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ANTI- HIV DRUGS FROM NATURAL SOURCES

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ABSTRACT

Anti-HIV agents are urgently required due to global and widespread infection of HIV/aids. Most of the clinically useful anti HIV agents are nucleosides but their use is limited owing to their severe toxicity, adverse effect and emergence of drug resistance. This has driven many scientists to look for new anti retroviral with better efficiency safety and affordability. There are several natural products, mostly of plant origin have been shown to possess promising activities that could assist in prevention and control of disease. The natural products that have potent anti-HIV activities were reviewed in this article. these compounds, isolated mainly from medicinal plants have been classified as alkaloids, coumarine, phenolics, proteins, sugars, flavanoids etc. the aim of this review is to report new discoveries and updates pertaining to anti HIV natural products.

Keywords: AIDS, NATURAL ANTI- HIV DRUGS, HIV

1. INTRODUCTION

The Acquired Immunodeficiency syndrome (AIDS) is characterized by abnormal host defense mechanism that predispose to infections with opportunistic organisms or the occurrence of B cell lymphoma or Kaposi's sarcoma as well as profound decrease in the count of CD4+T cells. AIDS appeared in distant and various areas of the Earth during second half of 20th century, at a moment when the immune systems of humans, as well as other bodily systems, were already saturated with exposure to a great variety of stressor agents. In AIDS the immune system is devastated & collapsed. As an estimate, 70 million people, world wide were infected with HIV since 1980 when it was recognized as an emerging disease.

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India has had a sharp increase in estimated number of HIV infections, from the first reported case in 1986 in Chennai (a commercial sex worker), then escalating to several thousands in early 1990 to around 5.7 million adults and children in 2005. With a population of over one billion, the HIV epidemics in India will have a major impact on the overall spread of HIV in Asia and the Pacific and indeed worldwide. HIV surveillance data collected by NACO is through annual unlinked anonymous testing of prenatal clinic (or antenatal clinics) and sexually transmitted infection clinic attendees.

There are two major types of HIV have been found, HIV-1 and HIV-2. HIV-1 is the cause of the world wide epidemic and is most commonly known as HIV. It is highly variable in nature and mutates readily. There are many different strains of HIV-1, which are further classified in to groups and subtypes; there are two groups – M & O. In group M there are ten genetically distinct subtypes of HIV-1, which are subtypes

A to J. group O contains another distinct group of heterogeneous virus. HIV-2 is much less pathogenic and occurs rarely mostly in West Africa.

There is urgent need of medicinal agents capable of specifically inhibiting HIV due to its globally widespread infection. Most of the clinically useful anti HIV agents are nucleosides but their use is limited due to their severe toxicity and emerging drug resistance. Natural products, of which structural diversity is so broad, are good sources for the effective discovery of anti HIV agents with decreased toxicity. Natural products having potent anti HIV activities isolated mainly from medicinal plants, which belongs different chemical classes [1-5].

2. Anti-HIV drugs of natural origin:

Nature always provides a source of drugs for various ailments. There are a number of medicinal plants, which have been reported to have anti-HIV properties. Various types of secondary metabolites obtained from natural origin showed moderate to good anti-HIV activity.

2.1 Anti-HIV drugs from Plants:

Coumarins: Coumarins such as calanolides are non-nucleoside specific reverse transcriptase inhibitors of HIV. These are obtained from various species of a tropical tree Callophyllum (family: Clusiaceae)[6]. Calanolide A**(1)**, Calanolide B**(2)** and its dihydro derivative;7,8 dihydrocalanolide B is obtained from *C. lanigerum*. These compounds protects cells from cytopathic effects of HIV-1 but inactive against HIV-2[7].Structural analogous of Calanolides; Cordatolide A and B isolated from *Callophylum cordato-oblongum* have potent inhibitory activity against HIV-1 replication[8]. Suksdorfin **(3)** is a pyrocoumarin derivative isolated from fruits of *Lomatium suksdorfii* (Family: Apiaceae) and *Angelica morii* (Family: Apiaceae) has been found to be active against HIV replication in T cell line[9-10]. Coriandrin is a type of isocoumarine is obtained from *Coriandrum sativum* and have anti-HIV as well as other antiviral activities[11]. Imperatorin is a type of furanocoumarin and isolated from *Ferula sumbul* (Family: Umbelleferae) have anti-HIV activity[12].

2.1.1 Alkaloids: HIV inhibitory activity have been found in the various types of alkaloids.There are some glycoalkaloids which are also known as sugar analogue alkaloids act by impairing the binding between CD4 and gp-120 of HIV virus and interfere the synthesis of glycoproteins; like Castanospermine **(4)** which is a indolizidine alkaloid obtained from *Castanospermum australe* (Family: Fabaceae). It inhibits the enzyme α-glucosidase as well as synergistic with Zidovudine against HIV-1 and HIV-2 without any toxicity. A sugar alkaloid 1-deoxynojirimycin which is piperidine type alkaloid obtained from Morus sp. (Mulberry) acts in the same manner[13-14]. Papaverine, an alkaloid obtained from Papaver sominiferum (Family: Papaveraceae) is reported to inhibit HIV replication in vitro. It has been also found that the production of HIV proteins is also reduced[9]. Michellamine B **(5)** is atype of atropisomeric naphthylisoquinoline alkaloid dimers isolated from the leaves of *Ancistrocladus korupensis* (Family: Ancistrocladaceae}. It act at both at early stage of the HIV life cycle by inhibiting reverse transcriptase, and at later stage by inhibiting cellular fusion and syncytium formation[15].

Buchapine is atype of quinolone containing two isoprene units and its structural isomer obtained from *Eodia roxburghiana*, inhibits cytopathic effects of HIV-1 in vitro[16]. Nitidine

is obtained from roots of *Toddalia asiatica* (Family: Rutaceae) have significant anti-HIV activity[17]. A piperidine flavone related alkaloid O-demethylbuchenavianine obtained from *Buchenavia capitata* (Family: Combretaceae) have both anti-HIV and anti-cancer activity[18]. Harmine is obtained from *Symplocos setchuensis* inhibits HIV replication in H9 lymphocytes[19]. 1-Methoxy canthionone is isolated from *Leitneria floridana* have potent anti-HIV activity[20]. Troponine A, TroponineB, and HypoglaumineB are sesquiterpene pyridine alkaloids obtained from *Trypterygium hypoglaucum* and *T. wilfordii* have potent anti-HIV activity in vitro[21]. FK-3000, a morphine-related compound obtained from methanolic extract of root tubers of *Stephania cepharantha* (family Menispermaceae12), inhibited the cytopathic effects of HIV-1on MT-4 cells. Cepharanthine isolated from the same plant, has been reported to have antiallergic, anti-inflammatory and immunomodulatory activity and also can potently inhibit HIV-1 replication[22].

2.1.2 Lignans: A number of lignans have been shown to possess antiviral activities[23]. Phyllamyricin B (**6**) and its lactone retrojusticidin B (**7**) isolated from chloroform extract of *Phyllanthus myrtifolius*/*P. urinaria* (Family: Euphorbiaceae), exhibited strong inhibition of HIV-RTase[24]. Dibenzylbutadiene lignans, anolignan A and anolignan B isolated from *Anogeissus acuminata*, showed HIV-1 RTase inhibitory activity[25]. Dibenzylbutyrolactone-type lignanolide, (–)-arctigenin (**8**) isolated from *Ipomoea cairica* and *Arctium lappa* showed anti-HIV activity that was primarily due to inhibition of HIV proviral DNA and not related to interference with HIV-1 RTase[26]. (–)Gomisin isolated from *Kadsura interior* has been found to be the most potent inhibitor of HIV replication[27]. Kadsulingnan M isolated from *Kadsura coccinea* showed an anti-HIV activity *in vitro*[28]. Demethoxyepiexcelsin obtained from methanolic extract of leaves and twigs of *Litsea verticillata* (Family: Lauraceae) showed good anti-HIV activity[29]. The ethanolic extract of the fruit rind of *Terminalia bellerica* (Family: Combretaceae), also yielded anolignan B and other lignans, which showed anti-HIV activity in vitro[30]. Globoidnan A, a lignan isolated from the methanolic extract of buds of *Eucalyptus globoidea*, inhibited the combined 3¢-processing and strand-transfer activity of HIV integrase[31].

2.1.3 Phenolics: There are several tannins and related phenolic substances which show virucidal effects in several viral systems. Several hydrolysable tannins such as chebulagic acid, punicalin and punicalagin from *Terminalia chebula* show anti-HIV activity. Corilagin and 1,3,4,6-tetra-*O*-galloyl-*b*-D-glucopyranose isolated from *Chamaesyce hyssopifolia* inhibited HIVRTase. A dimeric, hydrolysable tannin, cornusin A isolated from fruits of *Cornus oficinalis* (Family: Cornaceae) inhibited RTase from avian myeloblastosis virus[32]. Theasinensin D exhibited moderate anti-HIV activity[33].8-*C*-ascorbyl (–)-epigallocatechin showed potent anti-HIV activity[34]. Gossypol and 1,1-dideoxygossylic acid, yellow pigments from the cotton plant, are also reported to have anti-HIV activities[35]. Repandusinic acid isolated from *Phyllanthus niruri* (family Euphorbiaceae) inhibited HIV-1 RTase[36]. Monosodium and monopotassium salts of isomeric caffeic acid tetramer isolated from the aqueous acetone extract of *Arnebia eucbroma* (Boraginaceae) showed potent inhibitory activity against HIV replication[37]. Vismiaphenone D (**9**) isolated from *Vismia cayennensis* exhibited activity in the primary anti-HIV screens[38], while guttiferone A (**10**), isolated from *Symphonia globulifera* (Family: Guttiferae), provided cytoprotection of CEM-SS cells from HIV-1 infection[39]. 1,3,4,5-tetra-

O-galloylquinic acid isolated from the stem bark of the *Lepidobotrys staudti* (family Lepidobotryaceae), showed significant anti-HIV activity. Camellia-tannin H isolated from the pericarp of *Camellia japonica* showed a potent HIV-1 protease inhibitory activity. Gallic acid and galloyl glucoses isolated from *Terminalia chebula* (Family: Combretaceae) exhibited HIV integrase inhibitory activity[40-41].

A large number of macrocarpals (A–E) isolated from *Eucalyptus globulus* possessed anti-HIV RTase inhibitory activity, amongst these, macrocarpal B (**11**) was found to be most potent[42]. Mallotojaponin, a dimeric phloroglucinol derivative isolated from the pericarps of *Mallotus japonicus*, inhibited HIV-1 RTase noncompetitively as well as laxifloranone isolated from *Marila laxiflora*, showed moderate inhibition of the cytopathic effects of in vitro HIV infection[43]. The curcuminoids isolated from rhizomes of *Curcuma longa* showed modest HIV-1 and HIV-2 protease inhibitory activity[44]. Balanocarpol, hydroxylated stilbene compound isolated from *Hopea malibato* (Family: Dipterocarpaceae) exhibited modest HIV inhibitory activity[45]. Bergenin, norbergenin and methyl norbergenin isolated from methanolic extract of the aerial parts of *Ardisia japonica*(Family: Myrisinaceae) showed moderate anti-HIVactivity[46]. Phenylethanoid glycoside, calceolarioside B isolated from *Fraxinus sieboldiana* var. *angustata*, showed moderate anti HIV activity[47]. Diprenylated bibenzyl isolated from *Glycyrrhiza lepidota* (Family: Fabaceae) showed moderate anti-HIV-1activity[48]. Prenylated catechol dimer, the peltatol A isolated from *Pothomorphe peltata* (Family: Piperaceae) showed strong anti-HIV activity[49]. *Detarium microcarpum* (Family: Caesalpiniaceae) contains (-) epicatechin-3-O-gallate which blocks the binding of gp-120 to CD4(-). It is very common to other tannins and also an inhibitor of HIV Reverse Transcriptase but inhibition is not specific[50].

2.1.4 Flavonoids: These have been reported to possess a number of biological activities and are well known for their antioxidant properties. The antiviral activity of various flavonoids against several viruses in cell cultures and in animal models has been found.

Prenylated flavonoids, 6,8-diprenylaromadendrin and 6,8-diprenylkaempferol isolated from the extract of *Monotes africanus* exhibited HIV-inhibitory activity in the XTT-based, whole-cell screen[51]. Quercetin 3-*O*-(2-galloyl) *a*-L-arbinopyranose and flavonoid gallate ester isolated from ethanolic extract of *Acer okamotoanum* (Family: Aceraceae), possessed anti-HIV-1 integrase activity[52]. Biflavonoids, robustaflavone (**12**) and hinokiflavone (**13**) isolated from methanolic extracts of twigs and leaves of *Rhus succedanea* (Family: Anacardiaceae), showed strong inhibition of the polymerase of HIV-1 RTase in in vitro assay[53]. Another biflavonoid, wikstrol B obtained from extracts of roots of *Wikstroemia indica* (Family: Thymelaeaceae), showed good activity against HIV-1 in in vitro studies[54]. HIV-inhibitory pterocarpans and isoflavonoids have been reported from plants of genus *Erythrina*[55].Xanthohumol (**14**), a prenylchalcone recently isolated from hops *Humulus lupulus*, has shown HIV-1 inhibitory activity [56].

2.1.5 Quinones: Several naphthoquinones such as 1,4-naphthoquinone, vitamin K3, juglone and plumbagin showed HIV inhibitory activity[57]. A trimeric naphthoquinone, conocurvone isolated from *Conospermum incurvum* (Family: Proteaceae) showed potent anti-HIV activity[58]. A polycyclic aromatic dianthroquinone, hypericin obtained from *Hypericum perforatum* showed activity

against non-human retroviruses as well as human retroviruses in lymphocytes. It has also inhibited HIV-1 RTase[59].

2.1.6 Saponins: Actein, a tetracyclic triterpenoid saponin isolated from the rhizome of *Cimicifuga racemosa* (black cohosh), showed potent anti-HIV activity[60]. Escins, the triterpenoid saponin mixture extracted from the seeds of *Aesculus chinensis* (Family: Hippocastanaceae), was found to show moderate anti-HIV-1 protease activity[61]. Soybean saponins isolated from soybean seeds inhibited HIV-1 replication in MT-4 cells. They possess narrow therapeutic index and did not inhibit HIV-1 RTase. One of the saponins (B1) inhibits HIV-induced cell fusion in MOLT- 4 cells[62].

2.1.7 Xanthones: Swertifrancheside, a flavonone–xanthone glucoside isolated from *Swertia franchetiana* was found to inhibit HIV-1 RTase[63]. The prenylated xanthone, macluraxanthone B isolated from *Maclura tinctoria* (Family: Moraceae) exhibited moderate anti-HIV activity64.

2.1.8 Terpenes: Betulinic acid, platanic acid and oleanolic acid isolated from the leaves of *Syzigium claviflorum*, exhibited anti-HIV activity in H9 lymphocyte cell. Modified form of betulinic acid and dihydrobetulinic acids has increased anti-HIV activity, like esterification at C-3 hydroxyl resulted in more potent compounds 3-*O*-(3,3-dimethylsuccinyl) betulinic acid with tremendously improved TI values[65-66]. Uvaol (**15**) and ursolic acid (**16**) isolated from the methanolic extract of leaves of *Crataegus pinatifida* (Family: Rosaceae), showed potent inhibitory activity against HIV-1 protease[67]. Oleanolic acid isolated from methanolic extract of wood of *Xanthoceras sorbifolia* (Family: Sapindaceae), inhibited HIV-1 replication in acutely infected H9 cells. Esterification at C-3 hydroxyl of oleanolic acid resulted in 3-oxotirucalla-7,24-dien-21-oic acid with improved activity[68-69]. Moronic acid isolated from *Myrceugenia euosma* (Family: Myrtaceae), showed significant anti-HIV activity[70]. Maslinic acid isolated from *Geum japonicum*, showed potent inhibitory activity against HIV-1 protease[71]. Pentacyclic triterpenes, 1*b*-hydroxymaprounic 3-*p*-hydroxybenzoate, and 2*a*-hydroxymaprounic acid 2,3-*bis*-*p*-hydroxybenzoate isolated from the roots of *Maprounea Africana* Muell.-Arg. (Euphorbiaceae), active against HIV-1 RTase[72]. Celasdin B isolated from ethanolic extract of *Celastrus hindsii* (Family: Celastraceae), showed anti-HIV replication activity in H9 lymphocyte cells in vitro[73]. The protostanes, garcisaterpenes A and C isolated from ethyl acetate extract of bark and stems of *Garcinia speciosa*, showed significant inhibitory activities against HIV-1 RTase[74].Lanostane-type triterpene, suberosol isolated from ethanolic extract of the stems and leaves of *Polyalthia suberosa* (Family: Annonaceae) showed anti-HIV replication activity in H9 lymphocyte cells[75]. Oxygenated triterpenes, such as ganoderic acid-*a*, ganoderiol F, ganodermontriol, ganoderic acid B, ganoderiol B, and ganoderic acid C1 isolated from methanolic extracts of *Ganoderma lucidum* (Family: Polyporaceae), were found to inhibit HIV-1 induced cytopathic effects in MT-4 cells and also possessed HIV-1 protease inhibitory activity[76]. A ring-secocycloartene triterpenoid, nigranoic acid isolated from the stems of *Schisandra sphaerandra*, inhibited HIV-1 RTase and HIV-2 RTase[77]. Triterpene lactone, lancilactone C isolated from stems and roots of *Kadsura lancilimba*, also possessed inhibitory activity against HIV replication in H9 lymphocytes[78].An antimalarial sesquiterpene lactone, artemisinin (**17**), isolated from *Artemisia anuua* L. showed anti-HIV activity[79]. Shinjulactone C, isolated from *Brucea javanica* and *Brucea antidysenterica*, showed anti-HIV activity[80]. Kaurane diterpenoid, 16*b*,17-dihydroxy-*ent*-kauran-19-

oic acid (**18**) isolated from methanolic extracts of the fresh fruits of *Annona squamosa* L. (Annonaceae), significantly inhibited HIV[81]. Linearol (**88**), an *ent*-kaurane diterpenoid isolated from *Sideritis akmanii* and its semisynthetic derivatives showed significant anti-HIV activity against HIV-1 replication in H9 lymphocyte cells[82]. Phorbol ester, prostratin isolated from *Homalanthus nutans* (Family: Euphorbiaceae), showed potent HIV inhibitory property. Another phorbol diester, 12-*O*-tetradecanoylphorbol-13- acetate (TPA) isolated from methanolic extract of *Croton tiglium* (Euphorbiaceae) inhibited HIV-1-induced cytopathic effects[83]. 12-Deoxyphorbol 13-(3*E*, 5*E*-decadienoate), isolated from leaves and stems of *Excoecaria agallocha* inhibited HIV-1 RTase[84].

Diterpene lactone, andrographolide (**19**) isolated from *Andrographis paniculata* inhibited HIV-infected cells[85]. Nortripterifordin isolated from *Tripterygium wilfordii* inhibited HIV replication in H9 lymphocytes[86]. Glycyrrhizin from licorice root has shown anti-HIV-1 activity in MT-4 cells[87]. Diterpenes from *Homolanthus acuminatus* and *Chrysobalanus icaco* have shown HIV-inhibitory activity in *in vitro* screening[88]. Limonin and nomilin isolated from *Citrus* spp. (Family: Rutaceae) exhibited anti-HIV-1 activity in different cell-based assays[89]. A limonoid, clausenolide-1-ethyl ether isolated from rhizomes of *Clausena excavate* (Rutaceae), exhibited HIV inhibitory activity in 1A2 cell line in syncytium assay90.

2.1.9 Peptides: Palicourein, a cyclic polypeptide, isolated from organic extract of the tropical tree *Palicourea condensata* (Family: Rubiaceae), inhibits the *in vitro* cytopathic effects of HIV-1RF infection of CEM-SS cells[91]. Macrocyclic peptides, cycloviolins isolated from tropical plant *Leonia cymosa* and circulins, a group of cyclic peptides isolated from *Chassalia parvifolia* (Rubiaceae), exhibited anti-HIV activity92-93.

2.1.10 Proteins: Ribosome inactivating proteins (RIPs) are those that specifically interfere with eukaryotic protein translation. RIPs are widely distributed in nature but are found predominantly in plants, bacteria and fungi. They vary greatly in their physical properties and cellular effects. Trichosanthin, *b*-momorcharin and L-momorcharin inhibited HIV replication in acutely and chronically infected cells of lymphocyte and mononuclear phagocyte lineageand some other cells. Saporin and luffin, also exhibited anti- HIV integrase activity[94]. Anti-HIV proteins, MAP30, TAP29 isolated from *Momordica charantia* seeds and *Trichosanthes kirilowii* tubers, exhibited a dose-dependent inhibition of cell-free HIV-1 infection and replication[95]. GAP31 isolated from *Gelonium multiflorum* inhibited HIV-1 integrase[96]. *Myrianthus holstii* lectin (MHL), a 9284-Da, cysteine-rich protein isolated from aqueous extract of *M. holstii* (Family: Moraceae), showed anti-HIV activity[97].

2.1.11 Carbohydrates: A polysaccharide fraction isolated from *Thuja occidentalis* (Family: Cuppressaceae), exhibited HIV-1 reverse transcriptase activity[98]. Several sulphated polysaccharides were shown to inactivate HIV by binding with the surface envelope glycoprotein gp120. Niruriside, isolated from the methanolic extract of leaves of *Phyllanthus niruri* L, is a novel specific inhibitor of REV protein/RRE RNA[99].

2.2 Anti-HIV drugs from microorganisms:

Complestatin A and B, isocomplestatin and chloropeptin isolated from the fermentation broth of *Streptomyces* sp. MA7234 showed anti-HIV activities[100]. Siamycins, polypeptides isolated from *Streptomyces* were found to

inhibit HIV infection *in vitro*[101]. Tat is a small HIV protein essential for both viral replication and progression of HIV disease. Durhamycin A isolated from the methyl ethyl ketone extract of fermentation broth of *Actinoplanes durhamensis*, was found to be a potent inhibitor of tat transactivation[102]. Equisetin, obtained from the fungus *Fusarium heterosporum*, inhibits HIV-1 replication[103]. Integrastatins A and B, isolated from an endophytic fungus *Ascochyta* sp., inhibited the strand-transfer reaction of HIV-1 integrase[104]. Integracins A–C are three novel dimeric alkyl aromatic inhibitors of HIV-1 integrase, discovered from the *in vitro* assay[105]. Integracides A and B, isolated from the fermentation broth of a *Fusarium* sp. exhibited potent inhibitory activity against strand-transfer reaction of HIV-1 integrase[106]. [Ile7]surfactin and [Leu7]surfactin isolated from *Bacillus subtilis natto* are cyclic depsipeptides, exhibited moderate anti-HIV activities for HIV-1 cytopathic effects in XTT formazan assay[107]. Cytosporic acid (**20**) isolated from fermentation broth of filamentous fungus *Cytospora* sp. exhibited HIV-1 integrase activity[108].

2.3 Anti-HIV drugs from marine organisms:

Marine organisms have yielded a number of compounds exhibiting a range of biological activities. Several marine natural products have shown anti-HIV activity.

2.3.1Sterols: Marine sponges are known to produce a variety of steroids among which polyoxygenated steroids have remarkable biological and pharmacological activities. In particular, sulphated steroids have been examined for their anti-HIV activity. Haplosamates A and B, sulphated sterols isolated from Philippine sponge *Xestospongia* sp. inhibited HIV integrase, as well as clathsterol isolated from red sea sponge, *Clathria* sp. inhibited HIV-1 RTase[109-110]. Halistanol sulphates G and H isolated from marine sponge *Pseudoaxinissa digitata* have shown cytoprotective effect against HIV-1[111].

2.3.2 Terpenes: A diterpene, Cyanthiwigin B, isolated from Jamaican sponge *Myrmekioderma styx* was active against HIV-1 and cembrane diterpenoids, lobohedleolides exhibited moderate anti-HIV inhibitory activity *in vitro*[112]. Avarone (**21**) and avarol (**22**) isolated from the sponge *Dysidea avara* showed anti-HIV activity. Illimaquinone isolated from red sea sponge *Smenospongia* sp. also exhibited anti-HIV activity by inhibiting specifically RNase H[113].

2.3.3 Alkaloids: Sponge-derived polycyclic guanidine alkaloids exhibit a range of biological activities, including anticancer, antifungal, antimicrobial and antiviral activities. Dehydrocrambine and A Crambescidin 826 inhibited HIV-1 envelope-mediated fusion in vitro[114]. An unusual red pigment, Trikendiol isolated from the sponge *Trikentrion loeve,* was found to be active in a CEM- 4 HIV-1 infection assay,that measures inhibition of cytopathogenic effect of the virus[115]. Batzelladines A and B isolated from the bright red Caribbean sponge of genus *Batzella* were found to be active in the cell-based assay that measures the binding of gp120 to CD4-positive T-cells[116]. Manzamine alkaloids, ent-12,34-oxamanzamine E, ent-12,34-oxamanzamine F and 12,34-oxamanzamine A isolated from sponge *Cryptosporidium parvum* and *Toxoplasma gondii*), were active against AIDS OI-pathogens[117].

2.3.4 Carbohydrates: Several sulphated polysaccharides were found to be inhibitors of the replication of HIV-1 *in vitro*, due to presence of polyanionic charges[118]. Sulphated

water-soluble polysaccharides such as agarocolloids and carageenans, isolated from gametic, carposporic and tetrasporic stages of the Mediterranean red alga *Asparagopsis armata* were found to be HIV inhibitors and inhibited HIV replication in cell culture without any toxicity to the host cells[119]. A galactan sulphate, isolated from an aqueous extract of the red seaweed *Aghardhiella tenera*, exhibited inhibition of the cytopathic effect of HIV-1 and HIV-2 in MT-4 cells[120]. A natural sulphated polysaccharide Rhamnan sulphate, isolated from Chlorophyta, *Monostroma latissimum* is exhibited antiviral activity against HSV-1, HCMV and HIV-1[121]. Various compounds of sulphated polysaccharides obtained from species of algae (Family: *Gigartaceae* and *Solieriaceae*) inhibit HIV replication in vitro by blocking the absorption of virus particles to cell through a selective action[122].

2.3.5 **Peptides:** Microspinosamide, a cyclic depsipeptide, was isolated from extracts of the marine sponge *Sidonops microspinosa*, exhibited the inhibition of the cytopathic effect of HIV-1 infection in an XTT-based *in vitro* assay[123]. A cyclic depsidecapeptide, callipeltin A was isolated from a shallow water sponge of the genus *Callipelta*, exhibited anti- HIV activity[124].

2.3.6 Proteins: Cyanovirin-N is a 11-kDa protein, isolated from the cyanobacterium (blue-green alga) *Nostoc ellipsosporum.* It irreversibly inactivates both laboratory strains and primary isolates of HIV-1 and HIV-2 at low nanomolar concentrations, as well as, it aborts cell-to-cell fusion and transmission of HIV infection[125].

2.4 Anti-HIV drugs from minerals:

Colloidal silver solution have been used for HIV pathogens, it kills not only the present virus form, but future forms as well due to its catalytic nature[126]. Ozone also inactivates extracellular HIV at non- cytotoxic concentrations, it disrupts viral particle, inactivates reverse transcriptase and a perturbation of the virus ability to bind its receptor on target cells[127].

2.5 Miscellaneous natural Anti-HIV agents:

There are some naturally occurring substances that could help in more effective treatments for AIDS. Lysozyme is a potent AIDS-fighting protein naturally found in tears, saliva and urine of pregnant women, and breaks down the AIDS virus. It has been suspected that lysozyme together with ribonuclease of urine, break down the genetic material of the HIV and prevent the replication of virus[128].
Bovine milk contains a number of proteins such as lactoferrin, lactoperoxidase, glycolactin, lactogenin, lactoglobulin, casein etc . These proteins inhibited HIV-1 reverse transcriptase, protease and integrase to different extents[129].
Various types of antifungal proteins were isolated from seeds of leguminous plants, including french bean, cowpea, field bean, mung bean, peanut and red kidney bean, have high potency in inhibiting HIV-1 protease HIV-1 integrase, HIV-1 reverse transcriptase[130].

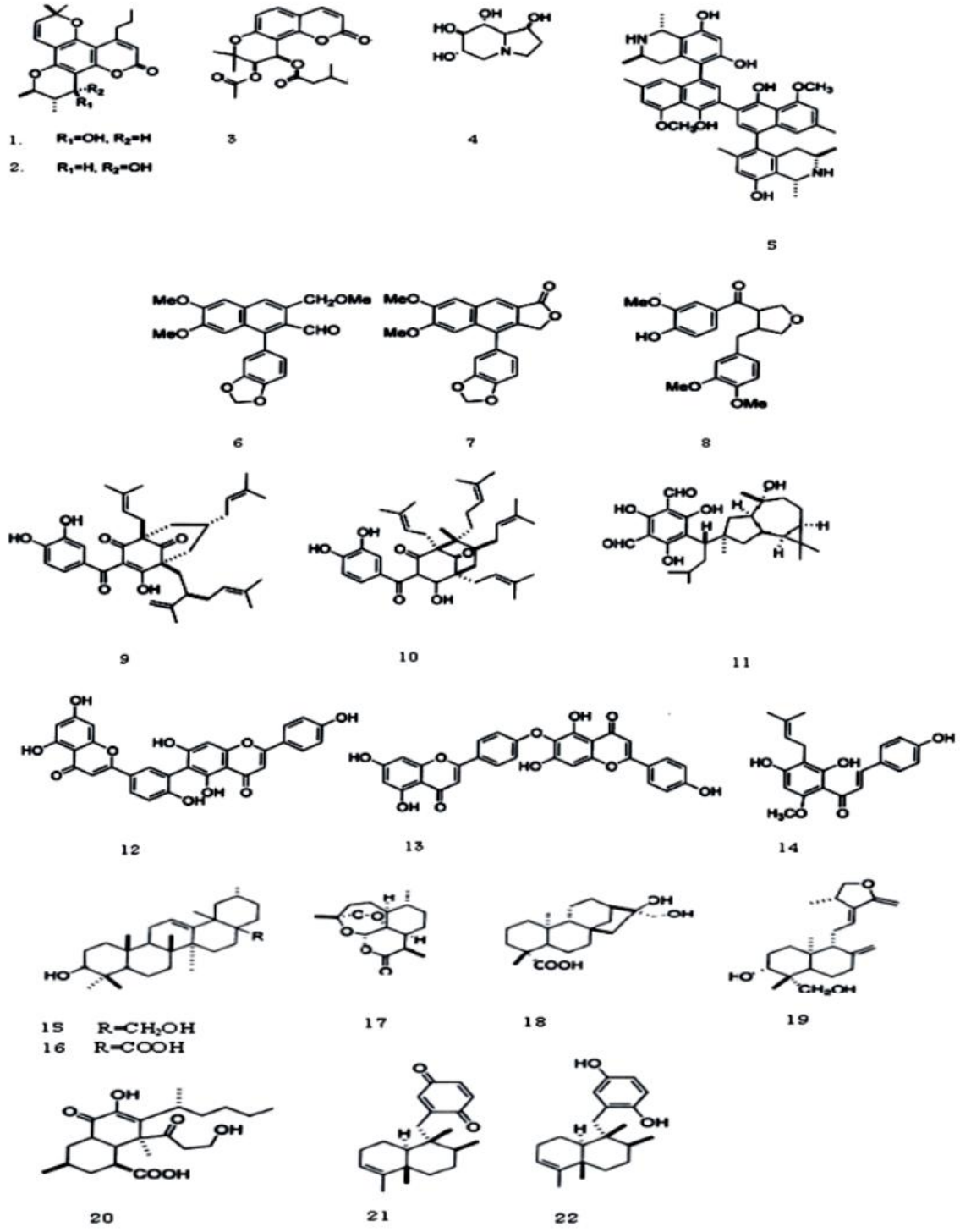

FIG: ANTI- HIV DRUGS FROM NATURAL SOURCES

3. Conclusion

Biodiversity of the plant kingdom has always provided a source of new drug candidates for almost all disease areas. The number of compounds exhibiting anti-HIV activity and isolated from natural sources is increasing steadily. In the era of extensive research, great progress has been achieved in the discovery of potent anti-HIV agents from nature. A number of natural products have been used as lead compounds because of their specific activity and low toxicity. Given the escalating incidence of HIV-1 resistance to standard antiretroviral drugs and the need for agents that are less toxic and expensive than the ones currently in use, the search for new treatments amongst these natural products is warranted.

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