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Evaluation of phytochemicals from Indian traditional medicinal plants as anti-HIV-1 Drugs

Abstract

According to a global estimate, the growing infection by Human Immunodeficiency Virus type 1 (HIV-1) causing development of a dreaded disease i.e., Acquired Immuno-Deficiency Syndrome (AIDS) has been a major health risk resulting into loss of lives of about 25 million people in the last 25 years. The information available on basic biological processes in the HIV life-cycle suggest that it destroys a subpopulation of T-lymphocytes containing CD4 receptor and CXCR4 or CCR5 as a coreceptor on their surface. These molecules on cell surface are required by the virus for docking and internalization. Since the availability of a suitable vaccine against this virus is currently far from reach and the presently available synthetic anti-HIV therapeutics exhibit severe toxicity and induce emergence of drug resistant mutations, it was imperative to explore plant-based principles targeting specific steps in the viral life-cycle. Moreover, the advancement in separation, purification and chemical characterization technologies for identification of natural compounds has offered promises for the usage of medicinal plants in modern drug discovery. With a few newly discovered natural products demonstrating anti-HIV potential in comparison to a vast number of previously known natural products exhibiting activity against HIV, a multiplex approach is required for exploring cost effective, safe, and efficient plant based anti-HIV drugs with very small LD_{50} value exhibiting efficacy at nanomolar / picomolar range. This article illustrates an updated account of information on the anti-HIV-1 efficacy of some bioactive molecules isolated from different medicinal plants. Furthermore, the article highlights some chemical compounds isolated from weeds showing activity against functions of viral reverse transcriptase (HIV-1RT), protease and integrase enzymes.

Keywords: phytochemicals, human immunodeficiency type 1 reverse transcriptase (HIV-1RT), highly active antiretroviral therapy (HAART), CD4+ve lymphocyte, toxicity, anti-HIV-1 drugs resistance, chemotherapeutics

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Abbreviations: HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; ART, anti-retroviral therapies; EGCG, epigallocatechin-3-gallate; LCC, lignin-carbohydrate complex; TXE, trigonostema xyphophylloides; VAD, vatica astrotricha

Introduction

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS). CD4+ T lymphocytes are the natural target of HIV-1 infection.[1] The information available on basic biological processes in the HIV life-cycle suggest that the virus binds to a subpopulation of CD4 receptor of T lymphocytes and chemokine receptors CXCR4 or CCR5 as a coreceptor present on host's surface. These molecules on host's cell surface are required by the virus for docking and internalization. The cDNA synthesized by HIV-1RT using viral genetic material i.e. mRNA enters the nucleus and is covalently integrated into the genome of the host cell by the virally encoded enzyme, integrase (IN).[2–4]

The complete HIV-1 life cycle stages (docking, internalization, uncoating, reverse transcription, synthesis of a proviral cDNA, integration of cDNA, replication, transcription, synthesis of a viral polyprotein chain, processing of this chain by viral protease into virus specific fragments, assembly of viral particles, release of viral particles and maturation) are now well established and serve as targets for development of an efficient drug to arrest virus proliferation.

The goal of HIV-1 treatment is to reduce the number of virions in the body of infected individuals and to prevent rapid destruction of CD4+ T-lymphocyte cells, thus protecting the immune system. The current strategy for the treatment of HIV infection is called as Highly Active Antiretroviral Therapy (HAART), which involves the use of a combination of inhibitors of reverse transcriptase and protease. The HAART has caused significant reduction in the mortality rate of HIV-1 infected individuals.[5] Current anti-retroviral therapies (ART) available for symptomatic treatment of AIDS are expensive and unaffordable by a common person and are associated with rapid emergence of drug resistance.

Medicinal plants play an important role in supporting healthcare system throughout the world. According to the World Health Organization (WHO), 80% of the rural population in developing countries mainly utilizes locally available medicinal plants for their primary healthcare needs.[6] In support, the recent reports suggest that application of plant-based principles may prove to be highly useful, affordable, and efficient to arrest the HIV-1 progression. The medicinal plants may be accelerative in transition from development to usage with easily manageable toxicological issues as these plant-ingredients are suitably metabolized and excreted out of body without much accumulation in human organs.

An important highlight is that a number of promising anti-HIV natural products have paved the way to clinical trial and are anticipated to be available for the patients use in near future.[7] This article presents a brief account of certain biomolecules extracted from some Indian Medicinal plants active against different enzymes of HIV-1 and indicates the need of an extensive research to be conducted to explore the potentially active, cost effective and safe plant based anti-HIV-1 agents.

Bioactive molecules from the herbs and plants as Anti-HIV agents: Certain plant extracts such as green tea containing ((-)-Epigallocatechin-3-gallate (EGCG)), Brazil nut and *Cao cao* contain immune potentiators which help maintain the immunity. The cacao mass lignin-carbohydrate complex (LCC) has been found to possess Anti-HIV and immunomodulation properties. Cacao mass LCC and LPS may synergistically stimulate iNOS protein expression, suggesting a different point of action. Further, the skin and seed of grapes, berries, peanuts and red wine containing resveratrol, a polyphenolic plant-derived antioxidant, indicated that this molecule protected the AZT induced concentration-dependent cell death.[8]

Pinus yunnanensis can inhibit the fusion between normal cells and HIV-1 infected cells, and the activity of recombinant HIV-1 reverse transcriptase. The extract of pine cone from *Pinus yunnanensis* have been shown to possess some key molecules which may exert strong anti-HIV-1 activity either in isolation or in combination mode.[9]

Curcumin contains diferuloyl methane, which has significant inhibitory effect on the viral enzymes by direct binding to their active sites. It interacts with the catalytic core of the integrase (IN) enzyme and thus inhibits the function of HIV-1 IN.[10] Barthelemy et al[11] reported that curcumin from *C. longa* inhibited HIV-1 integrase and Tat mediated transactivation of HIV-1 long terminal repeat.

Phyllanthus amarus possess antiviral and anticancer properties.[12] Further, screening of antiviral activity of *Phyllanthus amarus* along with other species of Phyllanthus genus have evaluated against Herpes Simplex Virus type-1 and Herpes Simplex Virus type-2 in Vero cells by quantitative polymerase chain reaction (RT-PCR). The extracts from the stem of Euphorbiaceae, *Trigonostema xyphophylloides* (TXE) and the stem of Dipterocarpaceae, *Vatica astrotricha* (VAD) inhibited HIV-1.

Allium sativum contains flavonoids, peptides, phenols, terpenoids and steroids. These alkaloids are responsible for various biological activities, replication without evident effects on cell proliferation and cell survival.[13] *A. sativum* was found to be effective against HIV infection by inhibiting virus replication.[14]

Withania somnifera, a good source of sugar compounds, hydrocarbons, ether compounds, nitrogen compounds, fatty acids, fatty acid esters, alcohols, and alkaloids. The bioactive constituents of plants have been shown to contain antimicrobial and anti-HIV-1 activity.[15] Some workers have revealed by MTT assay that the use of *W. somnifera* may cause significant increase ($p < 0.001$) in the normal lymphocyte proliferation at all concentration's tested i.e. 25 mg/ml with SI (6.06) and at 50 mg/ml with SI (5.8). Using PCR, they have shown a marked viral load reduction after treatment by ASH-WX at concentration 25 mg/ml to 6.241×10^3 IU/mL. These workers have revealed by Molecular docking analysis a good prediction of binding between Ashwagandha and NS5B, thereby significantly decreasing the rate of HIV proliferation significantly.

Punica granatum (pomegranate) juice has been reported to act as an inhibitor of HIV-1 entry. In 2005, Neurath and coworkers screened various fruit juices for their inhibitory activity against HIV-1 IIIB using CD4 and CXCR4/CCR5 as cell receptors. They observed that the pomegranate juice contained the chemical constituents with abilities to inhibit HIV-1 progression via blocking its docking and entry into the CD4+ve lymphocytes. The inhibitory potential of the pomegranate juice was also observed towards infection by primary virus clades A to G and group O.[16]

Ocimum sanctum L. (also known as *Ocimum tenuiflorum*) is an aromatic plant species belonging to family Lamiaceae. Ethanolic leaf extract of *O. sanctum* showed significant inhibition of recombinant HIV 1 reverse transcriptase (HIV1-RT) activity.[17] The extracts of Ocimum kilimandscharicum prepared in methanol and water inhibited HIV-1RT at an MIC range from 25-100µg/ml. The methanol and aqueous extract of Rubia cordifolia, methanol extract and aqueous extracts of *Ocimum kilimandscharicum* and *Plectranthus amboinicus* were immunostimulatory and non-cytotoxic at these levels.[18–21]

Phyllanthus emblica have immunomodulatory and HIV1-RT inhibitor activity. Mekkawy et al[18] have reported that Putranjivain, an active compound from its phenolic compound, was exhibiting ability to inhibit the activity of HIV1-RT.[19] Their studies seem to justify the traditional use of medicinal plants for the treatment of infectious disease of viral origin. However, in order to assess the usefulness of this herb, it is necessary to isolate the active principle(s) from the crude and fractions, identify them and study their mechanism of action. The *Aegle marmelos* fruits have been found to contain alkaloids and marmelene which are active against HIV-1. They may act as anti-inflammatory and antioxidant agents.[19]

Tinospora cordifolia leaves phenolic compounds which have been found to act against HIV-1 progression by creating interference in docking between the gp120 and CD4 receptor. These molecules have also been observed to inhibit the activity of HIV-1RT.[19] *Momordica charantia* fruits protein, MAP30, was found to be active against the activities of HIV-1 integrase and HIV-1 RT.[19] *Papaver somniferum* leaves contain alkaloids, morphine, codeine, and papaverine which have been found to modulate the structure and function of HIV-1 gp120.[19] *Psidium guajava* leaves contain alkaloids, β-sitosterol, uvaol, oleanolic acid, Procyanidine B2, and ursolic acid. These molecules exhibit the potential to inhibit the activity of HIV-1RT.[19]

Stephania cepharantha leaves and fruits contain alkaloids, palmatine and isocorydione which have been reported to inhibit the progression of HIV-1 and HSV-1. These molecules possess immunomodulatory and antioxidant functions.[19] *Eugenia jambolona* bark contain phenolic oleanolic acid, ursolic acid and β-sitosterol which show significant activities against activity of HIV-1 protease.[19] *Parthenium hysterophorus* leaves were found to possess anti-HIV-1RT properties in its aqueous extract.[20–24] Though the current information on P. hysterophorus indicates the ethnopharmacological implications of extracts of this plant, more systematic and extensive studies are still required to properly understand the contribution of its specific chemical constituents responsible for their various medicinal properties.[25] A list of herbal plants with their biological activities has been shown in Table 1.

Table 1 Some Indian medicinal plants known for their anti-HIV potential

Plants	Parts of the plant used	Class of compounds	Virus	Biological Activity and mechanism of action	References
Withania somnifera	Root, Leaves	Alkaloids, Lactones	HIV-1	Cell Mediated Immunity, Antioxidant	15
Cao cao	Leaves	((-)-Epigallocatechin-3-gallate (EGCG))	HIV-1	Immunopotentiator and	19,20
Allium sativum	Leaves or fresh dried	Flavonoids, peptides, phenols, terpenoids and steroids	HIV-1	inhibiting virus replication	14

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Table Continued...

Plants	Parts of the plant used	Class of compounds	Virus	Biological Activity and mechanism of action	References
Pinus yunnanensis	Leaves	Alkaloids, Flavonoids, Terpenoids	HIV-1	Inhibit the fusion between normal cells and HIV-1 infected cells, and the activity of recombinant HIV-1RT.	8
Aegle marmelos	Fruit	Alkaloids, Marmelene	HIV-1	Anti-inflammatory, Antioxidant	19, 21
Ocimum sanctum	Leaves	Resins, Alkaloids, Tannins	HIV-1	Immunomodulation	17
Tinospora cordifolia	Leaves	Phenolic	HIV-1	Immunomodulation (Interference with the gp120 / CD4 interaction, inhibition of HIV-reverse transcriptase	19,22
Curcuma longa	Roots	Phenolic diferuloyl methane molecule	HIV-1	Inhibitory effect on HIV1 Integrase and Protease	10, 11
Momordica charantia	Fruits	Protein, MAP30	HIV-1	Inhibition of HIV-1 integrase, HIV-1 RT	19, 22
Papaver somniferum	Leaves	Alkaloids, Morphine, codeine, Papaverine	HIV-1	Interfere with HIV-1glyco protein120	19
Psidium guajava	Leaves	Alkaloids β-sitosterol, uvaol, oleanolic acid, Procyanidine B2 and ursolic acid	HIV-1	Inhibit HIV RT	19, 22
Stephania cepharantha	Leaves, Fruit	Alkaloids palmatine, isocorydione	HIV-1 HSV-1	Immunomodulation, antioxidant	19
Eugenia jambolona	Bark	Phenolic oleanolic acid, ursolic acid, β-sitosterol	HIV-1	Inhibition of HIV protease	19
Phyllanthus emblica	Leaves	Putranjivain,	HIV-1	Immunomodulatory and HIV1-RT inhibitor activity	18, 20
Parthenium hysterophorus	Leaves	Polyphenols, flavonoids, alkaloids, terpenes, flavones, parthenin	HIV-1	AntiHIV-1RT activity, antioxidant and antimicrobial properties	23-25

Conclusion

The chemical ingredients from many medicinal plants are known to maintain the vitality of individuals and cure various diseases. The effective approach needs to be continued for the discovery of potential anti-HIV drugs isolated from natural sources, which could arrest the activities of virus enzymes such as RT, integrase, and protease. It is expected that the phytochemicals with slight modification may enhance the activity of parent compounds and inhibit the activities of virus enzymes relatively more effectively. The bioactive molecules isolated from different Indian medicinal plants may be able to serve as effective immunopotentiators and serve as an excellent source of novel drug candidates with anti-HIV properties. However, an extensive investigation is required to assess their bioactivity, pharmaco-therapeutic properties and doses, toxicity and margin of safety, standardization, clinical trial, and mechanism of action. The application of plant based anti-HIV drugs could prove to be cost effective, efficient, and safe to the AIDS patients.

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Conflicts of interest

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