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Ethnomedicinal plants and other natural products with anti-HIV active compounds and their putative modes of action

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The use of ethnomedicines to manage HIV/AIDS has recently gained public interest, although harmonization with official HIV/AIDS policy remains a contentious issue in many countries. Plants and other natural products present a large repertoire from which to isolate novel anti-HIV active compounds. In this literature survey, 55 plant families containing 95 plant species, and other natural products, were found to contain anti-HIV active compounds that included diterpenes, triterpenes, biflavonoids, coumarins, caffeic acid tetramers, hypericin, gallotannins, galloylquinic acids, curcumins, michellamines, and limonoids. These active compounds inhibited various steps in the HIV life cycle. However, further studies are needed to determine their interactions with current regimes of antiretroviral drugs. More clinical trials of candidate drugs developed from these novel compounds are also encouraged.

Key words: Anti-HIV active compounds, other natural products, plants.

INTRODUCTION

In 2008, an estimated 2.7 million new HIV infections occurred worldwide; this was 30% lower than the 3.5 million new infections at the peak of the epidemic in 1996 (UNAIDS, 2009). Sub-Saharan Africa remains the most heavily affected region, accounting for about 71% of all new HIV infections in 2008. There are two related but distinct types of HIV: HIV-1 and HIV-2 (Fletcher et al., 2002). HIV-1 is the most pathogenic and causes over 99% of HIV infections (Cos et al., 2004). HIV-2 is also known to cause AIDS but is much less prevalent, being present in fewer and isolated geographic locations such as West Africa. Therefore, most research is done on HIV-1 (Klos et al., 2009).

AIDS-related diseases remain one of the leading causes of death globally. According to UNAIDS, the number of people living with HIV/AIDS worldwide was estimated at 33.4 million in 2008; >20% higher than the

number in 2000 (UNAIDS, 2009). It was estimated that 2million deaths due to AIDS-related illnesses occurred worldwide in 2008; this was ~10% lower than in 2004 (UNAIDS, 2009). The declines in new infections and AIDS-deaths may be attributed to the scale-up of anti-retroviral therapy (ART) programmes, especially in the developing world. As of December 2008, approximately 4 million people in low- and middle-income countries were on ART, representing a 10-fold increase over five years (UNAIDS, 2009). In eastern and southern Africa, ART coverage rose from 7% in 2003 to 48% in 2008 (UNAIDS, 2009).

Despite this impressive progress, Chinsembu (2009) reports that poverty in southern Africa still plays a major role in the dynamics of the HIV/AIDS. There are concerns that free public sector ART programmes are not sustainable due to their heavy reliance on donor funding. Besides funding, access to treatment still has many shortcomings, including lack of confidentiality, lack of bed space, lack of transport to hospitals, shortages of qualified health workers, long queues, the criterion of treatment supporter, and serious side-effects now causing new forms of stigma (Chinsembu, 2009). ART of

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HIV-infected patients has also been associated with the development of lipodystrophy (LD). LD is characterized by peripheral fat loss (lipoatrophy) and central fat accumulation which may result in thin facial pads, thin arms and legs, pot-bellies, or 'buffalo humps', leaving patients stigmatized (Lindegard et al., 2004). Thus, while acknowledging that current antiretroviral drugs are vitally important in improving the quality and prolonging the life of HIV/AIDS patients, the drugs still have many disadvantages including resistance, toxicity, limited availability, high cost and lack of any curative effect (Vermani and Garg, 2002). These shortcomings of conventional ART continue to open new vistas in the use of ethnomedicinal plants and other natural products for the management of HIV/AIDS.

In many countries, the inclusion of anti-HIV ethnomedicines and other natural products in official HIV/AIDS policy is an extremely sensitive and contentious issue (Chinsembu, 2009). It is sensitive because anti-HIV ethnomedicines and other natural products can easily become a scapegoat for denial and inertia to roll-out ART (Chinsembu, 2009). It is also contentious because in various resource-poor settings, government-sponsored ART programmes discourage the use of traditional medicines, fearing that the efficacy of antiretroviral drugs may be inhibited by such natural products, or that their pharmacological interactions could lead to toxicity (Hardon et al., 2008; Chinsembu, 2009). Reliance on anti-HIV plants and other natural products can also lead to poor adherence to ART (Langlois-Klassen et al., 2007). Thus, many governments still have contradictory attitudes towards the use of anti-HIV plants and other natural products in the management of HIV/AIDS, discouraging them within ART programmes, and supporting them within other initiatives of public health and primary health care (Chinsembu, 2009).

In essence, many HIV-infected persons have access to antiretroviral drugs, but some still use ethnomedicinal plants and other natural products to treat opportunistic infections and offset side-effects from antiretroviral medication (Hardon et al., 2008). Medicinal plants and other natural products including mushrooms are used as primary treatment for HIV-related problems such as skin disorders, nausea, depression, insomnia, and body weakness (Babb et al., 2004). In the case of rural communities, formal biomedical services are also hardly accessible. Thus, whilst the majority of HIV/AIDS patients rely on ART, some still have faith in the use of traditional medicines. Understandably, HIV/AIDS patients are vulnerable in their choice of treatments (Hardon et al., 2008), such that some of them do vacillate from conventional ART programmes to traditional medicines and vice versa; they want to have the best of both worlds (Hardon et al., 2008; Chinsembu, 2009).

As early as 1989, the World Health Organization (WHO) had already voiced the need to evaluate ethnomedicines and other natural products for the manage-

ment of HIV/AIDS: "In this context, there is need to evaluate those elements of traditional medicine, particularly medicinal plants and other natural products that might yield effective and affordable therapeutic agents. This will require a systematic approach", stated a memorandum of the WHO (1989a). Thus, African governments expressed the need for a concerted, systematic and sustained effort at both local and regional levels to support and biochemically validate African traditional medicines (UNAIDS, 1998). To popularize this commitment, the Organization of African Unity (African Union) Heads of State and Government declared the period 2000-2010 as the Decade of African Traditional Medicine. In addition, the Director General of WHO, declared 31st August of every year as the African Traditional Medicine Day (Homsy et al., 2004). All these initiatives demonstrate the need to mainstream and institutionalize traditional medicine into the formal health care system.

The importance of investing in the high growth sectors of biotechnology and phytomedicine was also articulated in the founding document of the New Partnership for Africa's Development (NEPAD), and adopted by the African Biosciences Initiative (NEPAD, 2001; African Biosciences Initiative, 2005). Herbal medicines provide rational means for the treatment of many diseases that are obstinate and incurable in western systems of medicine (Vermani and Garg, 2002). Phytomedicines are regaining patient acceptance because they have fewer side effects, are relatively less expensive, are easy to use (Short, 2006), and have a long history of use (Vermani and Garg, 2002). Medicinal effects of plants tend to normalize physiological function and correct the underlying cause of the disorder (Murray and Pizzorno, 1999). Furthermore, medicinal plants are renewable in nature unlike the synthetic drugs that are obtained from non-renewable sources of basic raw materials such as fossil sources and petrochemicals (Samanta et al., 2000). Cultivation, gathering, and selling of medicinal plants can also be a source of income for poor families (Reihling, 2008).

Due to the renewed public interest in phytomedicines, NEPAD's Southern Africa Network for Biosciences (SANBio) has launched a flagship project to validate ethnomedicines for effective and affordable treatment of HIV/AIDS. Scientific validation of putative herbal plants used in the management of HIV/AIDS is done at the Council for Scientific and Industrial Research (CSIR) in Pretoria, South Africa. Prior to this NEPAD/SANBio initiative, there existed only a handful of workers in Africa that had attempted to screen medicinal plants for anti-HIV active compounds: Moore and Pizza (1992); Iwu (1993); Boyd et al. (1994); Muanza et al. (1995); Matsuse et al. (1999); Bessong et al. (2005); Mills et al. (2005); Abere and Agoreyo (2006); Kisangau et al. (2007); Moore et al. (2007); Quattara et al. (2007); Igbinosa et al. (2009) and Klos et al. (2009).

Sub-Saharan Africa has rich plant biodiversity and a

long tradition of medicinal use of plants with over 3,000 species of plants used as medicines (Van Wyk and Gericke, 2000; Scott et al., 2004). Several of these plants may contain novel anti-HIV compounds. In the past decade, there has been a sustained bioprospective effort to isolate the active leads from plants and other natural products for preventing transmission of HIV and management of AIDS (Asres et al., 2001; Vermani and Garg, 2002). Screening of plants based on ethnopharmacological data increases the potential of finding novel anti-HIV compounds (Farnsworth, 1994; Fabricant and Farnsworth, 2001). Indigenous knowledge of medicinal plant use also provides leads towards therapeutic concept thereby accelerating drug discovery; this is now being called reverse pharmacology (Chinsebu, 2009; Kaya, 2009). Thus, it is important to search for novel antiretroviral agents which can be added to or replace the current arsenal of drugs against HIV (Klos et al., 2009).

Despite the rich African repertoire from which to select medicinal plants, traditional herbal medicines are still not well-researched (Mills et al., 2005), and African knowledge of herbal remedies used to manage HIV/AIDS is scanty, impressionistic and not well documented (Kayombo et al., 2007). Africa is also awash with fake AIDS cures (Amon, 2008). HIV/AIDS is a relatively new human disease, with few ethnobotanical treatments, but logical associations of treatments for other likely viral infections (such as hepatitis B) and closely linked disease states or symptoms (wasting, diarrhoea, lymphadenopathy, skin lesions, cough, and genital ulcers) can increase the prospect of finding new plant leads as potential anti-HIV agents (WHO, 1989ab; Cardellina and Boyd, 1995; Lewis and Elvin-Lewis, 1995). Natural products can be selected for biological screening based on ethnomedical use, random collection and a chemotaxonomic approach i.e. screening of species of the same botanical family for similar compounds. However, the follow-up and selection of plants based on literature leads would seem to be the most cost-effective way of identifying plants with anti-HIV activity (WHO, 1989a).

The general objective of this study was to carry out a desktop survey of the literature for plants and other natural products with anti-HIV activity. Such a desktop survey is an important prerequisite and starting point in the search for novel HIV/AIDS treatments in and outside Africa. The specific objectives of the current study were to search for: (a) plants and other natural products with known active compounds and mechanisms of action, and (b) plants and other natural products with known or unknown active compounds and/or known or unknown mechanisms of action against HIV and AIDS-related opportunistic infections.

METHODOLOGY

The key words "plants with anti-HIV activity" were searched in PubMed Central, the United States of America National Library of

Medicine's digital archive of biomedical and life sciences journal literature. During the literature search which lasted 3 months, between 224 - 250 journal publications were reviewed. Wherever possible, families and species of plants and other natural products, their active compounds and modes of action, were listed in tables according to their taxonomic families, in alphabetical order. Evidence of use of plants and other natural products against HIV/AIDS was also documented.

RESULTS

Plants and other natural products with known active compounds and mechanisms of action

The search documented 40 plant families containing 65 plant species, two fungal families containing four mushroom species (*Ganoderma lucidum*, *G. frondosa*, and *G. pfeifferi*; and *Inonotus obliquus*), and one blue-green algae (*Nostoc ellipsosporum*), respectively, with known anti-HIV active compounds. Interestingly, some of the ethnopharmacological data that was downloaded (dating as far back as 1989) had not been included in previous reviews. The families (in alphabetical order) and species of plants and other natural products with known active compounds and their modes of action are listed in Table 1.

Plants and other natural products with known or unknown active compounds and/or known or unknown mechanisms of action against HIV and AIDS-related opportunistic infections

A total of 30 plant species from 15 families were reported to have activities against HIV or HIV related sicknesses, and also against other diseases such as cancer (*Mangifera indica*) (Muaza et al., 1995), fungal infections (*Fragaria virginiana* and *Potentilla simplex*) (Webster et al., 2008), inflammation, and general microbial opportunistic infections (Iwu, 1993) (Table 2). However, their active compounds or modes of actions were not well understood. Aqueous and ethanol extracts of *Baissea axillaries* (Abere and Agoreyo, 2006), *Melissa officinalis* (Geuenich et al., 2008), and *Leonotis leonurus* (Klos et al., 2009) were reported to possess activities against HIV-1.

Several unknown active components of plants belonging to the family Euphorbiaceae (*Jatropha curcas*, *J. multifida*, *Spirostachys africana* and *Trigonostema xyphophylloides*) were found to possess anti-HIV activities by inhibiting HIV-1 cell entry (Park et al., 2009). *Jatropha* species were also found to inhibit HIV-induced cytopathic effects (Igbinosa et al., 2009; Matsuse et al., 1999) but caused genotoxicity during ART (Muaza et al., 1995; Van den Beukel et al., 2008) (Table 2).

DISCUSSION

Several chemical compounds were found to interfere with

Table 1. Plants and other natural products with known active compounds and modes of action against HIV

Family species	Active constituents	Mechanism of action	References
Acanthaceae			
<i>Andrographis paniculata</i>	Aqueous extracts of leaves	Inhibition of HIV protease and reverse transcriptase.	Otake et al., 1995
	Diterpene lactones (andrographolide)	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	Calabrese, 2000
Aceraceae			
<i>Acer okamotoanum</i>	Flavonoid gallate ester	Anti-HIV-1 integrase activity	Kim et al., 1998
Agaricaceae			
<i>Lentinus edodes</i> (Berk.) Singer	Sulfated lentinan	Prevent HIV-induced cytopathic effect	Suzuki et al., 1989
Amaryllidaceae			
<i>Galanthus nivalis</i> L.	Plant lectins: <i>G. nivalis</i> agglutinin (GNA),	Potent inhibitors that stop the spread of HIV among lymphocytes by targeting gp120 envelope glycoprotein; most prominent anti-HIV activity is found among MBLs; GNA has specificity for terminal $\alpha(1-3)$ -linked mannose residues; HHA recognizes both terminal and internal $\alpha(1-3)$ - and $\alpha(1-6)$ -linked mannose residues	Saidi et al., 2007
<i>Hippeastrum</i> hybrids	<i>Hippeastrum</i> hybrid agglutinin (HHA), and monocot mannose-binding lectins (MBLs)		Cited in Balzarini et al., 2004
Anacardiaceae			
<i>Rhus succedanea</i> L.	Biflavonoids, robustaflavone and hinokiflavone	Strong inhibition of the polymerase of HIV-1 reverse transcriptase	Lin et al., 1997
Ancistrocladaceae			
<i>Ancistrocladus korupensis</i>	Michellamines A and B	Anti-HIV -1 and anti-HIV-2 activities. Act at early stage of the HIV life cycle by inhibiting reverse transcriptase and at later stages by inhibiting cellular fusion and syncytium formation	Boyd et al., 1994 Manfredi et al., 1991
Annonaceae			
<i>Polyalthia suberosa</i>	Lanostane-type triterpene, suberosol	Anti-HIV replication activity in H9 lymphocytes cells <i>in vitro</i>	Li et al., 1993
Apiaceae			
<i>Lomatium suksdorfii</i>	Suksdorfii	Suppress HIV-1 viral replication in H9 lymphocyte cells	Yu et al., 2007

Table 2. Contd.

Araliaceae			
<i>Panax ginseng</i> C.A. Meyer	-	Increases CD4/8 cells; has serious side effects	Sung et al 2005
Areschougiaceae			
<i>Agardhiella tenera</i> (J. Agardh) F. Schmitz	Sulfonated polysaccharides	inhibit the cytopathic effect of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) in MT-4 cells	Witvrouw et al., 1994
Asphodelaceae			
<i>Bulbine alooides</i>	Aqueous and ethanol extracts	Extracts of <i>B. alooides</i> , <i>H. sobolifera</i> , Extracts of <i>B. alooides</i> retained HIV-1 protease inhibition after dereplication to remove non-specific tannins/polysaccharides	Klos et al., 2009
Asteraceae			
<i>Achyrocline satureioides</i> (Lam.) DC (Marcela);	Two dicaffeoylquinic acids: 3,5-dicaffeoylquinic acid, and 1-methoxyoxalyl-3,5-dicaffeoylquinic acid	Potent and irreversible inhibition of HIV-1 integrase	Zhu et al., 1999; Robinson et al, 1996
<i>Arctium lappa</i> (Burdock)	Wedelolactone (a coumarin derivative); orobol (an isoflavone derivative)	Inhibit HIV-1 replication, block cell-to-cell transmission of HIV-1	Yao et al., 1992
Boraginaceae			
<i>Arnebia euchroma</i> (Royle) Jonst	Monosodium and monopotassium salts of isomeric caffeic acid tetramer	Inhibitory activity against HIV replication in acutely infected H9 cells	Kashiwada, 1995
Cannabaceae			
<i>Humulus lupulus</i>	Xanthohumol	HIV-1 inhibitory activity as well as HIV-1-induced cytopathic effects, production of viral p24 antigen and reverse transcriptase in C8166 lymphocytes.	Wang et al., 2004
Celastraceae			
<i>Tripterygium hypoglaucum</i>	Triptonine A and Triptonine B	Exhibit potent <i>in vitro</i> anti-HIV activity	Duan et al., 2000
<i>Celastrus hindsii</i>	Celasdin B	Anti-HIV replication activity in H9 lymphocytes cells <i>in vitro</i> Inhibit HIV replication in H9 lymphocytes	Kuo and Kuo, 1997
<i>Tripterygium wilfordii</i> Hook F	Diterpene lactones (nortriptiferodin)		Duan et al., 1999

Table 1 Contd.

Clusiaceae			
<i>Callophyllum cordato-oblongum</i>	Cordatolide A and B	Inhibitory activity against HIV-1 replication	Dharmaratne et al., 2002 Buckheit 1999
	(+)-calanolide A	Inhibit cytopathic effects of HIV-1 in T-cell lines, including both CEM-SS cells and MT-2 cells	Xu et al., 2000
<i>Marila laxiflora</i>	Laxofloranone	Novel non-nucleoside reverse transcriptase inhibitor with potent anti-HIV-1 activity	Bokesch et al., 1999
<i>Symphonia globulifera</i>	Guttiferone A	Inhibition of the cytopathic effects of in vitro HIV infection	Gustafson, 1992
<i>Hypericum perforatum</i> L.	Hypericin, 3-hydroxy lauric acid	Cytoprotection of CEM-SS cells from HIV-1 infection; inhibition of HIV-1 replication; anti-HIV activity with little or no cytotoxicity	Birt et al., 2009 Maury et al 2009
Combretaceae			
<i>Combretum molle</i> R.Br. ex G. Don	Gallotannin	Inhibits RNA-dependent-DNA polymerase activity of HIV-1 reverse transcriptase.	Bessong et al., 2005
<i>Terminalia chebula</i>	Gallic acid and galloyl glucose	Inhibits ribonuclease H activity of reverse transcriptase; also has HIV integrase inhibitory activity.	Ahn, 2002
Dipterocarpaceae			
<i>Monotes africanus</i>	Prenylated flavonoids,	HIV-inhibitory activity in XTT-based, whole cell screen	Meragelman et al., 2001
<i>Vatica astrotricha</i>	6,8-diprenylaromadendrin and 6,8-diprenylkaempferol Prostratin, a 12-deoxyphorbol	Inhibition of HIV-1 entry; blocks HIV-1 replication at the entry step	Park et al., 2009 Birt et al., 2009
Euphorbiaceae			
<i>Homalanthus nutan</i> (G. Forst.)	Prostratin, a 12-deoxyphorbol	Putative mechanisms 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-cells; hence it is used to flush out latent HIV from lymph nodes during antiretroviral therapy	Cited in review by Vermani and Garg, 2002 Johnson et al., 2008; Cited in review by Gupta et al, 2005

Table 1. Contd.

Fabaceae			
<i>Acacia auriculiformis</i> A. Cunn. ex. Benth.	Saponins, alkaloids	Anti-HIV activity	Mandal et al 2005; Singh et al., 2005; Parekh and Chanda 2006 ;
<i>Peltophorum africanum</i> Sond.	Gallotannin	Inhibits RNA-dependent-DNA polymerase activity of HIV-1 reverse transcriptase; inhibits ribonuclease H activity of reverse transcriptase	Bessong et al., 2005
Ganodermataceae			
<i>Ganoderma lucidum</i>	Ganoderiol Ganodermanontriol, Ganoderic acid.	and Inhibition of HIV-1 induced cytopathic effect in MT-4 cells.	Lindequist et al., 2005
<i>Ganoderma</i> species including <i>G. lucidum</i> , <i>G. frondosa</i> , and <i>G. pfeifferi</i>	Several triterpenes such as ganoderiol F (6a), ganodermanontriol (7a), and ganoderic acid B (8a); immunomodulators such as (1-6)- β -D-glucan, heteropolysaccharides, polysaccharide-protein complex, glycoproteins, (1-3)- β -D-glucan with (1-6)- β -D-glucosyl branches, complex mixture of polysaccharides and lignin, heteroglucans, glucoronoxylomannans, and lectins	Inhibits HIV-1 protease. Antiviral agents against HIV-1: ganoderiol F (6a) and ganodermanontriol (7a) inhibit HIV-1 induced cytopathic effect; ganoderic acid B (8a) inhibits HIV-1 protease. Lignins inhibit HIV protease; Sulfated (1-3)- β -D-glucan with (1-6)- β -D-glucosyl branches prevent HIV-induced cytopathic effect; polysaccharide-protein complexes inhibit HIV-1 gp120 binding to CD4 receptors and reverse transcriptase	Cited in review by Lindequist et al., 2005
Gentianaceae			
<i>Swertia franchetiana</i>	Flavonone-xanthone glucoside	Inhibits HIV-1 reverse transcriptase	Wang et al., 1994
Guttiferae			
<i>Calophyllum teysmannii</i> Miq.	(-)-calanolide B	Less activity than the A form	Cited in review by Gupta et al., 2005
Hymenochaetaceae			
<i>Inonotus obliquus</i>	Water-soluble lignins	Inhibit HIV-1 protease	Ichimura et al., 1998
Hypericaceae			
<i>Garcinia speciosa</i>	Protostanes, garcisaterpenes A and C	Inhibitory activity against HIV-1 reverse transcriptase	Rukachaisirikul, 2003

Table 1 Contd.

Lamiaceae			
<i>Melissa officinalis</i>	Rosmarinic acid	Inhibit HIV-1 virions carrying different X4 and R5 HIV-1 Envs as well as the heterologous VSV-G, interferes with MoMLV infection; inhibit fusion of HIV-1 particles with cells.	Geuenich et al., 2008
<i>Mentha piperita</i> L. <i>Prunella vulgaris</i> L.	Sulfonated polysaccharides	Inhibit HIV-1 particles carrying R5 Envs; inhibit HIV-1 replication; target HIV-1 virion (virucidal).	Hauber et al., 2009; Yao et al., 1992;
<i>Sideritis akmanii</i>	Linearol	Anti-HIV replication in H9 lymphocyte cells	Bruno et al., 2002
Magnoliaceae			
<i>Magnolia</i> spp.	Neolignans e.g. magnolol 1 and honokiol 2	Antioxidant, antidepressant, induces apoptosis in tumor cells, weak anti-HIV-1 activity	Amblard et al., 2007
Menispermaceae			
<i>Epinetrum villosum</i> (Exell) Troupin	Cycleanine, bisbenzylisoquinoline alkaloid	a Acts against HIV-2 but is 10-times less active against HIV-1	Otshudi et al., 2005
<i>Stephania cepharantha</i>	Cepharanthine	Potently inhibit HIV replication	Ma et al., 2002
Musaceae			
<i>Musa acuminata</i>	BanLec, a jacalin-related lectin	Binds to glycosylated viral envelopes and blocks viral entry, hence is a good microbicide; potent inhibitor of HIV-1 replication	Swanson et al., 2010
Myrothamnaceae			
<i>Myrothamnus flabellifolius</i> (Welw.)	Polyphenols, gallotannins, 3,4,5-tri-O-galloylquinic acids	Polyphenols protect cell membranes against free radical-induced damage; gallotannins have anti-burn properties; 3,4,5-tri-O-galloylquinic acids have anti-HIV reverse transcriptase activity	Moore et al., 2005; Moore et al., 2007
Nostocaceae			
<i>Nostoc ellipsosporum</i>	Cyanovirin-N, an 11 KDa anti-HIV-1 protein	Inhibits HIV-1 replication through its vivid binding to HIV-1 gp120 and as a result, inactivates the viruses and blocks the fusion of viruses to the cell membrane	Gustafson et al., 1997; cited in Balzarini et al., 2004
Phyllanthaceae			
<i>Phyllanthus niruri</i> L.	Niruriside	Specific inhibitor of REV protein/RRE RNA	Qian-Cutrone, 1996
Physalacriaceae			
<i>Flammulina velutipes</i> (Curt.: Fries) Singer	Velutin	Inhibition of HIV-1 reverse transcriptase	Wang and Ng, 2001

Table 1 Contd.

Phytolaccaceae			
<i>Phytolacca Americana</i> L	Pokeweed antiviral protein (PAP)	PAP has broad spectrum antiviral activity against HIV; it is used as an antiviral microbicide; its anti-HIV-1 activity is superior <i>in vitro</i> compared to zidovudine (AZT)	Tumer et al., 1997; Uckun et al., 1998; D'cruz et al., 2004
Pinaceae			
<i>Pinus parviflora</i> Siebold & Zucc	PC6, an extract from cones, has potent immune modulatory activities	Inhibits replication of HIV-1 via reverse transcriptase and modification of microenvironment	Tamura et al., 1991
<i>Pinus parviflora</i> Siebold & Zucc	PC6, an extract from cones, has potent immune modulatory activities	Inhibits replication of HIV-1 via reverse transcriptase and modification of microenvironment	Tamura et al., 1991
Punicaceae			
<i>Punica granatum</i> L	PJ-S21	PJ-S21 inhibits binding of gp120 III-CD4 complexes to cells expressing CXCR4; inhibitor of X4 and R5 virus binding to the cellular receptor CD4 and co-receptors CXCR4/CCR5	Neurath et al., 2004
Rosaceae			
<i>Crataegus pinatifida</i>	Uvaol and ursolic acid	Inhibitory activity against HIV-1 protease	Min et al., 1999
<i>Geum japonicum</i>	Maslinic acid	Inhibitory activity against HIV-1 protease	Xu et al., 1996
Rubiaceae			
<i>Oldenlandia affinis</i>	Circulins	Anti-HIV activity	Cited in Jennings et al., 2001
<i>Palicourea condensate</i>	Palicourein	Inhibits the <i>in vitro</i> cytopathic effects of HIV-1 infection of CEM-SS cells	Bokesch et al., 2001
Rutaceae			
<i>Citrus paradisi</i>	6',7'-dihydroxy-bergamottin	Enhances bioavailability of HIV protease inhibitor (e.g. saquinavar) by inhibiting cytochrome P450 iso-enzyme 3A4 in liver and gut	Kupferschmidt et al., 1998
<i>Citrus</i> spp.	Limonin and nomilin	Inhibit HIV-1 protease. Inhibit the production of HIV-1 p-24 antigen in infected monocytes and macrophages	Battinelli et al., 2003
<i>Clausena excavate</i>	Limonoid (clausenolide-1-ethyl ether)	HIV inhibitory activity in 1A2 cell line in syncytium assay	Sunthitikawinsakul et al., 2003
<i>Euodia roxburghiana</i> (Cham.) Benth.	Buchapine	Protect CEM-SS cells from cytopathic effects of HIV-1 <i>in vitro</i>	McMormick et al., 1996
<i>Toddalia asiatica</i> (L.) Lam.	Nitidine	Inhibit HIV-reverse transcriptase	Tan et al., 1991

Table 1 Contd.

Sapindaceae			
<i>Xanthoceras sorbifolia</i>	Oleanolic acid	Inhibit HIV-1 replication in acutely infected H9 cells.	Sakurai, 2004
Schisandraceae			
<i>Schisandra sphaerandra</i> f.	Nigranoic acid	Inhibit HIV-1/2 reverse transcriptase	Sun, 1998
<i>Schizymania pacifica</i> (Kylin) Kylin	Sulfated polysaccharide	Inhibit reverse transcriptase	Nakashima, 1987
<i>Kadsura lancilimba</i>	Triterpene lactone, lancilactone	Inhibitory activity against HIV replication in H9 lymphocytes	Chen et al., 1999
Symplocaceae			
<i>Symplocos setchuensis</i>	Harmine	Inhibit HIV replication in H9 lymphocyte cells.	Ishida et al., 2001
Theaceae			
<i>Camellia japonica</i>	Camellia-tannin H	HIV-1 protease inhibitory activity	Park, 2002
<i>Camellia sinensis</i>)	Polyphenol epigallocatechin-3-gallate	Inhibit semen-derived enhancer of virus infection (SEVI) activity and abrogates semen-mediated enhancement of HIV-1 infection	Hauber et al., 2009
Zingiberaceae			
<i>Curcuma</i> species including <i>C. longa</i> L.	Curcumin	Inhibits HIV-1 integrase, HIV-1 and HIV-2 protease, and HIV-1 Long Terminal Repeat-directed gene expression	Itokawa et al., 2008

HIV entry into cells while others were active against HIV reverse transcriptase, integrase, protease, and general replication. Some phytochemicals were also potent activators of HIV replication and expression in latently-infected T-cells, and others were known to inhibit syncytia formation (Table 1). Most of the entry inhibitors were lectins such as: agglutinins from *Galanthus nivalis* and *Hippeastrum* hybrid stopped the spread of HIV among cells (Saidi et al., 2007); BanLec, a jacalin-related lectin that binds to glycosylated viral envelopes blocked HIV-1 entry into cells (Swanson et al., 2010); cyanovirin, an 11

KDa protein isolated from *Nostoc ellipsosporum*, targeted gp120 proteins and blocked fusion of HIV-1 to lymphocyte membranes (Gustafson et al., 1997; Balzarini et al., 2004); glycoprotein complexes from *Ganoderma* mushrooms inhibited HIV-1 gp120 binding to CD4 cells (Lindequist et al., 2005); a code-named compound, PJ-S21, from *Punica granatum* inhibited the binding of gp120 to cells expressing CXCR4 receptors (Neurath et al., 2004); and *Phytolacca americana* pokeweed antiviral protein (PAP), a 29 KDa ribosome-inactivating protein that removes adenine from rRNA of prokaryotic and eukaryotic

ribosomes was found to be a potent microbicide (Tumer et al., 1997; Uckun et al., 1998; D'cruz et al., 2004). Other active constituents included: diterpene lactones (Calabrese, 2000) and a coumarin named wedelolactone (Yao et al., 1992) inhibited cell-to-cell transmission of HIV-1; prostratin, a 12-deoxyphorbol, inhibited HIV-1 entry into lymphocytes (Park et al., 2009); and rosmarinic acid isolated from *Melissa officinalis* inhibited fusion of HIV-1 to cells (Geuenich et al., 2008). Twenty-eight different chemical compounds were known to be active against HIV reverse transcriptase (Table 1). Some HIV reverse

Table 2. Plants and other natural products with known or unknown active compounds and/or known or unknown mechanisms of action against HIV and AIDS-related opportunistic infections

Family species	Active constituents	Mechanism of action	References
Anacardiaceae <i>Mangifera indica</i> L.	-	Anti-cancer	Muaza et al., 1995
Apocynaceae <i>Baijsea axillaries</i> Hua	Unknown aqueous and ethanol extracts contain alkaloids, tannins and cyanogenetic glycosides	Antimicrobial activity against clinical strains associated with HIV/AIDS-diarrhoea; shows toxicity at dose of 500 mg/kg	Abere and Agoreyo, 2006
Asteraceae <i>Artemisia absinthium</i> L.	Cardamonin, a known 2',4'-dihydroxy-6'-methoxychalcone	Anti-inflammatory, anti-cancer, antioxidant, antiviral, antifungal, antibiotic	Hatziieremia et al., 2006
<i>Baccharis dracunculifolia</i>	Brazilian propolis called Alecrim propolis and red coloured propolis from Cuba and Venezuela: contain phenolics, triterpenoids, isoflavonoids, prenylated benzophenones and a naphthoquinone epoxide	Antimicrobial activity and radical scavenging activity; an inseparable mixture of double bond isomers 3-methyl-2-butenyl and 3-methyl-3-butenyl is the active anti-HIV principle	Trusheva et al., 2006
<i>Eclipta prostrate</i> L. Hassk.		Anti-HIV-1 activity against integrase	Tewtrakul et al., 2007
Balanophoraceae <i>Thonningia sanguinea</i> Vahl	-	Stops HIV/AIDS-related diarrhoea, skin diseases and mycoses	Quattara et al., 2007
Betulaceae <i>Alnus viridis</i> DC <i>Betula alleghaniensis</i> Britt.	-	Anti-yeast activity	Webster et al., 2008
Cucurbitaceae <i>Momordica charantia</i>	1-monopalmitin, a simple monoglyceride with an abundant fatty acid chain	Major inhibitor of P-glycoprotein	Konishi et al., 2004

Table 2. Contd.

Euphorbiaceae				
<i>Jatropha curcas</i> L.	-		Inhibits HIV induced cytopathic effect; moderate cytoprotective effect against HIV.	Igbiosa et al., 2009; Matsuse et al., 1999
<i>Jatropha multifida</i> L.	-		Genotoxicity during HAART	Muaza et al., 1995
<i>Spirostachys africana</i> Sonder	-		Genotoxicity during HAART	Van den Beukel et al., 2008
<i>Trigonostema xyphophylloides</i>			Inhibition of HIV-1 entry	Park et al., 2009
Geraniaceae				
<i>Pelargonium sidoides</i> (DC), and <i>P. reniforme</i> (Curt)	-		Anecdotal ethnomedicinal uses reported for management of HIV/AIDS-related opportunistic infections in Southern Africa	Cited in review by Reihling, 2008
Fabaceae				
<i>Castanospermum australe</i>	Castanospermine		Blocks glycoprotein processing via inhibition of glucosidase I located in the endoplasmic reticulum.	Ruprecht, 1989
<i>Peltoporum africanum</i>	(+)-Catechin (flavonoid), bergenin (a C-galloyl-glycoside), betulinic acid		Used to treat diarrhoea, dysentery, sore throat wounds, HIV/AIDS, STIs,; betulinic acid had highest anti-HIV activity	Theo et al., 2009; Kashiwada et al., 2000
<i>Sutherlandia frutescens</i>	L-canavanine, GABA, and D-pinitol		L-canavanine has anti-viral activity against HIV and interacts with efflux of nevirapine; D-pinitol has been suggested as a treatment for wasting in cancer and AIDS patients though evidence is scanty	Brown et al., 2008
Guttiferae				
<i>Garcinia kola</i> Heckel	Biflavonoids, xanthones, benzophenones.		Anti-inflammatory, anti-microbial, antihepatotoxic, and antiviral activities	Iwu, 1993
<i>Hypericum chinense</i> L. var. <i>salicifolium</i>	Biyouyanagin A, which contains sesquiterpene, cyclobutane and spiro lactone moieties		Significant activity against HIV	Tanaka et al., 2005

Table 2. Contd.

Hypoxidaceae					
<i>Hypoxis hemerocallidea</i> and <i>H. colchicifolia</i>	Hypoxoside, glycosides	sterols,	and	Hypoxoside is converted to its aglycone, <i>rooperol</i> , a potent antioxidant; also affects cytochrome P-450 system, P-glycoprotein, and the pregnane X receptor (PXR)	Cited in review by Mills et al., 2005
<i>Hypoxis rooperi</i>				Used by persons with moderate or advanced AIDS	Babb et al., 2004
Lamiaceae					
<i>Melissa officinalis</i>	Aqueous extracts			Exhibited a high and concentration-dependent activity against HIV-1 infection in immune cells; active against virions carrying diverse envelopes X4 and R5. Ethanol extract of <i>L. leonurus</i> inhibit HIV-1 by 33%; and	Geuenich et al., 2008
<i>Leonotis leonurus</i>	aqueous and ethanol extracts			<i>L. leonurus</i> inhibit HIV-1 reverse transcriptase in a non-specific way due to tannins/polysaccharides; Extracts of <i>B. alooides</i> and <i>L. leonurus</i> retained HIV-1 protease inhibition after dereplication to remove non-specific tannins/ polysaccharides	Klos et al., 2009
Rosaceae					
<i>Fragaria virginiana</i> Duchesne	-			Antifungal potential	Webster et al., 2008
<i>Potentilla simplex</i> Michx.				Antifungal potential	Webster et al., 2008
Sterculiaceae					
<i>Sterculia Africa</i> (Lour) Fiori	-			Genotoxicity during HAART	Moshi et al., 2007

transcriptase inhibitors included: michellamines (Boyd et al., 1994); triterpene (Li et al., 1991); coumarins and isoflavone derivatives (Yao et al., 1992); caffeic acid tetramers (Kashiwada, 1995); (+)-calanolide A (Xu et al., 2000); hypericin and 3-hydroxy lauric acid (Birt et al., 2009); gallotannin (Bessong et al., 2005); flavonone-xanthone glucoside (Wang et al., 1994); linearol (Bruno et

al., 2002); catechins 1-5 (Moore and Pizza, 1992); cepharanthine (Ma et al., 2002); galloylquinic acids (Moore et al., 2005; 2007); velutin (Wang and Ng, 2001); nitidine (Tan et al., 1991); oleanolic acid (Sakurai, 2004); nigranoic acid (Sun, 1998); sulfated polysaccharides (Nakashima, 1987); triterpene lactone (Chen et al., 1999); and harmine (Ishida et al., 2001).

Four of the identified active compounds were known to be HIV integrase inhibitors: flavonoid gallate ester from *Acer okamotoanum* of the Aceraceae family (Kim et al., 1998); dicaffeoylquinic acids from *Achyrocline satuireioides* of the Asteraceae family (Robinson et al., 1996; Zhu et al., 1999); gallic acid and galloyl glucose from *Terminalia chebula* of the Combretaceae

family (Bessong et al., 2005); and curcumin from *Curcuma* species in the Zingiberaceae family (Itokawa et al., 2008).

Six active compounds were observed to be HIV protease inhibitors: ganoderiol, ganodermanontriol, and ganoderic acid B (a triterpene) from *Gonoderma* mushrooms (Lindequist et al., 2005); lignins from *Gonoderma* and *Inonotus obliquus*, commonly known as chaga mushroom belonging to the Hymenochaetaceae family (Ichimura et al., 1998); uvaol and ursolic acid from *Crataegus pinatifida* (Min et al., 1999), and maslinic acid (a triterpene acid) from the plant *Geum japonicum* (Xu et al., 1996), both from the Rosaceae family; limonoids (Manners, 2007), including limonin and nomilin, secondary metabolites from citrus fruit species belonging to the Rutaceae family (Battinelli et al., 2003); and curcumin from *Curcuma* species (Itokawa et al., 2008). Curcumin was also shown to be active against HIV-1 integrase (Itokawa et al., 2008).

Many active compounds were known to inhibit general HIV replication (Table 1). Diterpene lactones from *Andrographis paniculata* (Otake et al., 1995) and *Tripterygium wilfordii* (Duan et al., 1999); triterpene lactone and lancilactone from *Kadsura lancilimba* (Chen et al., 1999); biflavonoids from *Rhus succedanea* (Lin et al., 1997); lanostane-type triterpenes from *Polyalthia suberosa* (Li et al., 1993); suksdorfins from *Lomatium suksdorfii* (Yu et al., 2007); wedelolactone (a coumarin) and orobol (an isoflavone derivative) from *Arctium lappa* (Yao et al., 1992); caffeic acid tetramers from *Arnebia euchroma* (Kashiwada, 1995); celastrol from *Celestrus hindsii* (Kuo and Kuo, 1997); cordatolides from *Callophyllum cordato-oblongum* (Dharmaratne et al., 2002); hypericin and 3-hydroxy lauric acid from *Hypericum perforatum* (Birt et al., 2009); sulfonated polysaccharides from *Mentha piperita* and *Prunella vulgaris* (Hauber et al., 2009); linearol from *Sideritis akmanii* (Bruno et al., 2002); cepharanthine from *Stephania cepharantha* (Ma et al., 2002); cyanovirin from *Nostoc ellipsosporum* (Gustafson et al., 1997); oleanolic acid from *Xanthoceras sorbifolia* (Sakurai, 2004); and harmine from *Symplocos setchuensis* (Ishida et al., 2001). Prostratin, a 12-deoxyphorbol from *Homalanthus nutan*, was a potent activator of HIV replication and expression in latently-infected T-cells (Gupta et al., 2005; Johnson et al., 2008). Prostratin was therefore used to bring out latent HIV from lymph nodes so that the virus was exposed to lethal concentrations of the drugs (Gupta et al., 2005; Johnson et al., 2008).

Some active compounds were found to inhibit syncytia formation, a property of HIV that makes infected and healthy CD4 cells to fuse and form one giant cell with as many as 500 nuclei. Syncytia-inhibiting compounds included: diterpene lactones (Calabrese, 2000); michellamines A and B (Boyd et al., 1994; Manfredi et al., 1991); and limonoids (Sunthitikawinsakul et al., 2003). Eight natural compounds prevented HIV-induced cytopathic effect: sulfated lentinan (Suzuki et al., 1989); sulfonated polysaccharides (Witvrouw et al., 1994);

xanthohumol (Wang et al., 2004); cordatolides (Dharmaratne et al., 2002); laxofloranone (Bokesch et al., 1999); ganoderiol, ganodermanontriol, and ganoderic acid (Lindequist et al., 2005); sulfated (1-3)- β -D-glucan with (1-6)- β -D-glucosyl branches (Lindequist et al., 2005); and palicourenin (Bokesch et al., 2001).

Some plant-derived compounds were reported to possess activities against HIV-related symptoms. Castanospermine from *Castanospermum australe* blocked glycoprotein processing via inhibition of glucosidase I located in the endoplasmic reticulum (Ruprecht, 1989). L-canavanine from *Sutherlandia frutescens* had anti-viral activity against HIV but interacted with the efflux of nevirapine (Brown et al., 2008). D-pinitol, also from *Sutherlandia frutescens*, had been suggested as a treatment for wasting in cancer and AIDS patients though evidence was scanty (Brown et al., 2008). (+)-Catechin (flavonoid), bergenin (a C-galloyl-glycoside) and betulinic acid from *Peltophorum africanum* were used to treat diarrhoea, dysentery, sore throat wounds, HIV/AIDS, and other sexually transmitted infections (Theo et al., 2009; Kashiwada et al., 2000).

Coumarins and naturally occurring benzopyrene derivatives from several plant species were reported to possess antioxidant, anti-inflammatory, antithrombotic, antiviral, anticarcinogenic, antiallergic, hepatoprotective, and anti-HIV properties (Kostova et al., 2006). Furthermore, 50 different compounds (belonging to tannins, terpenoids, flavonoids, flavones, alkaloids, coumarins, lignans, lignin-polysaccharide complexes, and lectins), found in 40 different plant species, were reported to inhibit adsorption, viral fusion, HIV reverse transcriptase, integrase, protease, syncytium formation, interference with cellular factors, and some unknown targets (Cowan, 1999).

Castanospermine, hypericin, pseudohypericin, interferons, glycyrrhizin, avarone and avarone inhibited replication of HIV-1 and other retroviruses (Lin et al., 1989). Gossypol, a polyphenolic bisessquiterpene isolated as a racemic mixture from cottonseed has selective activity against HIV-1 but the exact mechanism was unknown (Lin et al., 1989). Flavonoid derivatives inhibited HIV-1 reverse transcriptase (Moore and Pizza, 1992). Suramin inhibits HIV-1 reverse transcriptase in a non-specific way (Moore and Pizza, 1992). Sulphated polysaccharides were potent *in vitro* inhibitors of HIV-1 and HIV-2 adsorption, fusion or penetration, induced cytopathogenicity, and antigen expression (Talyshinsky et al., 2002). They also inhibited reverse transcriptase and RNAase H, essential enzymes for retrovirus replication (Talyshinsky et al., 2002).

A wide variety of organisms including single-celled microbes, insects and other invertebrates, plants, amphibians, birds, fish, and mammals including humans had been shown to possess antiviral peptides that suppress HIV gene expression. Magainin from frogs and cecropin from insects suppressed HIV gene expression (Jensen et al., 2006). Dermaseptin from frogs disrupted HIV membranes while indolicidin from bovine inhibited

HIV integrase (Jenssen et al., 2006; Kim et al., 2002). Gordon and Ramanowski (2005) found that P113, isolated from human saliva, was a good mouth-rinse against *Candida albicans* in HIV/AIDS patients (Table 2). Plants such as *Viola yedoensis*, *Epimedium grandiflorum*, *Glycyrrhiza uralensis* and *Castanospermum australe* were used to manage HIV/AIDS opportunistic infections (WHO, 1989b), but their pharmacological interactions with ART were not well understood. Kisangau et al. (2007) documented 75 plant species (in 66 genera and 41 families) used in the management of HIV/AIDS opportunistic infections in one district of Tanzania, however their study did not report on the compounds that are active against HIV and did not report on their modes of action against HIV.

Conclusion

The literature survey revealed several anti-HIV active compounds such as terpenoids, coumarins, polyphenols, tannins, proteins, alkaloids, and biflavonoids that inhibit various steps of the HIV life cycle. These active compounds were isolated from 55 families of plants and other natural sources such as mushrooms (Ganodermaaceae), cyanobacteria, and marine organisms. Phylogenetic analysis and other bioinformatics tools may shed light on unidentified but related plants and other organisms that may contain similar active compounds. Primary data of known active compounds and mechanisms of action were available from studies mostly done outside Africa. Most of the studies done in Africa were inconclusive about either the active compounds or mechanisms of action, or both. Pharmacological interactions of unknown active ingredients from herbal medications remain a source of great medical concern. Throughout the survey, it was clear that although Africa had a wealth of medicinal plants, most of the research on screening of plants and isolation of active compounds was carried out elsewhere in Asia, Europe and the Americas. Lack of long-term funding and infrastructure have conspired to exacerbate Africa's dependency on overseas laboratories for screening of plants for active compounds, *in vitro* tests against HIV, and mechanisms of action. Such a situation is a perfect recipe for biopiracy. There is also an urgent need to fast-track HIV/AIDS clinical trials of candidate drugs developed from novel compounds isolated from plants and other natural sources. This will ensure that the millions of people that require HIV/AIDS treatment will have access to newer, more effective, and less toxic drugs.

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