ORIGINAL PAPER

A Survey of Plants with Anti-HIV Active Compounds and their Modes of Action

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ABSTRACT

***Background*:** Several limitations of current antiretroviral therapy (ART) programmes will continue to push patients towards the use of plants to manage HIV/AIDS. However, evidence about the use of anti-HIV plants is anecdotal.

Objectives: Search the literature for research articles that document plants with anti-HIV properties; and document the taxonomic families and species of plants with anti-HIV properties, their active ingredients, and modes of action against HIV.

***Methodology*:** Literature search for the key words "plants with anti-HIV activity" in PubMed Central.

***Results*:** The literature survey documented about 36 plant families containing 46 plant species with known anti-HIV active compounds and known modes of action. Anti-HIV active compounds such as terpenoids, coumarins, polyphenols, tannins, proteins, alkaloids, and biflavonoids inhibit various steps of the HIV life cycle.

***Discussion*:** Most studies that revealed anti-HIV active compounds and their modes of action were conducted outside Africa. A new initiative under NEPAD will help validate African medicinal plants used to manage HIV/AIDS.

***Conclusions*:** The review presents evidence that several plant families and species contain anti-HIV active compounds that could be developed into newer drugs to manage HIV/AIDS. This evidence should persuade further research and public interest into the isolation of anti-HIV active compounds from plants.

***Recommendation*:** There is an urgent need to fast-track HIV/AIDS clinical trials of candidate drugs developed from novel compounds isolated from plants.

BACKGROUND

At the end of 2009, 68% of the 330,000 Zambians needing antiretroviral therapy (ART) were receiving it and a third of all health facilities in the country were able to offer treatment[1]. Despite this impressive progress, Zambia's ART programme is like a candle in the wind as it battles to glimmer against the inevitable possibility of dying from another form of AIDS- 'Acquired Income Deficiency Syndrome'. There are concerns that the country's free public sector ART programme is not sustainable due its heavy reliance on donor funds. Besides funding, access to treatment in Zambia is challenged by inadequacy of the healthcare system, which suffers from high patient numbers, lack of physical space and infrastructure, and attrition of health workers[2,3]. Notably, there is a critical shortage of doctors. In 2006, there were only about 646 doctors; this was under a third of the doctor-patient ratio recommended by the World Health Organization (WHO)[2].

ART is also associated with serious side-effects now causing new forms of stigma. For example, ART has been associated with the development of lipodystrophy (LD). Lipodystrophy is characterized

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by peripheral fat loss (lipoatrophy) and central fat accumulation which may result in thin facial pads, thin arms and legs, pot-bellies, and 'buffalo humps', leaving patients stigmatized[4]. 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, and lack of any curative effect[5]. Limitations of conventional ART continue to open new avenues in the use of ethnomedicinal plants for the management of HIV/AIDS.

The World Health Organization (WHO) recommended that traditional healers be included in national responses to HIV/AIDS[6]. As early as 1989, WHO had already voiced the need to evaluate ethnomedicines for the management 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[7].

Although there are a good number of reports on traditional uses of plants to treat various diseases, knowledge of herbal remedies used to manage HIV/AIDS is scanty, impressionistic and not well documented[8,9,10]. Zambia has rich plant biodiversity and a long tradition of medicinal use of plants. Several of these plants may contain novel anti-HIV compounds. Thus, it is important to search for novel antiretroviral agents that can be added to or replace the current arsenal of drugs against HIV[11]. A literature survey of plants with anti-HIV activity is an important prerequisite in the quest to quicken the search for novel HIV/AIDS treatments in Zambia and beyond. Therefore, the current effort is a modest attempt to review the taxonomic families and species of plants with anti-HIV active compounds and their modes of action.

OBJECTIVES

The goal of the current study is to provide empirical evidence that several plants possess anti-HIV active compounds, help refocus the attention of researchers towards the study of herbal plants with anti-HIV activity, and re-inspire public and research interest in the use of plants with anti-HIV properties. This goal was approached through the following objectives:

1. To search the literature for research articles that document plants with anti-HIV properties;
2. To document the taxonomic families and species of plants with anti-HIV properties, their active ingredients, and modes of action against HIV.

METHODOLOGY

We searched for the key words "plants with anti-HIV activity" in PubMed Central, the United States of America National Library of Medicine's digital archive of biomedical and life sciences journal literature. Within the process of the literature search that lasted 2 months, we reviewed only-peer reviewed journal articles written in English language (excluding journal abstracts and conference abstracts), from all over the world. Pay-to-view articles were not included. Taxonomic families and species of plants, active compounds and their modes of action, were documented from primary literature sources. The search was not restricted to any time frame but did not cover the period before 1989. The inclusion criteria were: (a) plants should have been known by their scientific names; (b) anti-HIV active ingredients were isolated and known; and (c) mode of action for active ingredients were known.

RESULTS

Of the 150 journal articles found during the search, only 47 met our pre-determined inclusion criteria. Most of the studies, especially from Africa, were not included as they failed to meet the inclusion criteria. Therefore, out of the total number of articles reviewed, only about a third were included in this study.

The literature survey documented about 36 plant families containing 46 plant species with known anti-HIV active compounds and known modes of action. Several anti-HIV active compounds such as terpenoids, coumarins, polyphenols, tannins, proteins, alkaloids, and biflavonoids inhibit various steps of the virus life cycle. Details of the plant families and species, active compounds, modes of

action, and literature sources are listed in Table 1. Five chemical compounds were found to interfere with HIV entry into cells[16, 23,35,43,46]. Most of the entry inhibitors were agglutinins from *Galanthus nivalis* and *Hippeastrum*[16]. A coumarin called wedelolactone inhibited cell-to-cell transmission of HIV-1[23]. BanLec, a jacalin-related lectin that binds to glycosylated viral envelopes blocked HIV-1 entry into cells[43], and *Phytolacca americana* pokeweed antiviral protein (PAP), a 29 KDa ribosome-inactivating protein that removes adenine from rRNA was found to be a potent microbicide[46].

Table 1: Plants with active compounds and modes of action against HIV

Family *species*	**Active constituents**	**Mechanism of action**	**References**
Acanthaceae			
Andrographis paniculata	Aqueous extracts of leaves	Inhibits HIV protease and reverse transcriptase	12
	Diterpene lactones (andrographolide)	Inhibit cell-to-cell transmission, viral replication and syncytia formation in HIV-infected cells	13
Aceraceae			
Acer okamotoanum	Flavonoid gallate ester	Anti-HIV-1 integrase activity	14
Agaricaceae			
Lentinus edodes (Berk.) Singer	Sulfated lentinan	Prevents HIV-induced cytopathic effect	15
Amaryllidaceae			
Galanthus nivalis L.	Plant lectins: *G. nivalis* agglutinin (GNA),	Stops spread of HIV among lymphocytes; most prominent anti-HIV activity is found among MBLs; GNA has specificity for terminal α(1-3)-linked mannose residues; HHA recognizes both terminal and internal α(1-3)- and α(1-6)-linked mannose residues	16
Hippeastrum hybrids	*Hippeastrum* hybrid agglutinin (HHA), and monocot mannose-binding lectins (MBLs)		
Anacardiaceae			
Rhus succedanea L.	Biflavonoids, robustaflavone and hinokiflavone	Inhibits HIV-1 reverse transcriptase	17
Ancistrocladaceae			
Ancistrocladus korupensis	Michellamines A and B	Inhibits reverse transcriptase, cellular fusion and syncytium formation	18
Annonaceae			
Polyalthia suberosa	Lanostane-type triterpene, suberosol	Anti-HIV replication activity	19
Apiaceae			
Lomatium suksdorfii	Suksdorfin	Suppresses HIV-1 viral replication	20
Areschougiaceae			
Agardhiella tenera (J. Agardh) F. Schmitz	Sulfonated polysaccharides	Inhibits HIV cytopathic effect	21

Asteraceae			
Achyrocline satureioides (Lam.) DC (Marcela);	Dicaffeoylquinic acids: 3,5-dicaffeoylquinic acid, and 1-methoxyoxalyl-3,5-dicaffeoylquinic acid	Irreversible inhibition of HIV-1 integrase	22
Arctium lappa (Burdock)	Wedelolactone, a coumarin derivative; orobol (an isoflavone derivative)	Inhibits HIV-1 replication; blocks cell-to-cell transmission of HIV-1	23
Boraginaceae			
Arnebia euchroma (Royle) Jonst	Monosodium and monopotassium salts of isomeric caffeic acid tetramer	Inhibits HIV replication	24
Cannabaceae			
Humulus lupulus	Xanthohumol	Inhibits HIV-1-induced cytopathic effects	25
Celastraceae			
Celastrus hindsii	Celasdin B	Anti-HIV replication activity	26
Tripterygium wilfordii Hook F	Diterpene lactones (nortripterifordin)	Inhibits HIV replication	27
Clusiaceae			
Callophyllum cordato-oblongum	Cordatolide A and B	Inhibits HIV-1 replication	28
	(+)-calanolide A	Inhibits cytopathic effects of HIV-1	29
Marila laxiflora	Laxofloranone	Inhibits reverse transcriptase	30
Symphonia globulifera	Guttiferone A	Inhibits cytopathic effects of HIV Inhibits HIV-1 replication	31
Hypericum perforatum L.	Hypericin, 3-hydroxy lauric acid		32
Combreataceae			
Combretum molle R.Br. ex G. Don	Gallotannin	Inhibits HIV-1 reverse transcriptase	33
Terminalia chebula	Gallic acid and galloyl glucose	Inhibits HIV reverse transcriptase and integrase	34
Dipterocarpaceae			
Vatica astrotricha	6,8-diprenylaromadendrin and 6,8-diprenylkaempferol	Inhibits HIV-1 entry and replication	35
Fabaceae			
Peltophorum africanum Sond.	Gallotannin	Inhibits HIV-1 reverse transcriptase	33
Gentianaceae			
Swertia franchetiana	Flavonone-xanthone glucoside	Inhibits HIV-1 reverse transcriptase	36
Hymenochaetaceae			
Inonotus obliquus	Water-soluble lignins	Inhibits HIV-1 protease	37

Hypericaceae *Garcinia speciosa*	Protostanes, garcisaterpenes A and C	Inhibits HIV-1 reverse transcriptase	[38]
Lamiaceae *Sideritis akmanii*	Sulfonated polysaccharides; linearol	Anti-HIV replication	[39]
Leguminosae *Detarium microcarpum*	Catechins 1-5	Inhibit HIV-1 reverse transcriptase activity in a non-specific way	[40]
Magnoliaceae *Magnolia* spp.	Neolignans e.g. magnolol 1 and honokiol 2	Antioxidant; induces apoptosis in tumor cells, weak anti-HIV-1 activity	[41]
Menispermaceae *Stephania cepharantha*	Cepharanthine	Inhibits HIV replication	[42]
Musaceae *Musa acuminata*	BanLec, a jacalin-related lectin	Blocks HIV entry, hence is a good microbicide; potent inhibitor of HIV-1 replication	[43]
Myrothamnaceae *Myrothamnus flabellifolius* (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	[44]
Physalacriaceae *Flammulina velutipes* (Curt.: Fries) Singer	Velutin	Inhibits HIV-1 reverse transcriptase	[45]
Phytolaccaceae *Phytolacca Americana* L	Pokeweed antiviral protein (PAP)	Broad spectrum microbicide	[46]
Rosaceae *Crataegus pinatifida*	Uvaol and ursolic acid	Inhibits HIV-1 protease	[47]
Geum japonicum	Maslinic acid	Inhibits HIV-1 protease	[48]

About 28 different chemical compounds were known to be active against HIV reverse transcriptase and replication. Some of these HIV reverse transcriptase inhibitors included: biflavonoids from *Rhus succedanea*[17], michellamines from *Ancistrocladus korupensis*[18], lanostane-type triterpenes from *Polyalthia suberosa*[19], suksdorfin from *Lomatium suksdorfii*[20], caffeic acids from *Arnebia euchroma*[24], celasdin B from *Celastrus hindsii*[26], calanolide A from *Callophyllum cordato-oblongum*[29], gallotannin from *Combretum molle*[33], flavonone-xanthone glucoside from *Swertia franchetiana*[36], protostanes from *Garcinia speciosa*[38], catechins from *Detarium microcarpum*[40], cepharanthine from *Stephania cepharantha*[42], galloyquinic acids from *Myrothamnus flabellifolius*[44], velutin isolated from *Flammulina velutipes*[45], oleanolic from *Xanthoceras sorbifolia*[51], nigranoic acid from *Schisandra sphaerandra*[52], triterpene lactone from

Kadsura lancilimba[53], and harmine isolated from *Symplocos setchuensis*[54].

Three of the identified active compounds were known to be HIV integrase inhibitors: flavonoid gallate ester from *Acer okamotaanum* of the Aceraceae family[14], dicaffeoylquinic acids from *Achyrocline satureioides* of the Asteraceae family[22], and curcumin from *Curcuma longa* in the Zingiberaceae family[56]. Six active compounds were found to be HIV protease inhibitors: water-soluble lignins from *Inonotus obliquus*[37], uvaol and ursolic acid from *Crataegus pinatifida*[47], maslinic acid from *Geum japonicum*[48], limonin and nomilin from *Citrus* spp.[49], camellia-tannin H from *Camellia japonica*[55], and curcumin[56], which was also shown to be active against HIV-1 integrase[56].

Two 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[13], and michellamines A and B[18]. Seven plant compounds prevented HIV-induced cytopathic effect: sulfated lentinan[15], sulfonated polysaccharides[21], xantholhumol[25], (+)-calanolide A[29], guttiferone A[31], palicourein[30], and nitidine[50]. *Magnolia* spp.[41] and the Namibian resurrection plant *Myrothamnus flabellifolius*[44] were found to have anti-oxidant properties.

DISCUSSION

The data presented above are mostly from laboratory studies conducted in Asia, America and Europe. Most research on the use of medicinal plants in Africa does not reveal the active ingredients and their modes of action against HIV. For example, a study in Tanzania documented about 74 different plant species used in the management of HIV/AIDS[57] but the researchers did not go further to isolate the active ingredients from such plants. Isolation of active ingredients from plants and determination of their modes of action require expensive equipment which most government-funded research laboratories in Africa are lacking[8,9]. Responding to the compelling need for evidence regarding traditional medicines, NEPAD and Southern African Network for Biosciences (SANBio) launched a flagship project to validate ethnomedicines for the affordable treatment of HIV/AIDS and related opportunistic infections. Under this project, Zambia's Sondashi formula (SF-2000), invented from four plants by Dr. Ludwig Sondashi, is undergoing scientific validation at the Council for Scientific and Industrial Research (CSIR) in Pretoria, South Africa. Anti-HIV active compounds from the plants have been isolated, and a clinical trial is now being planned.

On the other hand, the inclusion of anti-HIV herbal medicines in official HIV/AIDS policy is an extremely sensitive and contentious issue. It is sensitive because anti-HIV plant products can easily become a scapegoat for denial and inertia to roll-out ART. 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.

Although no plant-derived drug is currently in clinical use to treat HIV/AIDS, phase II clinical trials were conducted for calanolide A[58]. The data from these clinical trial are not known to us. Other than calanolide A and two other molecules code-named PA-457 and PA-334B, our literature survey revealed no other report of clinical trials with anti-HIV drugs derived from plants. Prior to 2005, there had been a decline in the use of plant products as starting materials for drug discovery[59]. The lack of interest in utilizing plant products was attributed to rediscovery problems due to technical difficulties, issues of access and benefit sharing, and intellectual property rights, especially when working with plants found across national borders and cultures[59].

CONCLUSION

Plants are an important source of anti-HIV chemical compounds, and several plant families and species contain anti-HIV active compounds that could be developed into newer drugs to manage HIV/AIDS. Therefore, the current literature survey provides an evidence-based contribution to our understanding of plants that can be used in the management of HIV/AIDS. This evidence should persuade further research and public interest into the isolation of anti-HIV active compounds from plants.

RECOMMENDATIONS

There is need to increase the screening of plants based on ethnopharmacological data and indigenous knowledge; this will quicken the search for novel anti-HIV compounds. There is also an urgent need to fast-track HIV/AIDS clinical trials of candidate drugs developed from novel compounds isolated from plants. Post-genomics, phylogenetic analysis and other bioinformatics tools may shed light on other related plants that may contain similar active compounds.

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