

## ADVANCES IN HIV HERBAL RESEARCH: SUCCESSES/ADVERSE EFFECTS

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### ABSTRACT

An estimated number of 33.4 million people around the world are said to be living with HIV with more than twenty-five million deaths due to AIDS-related diseases recorded since the beginning of the epidemic. Complete cure for the disease has been diligently pursued by scientists around the world, but there has been no report of absolute success while the highly active anti-retroviral therapy (HAART) remains the only current treatment modality. This treatment guideline, though very effective in suppressing replication of the virus and reducing the mortality of HIV/AIDS patients, it does not offer an ultimate cure to the disease. This realization, coupled with other side effects associated with the drug including failure of HIV vaccines and microbicides, have urgently called for the need to develop inexpensive alternative anti-HIV/AIDS therapies. In the search for drugs and new cures for human and animal ailments, medicinal plants are definitely the most popular targets and Nigeria is endowed with a variety of these that could serve as veritable alternatives in the management of HIV/AIDS. Efforts are however required to determine the safety; efficacy and pharmacological profile of many of the herbal compounds with a view to fully understanding what remedies are in use for HIV and to educate those providing alternative medical services against unsafe practices.

**KEY WORDS:** Herbs; HIV; HAART, Immune system; AIDS; Anti-HIV activity

### INTRODUCTION

An estimated number of 33.4 million people around the world are now said to be living with HIV with more than 25 million deaths due to AIDS-related diseases recorded since the beginning of the epidemic (UNAIDS, 2009). Although HIV and AIDS are found in all parts of the world, some areas are more afflicted than others with Sub-Saharan Africa, with its estimated 22.5 million cases (around two thirds of the global total), 1.3 million deaths and 1.8 million new infections in 2009 alone, topping the list of the worst affected regions. Similarly, the epidemic is spreading most rapidly in Eastern Europe and Central Asia, where the number of people living with the virus has increased to 67% between 2001 and 2008 (UNAIDS, 2009), while in Latin America around 2 million people were said to be living with the virus at the end of 2008 with 77,000 deaths and an estimated 170,000 new infections (WHO, 2010).

In Nigeria, an estimated 3.6 percent of the population is said to be living with HIV/AIDS with approximately 192,000 deaths due to AIDS recorded in the country in 2009. With the disease claiming this number of lives, it could be said that Nigeria's life expectancy has declined significantly from 54 years and 53 years respectively for women and men in 1991 to the respective years of 48 and 46 in 2009 (CIA World Factbook, 2010).

Complete cure for HIV infection/AIDS has been diligently pursued by scientists around the world, yet there has been no report of absolute success (Wu, 2004). The highly active anti-retroviral therapy (HAART) is



however the current and only HIV/AIDS treatment modality. Despite the fact that this treatment guideline is very effective in suppressing HIV-1 replication and reducing the mortality of HIV/AIDS patients, it has become increasingly clear that the drug does not offer an ultimate cure to the disease (In-Woo *et al.*, 2009). In addition, the high cost of the HAART regimen has impeded its delivery to over 90% of the HIV/AIDS population in the world. Furthermore, the drugs are known to make patients very dependent on them such that once stopped, patient deterioration becomes rapid, since they could no longer generate enough immunity or resistance (Dybul *et al.*, 2002). Finally the drugs are known to possess a large dose of unpleasant side effects that could also pose another set of health crises to patients (McNicholl, 2005). These realities have urgently called for the need to develop inexpensive alternative anti-HIV/AIDS therapies, a need further manifested by recent clinical trial failures in anti-HIV-1 vaccines and microbicides (In-Woo *et al.*, 2009).

Consequently, the search for selective antiviral agents, principally focused on anti-HIV agents, has been vigorous in recent years with African herbal medicine being in the forefront of this new research against the scourge. Despite a paucity of evidence on effectiveness, and the possibility of harm however, the Ministries of Health of several African nations currently promote traditional medicines for the treatment of HIV and associated symptoms. Worldwide there is also a growing trend towards herbal medicines as supplements and/or treatments for HIV/AIDS (MacPhail *et al.*, 2002).

#### ADVANCES IN HIV HERBAL RESEARCH

Admittedly the highly active anti-retroviral therapy (HAART) is the current HIV/AIDS treatment modality. Despite the fact that this HAART is very effective in suppressing HIV-1 replication and reducing the mortality of HIV/AIDS patients, it has become increasingly clear that drug does not offer an ultimate cure to HIV/AIDS. The high cost of the HAART regimen has impeded its delivery to over 90% of the HIV/AIDS population in the world. This reality has urgently called for the need to develop inexpensive alternative anti-HIV/AIDS therapy. This need was further heightened and later manifested by the recent clinical trial failures in anti-HIV-1 vaccines and microbicides (In-Woo *et al.*, 2009).

In the search for drugs and new cures for human and animal ailments, medicinal plants are definitely the most popular targets. Consequently, all parts of the plant body and in fact, various plant products including their extracts, oils, juices and sap have been used in one form or the other in traditional and conventional medicine (Khan *et al.*, 1988). Herbal approach to viral infection occurs in two ways: stimulation of the immune system and thus production of more immune cells and immune chemicals; and disruption of the viral replication cycle so that the virus will not survive (Falodun, 2010). Hence there is reason to believe that some herbs and spices could attack HIV directly as various studies have indicated.

Using a well-established HIV-1 replication system, In-Woo *et al.*, (2009) screened extracts of traditional Chinese medicinal herbal plants for their anti-HIV activities and reported that extracts from the stem of *Euphorbiaceae*, *Trigonostema xyphophylloides* (TXE) and the stem of *Dipterocarpaceae*, *Vatica astrotricha* (VAD) inhibited HIV-1 replication without apparent effects on cell proliferation and cell survival. The report further had it that the inhibitory effects of these two extracts were corroborated by the finding that the extracts prevented HIV-infected cells from forming syncytia, potently blocked HIV-1 from entering its target cells, and had little effects on post-entry HIV-1 gene expression. The researchers claimed they also obtained similar results with the primary isolate, HIV-1 89.6, which displayed dual tropism, using both CXCR4 and CCR5 for entry into cells.



In addition, ethanolic and aqueous extracts of 15 medicinal plants widely used in the folk medicine of the Iberian Peninsula were evaluated *in vitro* and it was reported that most of the extracts tested were relatively nontoxic to human lymphocytic MT-2 cells, while the extracts of *Tuberaria lignosa* and *Sanguisorba minor magnolii* exhibited anti-HIV activity in an *in vitro* MTT assay. The aqueous extracts of the plants showed inhibitory effects against HIV-1 induced infections in MT-2 cells at concentrations ranging from 12.5 to 50 µg/ml and 50 µg/ml, respectively (Bedoya et al., 2001).

In his contribution, Ho et al., (1993) disclosed the use of an extract from a mixture of herbs for the *in vitro* inhibition of HIV infection in human T lymphocyte cells and mononuclear phagocytic lineage cells. The activity was based on the test results of a water extract from a mixture of three herbs: *Isatis tinctoria* (or *Isatis indigotica*), *Lonicera japonica*, and *Polygonum bistorta*.

In addition, water extract of *Prunella vulgaris* (boiling 3 g in 100 mL water for 45 minutes) has also been reported to have anti-HIV (strain H9/3B) activity with the extract exhibiting synergistic anti-HIV activity with zidovudine (AZT) and didanosine (ddl) and a slight additive effect on zalcitabine (ddC) (John and Rosenthal, 1994).

Contributing to this search for a possible herbal cure for HIV/AIDS, Yamasaki et al., (1993) evaluated, *in vitro*, two hundred and four (204) crude drugs of common use in Japan for anti-HIV-1 activity and reported that the hot water extract of *Prunella vulgaris* (spike) showed a strong *in vitro* anti-HIV-1 activity with an IC<sub>100</sub> of 16 µg/mL. The importance of *P. vulgaris* as a veritable anti-HIV agent was further demonstrated in detail by Yao et al., (1992) who reported that water extract of the dried entire plant of *Prunella vulgaris* was active *in vitro* in inhibiting HIV-1 replication with relatively low cytotoxicity towards the MT-4 cells. The extract was also reported to be active in reverse transcriptase inhibition. The active factor prunellin was purified and identified as anionic with a molecular weight of approximately 10,000 Dalton. The purified extract inhibited HIV-1 replication in the lymphoid cell line MT-4, in the monocytoid cell line U937, and in peripheral blood mononuclear cells (PBMC) at effective concentrations of 6, 30, and 12.5µg/mL, respectively. Pretreatment of uninfected cells with the extract prior to viral exposure did not however prevent HIV-1 infection while preincubation of HIV-1 with the purified extract dramatically decreased infectiousness. The purified extract was also able to block cell-to-cell transmission of HIV-1, prevent syncytium formation, and interferes with the ability of both HIV-1 and purified gp120 to bind to CD4. PCR (polymerase chain reaction) analysis confirmed the absence of HIV-1 proviral DNA in cells exposed to virus in the presence of the extract. Their results suggested that the purified extract antagonized HIV-1 infection of susceptible cells by preventing viral attachment to the CD4 receptor.

In his own study Tabba et al., (1989) isolated and partially characterized an anti-HIV component, prunellin, from aqueous extracts of *Prunella vulgaris*. Prunellin was reported to be a carbohydrate with an MIC of 2.2µg/mL against HIV-1 *in vitro*. It was identified as a partially sulfated polysaccharide with a molecular weight of about 10,000 Dalton.

Of 30 Indonesian plant extracts tested for their human immunodeficiency virus type-1 (HIV-1) inhibitory activities, six were shown to be effective by assays using HIV-1-infected MT-4 cells: a methanol extract of mahoni (bark of *Swietenia mahagoni*) and water extracts of benalu teh (stems and branches of *Loranthus parasiticus*), kiules (fruit of *Helicteres isora*), supratul (fruits of *Sindora sumatrana*), sambiloto (leaves of *Andrographis paniculata*) and temu ireng (rhizoma of *Curcuma aeruginosa*). Their ED<sub>50</sub> values ranged from



4.2 to 175  $\mu\text{g/mL}$ . The samples also suppressed the formation of syncytia in co-cultures of MOLT-4 and MOLT-4/HIV-1 cells. The most potent inhibitor was a methanol extract of mahoni, which also showed a significant inhibition of HIV-1 protease (Otake *et al.*, 2010).

The use of traditional medicine and natural health products (NHPs) is indeed widespread among those living with HIV infection (Fairfield *et al.*, 1998), since many of the patients take a broad range of the products in addition to their conventional therapeutic drugs (Babb *et al.*, 2004). In Africa, traditional herbal medicines are often used as primary treatment for HIV/AIDS and for HIV-related problems including dermatological disorders, nausea, depression, insomnia, and weakness (Babb *et al.*, 2004). Some of these herbal and traditional medicines are however not well-researched, poorly regulated, and may contain adulterated products which may produce adverse effects (Peters *et al.*, 2004). Notwithstanding these concerns, the use of traditional medicines by Africans living with HIV is believed to be widespread, although insufficiently documented (McPhail *et al.*, 2002).

Magadula and Suleiman (2010) studied the anti-HIV and cytotoxic activities of some crude extracts from the *Garcinia* plant species growing in Tanzania and reported that out of sixteen extracts tested in an HIV-1 viral replication assay, two (fruit extracts of *G. semseii* and *G. livingstoneii*) showed moderate to mild anti-HIV activities, respectively. The literature indicated that some polyisoprenylated benzophenone derivatives isolated from *Clusia* (Piccinelli *et al.*, 2005) and *Garcinia* (Gustafson *et al.*, 1992) genera exhibited potent anti-HIV-1 activities. Similar findings have been reported by Gustafson, *et al.*, 1992 of the isolation of guttiferones, benzophenone compounds with anti-HIV activities from *Garcinia* plants.

*Hypoxis*, a well-known genus of the family *Hypoxidaceae* which is easily recognized by its bright yellow, star-shaped flowers and strap-like leaves, has a long history of medicinal use on the African continent. This has been demonstrated by the South African primary health care community which is currently using *the plant material* as an immunostimulant for patients with HIV/AIDS. A daily dose of 2,400 mg of raw plant is purported to be therapeutically effective (Albrecht *et al.*, 1995). Within the genus, two species, *H. hemerocallidea* and *H. colchicifolia* are particularly popular both as African traditional remedies and for the preparation of herbal teas and tinctures (Mills *et al.*, 2005). An important constituent of the plant is a nor-lignan glycoside called hypoxoside, which, once in the human gut, readily converts to the aglycone, *rooperol*, a biologically active compound that is purported to have medicinal properties (Albrecht *et al.*, 1995). The plant also contains various sterols ( $\beta$ -sitosterol, stigmasterol) and their glycosides (sterolins) such as  $\beta$ -sitosterol glycoside and stanols such as sitostanol also called stigmastanol, which have also been purported to have important biological activity (Bouic *et al.*, 2001).

Another flowering shrub, *Sutherlandia frutescens*, which is a member of the *Fabacea* family, has been used in the treatment of cancer, tuberculosis, diabetes, chronic fatigue syndrome, influenza, rheumatoid arthritis, osteoarthritis, peptic ulcers, gastritis, reflux esophagitis, menopausal symptoms, anxiety, clinical depression and HIV infection (Dalvi, 2003). The plant has a recommended therapeutic dose of 9 mg/kg/day (Seier *et al.*, 2002) in humans, thus prompting the South African Ministry of Health, based on primate safety studies, to conclude that the plant product is safe (Mills *et al.*, 2005). The principal constituents purported to be active include L-canavanine, GABA, and D-pinitol. L-canavanine is an arginine analogue and has been reported to have anti-viral activity against influenza and retroviruses, including HIV (Green, 1988). A US patent registered in 1988 claimed that 95% of HIV-infected lymphocytes were selectively destroyed *in vitro*. Unfortunately, no further studies of the effect of this herb on HIV have confirmed this



claim. D-pinitol another important constituent of the plant has also been suggested for the treatment of wasting in cancer and AIDS patients although evidence is minimal (Green, 1988).

Eighteen ethanol extracts from some *Garcinia* species in the *Guttiferae* (*Clusiaceae*) family collected in Tanzania were investigated for their HIV-1 protease (HIV-1 PR) inhibitory activities using high performance liquid chromatography (HPLC). Among the tested extracts, the fruit hulls of *Garcinia semseii* showed the most potent inhibitory activity against HIV-1 PR with an  $IC_{50}$  value of 5.7  $\mu\text{g/ml}$  followed by the stem bark extracts of *Garcinia edulis* and *Garcinia kingaensis* with  $IC_{50}$  values of 9.2 and 15.2  $\mu\text{g/ml}$ , respectively. Phytochemical screening of the extracts indicated mostly the presence of phenolic and steroidal compounds (Magadula and Tewtrakul, 2010).

Nigeria is not left out in this initiative at finding herbal cure for HIV/AIDS (Amadi et al., 2009) since the country is endowed with a variety of traditional herbs and spices which are consumed by the various ethnic groups for different reasons. The use of local plant extracts in the treatment of diseases is indeed widespread in the country today. In fact, there is a general belief that more than 60% of the population particularly in the rural areas, depend on traditional medicine for their health care needs in the absence of modern medical facilities. Most of the traditional healers being patronized employ a variety of these extracts in concoctions as remedies for various ailments. Claims of potency of the different extracts used in these therapies have generated increased interest in some herbs and spices, leading to research and laboratory analysis of the extract from such plants (Ghani and Mbou, 1998; Adelaja and Fasidi, 2003).

#### ADVERT EFFECTS

Some forms of complementary and alternative medicine can cause harmful side effects. Consequently words like “natural” and “traditional” are certainly no guarantee of safety. Herbal or nutritional therapies (notably St John’s Wort) may also interact with other medications, making them less effective or worsening their side effects. In addition, herbal remedies and dietary supplements are not covered by the strict regulations that govern pharmaceutical drugs. Furthermore quality is inconsistent even among popular commercial formulations since tests have shown that the concentrations of active ingredients can vary greatly from the amounts listed on the packaging. The standard of complementary and alternative practitioners is similarly uneven. Although some countries regulate certain types of practitioners, many people still practice without any formal qualifications. Even if a therapy carries little risk of direct physical harm, it may still turn out to be a waste of time and money. Finally relying on alternative medicine instead of scientifically proven treatment can have very serious consequences because once HIV has severely weakened the immune system, antiretroviral drugs are less likely to be life-saving (Mills, 2006).

#### CONCLUSION

The market is crammed with varieties of herbs and spices that form an important part of human diets. Worldwide there is a growing trend towards herbal medicines as a supplement and/or treatment for HIV/AIDS. African herbal medicine, however, remains in the forefront of new researches against the scourge. Herbs and spices are indeed safe, natural and cheap remedies available to rid the body of microbial and parasitic infections, including retroviruses and other enemies of the immune system. The nutritional content of herbs and spices varies considerably, though generally they contain a small proportion of protein and fat and a relatively high proportion of vitamins, provitamins, dietary minerals, fiber and carbohydrates.





Many also contain phytochemicals made up of substances like alkaloids terpenes, phenolic compounds, basic metabolites, glycosides as well as secondary metabolites, which may have antioxidant, antibacterial, antifungal, antiviral and anti carcinogenic properties.

Government should therefore encourage researches into herbal remedies in order to create awareness to their efficacy. Furthermore these wonderful sources of cure could be compounded into tablets, injections and syrups to meet consumers' taste, whereby control measures as to production regulation would be enforced. However efforts are required to determine the safety, efficacy and pharmacological profile of many of the herbal compounds with a view to fully understanding what remedies are in use for HIV and to educate those providing alternative medical services against unsafe practices. Besides, improved sanitation and hygiene, safe sexual conduct (no sex outside marriage) can also help to prevent the spread of HIV/AIDS. The sooner this dimension is pursued, the better it will be for healthcare delivery against HIV/AIDS in this century.

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