International Journal of PharmaO2
Journal Home Page: http://www.ijpo.in/
(IJPO: A Peer-reviewed Bi-monthly online journal)

Review Article

A Review: Medicinal Plant Used in Treatment of the Human Immunodeficiency Virus

Mr. Bhaiyasaheb Shankar Wadate* **and Mr. Kiran A. Suryavanshi**

SMBT Institute of D. Pharmacy, Dhamangaon, Tal Igatpuri, Dist Nashik-422403, MS (India).

ARTICLE INFO

Article history:
Received: 28/01/2021;
Revised: 25/03/2021
Accepted: 07/04/2021;
Available online: 01/05/2021.

Key Words:
HIV, anti-retroviral, Natural product, Chemotherapy.

Please cite this article as: Wadate, B.S., *et al.* (2021). A Review: Medicinal Plant Used in Treatment of the Human Immunodeficiency Virus. 3(3), 0114-0120.

ABSTRACT

After the beginning of the epidemic, human immunodeficiency virus (HIV) has infected around 70 million people in world, most of who reside is sub-Saharan Africa. There have been very promising developments in the treatment of HIV with anti-retroviral drug cocktails. However, drug resistance to anti-HIV drugs is emerging, and many people infected with HIV have adverse reactions or do not have ready access to currently available HIV chemotherapies. Thus, there is a need to discover new anti-HIV agents to supplement our current arsenal of anti-HIV drugs and to provide therapeutic options for populations with limited resources or access to currently efficacious chemotherapies. Plant-derived natural products continue to serve as a reservoir for the discovery of new medicines, including anti-HIV agents. This review presents a survey of plants that have shown anti-HIV activity, both in vitro and in vivo.

*Corresponding author: Mr. Bhaiyyasaheb Shankar Wadate, S.Y. D. Pharmacy, SMBT Institute of D. Pharmacy, Dhamangaon, Nashik, Contact:+91 9923404306; e-mail: Wbs9923@gmail.com

Introduction

AIDS is as the development of very serious opportunistic infections or causes the ones that usually develop only in people with a CD4 count of less than 200 cells per microliter of blood. Know a day in world of science most of the HIV - infected patients are trying to get in treatment like ART Antiretroviral Therapy, bone marrow transplantation , but you take a herbal treatment , The periods of recovery is small and side effect is also less as compared to a ART ,That's why HIV-infected patients are seen to be recovering **.** The World Health Organisation estimates 73 million people globally have been infected with the human immunodeficiency virus (HIV), of which approximately 35 million are still alive and living with the infection. It is currently estimated that 26 million of these patients reside in Africa; 3.3 million in the Americas; 3.5 million in Southeast Asia; 2.4 million in Europe . Data from 2016 indicates that there were approximately two million new cases of HIV infections, and as many as one million deaths due to the disease. Importantly, these annual numbers are much reduced, as the numbers of newly infected patients has declined by 35% since

2000, and the mortality rate has also declined by almost 50%. The decline in HIV infections is thought to be due to increased use of condoms, a reduction in the prevalence of sexually transmitted infection, and the increased use of effective therapies, such as the three-drug therapy anti-retroviral therapy (ART). (Deeks S.G. et al., 2015).

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 (Kanta V., Unnatis, 2011). 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 cell 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. 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. 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 (Miceli MC, Parnes JR, 1993).

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.

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 viru-like particle. The formation of non-infectious particles does not require pol-encoded enzyme, viral genomic RNA and enveloped glycoproteins. Retroviral Gag proteins are responsible for targeting the nascent particles which are exported from the cell forming the framework of structural virion (Garzino-Demo A, 2007).

Transmission

The transmission of HIV requires contact with a body fluid that contains the virus or cells infected with the virus. HIV can appear in nearly any body fluid, but transmission occurs mainly through blood, semen, vaginal fluids, and breast milk. HIV is not transmitted by casual contact (such as touching, holding, or dry kissing) or by close, nonsexual contact at work, school, or home (Gouws E, et al., 2006).

Symptoms

Lungs: Fever, cough, or shortness of breath
Brain: Headache, weakness, loss of coordination, or deterioration of mental function
Digestive tract: Pain, diarrhea, or bleeding
Kidneys: Kidney failure with swelling in the legs and face, fatigue, and changes in urination (more common in blacks than in whites), but often not until the infection is severe
Heart: Heart failure with shortness of breath, cough, wheezing, and fatigue (uncommon)

Pathophysiology

The HIV virus is a retrovirus that is able to integrate a DNA copy of the viral genome into the DNA of the host cells. The virus enters the cell through receptors that are expressed on the surface of T lymphocytes (activated T lymphocytes are preferred targets), monocytes, macrophages and dendritic cells (Deeks S.G. , Overbaughj, Phillips A, Buchbinder S, 2015). To gain entry to the host cell, HIV-1 binds to the chemokine receptor 5 or the CXC chemokine receptor 4 through interactions with the envelope proteins. After fusion and uncoating, single stranded RNA is reverse transcribed into HIV DNA, and then integrated into the host DNA. HIV DNA is transcribed to viral mRNA and exported to the cytoplasm where it is translated to viral Gag, Gag-Pol, and Nef polyproteins, which are then cleaved later during virion assembly and maturation at the cell surface or after relase of the new viral particles. Current therapies inhibit many of the steps in this process, such as entry inhibitors, reverse transcriptase inhibitors, integrase strand transfer inhibitors and protease inhibitors (Moir S., et al., 2011).

Diagnosis

Detection of the HIV virus in the blood is usually measured as viral RNA load and infection is associated with an acute symptomatic period that includes fever, general malaise, lymphadenopathy, rash, myalgias, however serious consequences such as meningitis have also been reported (Moir S, et al., 2011). During the period of acute infection, the plasma levels of HIV RNA are at their highest and the severity of symptoms is associated with the level of viral load. It has been suggested that viral characteristics and viral load determine both the replication and pathogenesis. Thus, the clinical outcomes and disease progression are dependent not only on the host, but also on the viral genotype . HIV is difficult to completely eradicate as it establishes a quiescent or latent infection within the memory CD4+ T cells, which have a stem-cell-like capacity for self-renewal. Once the HIV DNA is integrated into the host chromatin, the virus can repeatedly initiate replication as long as that cell exists. While ART can prevent new cells from becoming infected, it cannot eliminate infection once the DNA has successfully integrated into the target cell. The lymph nodes harbor the virus because of limited antiretroviral drug penetration, and limited host clearance mechanisms, and serves as a source of virus recrudescence in individuals who stop or interrupt their therapy. It has been suggested that ART therapy may be needed for several decades before the viral reservoir might decay to negligible levels (Harden V.A., et al., 2012).

Plant Extracts and Some Secondary Metabolites with Anti-HIV Activity

1. ***Vernonia amygdalina***

It is shurb used as traditional herbal medicines for the treatment of HIV ,It is a belong to family asteraceae and its commonly name of the plant is better leaf due to the better taste , The studies reported that vernonia amygdalina has the antioxidant activity in the HIV positive patients , when compared with the commercially available tablet immune . The Aquarius extract of fresh leaves of vernonia amygdalina where used along with ARTs to evaluate effect of Herbs on cd4 count cell for a period of 4 months , The result shows that cd4 cell count was increase in the patient who use the leaf extract or supplement . Leave of vernonia amygdalina have an immunological effect on hiv-infected patients and are used in HIV management , It has a nutritional and health improving property and is moreover this patient also recovered skin rashes and it is also act on nutritional supplement (Momoh M., et al., 2012).

2. *Hypoxis hemerocallidea*

It is important plant species in traditional medicine in South Africa is commonly known as African potato ,yellow star flower And its belong to family hypoxisdaceae , The African potato is commonly used as immune booster , Active ingredient of the plant which have anti HIV activity include phytosterol , hypoxides , aglycone, rooperol , perpinene , linoleic acid and bourbonene ,The African Primary Health Care community is used the root of hypoxis hemerocallidea as an immune stimulant in HIV patients and have significant potential to increase immunity. (Oguhtibeju, O., et al.,2016).

3. *Calendula officinalis*

In India, the flowers of *Calendula officinalis* are used in ointments for treating wounds, herpes, ulcers, frostbite, skin damage, scars and blood purification. The infusions prepared from the leaves have been used for treating varicose veins in traditional use. Dichloromethane-methanol (1:1) extract of *Calendula officinalis* flowers exhibited potent anti-HIV activity in in vitro (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide)(MTT)/tetrazolium-based assay. This activity was attributed to inhibition of HIV1-RT at a concentration of 1000 μg/mL as well as suppression of the HIV mediated fusion at 500 μg/mL. (Kalvatchev Z, et al., 1997) The organic and aqueous extracts of dried flowers from *Calendula officinalis* were examined for their ability to inhibit the human immunodeficiency virus type 1 (HIV-l) replication. Both extracts were relatively nontoxic to human lymphocytic Molt-4 cells, but only the organic one exhibited potent anti-HIV activity in an in vitro MTT ketrazolium-based assay. In addition, in the presence of the organic extract (500 pg/mL), the uninfected Molt-4 cells were completely protected for up to 24 h from fusion and subsequent death, caused by cocultivation with persistently infected U-937/HIV-1 cells. It was also found that the organic extract from *Calendula officinalis* flowers caused a significant dose- and time-dependent reduction of HIV-l reverse transcription (RT) activity. An 85% RT inhibition was achieved after a 30 min treatment of partially purified enzyme in a cell-free system. These results suggested that organic extract of flowers from *Calendula oflicinalis* are possessed anti-HIV properties of therapeutic interest. (Kashman Y., et al., 1992)

4. *Combretum molle* (R. Br. ex. G. Don.) Engl & Diels (Combretaceae)

In vitro anti-HIV activity of various extracts prepared from the stem bark of Combretum molle widely used in Ethiopian traditional medicine for the treatment of liver diseases, malaria and tuberculosis has been assessed against human imnmuunodeficiencvy virus type 1 (HIV-1) and type 2 (HIV-2). The extracts were prepared by percolation with petroleum ether, chloroform, acetone and the methanol extract was obtained by successive hot extraction using Soxhlet apparatus. Selective inhibition of viral growth was assessed by the simultaneous determination of the in vitro cytotoxicity of each of the extracts against MT-4 cells (375). The results obtained in this study indicate that the acetone fraction possessed the highest selective inhibition of HIV-1 replication. Phytochemical investigation of the acetone fraction has resulted in the isolation of two tannins and two oleanane-type pentacyclic triterpene glycosides. One of the tannins was identified as punicalagin (an ellagitannin), while the structure of the other (CM-A) has not yet been fully elucidated. On the other hand, both punicalagin and CM-A had displayed selective inhibition of HIV-1 replication with selectivity indices (ratio of 50% cytotoxic concentration to 50% effective antiviral concentration) of 16 and 25, respectively and afforded cell protection of viral induced cytopathic effect of 100% when compared with control samples. (Rashed K., et al., 2012)

5. *Tuberaria lignosa* (Sweet) Sampaio (Asteraceae)

Tuberaria lignosa was widely used in the folk medicine to treat diseases of viral origin of the Iberian Peninsula and the ethanolic and aqueous extracts were evaluated for its anti-HIV activity by inhibiting HIV replication. The toxicity of the extracts to MT-2 cells was also investigated. The ethanolic extract was especially toxic, which prevented the evaluation of their potential antiviral effects at higher concentrations. However, the aqueous extract of *T. lignosa* tested was relatively nontoxic to human lymphocytic MT-2 cells, but did show anti-HIV activity at

concentrations ranging from 12.5 to 50 μg/mL. In conclusion, terrestrial plants produce secondary metabolites for their chemical defense, which possess unique chemical structures and have played pivotal roles in human health. There is continuous need to introduce new drug candidates to treat diseases and the drug discovery process can be realized using both ancient and modern research methodologies in a complementary manner. Some medicinal plants are still unexplored; therefore there are numerous avenues of research for the determination of their biological activities. In this review, the anti-HIV activity of some plant extracts and their potential utilization for anti-HIV agents have been summarized. Among them *Calendula officinalis, Justicia gendarussa* and *Sceletium tortuosum* might be useful potential sources for new lead compounds in the development of new candidates with anti-HIV properties of therapeutic interest. These studies are considered to be one of the most important approaches toward effective therapy for AIDS (Bedoyol, A. M,, et al., 2001).

Case study

In which you will see how quickly the disease is cured by herbal treatment , This patients belong to Pune city , She is HIV positive patient her husband was also HIV positive patients ,both were taking their ART treatment but it didn't work for them . He was complaining of weakness and laziness , He was mentally disturbed and depressed After starting herbal medicine all complications and all the side effect of ARTs decrease and the patients immunity also increase from 319 to 1302 within one and half month. Today's patients living healthy and happy life

Date:- 25 July 2018 his CD4 count is 319 cell/MM3

07 September 2018 his CD4 count is increased 1302 cell /MM3

Conclusion

Focusing on phytochemicals that have reached clinical trials, if there are any; highlighting medicinal plants where high level of scientific evidence has been reached; future perspectives. Although there have been major accomplishments in HIV chemotherapy, there remains a need for new anti-HIV drug discovery, and medicinal plants can play an important role in this endeavor. Several plant species have shown remarkable anti-HIV activity, especially *Artemisia annua*, *Garcinia edulis*, *Justicia gendarussa*, *Phyllanthus pulcher*, *Rhus chinensis*, *Smilax corbularia*, *Terminalia paniculata*, and *Tuberaria lignosa*. These plant species are worthy of further study for the development of new anti-HIV chemotherapeutic options. In particular, in vivo testing and, ultimately, human clinical trials need to be carried out on key lead plants and phytochemical isolates. In addition, continuous evaluation of medicinal plants for anti-HIV activity should be pursued.

Acknowledgments

Authors are very thankful to management of SMBT Institute of Diploma Pharmacy, Dhamangaon Nashik for their valuable Support.

Conflict of interest

The authors declare no conflict of interest

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