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ANTI - HIV HERBAL DRUGS

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ABSTRACT

Acquired Immuno Deficiency Syndrome (AIDS) is a clinical syndrome that is the result of infection with Human Immuno Deficiency (HIV), which causes profound immunosuppression. Current therapies available for symptomatic treatment of AIDS are quite expensive. Herbal medicines can be developed as a safe effective and economical alternate. Herbal medicine provides rational means for the treatment of AIDS. The herbal drugs which are used for treatment of AIDS are kalmegh, Betel nut, Ipecac, Turmeric, Clove, Liquorices, Cotton seed, Sarpgandha, Ashoka, Arjuna etc. Many compound of plant origin that inhibits HIV during various stage of cycle these include several alkaloids carbohydrates, coumarine, flavonoids, phenolics, proteins, quinines, xanthenes, phospholipids and tannins. These candidates have the potentialto come up as drug for treatment for HIV infection. So the aim of this review article is to identity plants and their active principles possessing activity against Human immunodeficiency virus with objectives of providing an effective approach for prevention of transmission and treatment of these diseases.

KEYWORDS: HIV, AIDS, Immunosuppression, Syndrome.

INRTODUCTION

AIDS (Acquired immune deficiency syndrome) is the final stage of HIV disease which causes damage to the immune system. Acquired immuno deficiency syndrome (AIDS) of human is caused by two lenti viruses, immune deficiency viruses type 1 and 2 (HIV-1 the CDC – defined AIDS indicator illnesses. An HIV positive person can also receive an AIDS diagnosis on the basis of certain blood tests (CD4 counts) and may not have experienced any serious illnesses. A positive HIV test does not mean that a person has AIDS.

AIDS is a serious life threatening health problem since the first case was identified in 1981 and is the most quickly spreading disease of the century. Since the epidemic began. More than 60 million people has been infected with the virus and HIV/AIDS is now leading to death.

AIDS is a result of human immunodeficiency virus (HIV) infection which leads to severe for effective therapies is still of great importance. However besides the high cost, there are adverse effects and limitation associated with chemotherapy applied. Thus herbal medicines are frequently used as alternate therapy by individual living with HIV. Numerous plant derived compounds have been evaluated for inhibitory effects on HIV replications, and many have been found to inhibit different steps in HIV replication cycle HIV-AIDS remains among the world's great public health challenges worldwide resurgence of HIV is due to major problem outbreak of multi drug resistant HIV mutants can gain a competitive advantages over with respect to virus become the dormant quassispecies Thus; there is a persuasive need for anti HIV drugs with improved properties such as, Enhanced activity against MDR strains, reduced toxicity, shortened duration of therapy, low dose frequency, rapid mechanism of action and most important it will have been executing conformational adaptability and to increase flexibility to penetrate host cells and exerts anti-retroviral effect in the intra and extra cellular environment. The disease usually occurs in stages from a latent stage with initial symptoms such as fever, dizziness, weakness and joint pain, a rashes and generalized lymphadenopathy followed by asymptomatic latency period. In the middle stage symptoms such as fever, weight loss, night sweats, diahorrea, thrust, skin lesion and depression are common. Herbal medicines provide rational means for the treatment of many disease. In Europe herbal treatment have been considered as the most popular complementary medicine used by HIV infected individuals. Substantial amount of research has been done and a lot more is in progress to isolate the active leads from plants for prevention of transmission of HIV and treatment of AIDS.

HIV belongs to a special class of viruses called retrovirus. The average Human immunodeficiency virus (HIV), the virus presumed responsible for AIDS, is about 0.000031 inches (120 A^0) long and has an RNA core.

Types of HIV

Two major types of HIV have been identified so far,

1. HIV- 1: It is the cause of the worldwide epidemic and is most commonly referred to as HIV. It is a highly variable virus, which mutate readily. There are many different strains of HIV-1, which be classified according to groups and subtypes; M and O. within the group M, there are currently known to be at least ten genetically distinct subtypes which are A to J.
2. HIV-2: In addition, Group O contains another distinct group of heterogeneous viruses. HIV-2 is less pathogenic and occurs rarely, it is found mostly in West Africa.

HIV Infection Mechanism

HIV begins its infection by binding to the CD4 receptor on the host cell. CD4 is present on the surface of many lymphocytes, which are a critical part of the body's immune system. It is now known that a co-receptor is needed for HIV to enter the cell. Following fusion of the virus with the host cell, HIV enters the cell. The genetic material of the virus which is RNA, is released and undergoes reverse transcription into DNA. An enzyme in HIV called reverse discomforting illness. His or her everyday activity may be restricted and he or she is probably manifesting bouts of illness that require short-term or long term medical treatment in and out of the hospital.

Life Cycle and Replication of HIV/AIDS Virus

1. Viral entry

The HIV-1 envelope spikes complete trimers of non-covalently linked herterodimers consisting of surface glycoprotein gp120 and the transmembrane glycoprotein gp41 when triggered, these spikes initiate a cascade of comformational changes that culminates in fusion between the viral and host cell membranes and release of the viral core into the cyctoplasm. HIV-1 primarily infects CD* T cells and macrophages. An intial interaction between gp120 and the surface receptor CD4 induces the formation of a bridging sheet between the inner and outer domains of the gp120 monomer, exposing the binding site for a second cell surface molecule, typically CC- the gp120 monomer, exposing the binding site for a second cell surface molecule, typically CC- chemokine receptor 5 (CCR5). Engagement of this co-receptor leads to insertion of the fusion peptides, located at the amino terminus of gp41, into the cell membrane. This event triggers significant rearrangements of the trimerized amino and carboxy-terminal heptal repeat sequences within gp41. The formation of a six-helix hairipin structure and the apposition and fusion of the viral and host cell membrane. Initial cryo-electron tomography studies provided crucial glimpse of HIV-1 envelope and its

associated conformational flexibility, although the low resolution models that were generated left many key aspects of native structure unresolved glycoprotein constricts have been instrumental in developing entry inhibitors and clucidating the mechanistic basis of virus neutralization by antibodies. Recent studies have highlighted the striking flexibility of the crore gp120 structure, which allows extreme conformational changes following CD4 engagement without destabilizing the interaction with gp41CD binds gp120 at a depression formed between the inner and outer domains, where the CD4 residue Phe43 partially fills a hydrophobic cavity10. Small molecules designed to bind and extend further into the pocket display antiviral activity; thus, increasing the affinity of such molecule for gp120 might lead to the development of clinically useful inhibitors. Most antibiotic directed against gp120 are strains specific and, moreover, fail to neutralize the virus. However. Several groups recently described patient-derived gp120-reactive antibodies with broad HIV-1 neutralization activity 20-24. One group in particular took a structure- based approach to stabilize the CD4- bound conformation of gp120 using disulphide bonds, and redesigned its surface to mask that positions that are ecterior to the CD4- binding site using one such construct as bait and peripheral mononuclear cells from patients with AIDS.

Engagement of this co-receptor leads to insertion of the fusion peptide, located at the amino terminus of gp41, into cell membrane. This event triggers significant rearrangement of the trimerized amino- and carboxy- terminal heptad repeat sequences within gp41, the formation of a six-helix hairpin structure and the apposition and fusion of the viral and host cell membranes.

2. Post-entry events: uncoating to integration

The HIV core, which houses the replication enzymes RT and integrase (IN) as well as the viral genomic RNA, is encased by a cone-shaped shell 29 composed of the viral capsid (CA) protein. Recent work has revealed the interaction that occur among individual CA molecules and underline the structural integrity and functionally of the protective shell.

Uncoating

Partial CA shell dissolution, which is required for reverse transcription, is a recently verified therapeutic target. Moreover, the underlying features of the assembled shelf seems to determine its prospensity to uncoat. CA, which comprises independently folded N-terminal and C-terminal domains (NTD and CTD, respectively) connected by a flexible linker, can assemble into ring structures containing five or six promoters. The rings further congregate to

form a fullerene like one that is composed predominantly of hexamers, but also contains seven pentamers at the wide end five at the narrow end. This arrangement produces shape declination and the flexibility of intramolecular NTD-CTD and intramolecular CTD-CTD interaction further contributes to the curvature of the shell lattice. The high concentration of pentameric declinations that is expected at the narrow end of the cone may also ever serve to initiate uncoating.

Viral DNA synthesis

Reverse transcription and integration of the resultant linear viral DNA molecule into a host cell chromosome occur within the context of nucleoprotein complex structures that are derived from the viral core high resolution HIV-1 RT structures have been available for number of years, with initial drug and nucleic acid templates bound crystal HIV-1 RT is a heterodimer compound of p66 and p51 subunits, with p66 harbouring two functional active sites: an N-terminal RNA- and DNA- dependent DNA polymerase and a C-terminal RNase H that digests the RNA component Of RNA-DNA hybrids. The polymers domain resembles a right hand with four subdomains: fingers, thumbs, palm and connection. During DNA polymerization, Mg2+ cations coordinated by the catalytic residues ASP110, ASP185 and ASP186 from palm subdomain active the DNA primer 3 –hydroxy group and stabilize the hypothetical pentavalent a-phosphorus intermediate state within the substrate 2' –deoxyribonucleoside 5'triphophate (dNTP), incorporating the nucleotide into the growing DNA chain and liberating free pyrophosphate11.

Plants for Anti HIV activity

S.No.	**Family/species**	**Active Constituents**	**Mechanism of Action**
1.	**Acanthaceae** *Andrographis paniculata*	*Aqueous extract of leaves diterpene lactones (andrographolide)*	*Inhibition of HIV protease and reverse transcriptase. Inhibit HIV-infected cells from arresting in G2 phase in which viral replication is optimal. Inhibit cell-to-cell transmission, viral replication and syncytia formation in HIV –infected cells.*
2.	**Amaryllidaceae** *Galanthus nivalis Hippeastrum hybrids*	*Plants lectins G. nivalis agglutinin (GNA)* *Hippeastrum hybrid agglutinin (HHA) and monocot mannose Binding lectins (MBLs)*	*Potent inhibitors that stop the spread of HIV among lymphocytes by targeting gp120 envelope glycoprotein; most prominent anti-HIV activity is found MBLs; GNA has specificity for terminal –(1 -3) and –(1-6)- linked mannose residues.*
3.	**Anacardiaceae**	*Biflavonoids, robusta flavones and hinokiflavone*	*Strong inhibition of polymerase of HIV-1 reverse transcriptase*
4.	**Ancistrocladaceae**	*Mischellamines A and B*	*Anti-HIV and anti HIV-2 activities. Act at*

	Ancistrocladus Korupensis		*early stage of HIV life cycle by inhibiting reverse transcriptase and at later stages by inhibiting cellular fusion and syncytium transformation.*
5.	**Apocyanaceae** *Rauwolfia serpentina*	*Papaverine*	*Inhibition of HIV reverse transcriptase and HIV cell growth*
6.	**Asteraceae** *Achyrocline satureiodes* *Arctiun lappa*	*Two dicaffeoylquinic acids: 3,5-dicaffeoylquinic acid, and 1-methoxyoxalyl-3-5-dicaffeoylquinic acid Wedelolactone (a coumarin derivative); orobol*	*Potent and irreversible inhibition of HIV -1 integrase.* *Inhibit HIV-1 replication, block cell transmission of HIV.*
7.	**Boraginaceae** *Arnebia euchroma (Royle) Jonst*	*Monosodium and monopotassium salts of isomeric caffeic acid tetramer*	*Inhibitory activity against HIV replication is acutely infected H9 cell.*
8.	**Combretaceae** *Terminalia arjuna*	*Extract of stem bark*	*HIV protease inhibition*
9.	**Cannabaceae** *Humulus Lupulus*	*Xanthohumol*	*HIV-1 inhibitory activity as well as HIV-1-induced cytopathic effects, production of viral p24 antigen and reverse transcriptase in C8166 lymphoctes*
10.	**Clusiaceae** *Callophyllum* *Cordatooblongum* *Marila laxiflora* *Symphonia globulifera* *Hypericum perforatum L.*	*Cordatolide A amd B* *(+)- Calanolide A* *Laxofloranone* *Guttiferone A* *Hypericin, 3-hydroxy lauric acid*	*Inhibitory activity against HIV-1 Replication* *Inhibit cytopathic effects of HIV-1 in T-cell lines, including both CEM-SS cell and MT-2 cells* *Novel non-nucleoside reserve transcriptase inhibitor with potent anti-HIV-1 activity Inhibiton of the cytopathic effects of in virus HIV infection Cytoprotection of CEM-SS cells HIV-1 infection; inhibiton of HIV-1 replication; anti- HIV activity with little or no cytotoxicity*
11.	**Dipterocarpaceae** *Monotes africabus Vatica astrotricha*	*Prenylated flavonoids, 6,8 Diprenylaromadendrin and 6,8-diprenylkaempferol Prostratin, a 12-deoxyphorbol*	*Blocks HIV-1 replication at the entry step.*
12.	**Euphorbiacea** *Homalanthus nutan*	*Prostratin, a 12-deoxyphorbol*	*Putative mechanism are: down regulation of CD4 expression in CEM and MT-2 cells, interference in protein kinase C enzyme pathway. Prostratin is a potent activator of HIV replication and expression in latently infected T-cell; it is used to flush out latent HIV from lymph nodes during antimicrobial therapy.*

13.	**Fabacea** *Peltophorum africanum*	*Gallotamin*	*Inhibits RNA- depedents-DNA polymerase activity of HIV-1 reverse transcriptase; inhibits ribonuclease H avtivity of reverse transcriptase*
14.	**Gentianceae** *Swertia Franchetiama*	*Flavonone – xanthone glucoside*	*Inhibits HIV-1 reverse transcriptase*
15.	***Hypericea*** *Hypericum perforatum*	*Hypericin and pseudohypericin*	*Interference with assembly of virions and secondary spread, interaction with proviral DNA.* *Integration, interference with viral infection, prevention of virus spreading and budding*
16.	**Lamiaceae** *Melissa officinalis*	*Rosmarinic acid*	*Inhibits HIV-1 virions carrying different X4 and R5 HIV-1. Inhibits fusion of HIV-1 particles with cells.*
17.	**Leguminoseae** *G.glabra linn.* *Liquorice C*	*Glycyrrhizin, licohalcone A, Glycocoumarin, Licopyranocoumarin*	*Inhibition of giant cell formation of HIV-infected cells, interference with viral adsorption and protein kinsase C.*
18.	**Leguminoseae** *S.indica Linn***.**	*Extract of bark*	*HIV protease inhibiton*
19.	**Magnoliaceae** *Magnolia*	*Neolignans e.g. mangolol 1 and honokiol 2*	*Antioxidant, antidepressant, induces apoptosis in tumor cells, weak anti hiv 1*
20.	**Myrtaceae** *Eugenia carryophyllata Thun.*	*Tannis eugenin, casuaricitn, tellimargrandin, chromones bilflorin and isobiflorin*	*Inhibition of virus cell fusion, inhibition of syncytium formation*
21.	**Malvaceae** *Gossypium spp*	*Gossypol*	*Inhibiton of giant cell formation of HIV-infected cells, interference with viral absorption and protein kinase C.*
22.	**Physalacriaceae** *Flammulina velutipes*	*velutin*	*Inhibition of HIV-1 reverse transcriptase.*
23.	**Palmae** *Areca catechu*	*Seed extract, procyanidins, arececatannin*	*HIV protease inhibiton*
24.	**Rubiaceae** *Cephaelis ipecacuanha*	*Psychotrine O-methylpsychotrine*	*Inhibiton of reverse transcriptase*
25.	**Rosaceae** *Crataegus pinatifida*	*Uvaol and ursolic acid*	*Inhibitory activity against HIV-1 protease*
26.	**Sapindaceae** *Xanthocerus sorbifolia*	*Oleanolic acid*	*Inhibits HIV-1 replication is acutely infected H9 cells.*
27.	**Theaceae** *Camellia japonica* *Camellia sinensis*	*Camellia – tannin H polyphenol* *Epigallocatechin -3 - gallate*	*HIV protease inhibitory activity activity Inhibit semen derived enhancerof virus infection (SEVI)activity and abrogates semen- mediated enhancement of HIV-1 infection*
28.	***Umbelliferae*** *C. longa*	*Curcumin*	*Inhibiton of HIV-1 integrase, inhibiton of Tat-mediated transactivation of HIV-1 long terminal repeat.*
29.	**Zingiberaceae** *Curcuma species Including C.longa*	*Curcumin*	*Inhibits HIV-1 integrase, HIV-1 and HIV-2 protease, and HIV-long terminal repeat-directed gene expression.*

S.No	Phytoconstituents	Source
1.	**Alkaloids**	
	Buchapine	*Eodia roxburghiama*
	Cepharanthine	*Stephania cepharantha*
	Nitidine	*Toddalia asiatica*
	Berberine	*Berberise Aristata*
	Brucine, Strychinine	*Strynchos nuxvomica*
2.	**Coumarins**	
	(+)- Calanolide A	*Callophyllum lanigerum*
	(-)- Calanoide B	*C.lanigerum*
	Coriandrin	*Coriandrun sativum*
3.	**Flavonoids**	
	Robusta flavone	*R.succedanea*
	Wikstrol B	*Wikstroemia indica*
	Xanthohumol	*Humulus Lupulus*
4.	**Phenolics**	
	8-C-Ascorbyl (-)-epigallocatechin	*Green and black tea*
	Balanocarpol	*Hopea malibato*
	Caffeic acid tetramer salts	*Arnebia eucbroma*
5.	**Quinones**	
	Conocurvone	*Conospermum incurvum*
	Hypericin	*Hypericum perforatum*
6.	**Saponins**	
	Actein	*Cimicfuga racemosa*
	Saponin B1	*Soyabean seeds*
7.	*Terpenes/sterols*	
	Andrographolide	*Andrographis paniculata*
	Clasthsterol	*clasthria*
	Limonin	*Citrus spp.*
	Oleanolic acid	*S.claviflorum*

CONCLUSION

Acquired immunodeficiency syndrome, caused by human immunodeficiency virus is an immunosuppressive disease. Acquired immunodeficiency syndrome are gaining significant importance at present due to rapid spread of the diseases, high cost of treatment and increases risk of transmission of other STD & AIDS. Current therapies available for symptomatic treatment of AIDS are seeking help from quite expensive. Many patients of AIDS are seeking help from alternative system of medicines such as unani, ayurvedic, homeopathy. Since a long time medicinal plant have been used for the treatment of AIDS, research is in progress activity against sexually transmitted pathogens including human immunodeficiency virus with objective of providing an effective approach for prevention of transmission and treatment of this disease. Medicinal plants have a long history of use and their use is widespread in both developing and developed countries. Herbal medicine provides rational

means for the treatment of AIDS. Many compound of plant origin that inhibits HIV during various stage of cycle, include alkaloids, carbohydrates, coumarine, flavonoids, lignin, phenolics, protiens, quinens, xanthene, phospholipids and tannins. Plant derived microbicide and plant bodies are some of new approach for prevention of HIV. So, herbal medicines can be developed as a safe effective and economical alternate for AIDS.

REFERENCES

1. Lann PY, Jadhav PK, Eyemann CJ, et al. 1994. Rational design of potent, bioavailable, nonpeptide cyclic ureas as HIV protease inhibitors. Science, 263-380-34.
2. Karpas, Y.A, Fleet, G.W.J. and Dwek, R.A, Amino sugar derivatives as potential anti-HIV agents. Proc. Natl. Acad. Sci. USA, 1988; 85: 9229.
3. Tan, GT, Pezzuto, J.M, kinghorn, A.D. and Hughes, S.H, Evaluation of natural products as inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase. J. Nat. Prod, 1991; 54: 143-154.
4. Duan, H Takaishi, Y., Imakura, Y., Jia, Y., Li, D., cosentino, L.M and Lee, K, H., Sesquiterpene alkaloids from Triptergium hypoglaucumand Triptergyium wilforii: A new class of potent anti- HIV agents. j. Nat. prod., 2000; 63: 357-361.
5. Carillo A, Stewart KD, Desmyter J, et al. 1990. Potent and selective and characterization of human immunodeficiency virus type 1 variants with increased resistance to ABT-378, a novel protease inhibitors. J. Virol., 72: 7532-4.
6. Manfredi, K.P., Blunt, J.W., Cardellina, J.H.I., McMahon, J.B., pannell, L.K., Cragg, G.M. and Boyd, M.R., Novel alkaloids from the tropical plant Ancistrocladus abbtreviatus inhibit cellkilling by HIV-1 and HIV-2.J. Med chem., 1991; 34: 3402-3405.
7. Nakmura, M., kunimoto, S. and takahashi, Y., Inhibitory effectsof polyethers on human immunodeficiency virus replication. Antimicrob. Agents Chemother., 1992; 36: 492.
8. Sakurai, N. el., Anti-HIV agents. Acteria, an anti-HIV principlefrom rhizome of Cimicifuga racemosa (black cohosh), and theanti-HIV activity of related saponins, Bioorg. Med. Chem. Lett., 2004; 14: 1329-1332.
9. Yang X. W., Zhao, J and Cui, Y, X., Anti-HIV-1 protease triterpenoidsaponins from the seeds of Aesculus chinensis. J. Nat. Prod., 1999; 62: 1510-1513.
10. Groweiss, A., Cardellina, J.H and Boyd, M.R., HIV inhibitoryprenylated xanthones and flavones from masclura tinctoria. J. Nat. Prod., 63: 1537-1539.
11. Ghosh AK, Das AK, Patra KK. Studies on antifertility effect of rhizome of curcuma longa linn. Asian Journal of pharmacy and life sciences, 2011; 1(4): 349-53.

12. Higuchi, h., Mori, k. and Kato, A., Antiretoviral activities of anthraquinonesand their inhibitory effects on reverse transcription. Antiviral Res., 1991; 15: 205.
13. Singh IP, bharate SB, BHutani KK. Anti HIV Natural Product. Current Science, 2005 july 25; 89: 269-290.
14. Kashiwada Y. Anti-AIDS Agents: Sodium and Potassium Salts of Caffeic Acid Triterpenes from Arebia euchroma as Anti-HIV Agents. J Nat Prod., 1995; 58: 392-400.
15. Itokawa H, Shi Q, Akiyama T, Morris- Natschke SL, Lee KH Recent Advances in the Investigation of Curcuminoids. Chinese Med., 2008; 3: 11.
16. Tripathi KD. Essential of medical Pharmacology. 5th ed. New Delhi: Jaypee Brothers Medical Puiblisher (p) Ltd, 2003.
17. Kim HJ, Woo ER, Shin CG. A New Flavoured Glycoside Gallate Ester from Acerokamotoanum and Inhibitory Activity against Human Immunodeficiency Virus-1 (HIV-1) Integrase. J Nat prod, 1998; 61: 142-145.
18. Zhu K, Cordeiro ML, Atienza J, Robinson Jr EW, Chow S. Irreversible Inhibition of Human Immunodeficiency Virus type intergrase by Dicaffeolyquinic Acids. J Nat Prod, 1996; 59: 643-645.