REVIEW ARTICLE

Anti-HIV natural products from medicinal plants: A review

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Abstract

Present article explains human immunodeficiency virus (anti-HIV) activity of various bioorganic components isolated from various plant species. Plants possess enormous potential to fight against viruses and other microbial pathogens. Medicinal plants are large depository of antiretroviral agents which could be used for treatment of sexually transmitted diseases. Diseases caused by viruses are showing new trends in virulence, with high infectivity, morbidity, and mortality. Due to climatic effect and drug resistance and new mutations in pathogens, disease burden has been exacerbated enormously at global level. In the present article, plant-derived anti-HIV bioorganic constituents which display reverse transcriptase, protease, and integrase inhibition and obstruct virus cycle inside host have been highlighted with their activity. These plant origin drugs can be produced easily and inexpensively in developing countries and become affordable to poor people. This article suggests the use of natural products from medicinal plants to replace costly antiretroviral chemical drugs which cause cellular toxicity and impose multidrug resistance in viruses. There is an immense need to have most appropriate and highly effective plant origin organic and heterocyclic compound to suppress HIV progression in human cells. 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.

Key words: Anti-human immunodeficiency virus antibodies, anti-human immunodeficiency virus drugs, attachment inhibitor, human immunodeficiency virus, immunity boosters, protease inhibitors, replication inhibitors

INTRODUCTION

The human immunodeficiency virus (HIV)/acquired immuno-deficiency syndrome (AIDS) is an epidemic that is affecting people millions of people throughout the globe. This is one of most serious health challenges in young and middle age group. This is a life-threatening long-term chronic infectious disease caused by HIV1 and HIV 2 virus. AIDS causes multiple morbidities impose larger impact on the health and behavior of people. It is disturbing socioeconomic, human health, and biological survival of human being as treatment cost is very high and poor people cannot afford treatment in any case. On an estimate, more than 70 million people died due to HIV infection and millions which are hanging for their breath and near to death. Mutant strains of (HIV-1) (V106A, V179D, and Y181C) have been identified in clinical isolates.[1] These show resistance to non-nucleoside reverse transcriptase (RT) inhibitors and infectivity, pathogenicity and generate immunological abnormalities, and responsible for morbidities and mortalities in rural, suburban clusters, and urban population of African and American regions.[2]

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. Therefore, effective drug treatments are required to treat the infected people. Although, there are synthetic anti-retroviral drugs are available to combat HIV infection. HIV persists in low-and middle-income countries due to emerging drug resistance and insufficient drug accessibility. This is also true that existing medicare and treatment of AIDS patients are very costly and poor people cannot afford it. Among them, major categories are RT inhibitors, protease inhibitors, and replication

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inhibitors. RT 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. Although these chemical drugs show highly effective and suppress HIV, its cost is very high. There is also problem with the usage of these antiretroviral therapy (ART) drugs, low dose and repetitive long-term usage causes resistance in virus with several side effects.[3] Furthermore, cART does not target latently-infected CD4+T cells, which represent a major barrier to HIV eradication. The "shock and kill" therapeutic approach aims to reactivate provirus expression in latently-infected cells in the presence of cART and target virus-expressing cells for elimination.[4]

Plants are large depository of thousands of natural products which have shown promising anti-HIV activity. Plant natural products are important source of drugs like triterpenes and their analogs have demonstrated potential as pharmaceutical precursors for the treatment of HIV. Over the past decade, natural triterpenoids and analogs have been extensively studied to find new anti-HIV drugs.[5] Hence, this is the duty of researchers, pharmaceutical companies, health institutes, World Health Organization, 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.[6] Although these natural plant products possess different structure and biological activity and mode of action,[7] these can be easily tested for their anti-HIV activity, here is a question that how long we can wait for such novel molecules. There is a need to find out new antiviral agents with diverse structures and novel mechanisms of action remain a vital need for the management of HIV/AIDS. Due to emergence of emergence of multidrug resistance in viruses, new drugs and novel targets are needed. These plant origin drugs may more efficiently attack HIV reservoirs in the body such as brain and lymph nodes. Natural products and their derivatives found more efficient and displayed enormous therapeutic potential against HIV. If these active ingredients are provided in combination these will decrease viral load and increase the CD4+T-cell count in HIV-1 infected patients. This therapy cut down both morbidity and mortality and improves the quality of life of infected patients.[4] Finally, a complete eradication of HIV and AIDS from the human community could be achieved. Natural products or plant-originated compounds and plant extracts have enormous potential to become drug leads with anti-HIV and neuroprotective activity.[8]

These plant origin drugs can be produced efficiently and inexpensively in developing countries. Moreover, the use of natural products from medicinal plants can eliminate the concerns associated with ART drug-related toxicity and multidrug resistance. This article highlights use of plant origin anti-HIV biochemicals which could work as novel antiretroviral inhibitors with higher bioavailability, longer elimination half-life, more favorable side-effect profiles, fewer drug-drug interactions, and higher activities against circulating drug-resistant strains. Plants possess enormous genetic, molecular, and biochemical diversity that have the potential to block HIV virus life cycle. There is a need for the discovery of novel anti-HIV compounds from plants as a potential alternative in combating HIV disease.[9] 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. The review also provides an account photochemistry of anti-viral obtained from various plant species.

SOURCE OF INFORMATION

For writing, this comprehensive research reviews on anti-HIV plant natural products various databases which were searched. For collection of relevant information, specific terms such as medical subject headings and key text words, such as "anti-HIV plants," "biological and pharmaceutical effects," and "therapeutic uses" published until 2022 were used in Medline. Most specially for retrieving all articles pertaining to the use of anti-HIV plant origin phytochemicals, electronic bibliographic databases were searched and abstracts of published studies with relevant information on the anti-HIV plant natural products were collected. Furthermore, additional references were included through searching the references cited by the studies done on the present topic. Relevant terms were used individually and in combination to ensure an extensive literature search. For updating the information about a subject and incorporation of recent knowledge, relevant research articles, books, conferences proceedings, and public health organization survey reports were selected and collated based on the broader objective of the review. Most relevant information on this topic was acquired from various scientific databases, including Scopus, Science Direct Web of Science, and EMBASE, PubMed central, PMC, Publon, Swissprot, and Google search. From this common methodology, discoveries and findings were identified and summarized in this final review.

PHYTOCHEMICALS AS ALTERNATIVE MEDICINES

Plant origin natural RT HIV RT inhibitor has been discovered[10] These compounds belong to a wide range of different structural classes, for example, 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 RT are important drugs for the treatment of 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 such as alkaloids, flavonoids, polyphenols, terpenoids, proteins, and coumarins inhibit, interrupt life cycle of HIV virus and are immunity boosters.[11] These could be developed as complete drug as alternative medicine for suppressing the genomic association and integration with human genome[12] [Table 1 and Figure 1].

PLANT DERIVED ANTI-HIV AGENTS

There are so many plant species, that is, *Andrographis paniculata*, *Dioscorea bulbifera*, *Aegle marmelos*, *Wisteria floribunda*, *Lindera chunii*, *Xanthoceras sorbifolia,*[13] *Parthenium hysterophorus*,[14] and *Phyllanthus niruri* Linn[15] which displayed good anti-virus activity.[16] These could be used in alternative medicine for antiretroviral treatment.[17] *Jatropha curcas* displayed cytotoxicity and inhibit hemagglutinin protein of influenza virus.[18] Bioactive natural products derived,[19] *Hyptis verticillata* Jacq,[20] and *Artemisia annua* showed anti-HIV activity.[21] Moreover, natural products isolated from *Gnetum parvifolium* showed HIV-1 inhibitory activity.[22] Natural products from Canova act as immunomodulators.[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.[24] 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. The class includes cardenolides [Table 1]. Total 11 cardenolides have been isolated from milkweeds and other members of the Apocynaceae [Figure 1].

So far, studies have been done so many compounds with diverse anti-HIV activity have been isolated from different plant species.[25] Majority of them are multiple classes of either enzymes inhibitors or immunomodulators. Among them, important phytochemicals, that is, cyclotides,[26] trichosanthin,[27] diterpenes, and dimeric phloroglucinols showed very strong anti-HIV activity which targets the virus at its different sites.[28,29] Olean-18-ene triterpenoids,[30] phenolic alkaloid neferine, and its analogs also showed similar anti-HIV activities.[31] Besides this so many anti-HIV principles, that is, 1'S-1'-acetoxychavicol acetate from *Alpinia galanga*,[32] alkaloid, drymaritin, and C-glycoside flavonoid, diandraflavone, from *Drymaria diandra*,[33] Bis-andrographolide from *A. paniculata* nees,[34] carbazoles and a pyranocoumarin,[35] and eudesmanes from *Caragana intermedia* anti-HIV activity.[36] These mainly inhibit HIV 1 replication by blocking reverse transcription[32] [Table 1 and Figure 1].

Other inhibitory compounds which were found quite active against HIV virus[37] are tripterifordin[38] and acid has been isolated from,[39] suberosol, C31 lanostane-type triterpene from *Polyalthia suberosa*,[40] acacetin-7-O-beta-D-galactopyranoside from *Chrysanthemum morifolium*,[41] and taxol from *Taxol buccata* are strong anti-HIV agents/principles.[42] In addition, *Galloyl paeoniflorin*, acylated monoterpene glucoside from paeony root,[43] diterpenoids annosquamosins A and B from *Annona squamosa,*[44] and lignans from *Larrea tridentate*,[45] and harman from *Symplocos setchuensis* showed anti-HIV-1 activity.[46] Furthermore, two new sesquiterpenes, leitneridanins A and B, and the cytotoxic and anti-HIV principles were isolated from *Leitneria floridana*[47] Other anti-HIV compounds isolated are actein and saponins from the rhizome of *Cimicifuga racemosa* (black cohosh),[48] limonoid from *Clausena excavata*,[49] kaurane diterpenoids from *Annona glabra* (Chang *et al*., 1998),[50] and diterpene-benzoate macrolides from the Fijian red alga *Callophycus serratus*.[51] More often, coumarin derivatives.[52] oleanolic acid, pomolic acid, triterpenoids,[53,54] flavonoids, and their analogues,[53] moronic acid derivatives and the new melliferone-related triterpenoid isolated from Brazilian propolis (Ito *et al*., 2001),[55] betulinic acid, and platanic acid from Syzigium claviflorum are much potent anti-HIV agents.[56] HIV constituents pyranocoumarins have been isolated from *Calophyllum cordato-oblongum*[57] and *Euchresta formosana*.[58] These plant-derived compounds can be used for chemotherapy of HIV infection[59] [Table 1 and Figure 1].

Diterpenes isolated from Gnidia sericocephala showed potent anti-HIV and latency Reversing activity.[4] It contains four daphnane-type bio-organic compounds which inhibit viral replication and/or reverse HIV latency.[4] Similarly, plant species from tropical rain forests Venezuela are potent inhibitors of HIV-1 replication.[60] Few plant origin natural products Suksdorfin (Lee *et al*., 1994)[61] from Lomatium suksdorfii, circulin A and B macrocylic peptides,[62] pine cone,[63] *Hyssop officinalis* extracts,[64] *Dandelion* extract,[65] coumarins and xanthone, and inophyllums from Calophyllum inophyllum Linn inhibit HIV-1 RT activity.[66,67] Similarly, chlorogenic acids, compounds with cinnamoyl functional groups, and quinic acid were the most prominent compounds in the Helichrysum species with anti-HIV activity[68] [Table 1 and Figure 1].

HIV PROTEASE INHIBITION

Plant natural products are used for chemotherapy of HIV infection.[69] Aged garlic extract inhibited protease activity,[70] while Hypericum shows anti-viral and anti-inflammatory activity.[71] Methanol extracts of Chinese medicinal herbs[72] and Korean red ginseng showed HIV

Table 1: Anti-HIV plant natural products and derived bioorganic compounds used as alternative medicines

Name of plant species	Name natural product	Mechanism of action	Ant-retroviral therapy	References
Enzyme inhibitors				
Allium sativum garlic	Allicin, allyl polysulfides, and ajoene.	Strong HIV protease inhibitors, enterocytes into gastrointestinal lumen	Inhibited HIV-protease inhibitors.	(Berginc *et al*., 2010).
Salsola tetragona	Canthoside D a phenolic compound	Inhibition of the enzyme Na^+/K^+-ATPase	Antiviral	Ghorab *et al*. 2017
Stevia rebaudiana leaves	Steviol Geoside cardiac-active steroids	Inhibition of the enzyme Na^+/K^+-ATPase	Antiviral	Gonzalez *et al*. 2014
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	Xu *et al*. 2000
Phyllanthus niruri Linn	Flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins and saponins	Xanthine oxidase inhibition	HIV/AIDS and hepatitis B.	(Bagalkotkar *et al*. 2006).
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	(Jeong *et al*. 2013).
Allium sativum garlic	Allicin. iallyl polysulfides and ajoene.	Strong HIV protease inhibitors, enterocytes into gastrointestinal lumen	Inhibited HIV-protease inhibitors	(Berginc *et al*. 2010).
Combretum adenogonium Steud	*Saponins, glycosides,* Phenanthrenes, dihydrophenanthrenes	Inhibitors of protease activity	Anti-HIV-1	(Mushi *et al*. 2012)
Goniophlebium niponicum and *Gymnadenia conopsea*	Phenyl-β-D- Glucopyranoside	*Ring-ring/sugar-sugar interactions*	Bind to receptor subclass, hTAS2R16	Hwang; Lee, 2015
Immunomodulators				
Rheum palmatum L., *Rheum officinale*	Alkaloids, flavonoids, polyphenols, terpenoids, proteins and coumarins inhibit, interrupt life cycle of HIV virus and are immunity boosters	Immunomodulators to enhance the immune system of infected patients	Interrupt the life cycle of HIV as well as act as antiretroviral therapy (ART)	Laila *et al*. 2019
Canova	Immunomodulators	Brazilian medication produced with homeopathic techniques, composed of Aconitum, Thuya, Bryonia, Arsenicum, Lachesis	Monocyte activation, stimulate the host defense	(Smit *et al*. 2009).

(Contd...)

Table 1: *(Continued)*

Name of plant species	Name natural product	Mechanism of action	Ant-retroviral therapy	References
Caragana intermedia	4 (15)-eudesmene-1beta, 7alpha-diol (1), 4 (15)-eudesmene-1beta, 7beta-diol (2), 7-trinoreudesma-4 (15),8-dien-1beta-ol- 7-one (3) and others	Immunostimulant and immunosuppressant activities.	Anti-HIV activity	(Sun *et al*. 2004
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	(Bodiwala *et al*. 2009 and Chauthe *et al*. 2010).
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	(Zhao *et al*. 2009),
HIV-1 inhibitory activity				
Andrographis paniculata, Dioscorea bulbifera, Aegle marmelos,\	Alkaloids, flavonoids, polyphenols, terpenoids, proteins and coumarins	Antiretroviral therapy (ART)	Displayed significant anti-HIV activity, inhibit, interrupt life cycle of HIV virus and are immunity boosters	(Kaur *et al*. 2020)
Hypericum	Flavonoid	Antiretroviral treatment	Antiviral Activity *against* SARS-CoV-2	(Birt *et al*. 2009),
Artemisia annua	Artemisinin showed anti-HIV activity	Antiretroviral treatment	Human immunodeficiency virus type 1 (HIV-I) and type II (HIV-II)	(Lubbe *et al*. 2012).
Gnetum parvifolium showed	Resveratrol, isorhapontigenin, and pinosylvin	HIV-1 inhibitory activity	12d (trans-3, 4, 5, 4'-tetrahydroxystilbene) exhibits the most potent anti- HIV-1 activity	(Piao *et al*. 2010).
Inhibition of HIV replication/reverse transcriptase activity				
Alpinia galanga	1'S-1'-acetoxychavicol acetate	Inhibit HIV protease, integrase, and reverse transcriptase enzymes	Effective anti HIV-1 agents	(Ye *et al*. 2006),
Cassine xylocarpa and *Maytenus jelskii*.	Olean-18-ene triterpenoids	Act as inhibitors of enhancer-dependent transcription.	Modulate the selectivity and intensity of HIV inhibition	(Osorio *et al*. 2012),
Dandelion (*Taraxacum Officinale*	Inhibit HIV-1 life cycle at different stages	Inhibit HIV-1 replication and reverse transcriptase activity	Anti HIV-1 RT and inhibited both the HIV-1 vector and the hybrid-MoMuLV/ MoMuSV retrovirus replication	(Han *et al*. 2011)
Lomatium suksdorfii	Suksdorfin, circulin A and B macrocylic peptides	Suksdorfin's enhanced anti-HIV activity.	Inhibit HIV-1 replication	(Derua *et al*. 1996). Lee *et al*.,
Calophyllum inophyllum Linn	coumarins and xanthone and inophyllums from	inhibit HIV-1 reverse transcriptase activity	Anti-HIV activity	Patil *et al*. 1993; Dharmaratne *et al*. 2002).
Galloyl paeoniflorin	Acylated monoterpene glucoside from paeony root	Anticomplement effects	Anti-HIV activity	(Kang *et al*. 1991)

(Contd...)

Table 1: *(Continued)*

Name of plant species	Name natural product	Mechanism of action	Ant-retroviral therapy	References
Annona quamosa	Diterpenoids annosquamosins A and B from	HIV replication in H9 lymphocyte cells	Anti-HIV activity	(Wu *et al*. 1996)
Larrea tridentata	Lignans -anti-HIV compound FB2	Inhibit HIV replication	Anti-HIV activity	(Gnabre *et al*. 1996),
Symplocos setchuensis	Matairesinol (1) and harman (5)	Inhibit HIV replication in H9 lymphocyte cells	Anti-HIV activity	(Ishida *et al*. 2001
Cytotoxic				
Drymaria diandra	Alkaloid, drymaritin, and C-glycoside flavonoid, diandraflavone	Cytotoxic activity	Anti-HIV activities, exhibited anti-HIV effects in H9 lymphocytes	(Hsieh *et al*. 2004)
Violaceae, Rubiaceae, Cucurbitaceae, Fabaceae, and *Solanaceae* families.	Cyclotides, disulfide rich macrocyclic plant peptides	Cytotoxic activity Control anti-HIV information	Inhibitory activity against HIV infection	(Ireland *et al*. 2010)
Taxol buccata	Taxol	Cytotoxic	HIV agents/principles	(Cragg *et al*. 1993).
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	(Ji Sun Lee *et al*. 2003)
Andrographis paniculata nees	Bis-andrographolide ether (1) and six known compounds andrographolide	Cytotoxic activity	Anti-HIV and	(Reddy *et al*. 2005),
Jatropha curcas	Flavonoids, saponins and tannins.	Cytotoxicity	Inhibit hemagglutinin protein of influenza virus	(Patil *et al*. 2013)
Tripterygium wilfordii	Salaspermic acid, kaurane-type diterpene lactone, and tripterifordin,[1]	Cytotoxicity	Nti-HIV replication activity in H9 lymphocyte cells with an EC50 of 1 mg/mL.	(Chen *et al*. 1992).
Polyalthia suberosa	suberosol, C31 lanostane-type triterpene	Cytotoxicity	Anti-HIV replication activity in H9 lymphocyte cells	(Li *et al*. 1993)
Leitneria floridana	Two new sesquiterpenes, leitneridanins A and B	Cytotoxic and	Anti-HIV principles from	(Xu *et al*. 2000).
Parthenium hysterophorus	Alkaloids, terpenoids, lignans,	Cytotoxic and antioxidant agents	Reduction in mitochondrial membrane potential	(Kumar *et al*. 2013),
Rhizomes and roots of *Clausena excavata*	Carbazole derivatives, O-methylmukonal (1), 3-formyl-2,7-dimethoxycarbazole (2) and clauszoline J (3), and a pyranocoumarin, clausenidin (4),	Carbazoles and a pyranocoumarin and)	Anti-HIV-1 activity	(Kongkathip *et al*. 2005)
Red alga *Callophycus serratus*	Antineoplastic diterpene-benzoate macrolides	Cytotoxicity	Human tumor cell lines through specific apoptotic cell death	(Kubanek *et al*. 2005).
Cimicifuga racemosa (black cohosh)	Actein and saponins from the rhizome	Cytotoxicity	Anti-HIV activity	(Sakurai *et al*. 2004),

(Contd...)

Table 1: *(Continued)*

Name of plant species	Name natural product	Mechanism of action	Ant-retroviral therapy	References
Clausena excavate	Limonoid	Cytotoxic effect against KB and BC-1 cell lines	Anti-HIV activity	(Sunthitikawinsakul *et al*. 2003),
Annona glabra	Kaurane diterpenoids and annoglabasin A	Against HIV replication in H9 lymphocyte cells	Inhibition of HIV-reverse transcriptase.	(Chang *et al*. 1998).
Trigonella foenum-graecum, Allium sativum	Coumarin derivatives	Inhibit different stages in the HIV replication cycle.	Potent anti-HIV	Yu *et al*. 2003
Euchresta formosana	Tectorigenin (1), 3',4',5-trihydroxyisoflavone (3), and euchretin F (19)	Antiplatelet aggregation	Anti-HIV activities	Lo *et al*. 2003).
Syzigium claviflorum	Betulinic acid and platonic acid	Anti-HIV activity and the inhibition of PKC anti protein kinase C	Anti-HIV principles from are potent anti-HIV agents	(Fujioka *et al*. 1994).
Brazilian propolis	Moronic acid derivatives and the new melliferone- related triterpenoid	Anti-HIV activity in H9 lymphocytes.	Anti-HIV agent	(Ito *et al*. 2001),
Calophyllum cordato-oblongum	Pyranocoumarins ordatolide B-OMe and 11,12-anhydrocordatolide	Inhibit HIV-1 reverse transcriptase	Anti-HIV constituents	(Dharmaratne *et al*. 1998)

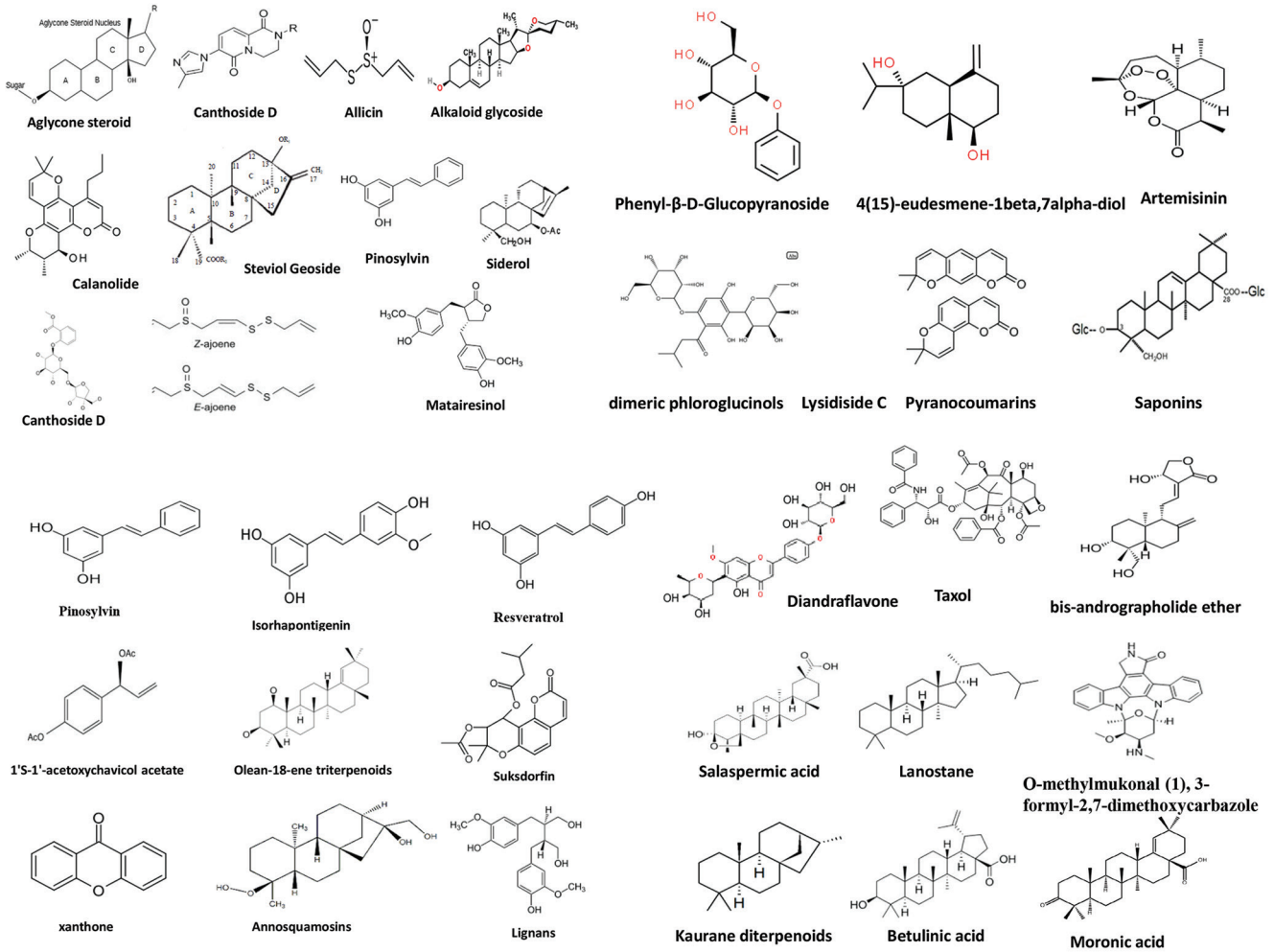

Figure 1: Various anti-HIV bio-organic compounds isolated from different plant species

type-1 protease inhibition activities.[73] Some triterpenes from the stems of Cynomorium songaricum and the woody part of *X. sorbifolia* showed inhibitory activity against HIV-1 protease.[74] while Hypericum,[71] *Combretum adenogonium* Steud[75] and garlic are strong HIV protease inhibitors.[70] Ginsenoside Rh1 eliminates the cytoprotective phenotype of HIV type 1-transduced human macrophages by inhibiting the phosphorylation of pyruvate dehydrogenase lipoamide kinase isozyme.[76] Korean plants also found to inhibit protease activity in HIV 1[77] [Table 1 and Figure 1].

At present, the derivatives of natural products available as anti-HIV-1 agents include zidovudine, an arabinonucleoside derivative of the Caribbean marine sponge (*Tectitethya crypta*), which inhibits the RT of the virus. This was the first antiviral agent approved for treatment of HIV infection. In addition, bevirimat isolated from *Syzygium claviflorum* and calanolide A from *Calophyllum* spp. is inhibitors of viral maturation and reverse transcription process, respectively.[78] Phytophores work against herpesviruses. Grape seed extract proanthocyanidins down regulate HIV-1 entry coreceptors, CCR2b, CCR3, and CCR5 gene expression by normal peripheral blood mononuclear cells[79] [Figure 1].

Moreover, heterodimer of guibourtinidol and planchol and palmitic acid have been isolated from crude extract of *Cassia abbreviate*.[80] Three compounds guibourtinidol-(4α→8)-epiafzelechin and cassiabrevone inhibit HIV-1 entry (IC_{50} of 42.47 μM and 30.96 μM, respectively), as well as that piceatannol interacts with cellular membranes. Cassiabrevone plays a major role of the crude extract of *CA* by blocking the binding activity of HIV-1 gp120 and CD4[81] [Figure 1].

There is an immense 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.[82] Korean red ginseng provides long-term survival to HIV type 1-infected patients.[83] Tat-activated, transduced interferon gene inhibits immunodeficiency virus type 1 replication by a targeted expression to HIV type 1-infected cells.[84] Inhibition of gp 120-CD4 interaction is also achieved using various plant extracts (Woo *et al*., 1997).[85] Special must be given to explore anti-virus molecules in plant extracts which are used in Ayurveda and other herbal medicinal preparations. These must be analyzed for NMR metabolomics[86] and anti-HIV action of activity determined. These must display high antiviral activity with low toxicity and high selectivity index values[87] [Table 1].

ANTI-HIV TOPICAL MICROBICIDES FROM PLANTS

Plant-derived compounds are used for chemotherapy of sexually transmitted diseases.[88,89] These could be used for antiretroviral treatment.[17] 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 micro bicide[90] and vaginal microbicides have been discovered.[91] In this direction, Praneem polyherbal vaginal tablet was found effective in HIV uninfected women and their male partners in Pune. Its trial has been successfully completed Phase I study in India.[92] These naturally plant derived anti-HIV microbicides are topically used which target the viral entry process.[93,94] These prevent sexually transmitted infections such as HIV and HSV-2.[95] Plant species mainly Achyranthes aspera and Rosa centifolia)[9], Acacia catechu, Rollinia Parviflora[96] and Croton tiglium[74] showed potent inhibitory effects on the proliferation of HIV-1 These also inhibit the functions of the viral protein [Table 1].

The human anti-HIV antibodies 2F5, 2G12, and PG9 do proteolytic degradation of HIV proteins. These antibodies can be generated in plant-based expression systems.[97] In addition, chimeric mouse-human antibody showed specificity for HIV gp120 and mediates the lysis of HIV-infected cells.[98] Similarly, chimeric gag-V3 virus-like particles of HIV induce virus-neutralizing antibodies.[99] Micro-RNA[100] and ribozymes are potential anti-HIV-1 therapeutic agents.[101] Few ribosome-inactivating protein also targets HIV-infected cells.[102] Besides this, bi-directional protein transduction systems are used for suppression of HIV-1 expression.[103] Inhibition HIV type 1 virus in human T-cells is also done by potent Rev response element decoy consisting of the 13-nucleotide minimal Rev-binding domain[104]). Similarly, chimeric HIV-1 virus-like particles containing gp120 epitopes as a result of a ribosomal frame shift elicit Gag-and SU-specific murine cytotoxic T-lymphocyte activities.[105] Further, for enhancing immunological potential and transduction, rotavirus enterotoxin fusion is done in transgenic potato to target HIV-1.[106] SIVmac Gag p27 capsid protein gene expression is also done in potato.[106] Synthetic HIV-1 Tat peptides are used to minimize the plasma viremia caused by chimeric simian/HIV 33 in rhesus macaques[107] [Table 1].

FUTURE DIRECTIONS

Plant-derived natural products continue to serve as a reservoir for the discovery of new medicines. 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. 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.[108] All plant origin compounds and their derivatives thereof are of paramount importance and need to be explored as well. At present, the biodiversity of the plant kingdom is being explored by several researchers for the discovery of potent anti-HIV drugs with different mechanisms of action. It is also true that highly active ART has cut down the occurrence deaths due to

AIDS and other associating diseases. These are too expensive and people from underdeveloped and developing countries cannot afford these drugs. To overcome the issues that greatly constrain the development of plant-produced pharmaceuticals, great efforts have been made to improve expression systems and develop alternative strategies to increase both the quantity and quality of the recombinant proteins. Hence, there is a need to explore focus effective plant-based natural products with remarkable anti-HIV activity. There is a need to prepare plant expression platforms, with special focus on the upstream designs and milestone achievements in improving the yield and glycosylation of the plant-produced pharmaceutical proteins.[108] Furthermore, toxicological aspects of such plant species need to be explored. The current antiretroviral therapies have achieved success in providing instant HIV suppression but with countless undesirable adverse effects. These should be screened and established for their mechanisms of action, structure-activity-relationships and IC_{50} values *in vitro* and *in vivo* assays.[13]

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 focus effective plant-based natural products with remarkable anti-HIV activity. Plant origin natural product or drug formulation 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. Repetitive use of antiretroviral drugs showed severe side effects and pose lifelong dependency and resistance. Natural products and their derivatives were found more efficient and showed very high therapeutic potential and can become an excellent option to treat HIV-infected patients. Plant natural products possess different classes of compounds, that is, nucleoside RT inhibitors, including chain terminators, delayed chain terminators, and nucleoside RT translocation inhibitors which can be used to make low cost and affordable antiretroviral agents for the treatment of HIV infections. Natural products and their derivatives found more efficient and displayed enormous therapeutic potential against HIV. If these active ingredients are provided in combination, these will decrease the viral load and increase the CD4+T=cell count in patients with HIV-1 infection. This therapy cut down both morbidity and mortality and improves the quality of life of infected patients. Hence, there is an immense need to explore plant-based natural products with remarkable anti-HIV activity. However, its toxicological and pharmacological properties and mechanism/s of action, structure-activity-relationships, and IC_{50} values *in vitro* and *in vivo* assays must be determined before use. Further, to understand the mechanisms of action of bioactive constituents, chemical profiles, receptor interactions, bioavailability, and cellular-signaling pathways are to be explored. The understanding of the action mechanisms of plant-derived compounds will help new ways to combat of this life-threatening disease.

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