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Emergence of Anti-HIV Phytoconstituents

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ABSTRACT

HIV (human immuno deficiency virus) is a virus that attack the immune system, making a person more vulnerable to other infections and diseases. It is unfurled by exposure with certain body fluids of a person with HIV, unprotected vaginal, anal or oral sex, by mother to baby by pregnancy, labour or nursing, by blood products (unclean needles or unscreened blood). People infected with HIV shows drug resistance to anti-HIV drugs and have adverse effects. So, plant derived natural products should discover for the management of disease. Medicinal plants and their phytochemical constituents can dramatically slow down disease progression and secondary infections. We acquaint 10 Indian medicinal plants and their anti-HIV effects and have been assessing in experimental studies. The review step into an attempt to investigating the anti-HIV activity of Indian medicinal plants

INTRODUCTION

Human immuno deficiency virus that damages the immune system. Immune system of body helps to fight off infections. HIV kills CD4 cells, which are type of immune cell called T cells. As the time is over, HIV kills more CD4cells, the body becomes catched with various types of infections and cancers. Stages of HIV: - Stage 1: Acute stage, the first few weeks after transmission. Stage 2: Clinical latency, or chronic stage. Stage 3: AIDS. HIV is transmitted through bodily fluids that include: Blood, Semen, Vaginal& Rectal fluids, Breast milk. HIV couldn't spread in air or water, or through casual contact. A person with HIV is likely to cause a serious condition called AIDS. HIV are of two types HIV-1(the most common), HIV-2 (relatively uncommon & less infectious) Strains of HIV-1 are of 4 groups. The major group M is the cause for global epidemic, above 90% cases of HIV is from infection with HIV-1 group M. The subtypes are A, B, C, D, F, G, H, J&K. Additional groups for HIV-2 are of 6. Each group have been just found in one person[1]

1.1. STRUCTURE OF HIV VIRUS

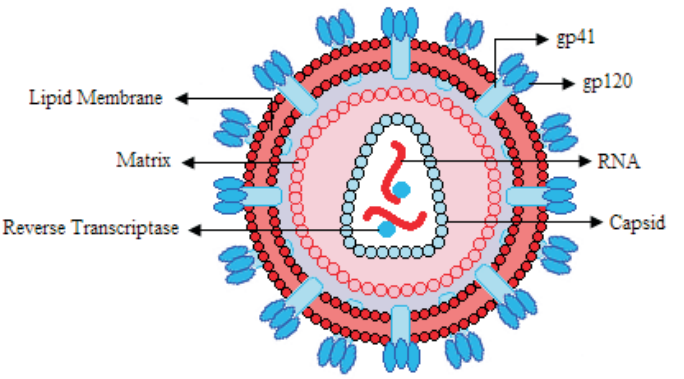

Fig 1 : Structure of HIV virus

Stages of HIV infections: First stage is acute HIV infection.

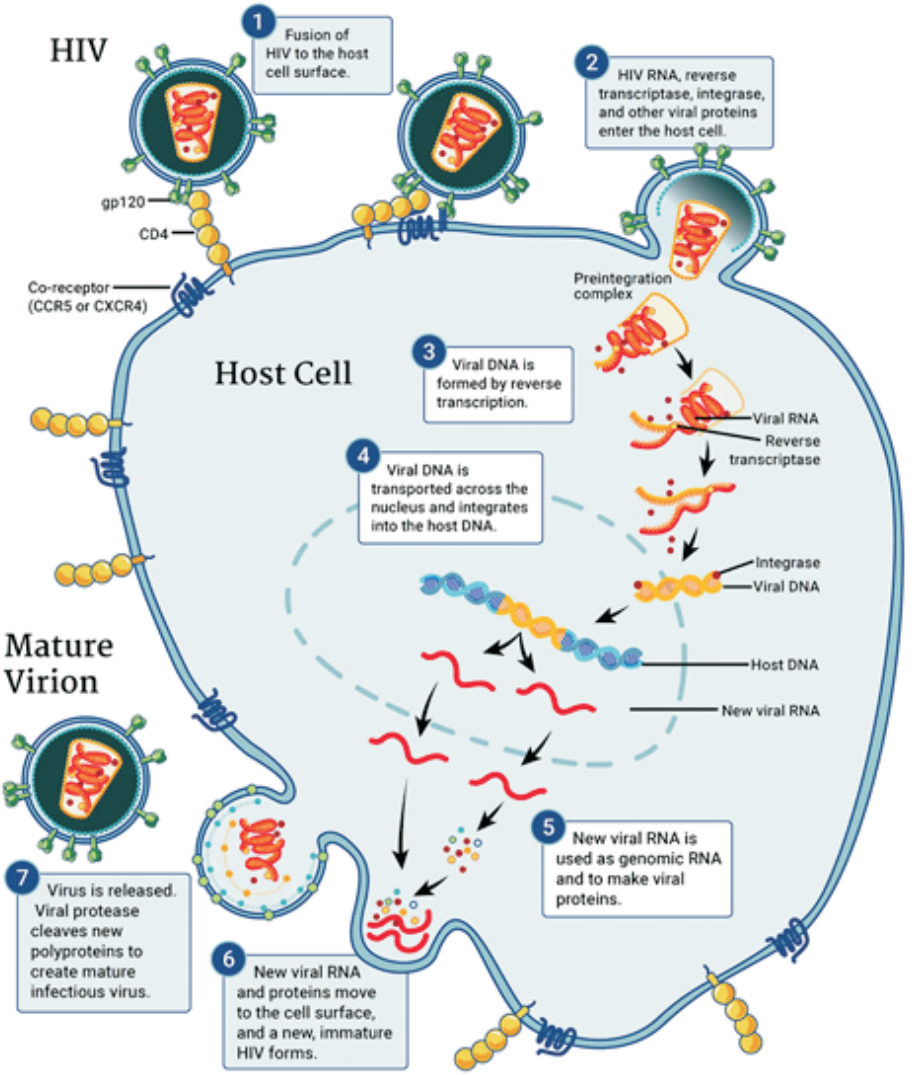

Fig 2 : HIV life cycle

Second stage is chronic HIV infection (asymptomatic HIV infection or clinical latency). AIDS is the final stage and is the most severe stage of HIV infection[2].

1.2. HIV LIFE CYCLE

HIV generally infects immune system and infected cells can generate hundreds of new copies of HIV. It specifically targets CD4+T cells, dendritic and macrophage cells[3].

HIV begins its life cycle when it binds to CD4 receptor. Then it fuses with host cells and releases RNA into the cell. Reverse transcriptase converts single stranded RNA into double stranded DNA. After carrying DNA into the cell, integrase enzyme hides the DNA into cells DNA and makes new protein. Integrated HIV DNA is called provirus which uses host enzyme called RNA polymerase and create copies of new genomic material (mRNA). Protease cuts long chains of HIV protein into smaller protein. Virus particles which is formed get assembled and bud off host cell to produce new virus. After this process new HIV maturation take place and infect new cells[4].

1.3. HIV TREATMENT

There is no cure for HIV/AIDS. But the antiretroviral therapy (ART) decreasing the rate of the disease progression and secondary infection. It introduced in 1996 and involves taking combination of medicines[5].

1.4. HIV DRUGS

There are seven classes of HIV drugs.

1. Nucleoside reverse transcriptase inhibitors (NRTIs)
2. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
3. Retroviral protease inhibitors (PIs)
4. Entry(fusion) inhibitors
5. CCR5 receptor inhibitors
6. Integrase strand transfer inhibitors (INSTIs)
7. Post attachment inhibitors[6].

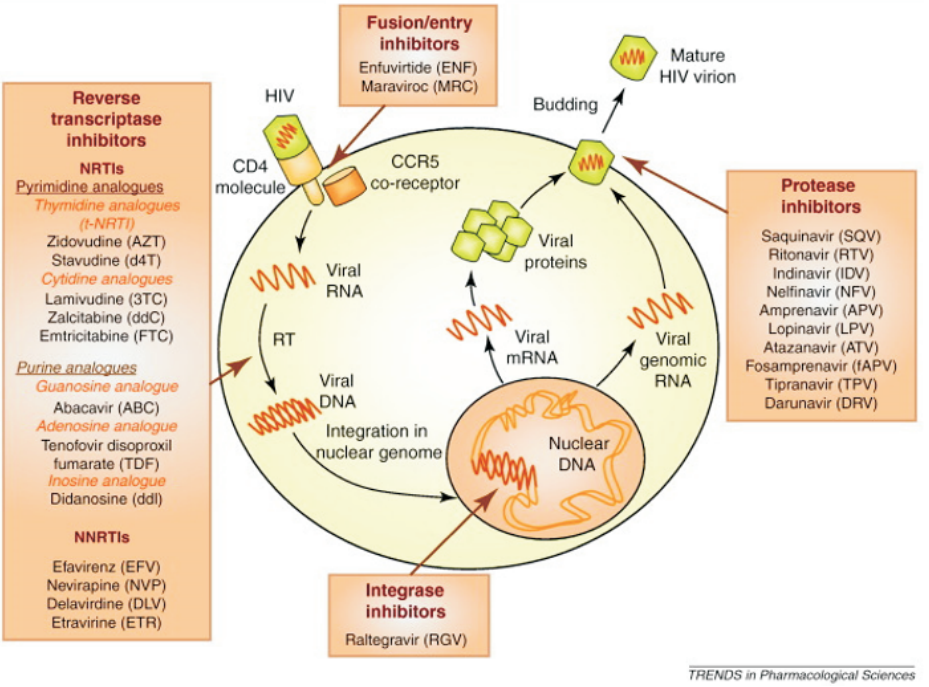

Fig 3 : Mechanism of Anti-HIV drugs

The antiretroviral therapy starting regimen[7],

- Bictegravir/tenofovir/emtricitabine
- Dolutegravir plus tenofovir/emtricitabine
- Raltegravir plus tenofovir/emtrcitabine
- Abacavir/dolutegravir/lamivudine[8]

1.5. HIV RESISTANCE:

One of the best medications used for HIV infection is Highly Active Antiretroviral Therapy (HAART), found combination of inhibitors of reverse transcriptase and protease. While HAART possess much reduced deaths from AIDS related disease, it frequently has side effects and not well allowed mostly in persons experience long term treatment and keeps the chance of developing multidrug resistance[9]. Besides, HAART is an exorbitant authority to be underdeveloped and developing countries where the drugs are unreachable to the HIV infected patients. So, there is a need for discovery of novel therapeutic strategies, which identify new anti-HIV compounds from natural sources of medicinal plants.

Reverse transcriptase (RT)-associated RNA-dependent DNA polymerase (RDDP) and ribonuclease H (RNase H) functions are essential for HIV-1 genome replication. Non-nucleoside reverse transcriptase inhibitors (NNRTI) among the HIV-1 RT inhibitors, constitute a prominent class of drugs for almost 20 years has served as the keystone of combination. NNRTI are small molecules that bind to HIV-1 RT at a site distinct from the DNA polymerase active site of the enzyme and block HIV-1 reverse transcription via an allosteric mechanism. The conformation of RT for RNA hydrolysis is clearly different from that for DNA synthesis and reveals a structural cavity which serves as a target for RT inhibition. Nevirapine was the first NNRTI approved in 1996 by the United States of America (USA) Food and Drug Administration (FDA) for the treatment of HIV-1 infection, followed by delavirdine in 1997, efavirenz in 1998, etravirine in 2008, and rilpivirine in 2011. About 21.7 million people were scattering cART in 2017 (UNAIDS, 2018). However, the efficiency of NNRTI is eroded by adverse events, poor drugdrug interactions, and drug resistant variants of HIV-1 RT. Even in naïve patients who are not yet on cART, HIV-1 mutant variants with residues that confer resistance to RT inhibitors form small pockets of the viral population. There are few other treatment options except regimens based on ritonavir boosted protease inhibitors for the people living with HIV. Protease and integrase inhibitors are less likely recommend by the current treatment protocols as it resulting in inferior virological outcomes and more HIV resistance. Severe liver toxicity affects 823% of HIV-infected patients receiving indinavir and tenofovir causes liver toxicity and in case of cART which cause nephrotoxicity. In order to overcome this drawback, it is important to discover alternative HIV-1 RT inhibitors from plants. Therefore, the current review details the chemical diversity and biological activity profiles of HIV1 RT inhibitors from plants. In the face of current challenges to cART, this review may inspire a new future where plants are the frontier for more efficacious HIV-1 RT inhibitors, in addition to creating a strong bioprospecting pipeline for innovative bioentrepreneurs to advance the invention of new HIV-1 RT drugs from medicinal plants[10].

2. NOVEL NATURAL LEADS IN THE TREATMENT OF HIV

Current issues to anti retro viral therapy have opened new views in search for novel drugs from the natural source[11].

Discovery of HIV-1RT inhibitors from plant source is important due to development of HIV resistance and some toxicity problems. Traditional plant should possess more potential to combat HIV disease.

2.1 Calendula officinalis

Extract of Calendula officinalis (Dichloromethane:methanol - 1:1) show potent anti-HIV activity in *in vitro* tetrazolium-based assay. At 1000 and 500µg/mL concentration inhibition of HIV1-RT and suppression of HIV mediated fusion occur respectively. The organic and aqueous extracts of dried flowers posse's ability to inhibit HIV-l replication[12]. By using *in vitro* MTT tetrazolium-based assay organic extract shows anti-HIV activity and also gives a significant dose- and time-dependent reduction of HIV-l reverse transcription (RT) activity. 85% of RT inhibition was attained after 30 min treatment of partially purified enzyme in the cell-free system. Organic extract of flowers has anti-HIV properties of therapeutic interest[13].

Fig 4 : Flower of Calendula officinalis

2.2. Justicia gendarussa

Justicia gendarussa, a medicinal plant which shows key role in treatment of HIV. Patentiflorin A is an arylnaphthalene lignan (ANL) glycoside, the main constituent present in this plant responsible for anti-HIV activity.

Fig 5 : Justicia gendarussa plant

It is isolated from the extracts of stems and roots of this plant. On its evaluation on both M-and T-tropic HIV-1 isolates it shows comparatively higher inhibitory effect than conventionally used Azidothymidine. Quinovopyranosyloxy group in the structure of patentiflorin is important in showing higher degree of anti-HIV activity. Moreover, it shows higher inhibitory effect against drug resistant HIV-1 isolates of Azidothymidine and Nevirapine. So, it can emerge as novel drug in the treatment of HIV[14].

2.3. Ricinus communis

Extracts of Ricinus communis were tested for their inhibitory effects on essential enzymes reverse transcriptase (RT), protease and alpha-glucosidase. Quantitative structure activity relationships (QSAR) *in silico* studies shows inhibition activity of major compounds of Ricinus communis.

In the anti-HIV-1 RT utilizing enzyme-linked oligonucleotide sorbent assay (ELOSA) method, water and methanol extracts (100ug/ml) of Ricinus communis exhibit strong activity. HIV-1 protease and alpha-glucosidase inhibition assay, neither water nor methanol extracts inhibited the activity of the enzyme to cleave any substrates as oligopeptides and oligosaccharide[15].

Finally observed that ricinine and quercitin (secondary metabolites) of ricinus communis is responsible for the inhibition of the RT *in vitro*.

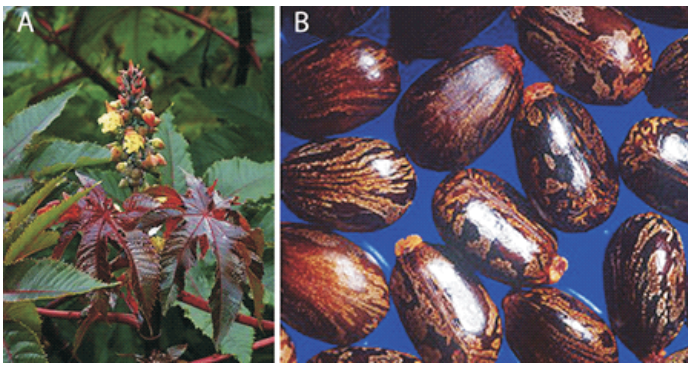

Fig 6 : Leaves, flowers and seeds of Ricinus communis

2.4. Hemidesmus indicus

Hemidesmus indicus (Indian sarsaparilla) is a medicinal plant used in Ayurveda tradition for the treatment of a wide spectrum of diseases, including bacterial and viral infection. HIV-1 Reverse

Fig 7 : Hemidesmus indicus plant

Transcriptase (RT)-associated Ribonuclease H (RNAse H) function and the cellular α-glucosidase, involved in the control mechanisms of N-linked glycoprotein's formation in the endoplasmic reticulum. Pentacyclic triterpenes area good class of HIV-1 inhibitors. Pentacyclic triterpene Lupeol, that inhibits the HIV-1 RT-associated RNAse H function[16]. By using combination studies shows that Lupeol and the active site RNase H inhibitor (RDS1759), blind docking calculations indicates that Lupeol binds to an HIV-1 RT allosteric pocket. The studies show that Hemidesmus indicus gives a constituent called Lupeol. Hemidesmus indicus was able to inhibit not only responsible for the RT-associated RNase H function, but also the HIV-1 RT-associated RNA dependent DNA polymerase activity and the cellular α-glucosidase.

2.5. Terminalia chebula

Terminalia chebula, family combretaceae is widely used in traditional medicine. Pharmacological studies revealed the inhibitory activity of Terminalia chebula on viral infections, such as human immuno deficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV) and influenza. Medicinal plants have important role in exhibiting various modes of action against viral infections. The extract of terminalia chebula has antibacterial, antifungal, anticarcinogenic, antiaging, antioxidant and antidiabetic activities. It contains constituents are tannis (chebulinic acid, chebulagic acid, gallic acid, ellagic acid corilagin), flavonoids, aminoacids, fructose, resin, fixed oil, sterols, etc. The inhibitory activity of Terminelia chebula against HIV-1 protease, reverse transcriptase and integrase inhibition is documented in literature.

Raltegravir, Elvitegravir and Dolutegravir are now used as integrase inhibitors in the market. Integrase inhibitory activity of Fruit extraction of Terminalia chebula has determined and showed the IC_{50} value of 84.81µg/ml. The standard integrase inhibitor Raltegravir showed the IC_{50} value of 17.8 nM, reported in literature. Chemical constituents present in the Terminalia chebula can be used as the basic pharmacophore to design a potent integrase inhibitor with anti-HIV activity[17].

Fig 8 : Fruits of Terminalia chebula

2.6. Curcuma longa

Curcuma longa, belongs to Zingiberaceae family has rhizomes under the ground. It has been used for thousands of years as a traditional remedy in Indian and folk medicine for the treatment of a large variety of diseases. Curcumin is a major active constituent (polyphenol) from the rhizome of turmeric (Curcuma longa). It has a wide range of pharmacological activities. Naturally occurring Curcumin demethoxycurcumin and bisdemethoxycurcumin isolated from C. longa have been showing an inhibitory activity towards glucosidase enzyme. From these naturally occurring constituents, bisdemethoxycurcumin is most potent and showing inhibitory effect at a concentration two-fold lesser than that of acarbose with an IC_{50} value of 23µM [18]. Curcumin's role has been studied as an antiviral agent, thoroughly in the case of viruses like HIV, Herpes simplex virus (HSV), Hepatitis viruses, influenza type A virus (IAV), and Ebola virus. Since curcumin's positive effects outweigh the negative effects and their role in targeting various cellular pathways, further inhibiting the growth and replication of viruses make it a candidate for an anti-viral drug.

Fig 9 : Plant of Curcuma longa

2.7. Allium sativum

Garlic, Allium sativum belongs to Alliaceae family. Aged garlic extract (AGE), a favoured herbal supplement that improve the immune system. Garlic and its constituents have antiviral activity. Allicin (diallyl-dithiosulfinate) is the major component of garlic and generally lay claim to behind the effects such as antibacterial, antiviral, antifungal and antioxidative. Garlic and its constituents have activity such as, opposing to coxsackie virus species, herpes simplex virus types1 and 2, influenza-B, para-influenza virus type 3, vaccinia virus, vesicular stomatitis virus, human immunodeficiency virus type1 and human rhinovirus type 2.

The order of virucidal activity of compounds was found to be ajoene> allicin> allyl methyl thiosulfate> methyl allyl thiosulfate, no activity was found for the polar fractions alliin, deoxy allii, diallyl disulfide, or diallyl trisulfide[19]. Ajoene isolated from extracts of garlic may inhibit adhesive interaction

Fig 10 : Bulbs of Allium sativum

and fusion of leukocytes [20]. Ajoene is found in large quantities in oil-macerated garlic only[23]. It intensifies natural killer-cell activity that demolish virus infected cells [20]. HIV infection leads to a pronounced oxidative stress, virus triggers reactive oxygen species production[21]. The effectiveness of antioxidant compounds found in garlic ethanol extract determined by antioxidant activity test[22].

2.8. Ocimum sanctum

Ocimum sanctum (synonym Ocimum tenuiflorum), also known as holy basil or Tulsi, is an aromatic perennial plant which belongs to the family Lamiaceae. Pepsin was used as a substitute for HIV-protease for the evaluation of inhibitory activity of ethanolic extract of Ocimim Sanctum linn. Pepsin has a close resemblance with HIV-protease in proteolytic activity. The inhibitory activity of Occimum sanctum could be attributed to flavonoid contents. Flavonoids also showed inhibitory activity against HIV protease inhibitors. The Phytochemical investigation of Ocimum sanctum revealed the presence of resins, alkaloids, tannins and also steroidal terpenes. These phyto-constituents showed compounds having anti-HIV activity. This plant has shown anti-HIV potential by three different mechanisms such as interference with the gp120 / CD4 interaction, inhibition of HIV-reverse transcriptase and probable inhibition of HIV-protease enzyme. Pepsin has a close resemblance in proteolytic activity with HIV-protease as both of them belong to same aspartate enzyme family. Hence in this study, pepsin was used as a substitute for HIV-protease[24].

Fig 11 : Plant of Ocimum sanctum

2.9. Azadirachta indica

Azadirachta indica is the member of meliaceae family. Which have wide variety of medicinal properties like antiacne, emetic, stimulent, anthelmintic, antiallergic, astringent, antibacterial etc. The hydroacetone extract of Azadirachta indica leaves were evaluated for their inhibitory effect on reverse transcriptase (RT) polymerase activity by syncytia formation assay and p24 antigen expression ELISA, it shows the extract blocked HIV-1 envelope mediated membrane fusion and inhibited HIV-1 replication in C8166 CD4+ cells in vitro by inhibiting the biochemical activity of HIV-1 reverse transcriptase, it results in the subsequent decrease of HIV p24antigen concentration. No cytotoxicity was observed in the effective dose range.

Azadirachta indica was also investigated for its immunomodulatory potentials by the expression of immune activation markers CD38 and CD69, it shows a dose dependent reduction in the CD38 and CD69 on phytohemagglutinin A (PHA)- stimulated human peripheral blood mononuclear cells (PBMC). The above results show that neem could impart health benefits to HIV/AIDS patients[25].

Fig 12 : Plant of Azadirachta indica

CONCLUSION

The conclusion of this study, which includes the extraction of phytochemical constituents from medicinal plant like Calendula officinalis, Justicia gendarussa, Ricinus communis, Hemidesmus indicus, Terminalia chebula, Curcuma longa, Allium sativum, Ocimum sanctum, and Azadirachta indica have antiviral activity against Human immuno deficiency virus infection (HIV). The chemical constituents used for the development of new era of antiviral drugs against human immuno deficiency virus.

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