampaio

Tuberaria lignosa belongs to the Asteraceae plant family. This plant was widely used in traditional medicine for the treatment of viral diseases. The anti-HIV activity of ethanolic and aqueous extracts of this plant by inhibiting the HIV replication. The study results showed that the tested *T. ligosa* aqueous extract was relatively nontoxic to human lymphocytic MT-2 cells without showing anti-HIV activity between 12.5 and 50 μg/mL concentrations range. The toxicity of ethanolic extract of this plant prevented the evaluation of their potent antiviral activity at increased concentrations.18, 37

5.2.18 *Astragalus membranaceus* Bunge

Astragalus membranaceus belongs to the Fabaceae plant family. It is a well known medicinal plant used in traditional Chinese medicine as an immunostimulant. Studies using *Astragalus* extracts demonstrated the augmentation or restoration of local graft versus host rejection in immunocompetent and immunosuppressed patients. The study results suggested the *Astragalus* extract as safe but nothing has been revealed about its mutagenicity. This remains to be investigated.38

5.2.19 *Dittrichia viscosa* (L.) Greuter

This plant belongs to Asteraceae family. The ability of *D. viscosa* aqueous extract to inhibit the HIV replication was tested using HIV infection of MT-2 cells for the detection of drug's antiviral effect against AIDS. The HIV-1 inhibitory effect of *D. viscosa* aqueous extract at concentrations ranging from 25 to 400 μg/mL has been observed in MT-2 cells induced with HIV-1 infection.39

5.2.20 *Momordica balsamina*

Momordica balsamina belongs to Cucurbitacae plant family. It is commonly used as antiviral agent due to its antiviral efficacy in poultry mainly in the northern part of Nigeria. The fruit pulp extract of this plant has been tested for its anti-HIV properties by in vitro studies and found to be potent anti-HIV-1 replication inhibitor. Further research on this plant fruit extract is required to study its therapeutic potential against retroviral infections in humans.40

6 CONCLUSION

Since the discovery of the causative agent of AIDS in the 1980s, researchers have been trying to develop drugs for the management of this devastating and deadly disease (Table 1). Although introduction of ARTs in the 1990s revolutionized the drug development for the cure of AIDS, safety concerns especially have motivated the search for new drugs which not only inhibit the virus replication but also restore the destroyed immune system, specifically CD4+ T-lymphocytes. This review article potentially suggests that herbal plants could be the hope for the drugs development with significant anti-HIV activities. Moreover, literature reviewed also explored that medicinal plants not only overcome the symptoms but also provide various constituents to treat HIV-infected patients. Further, medicinal plants are key sources of anti-HIV agents, immunomodulators, immunostimulants, antioxidant compounds as well as nutraceuticals which prevent the replication of viral particles as well as boost the immune system of infected one's. Therefore, the present literature review provides an evidence-based contribution to the understanding of medicinal plants for the novel drugs development in the management of HIV/AIDS. Moreover, further research is required to isolate the anti-HIV active agents, to find out the mechanism of actions of these compounds as well as to run clinical trial to explore the cytotoxicity of phytochemical constituents responsible for their beneficial effects. In future, medicinal plants should be continuously evaluated for their anti-HIV activity.

Table 1. Medicinal plants, their phytoconstituents and mechanism of action against HIV

Family & species	Active constituents	Mechanism of action	Reference
Amaryllidaceae *Glanthus nivalis*	Phytolectins, Glanthus nivalis agglutinin	It inhibits the HIV infection among lymphocytes and prevents this infection to target the gp120 envelope	39, 41
Anacardeaceae *Rhus succedanea*	Robustaflavone, hinokiflavone and bioflavonoids	It inhibits the polymerase of HIV-1 reverse transcriptase	42
Ancistrocladaceae *Ancistrocladus korupensis*	Michellamines a and b	It has both anti-HIV-1 and HIV-2 activity because it acts early and later stages and inhibit HIV infection	43
Apocyanaceae *Rauwolfia serpentine*	Papaverine	It inhibits HIV reverse transcriptase and HIV cell growth	44, 45
Boraginaceae *Arnebia euchroma* Jonst	Monopotassium and monosodium salt of isomeric caffeic acid	It has an anti-HIV replication activity	46
Cannabaceae	Xanthohumol	It has anti-HIV activity and induced the	47

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Citing Literature

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