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Mini Review

A Great Hope from Plant Origin Bio-Organic Anti-HIV Agents: Safety, Bio-Efficacy and Protection Issues

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Abstract

Present article signifies anti-HIV potential of various plant natural products. Till the date thousands of green biochemicals have been isolated and tested against HIV *in vitro*. Most of them have been displayed inhibition of reverse transcriptase, protease, integrase enzyme activity. These are also fusion inhibitors, CCR5 antagonists showed gp 120 attachment inhibition activity *in vitro* models. There is an immense need to have most appropriate and highly effective biochemical drug as a single compound or combinatorial drug or a complex of organic and heterocyclic compound to suppress HIV progression in human cells. Medicinal plants are large depository of antiretroviral agents which could be used for treatment of sexually transmitted diseases. Present review article tries to explore new possibilities of HIV control by suggesting important plant natural products which can be used for discovery and design of new drug candidates.

Keywords: *HIV; Anti-HIV Drugs; Attachment Inhibitor; Protease Inhibitors; Replication Inhibitors; Anti-HIV Antibodies; Immunity Boosters*

Introduction

AIDS is a life threatening long term chronic infectious disease caused by HIV1 and HIV 2. AIDS virus is hovering throughout the globe; its impact is so severe that people are making distance from their close relatives though it never spreads through air. It has put large impact on socio-economic and biological life of human being as more than 70 million people died due to HIV infection and millions are hanging for their breath and near to death. The poor third world countries are worst affected as they do not have sufficient health care facilities and are not able to manage large population of HIV infected patients. This is also true that existing medical care and treatment of AIDS patients is very costly and poor people cannot afford it. Hence, this is the duty of researchers, pharmaceutical companies, health institutes, WHO and government organizations to have more appropriate anti-HIV drugs of plant origin, so that poor people can get such treatments. There are many possibilities if we think about chemical structure and activity relationships of plant origin drugs to inhibit the virus replication inside human cells. These anti-HIV agents will work as immune-modulators and boost body resistance and immunity against infectious agents [1]. Though these natural plant products possess different structure and biological activity and mode of action [2], these can be easily tested for their anti-HIV activity, but here is a question that how long we can wait for such novel molecules.

Though, there are synthetic anti-retroviral drugs are available to combat HIV infection. Among them major categories are reverse transcriptase inhibitors, protease inhibitors and replication inhibitors. Reverse transcriptase inhibitors block transcription of reverse the

double-stranded viral DNA by obstructing transcriptase's enzymatic function and prevent its complete synthesis but there are two issues. One usage and cost of these drugs, long term usage cause resistance in virus and have so many side effects in patients [3]. There is an immense need of plant origin anti-HIV biochemicals which could work as novel antiretroviral inhibitors show higher bioavailability, minimum side-effects, fewer negative drug interactions, and higher biological activities against circulating drug-resistant microbial strains. Plants possess the ability to fight against any old virus, newly emerging or drug resistant strain of microbes. Plants possess enormous genetic, molecular and biochemical diversity parallel to microbial infective protein molecules and their novel molecules not only potentially block HIV virus life cycle but also life cycle of other dreadful viruses. This is true that we are lacking behind in finding these novel highly efficient and workable bio-molecules which can hit viruses at multiple sites. Present review article tries to explore new possibilities of HIV control by suggesting important plant natural products which can be used for discovery and design of new drug candidates.

Plant origin natural RT HIV reverse transcriptase (RT) inhibitor have been discovered [4]. These compounds belong to a wide range of different structural classes, e.g. coumarins, calanolide, flavonoids, tannins, alkaloids, lignans, terpenes, naphtho- and anthraquinones, and polysaccharides have been isolated from terrestrial and marine plants, micro-organisms, and marine animals. Inhibitors of HIV reverse transcriptase (RT) are important drugs for the treatment of acquired immuno-deficiency syndrome (AIDS). One approach to identify novel inhibitors of HIV-1-RT is the screening of natural compounds. Many natural products have been shown to be active as RT inhibitors. A, isolated from the terrestrial plant *Calophyllum lanigerum* (Guttiferae), has been discovered as the most interesting natural RT inhibitor. The promise of this natural product probably relates to a novel mechanism of action. The current review describes natural products from various sources that are able to inhibit HIV-RT. Phytochemicals like alkaloids, flavanoids, polyphenols, terpenoids, proteins and coumarins inhibit, interrupt life cycle of HIV virus and are immunity boosters [5]. These could be developed as complete drug as alternative medicine for suppressing the genomic association and integration with human genome [6].

Plant origin compounds used in virus chemotherapy showed least side effects, though, these are slow acting, and immunity booster and will provide longevity to the patients [7]. However, drugs derived or formulated from plant natural products should eliminate or destroy cellular HIV reservoirs and de-activate the infectious coat proteins genome binding proteins [8]. Hence, there is a need to explore focus effective plant-based natural products with remarkable anti-HIV activity. These should be screened and established for their mechanisms of action, structure-activity-relationships and IC_{50} values *in vitro* and *in vivo* assays [9] (Table 1).

There are so many plant species i.e. *Andrographis paniculata*, *Dioscorea bulbifera*, *Aegle marmelos*, *Wistaria floribunda*, *Lindera chunii*, *Xanthoceras sorbifolia* [9] and *Parthenium hysterophorus* [10], *Phyllanthus niruri* Linn [11] which displayed good anti-virus activity [8]. Strong HIV activity is reported in *Artemisia annua* [12], *Gnetum parvifolium* [13], *Combretum adenogonium* Steud [14]. These could be used as alternative medicine for antiretroviral treatment and [15] natural products and immunomodulators [16] (Table 1).

So far studies have been done throughout the globe compounds with diverse anti-HIV activity have been isolated from different plant species. Majority of them are multiple classes of inhibitors. Among them important phytochemicals are cyclotides [17], trichosanthin [18], diterpenes and dimeric phloroglucinols showed anti-HIV activity which target the virus at its different sites [19,20]. Olean-18-ene triterpenoids [21], phenolic alkaloid neferine and its analogues [22], 1'S-1'-acetoxychavicol acetate from *Alpinia galanga* [23], alkaloid, drymaritin, and C-glycoside flavonoid, diandraflavone, from *Drymaria diandra* [24], Bis-andrographolide from *Andrographis paniculata nees* [25], carbazoles and a pyranocoumarin [26] and eudesmanes from *Caragana intermedia* anti-HIV activity [27]. These successfully inhibit HIV 1 replication by blocking reverse transcription [23]. Phenyl β-D-glucopyranoside can be used: As a starting material for the synthesis of various derivatives of β-D-glucopyranosides with potential application as anti-HIV agents. [28]. Cardenolides are C(23)-steroids with methyl groups at C-10 and C-13 and a five-membered lactone (specifically a butenolide) at C-17. They are aglycone constituents of cardiac glycosides and must have at least one double bond in the molecule. These are mostly found in milkweeds and other members of the family Apocynaceae, aged garlic extract inhibited the activity of saquinavir. However, it enhanced the activity of darunavir, another

protease inhibitor [29]. Moreover, coumarins and xanthone and inophyllums from *Calophyllum inophyllum* Linn inhibit HIV-1 reverse transcriptase activity [30,31] (Table 1).

There are so many plant natural products which can be used for chemotherapy of human immunodeficiency virus (HIV). Among them are melliferone-related triterpenoid, tectorigenin, 3',4',5-trihydroxyisoflavone, and euchretin F Alkaloid, drymaritin, and C-glycoside flavonoid, diandraflavone, Cyclotides, disulfide rich macrocyclic plant peptides, taxol, apigenin 7-O-beta-D-(4'-caffeoyl)glucuronide, bis-andrographolide ether, Salaspermic acid, kaurane-type diterpene lactone, tripterifordin, diterpene-benzoate macrolides, sesquiterpenes, leitneridanins A and B, Alkaloid, drymaritin, and C-glycoside flavonoid, diandraflavone, carbazole derivatives, O-methylmukonal, 3-formyl-2,7-dimethoxycarbazole and clauszoline and a pyranocoumarin, clausenidin, limonoid, Kaurane diterpenoids and annoglabasin A and Kaurane diterpenoids and annoglabasin A, allicin. allyl polysulfides and ajoene, Canthoside D a phenolic compound, Steviol Geoside cardiac-active steroids, and Calanolides (Table 1).

To mitigate the chances of transfer of HIV virus from males to females or from females to males or vice versa effective plant origin spermicidal microbicide [32] and vaginal microbicides are highly required [33]. Praneem polyherbal vaginal tablet were found effective in HIV uninfected women; their male partners in Pune, India-Phase I study [34]. Naturally derived anti-HIV agents [35]. There is need of novel molecules which can stop T cell death and binding inhibitor for HIV virus in human cellular system. Hence, inhibition of depletion of CD 4 cells will restore the roles of cellular and humoral immunity [36] (Table 1 and figure 1).

Name of plant species	Name natural product	Mechanism of action	Ant-retroviral therapy
Allium sativum garlic	Allicin, allyl polysulfides and ajoene	Strong HIV protease inhibitors, enterocytes into gastrointestinal lumen	Inhibited HIV-protease inhibitors
Salsola tetragona	Canthoside D a phenolic compound	Inhibition of the enzyme Na^+/K^+-ATPase	Antiviral,
Stevia rebaudiana leaves	Steviol Geoside cardiac-active steroids	Inhibition of the enzyme Na^+/K^+-ATPase	Antiviral,
Calophyllum lanigerum var. austrocoriaceum (Whitmore) leaves and twigs of	Calanolides are tetracyclic 4-substituted dipyranocoumarins. Calanolide A, isolated from the	Selectively inhibits recombinant HIV type 1 RT but not cellular DNA polymerases or HIV type 2 RT	Antiviral Anti-HIV 1 activity
Phyllanthus niruri Linn	Flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins	Xanthine oxidase inhibition	HIV/AIDS and hepatitis B.
Panax ginseng C.A. MEYER, Araliaceae	Ginsenoside Rh1 eliminates the cytoprotective phenotype of human immunodeficiency virus type 1-transduced human macrophages	Inhibiting the phosphorylation of pyruvate dehydrogenase lipoamide kinase isozyme	Cytoprotective from Human immunodeficiency virus type 1 attack
Allium sativum garlic	Allicin. iallyl polysulfides and ajoene.	Strong HIV protease inhibitors, enterocytes into gastrointestinal lumen	Inhibited HIV-protease inhibitors.
Combretum adenogonium Steud	*Saponins, glycosides,* Phenanthrenes, dihydrophenanthrenes	Inhibitors of protease activity	Anti-HIV-1
Goniophlebium niponicum and *Gymnadenia conopsea*	Phenyl-β-D-Glucopyranoside	Ring-ring/sugar-sugar interactions	Bind to receptor subclass, hTAS2R16
Rheum palmatum L., *Rheum officinale*	Alkaloids, flavanoids, polyphenols, terpenoids, proteins	Immunomodulators to enhance the immune system of infected patients	Interrupt the life cycle of HIV
Canova	Immunomodulators	Brazilian medication produced with homeopathic techniques, composed of Aconitum, Thuya, Bryonia, Arsenicum, Lachesis	Monocyte activation, stimulate the host defense

Caragana intermedia	4(15)-eudesmene-1beta,7alpha-diol (1),	Immunostimulant and immunosuppressant activities.	Anti-HIV activity
Cannabis sativa, Cornus capitata	Diterpenes and dimeric phloroglucinols	Protect HIV infected human CD4+ T cell line	Anti-HIV activity showed which target the virus at its different sites
Trichosanthes kirilowii	Trichosanthin	Induce apoptosis, enhance the action of chemokines and inhibit HIV-1 integrase	Enhances the capabilities of chemokines to stimulate chemotaxis and G protein activation
Alpinia galanga	1'S-1'-acetoxychavicol acetate	Inhibit HIV protease, integrase, and reverse transcriptase enzymes	Effective anti HIV-1 agents
Cassine xylocarpa and Maytenus jelskii	Olean-18-ene triterpenoids	Inhibitors of enhancer-dependent transcription.	Modulate the selectivity and intensity of HIV inhibition.
Dandelion (*Taraxacum officinale*)	Alkaloids, flavanoids	Inhibit HIV-1 replication and reverse transcriptase activity	Anti HIV-1 RT.
Lomatium suksdorfii	Suksdorfin, circulin A and B macrocyclic peptides	Suksdorfin's enhanced anti-HIV activity	Inhibit HIV-1 replication
Calophyllum inophyllum Linn	Coumarins and xanthone and inophyllums from	Inhibit HIV-1 reverse transcriptase activity	Anti-HIV activity
Annona squamosa	Diterpenoids annosquamosins A and B from	HIV replication in H9 lymphocyte cells	Anti-HIV activity
Drymaria diandra	Alkaloid, drymaritin, and C-glycoside flavonoid, diandraflavone	Cytotoxic activity	anti-HIV activities, exhibited anti-HIV effects in H9 lymphocytes
Violaceae, Rubiaceae, Cucurbitaceae, Fabaceae, and Solanaceae families	Cyclotides, disulfide rich macrocyclic plant peptides	Cytotoxic activity Control anti-HIV information	inhibitory activity against HIV infection
Taxol buccata	Taxol	Cytotoxic	HIV agents/principles
Chrysanthemum morifolium	Apigenin 7-O-beta-D-(4'-caffeoyl) glucuronide (1),	Cytotoxic activity Acacetin-7-O-beta-D-galactopyranoside	Strong HIV-1 integrase inhibitory activity
Andrographis paniculata nees	Bis-andrographolide ether (1) and six known compounds andrographolide	Cytotoxic activity	Anti-HIV
Jatropha curcas	Flavonoids, saponins and tannins. T	Cytotoxicity	Inhibit hemagglutinin protein of influenza virus
Tripterygium wilfordii	Salaspermic acid, kaurane-type diterpene lactone, tripterifordin [1],	Cytotoxicity	Anti-HIV replication activity in H9 lymphocyte cells with an EC50 of 1 microgram/ml.

Polyalthia suberosa	Suberosol, C31 lanostane-type triterpene	Cytotoxicity	Anti-HIV replication activity in H9 lymphocyte cells
Leitneria floridana	Two new sesquiterpenes, leitneridanins A and B	Cytotoxic	Anti-HIV principles from
Parthenium hysterophorus	Alkaloids, terpenoids, lignans,	Cytotoxic and antioxidant agents	Reduction in mitochondrial membrane potential
Red alga *Callophycus serratus*	Antineoplastic diterpene-benzoate macrolides	Cytotoxicity	Human tumor cell lines via specific apoptotic cell death
Cimicifuga racemosa (black cohosh)	Actein and saponins from the rhizome	Cytotoxicity	Anti-HIV activity
Clausena excavata	limonoid	Cytotoxic effect against KB and BC-1 cell lines	Anti-HIV activity
Annona glabra	Kaurane diterpenoids and annoglabasin A	Against HIV replication in H9 lymphocyte cells	Inhibition of HIV-reverse transcriptase.
Trigonella foenum-graecum, Allium sativum	Coumarin derivatives	Inhibit different stages in the HIV replication cycle	Potent anti-HIV
Euchresta formosana	Tectorigenin (1), 3',4',5-trihydroxyisoflavone (3), and euchretin F (19)	Antiplatelet aggregation	Anti-HIV activities
Brazilian propolis	Moronic acid derivatives and the new melliferone-related triterpenoid	Anti-HIV activity in H9 lymphocytes.	Anti-HIV agent
Calophyllum cordato-oblongum	Pyranocoumarins ordatolide B-OMe and 11,12-anhydrocordatolide	Inhibit HIV-1 reverse transcriptase	Anti-HIV constituents

Table 1: *Anti-HIV potential of natural products isolated from different plant species.*

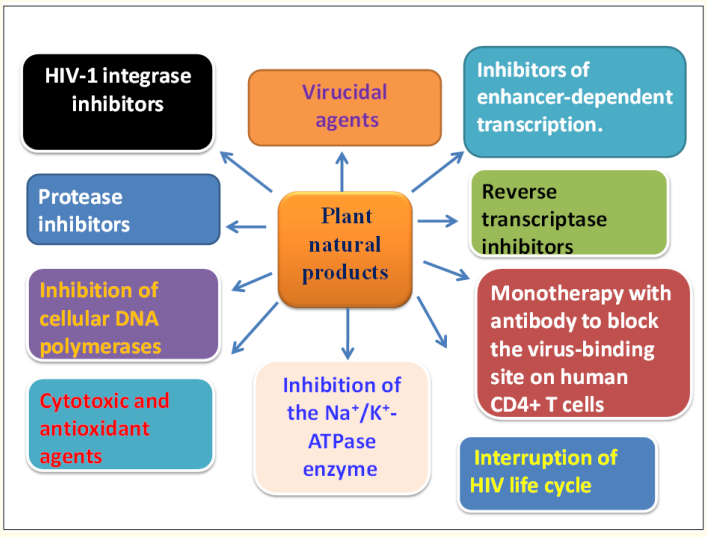

Figure 1: *Showing different targets of anti-HIV bioorganic compounds.*

Conclusion

However, drugs derived or formulated from plant natural products should eliminate or destroy cellular HIV reservoirs and de-activate the infectious coat proteins genome binding proteins. Hence, there is a need to explore effective plant-based natural products with remarkable anti-HIV activity. Plant origin natural product or drug formulations must possess the ability to counteract replication in HIV virus in a highly infectious condition. These plant origin compounds must show least side effects, during testing period, though, these are slow acting, and immunity booster and will provide longevity to the patients. Available chemical drugs showed severe side effects and pose lifelong dependency and resistance. Repetitive use of antiretroviral drugs lead to the transmission of resistant HIV. Hence, there is a need to explore effective plant-based natural products with remarkable anti-HIV activity. These should be screened and established for their mechanisms of action, structure-activity-relationships and IC_{50} values *in vitro* and *in vivo* assays to understand the mechanisms of action of bioactive constituents-in particular the cellular-signaling pathways and receptors. Though, it is very difficult to assess bioactivity and effects of interactions of their key constituents in vivo, Similarly, to assess the bioavailability of key constituents of these supplements and the effects of their complex chemical profiles is also very difficult. Plant natural products possess different classes of compounds which can be used to make low cost and affordable antiretroviral agents for the treatment of HIV infections.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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