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Review Article

Emerging need to use phytopharmaceuticals in the treatment of HIV

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ABSTRACT

Phytopharmaceuticals holds promise in the treatment of HIV because of its efficacy, lesser or no side effects coupled with no toxicity. Thus far, very few candidate species have been exploited for testing of anti-HIV activity. The plant kingdom being highly diverse holds many more biomolecules to be uncovered and explored for the treatment of HIV. For this, it becomes necessary to carry out extensive research and unearth new bioactive molecules. This review presents a comprehensive outlook into the presently available synthetic drugs and its vast side effects and hence, stresses on the importance of herbal therapy in the treatment regimen of HIV.

1. Introduction

Acquired Immunodeficiency Syndrome (AIDS), caused by Human Immunodeficiency Virus (HIV), is an immunosuppressive disease that results in life-threatening opportunistic infections and malignancies. Despite continuous advances made in antiretroviral therapy, AIDS has become the leading cause of death in Africa and fourth worldwide. The number of people with HIV is increasing at an alarming rate in India and Southeast Asia. The success of drug treatment is achieved at the cost of life-threatening adverse drug effects, drug–drug interactions and an inconvenience of life-long therapy. Since the disease has stepped into the third decade, there are several treatment experienced patients living either with drug toxicity or facing the threat of treatment failure due to multidrug resistance.[1] Moreover there is likelihood of newly infected untreated patients harboring HIV mutants that are already resistant to commonly used antiretroviral drugs.[2] As the epidemic continues to ravage the developing world, it becomes increasingly evident that diverse strategies are needed to confront the wide-ranging and complex, social, cultural, environmental and economic contexts in which HIV continues to spread must be researched and adopted. Today, interventions to stem the spread of HIV/AIDS throughout the world are as varied as the contexts in which we find them. Today, many research groups are exploring the biodiversity of the plant kingdom to find new and better anti-HIV drugs with novel mechanisms of action. Due to the adverse side effects of most of the chemical analogs used currently, plant derived drugs promise to be a more effective and safe therapy. This review is hence mainly focused on the currently used anti-HIV drugs, its side effects and also on the plant derived

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biomolecules which promise to be a major promising source of therapy for AIDS patients in the coming future having no or lesser side effects. This review stresses on the importance to focus and develop phytopharmaceuticals with extensive research which could provide a safer and cost-effective approach.

1.1. *AIDS and antiretroviral therapy*

The identification of a retrovirus, HIV, as the causative agent of AIDS, the steadily increasing incidence of various viral diseases in immunodeficient patients and the socio-economic impact of virus infections have all been important factors in boosting the search for new antiviral agents and new modalities of antiviral chemotherapy. A number of laboratories are actively involved in the development of antiviral agents that interfere with HIV at different stages of viral replication.[3,4] However, the rapid spread of the AIDS epidemic and the appearance of HIV strains resistant to the currently available drugs suggest that effective and durable chemotherapy of this disease will require the use of innovative combinations of drugs having diverse mechanisms of anti-HIV activity.[5–7] For this reason, there is a continuous need for alternative inhibitors. New chemical entities with such activities may be identified through a variety of approaches, one of them being screening of natural products. Over the last few years, antiviral researchers have also turned toward many of the traditional folk medicine, invariably a 'cocktail' of natural products, to uncover the scientific basis of their remedial effects. Ng, Vlietinck and Matthee[8–10] reviewed plant-derived anti-HIV compounds, which serves to underline the fact that selected medicinal plants with HIV-inhibitory activity are widely distributed in nature.[11,12] HIV-1 encodes three major enzymes, Protease (PR), Reverse Transcriptase (RT) and Integrase (IN). HIV-1 PR processes viral proteins into functional enzymes and structural proteins. HIV-1 RT is the multifunctional enzyme that transcripts viral RNA to viral DNA which is important for viral replication, whereas integrase is responsible for the integration of dsDNA transcribed from viral RNA into the host chromosome.[13] For HIV-1 PR, many inhibitors have been synthesized chemically and used intensively for AIDS treatments. However, their use is limited due to the emergence of drug resistance and toxicity.[14] Thus, screening of natural products provides an opportunity for the discovery of HIV-1 inhibitors with lesser or no toxicity and side effects.

1.2. *Antiretroviral therapy (ART)*

There are several steps in HIV virus replication in which antiretroviral drugs can interfere. The first step is adherence of the virus particle to the CD4 positive cell and consecutive fusion with the cell. The next step is transcription of the virus RNA by reverse transcriptase in a DNA strand, which is built into the DNA of the host cell with the enzyme Integrase. After integration of proviral DNA into the host cell, the cell produces a long protein chain. This protein chain has to be snipped into small protein chains with the enzyme protease. At the end of 1980's and the beginning of 1990's, the nucleoside reverse transcriptase (NRTIs) was the only anti-retroviral drugs available. Patients were treated with these drugs as monotherapy. Suboptimal suppression of the HIV virus resulted in resistance. Since then two other classes of antiretroviral drugs have emerged: The non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs). These classes of drugs interfere with different points in the viral life cycle, so the combination works synergistically.[15] Though these combination therapies have increased survival and quality of life enormously, there are also problems associated with these such as compliance, resistance, many interactions and serious side effects.

1.3. *Reverse transcriptase inhibitors*

Reverse transcriptase inhibitors act to inhibit the enzyme reverse transcriptase, thus, inhibiting the transcription of viral RNA into DNA. Reverse transcriptase inhibitors are both nucleoside and nucleotide reverse transcriptase inhibitors, and the non-nucleoside reverse transcriptase inhibitors. Patil et al, isolated, from the Malaysian tree *Calophyllum inophyllum* and also from the giant African snail *Achatina fulica* which feeds on its leaves, coumarin derivatives designated as inophyllums. Two of the compounds inhibited HIV-1 RT with IC_{50} values of 38 and 130 nm respectively and were active against HIV-1.[16]

1.4. *Nucleoside reverse transcriptase inhibitors*

HIV-1 reverse transcriptase uses nucleotides to reverse transcribe the RNA of the virus into proviral DNA so that this proviral DNA can be inserted into the DNA of the host cell. In the cell, the nucleoside RT inhibitors are then phosphorylated into nucleotides, which are then used by reverse transcriptase to convert RNA into DNA. When reverse transcriptase uses these faulty building blocks, the development of the DNA is terminated and cellular enzymes can destroy the virus particles. Cross resistance between the NRTIs is possible.[17]

1.4.1. *Side effects*

NRTIs, especially Zerit, Videx and Retrovir, are associated with lactic acidosis and hepatic steatosis.[18] Nucleoside reverse transcriptase inhibitors can cause hyperlactemia by disrupting the function of the mitochondria, known as mitochondrial toxicity. NRTI's can also cause hepatic steatosis. However, NRTIs are capable of causing a wide variety of long-term side effects, including myelotoxicity, lactic acidosis, polyneuropathy and pancreatitis. Long-term side effects are theorized to be related to mitochondrial toxicity (Brinkman et al, 1998). Fast-replicating cells may also be inhibited by NRTIs leading to blood disorders like anemia and neutropenia. Macrocytic anemia and myopathy may occur with Zidovudine and oral ulcers with Zalcitabine and Didanoside. Abacavir can cause severe hypersensitivity reactions and is a contraindication for further treatment. Long-term side effects of the NRTIs are lipoatrophy.[18] Nucleoside and nucleotide analogs have become the cornerstone of HAART (Highly Active Antiretroviral Therapy). Unfortunately, these drugs have shown to inhibit cellular polymerases, most notably mitochondrial DNA polymerase gamma. Studies of the NRTIs in enzyme assays and cell cultures demonstrate the following hierarchy of mitochondrial DNA polymerase gamma inhibition: Zalcitabine > Didanosine > Stavudine > Lamivudine > Zidovudine > Abacavir.