*Review Article* *Spatula DD. 2013; 3(4):127-140*

# The potential of complementary and alternative medicines in the management of HIV infection and related complications

## HIV infeksiyonunun ve ilişkili komplikasyonların tedavisinde tamamlayıcı ve alternatif ilaçların potansiyeli

*Mohamad Fawzi Mahomoodally, Luxcha Ragoo, Priyamka Dheeya Sreekeesoon, Shanoo Suroowan, Zubeyr Muhammad Khedoo*

Department of Health Sciences, Faculty of Science, University of Mauritius, Réduit, Mauritius.

**SUMMARY**

With more than 34 million of infected individuals, the prevalence of Human Immunodeficiency Virus (HIV) infection remains a perturbing pandemic that has been projected to one of the most serious significant public health concerns. Nonetheless, the introduction of highly active antiretroviral therapy (HAART) has significantly reduced Acquired Immune Deficiency Syndrome (AIDS) related morbidity and mortality. Although the quality of life of those infected has been improved, patients continue to experience physical and emotional discomforts due to the infection and/or co-infection and related treatment. The weak success of conventional biomedicine to find an effective cure for this infection has enticed patients to seek relief through the use of complementary and alternative medicine (CAM) though this means accepting certain levels of uncertainty in the hope to alleviate their suffering. Despite the widespread use of CAM, little is known about the characteristics of HIV-infected CAM users. Based on the lacuna of high-quality data reporting the use of CAM among HIV/AIDS patients, reviewing CAM use in patients on and off antiretroviral medications (ARV) is an essential baseline step to address challenges surrounding the use, safety and efficacy of CAM therapies. It therefore remains to the clinicians' obligation to inquire about CAM use when assessing, treating, and monitoring patients to ensure the effective use of CAM alongside preventing drug toxicity, treatment failure and ARV resistance. The present review has endeavoured to explore and provide updated information on the potential of common CAM therapies that have been shown to have positive health benefits in HIV/AIDS patients.

**Key words**: Human Immunodeficiency Virus; Acquired Immune Deficiency Syndrome; Complementary and alternative medicine.

**ÖZET**

Otuz dört milyon enfekte bireyle, en ciddi önemli halk sağlığı sorunlarından biri olan İnsan İmmün Yetmezlik Virüs (HIV) enfeksiyonunun prevalansı rahatsızlık verici bir pandemi olarak sürmektedir. Bununla birlikte, yüksek oranda aktif antiretroviral tedavilerin (HAART) kullanıma girmesi Kazanılmış İmmün Yetmezlik Sendromu (AİDS) ile bağlantılı morbidite ve mortaliteyi belirgin şekilde azaltmıştır. Enfeksiyonluların yaşam kalitelerinin geliştirilmiş olmasına rağmen, hastalar enfeksiyon ve/veya koenfeksiyon ve ilgili tedavi nedeniyle fiziksel ve duygusal rahatsızlıklar yaşamaya devam etmektedir. Bu enfeksiyon için etkin bir tedavi bulmaktaki konvansiyonel ilaçların başarısızlığı, sıkıntılarını hafifletmedeki belirsizliği kabul etmelerine rağmen, hastaları tamamlayıcı ve alternative tıp (CAM) kullanımını yoluyla yardım aramaya yönlendirmiştir. Tamamlayıcı ve alternatif tedavilerin yaygın olarak kullanılmasına rağmen, HIV ile enfekte CAM kullanıcılarının özellikleri hakkında bilinenler yetersizdir. HIV/AİDS hastaları arasında CAV kullanımını rapor eden yüksek kalitede ki bilgilerin olmamasına dayanarak, antiretroviral tedavilerin (ARV) varlığı ve yokluğunda hastalarda CAM kullanımının değerlendirilmesi, CAM tedavilerinin kullanımı, güvenliği ve etkinliğini çevreleyen zorlukları çözmek için gerekli temel bir adımdır. Bu nedenle, ilaç toksisitesinin, tedavide başarısızlığın ve ARV direncinin önlenmesinin yanısıra alternatif ilaçların etkin kullanımından emin olmak için, hastayı değerlendirirken, tedavi ederken ve takip ederken klinisyenlerin CAM kullanımı hakkında bilgi edinme zorunluluğu vardır. Bu değerdirme yazısı, HIV/AIDS hastalarında pozitif sağlık faydaları gösterilmiş olan sık kullanılan CAM tedavilerinin potansiyel hakkında güncel bilgileri saptamaya ve sunmaya çabalamıştır.

**Anahtar kelimeler:** İnsan immün yetmezlik virüsü, Kazanılmış immune yetmezlik sendromu, Tamamlayıcı ve alternative tıp.

**Corresponding Author:**
Dr. M. Fawzi Mahomoodally,
Department of Health Sciences, Faculty of Science, University of Mauritius, Réduit, Mauritius.
E-mail: f.mahomoodally@uom.ac.mu; mmfawzi@gmail.com

Received July 29, 2013; accepted October 25, 2013
DOI 10.5455/spatula.20131025123323
Published online in ScopeMed (www.scopemed.org).
Spatula DD. 2013; 3(4):127-140.

## INTRODUCTION

The human immunodeficiency viruses (HIV) designated as HIV-1 and HIV-2 are the infection agents in human, causing a syndrome known as acquired-immuno deficiency syndrome at the terminal stage of the disease. HIV/AIDS is a perturbing pandemic and one of the worst to affect humanity over the last century [1] with endorsing figures of 34 million of infected individuals in 2012 [2]. Panoply of conventional remedies including mainly antiretroviral medications (ARV) has been developed and used successfully [3]. Indeed, the massive and unprecedented scale-up of antiretroviral therapy (ART) in low and middle income countries in the last years is probably the most outstanding achievement in the global fight against HIV/AIDS [4]. Interestingly, combination of antiretroviral therapies (cART) has significantly reduced AIDS-related morbidity and mortality and new regimens offer benefits of fewer side effects and a low pill burden [5].

Despite laudable advances in the medical field over the recent years and the profusion of effective ARV that have been produced to combat HIV/AIDS, concerns associated with the use of ARVs do not cease to increase [6]. Indeed, it is of no denying to the blatant fact that even more than thirty years after the discovery of HIV; the virus can still not be managed and cured completely [7]. Additionally, accounts of HIV drug resistance, ranging from 27 to 50%, have also been reported. Furthermore, these drugs can be toxic, highly priced, and unaffordable by most people who need them in the developing world [8].

Given the magnitude of the HIV/AIDS epidemic among the world's population and the absence of an effective vaccine, timely and appropriate treatment has become critical in extending the length and quality of life of those infected [9]. Consequently, attention and interest in the use of CAM as an adjunct to HIV/AIDS treatment [10] has burgeoned in recent years and is still in its burgeoning stages [11]. Several studies have shown that CAM is widely used by people living with HIV/AIDS (PLWHA) as the primary treatment form for HIV/AIDS and for HIV-related complications [12].

Interestingly, CAM use has increased in popularity among HIV-positive individuals in recent years. Vitamins and dietary supplements, massage, and acupuncture are the most prominent CAM modalities used by these individuals [13]. Despite the widespread use of CAM, little is known about the characteristics of HIV-infected CAM users. Based on the lacuna of high-quality data reporting the use of CAM among HIV/AIDS patients, reviewing CAM use in patients on and off ARV is an essential baseline step to address challenges surrounding the use, safety and efficacy of CAM therapies.

### Pathogenesis of HIV/AIDS

HIV is a ribonucleic acid (RNA) virus first discovered in 1983 belonging to the retroviridae family of viruses. This virus contains a unique enzyme, reverse transcriptase, that converts viral RNA into complementary deoxyribonucleic acid (cDNA) which can then be integrated into the genome of the host cell it has infected [14]. One genus of retrovirus, lentivirus, includes subspecies HIV-1 and HIV-2. Lentivirus, known as slow virus characteristically, particularly attacks the immune system. Indeed, there is a long time interval between infection and onset of symptoms [15].

In the *Homo sapiens*, HIV is mainly spread through semen and vaginal fluid from unprotected sex. Alongside, mother to child transmission during pregnancy, birth and breast feeding and the use of un-cleaned needles among injecting drug communities remain significant routes of HIV transmission [16, 17]. HIV infection progresses to AIDS disease as the virus replicates in cells of the immune system (CD4+ cells). Immunologically, HIV infection suppresses levels of CD4+ cells via three mechanisms including: direct killing of infected cells; increasing rates of apoptosis in infected cells; killing infected CD4+ cells by CD8+ cytotoxic lymphocytes that recognise infected cells [18]. Sero-conversion of HIV occurs 2-4 weeks after viral entry in the human body and is either marked as asymptomatic or acute retroviral syndrome characterized by glandular fever-like illness with fever, rash, joint pains and lymphadenopathy is experienced. The pathogenic events of HIV enclose 4 clinical stages in the adult and adolescents (≥15 years) populations [19].

The clinical stage I is either asymptomatic or persistent generalised lymphadenopathy is observed and lasts for several years [19, 20]. During this symptomatic stage II, unexplained weight loss less than 10% of total body weight, recurrent upper respiratory tract infections such as sinusitis, bronchitis, otitis media, and pharyngitis and a range of dermatological conditions including herpes zoster flares, angular cheilitis, recurrent oral ulcerations, papular pruritic eruptions, seborrhoeic dermatitis and fungal nail infection are observed [19].The clinical manifestations of this stage III encompass weight

loss of greater than 10% of total body weight, prolonged unexplained diarrhea, unexplained persistent fever, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis, severe presumed bacterial infections including pneumonia, pyelonephritis, empyema, pyomyositis, meningitis, bone and joint infections, and bacteremia and acute necrotizing ulcerative gingivitis or necrotizing ulcerative periodontitis [19]. The last clinical stage leads to the development of AIDS and comprises of 22 opportunistic infections or cancers related to HIV including tuberculosis, wasting syndrome, pneumocystis pneumonia, candidiasis of trachea, bronchi and lungs and HIV encephalopathy. AIDS is developed when the CD4+ cell count of less than 200 per mm3 of blood [19, 21].

**The Management of HIV/AIDS**

**Antiretroviral medications**

ART is primarily aimed at reducing the plasma viral load by means of medication which generally target either reverse transcription of viral RNA into cDNA; the reverse transcriptase inhibitors; or virus assembly and maturation; the protease inhibitors [22]. The standard treatment consists of a combination of at least three drugs often called "highly active antiretroviral therapy" (HAART) that suppress HIV replication. The purpose of the combination is to reduce the probability of the virus developing resistance. As at the end of 2012, 9.7 million people had access to ART in low- and middle-income countries [23].

The World Health Organisation (WHO) has established guidelines for when to start the ART. In low income countries HIV-infected individuals should commence ART if they have WHO stage IV disease, stage III disease and a CD4+ lymphocyte cell count of ≤ 350 cells/μL, or stage I or II disease with CD4+ cell counts ≤ 200 cells/μL [24].

Besides increasing the longevity of patients, no cure for the infection has been found by researchers in over thirty years since the initial reports of AIDS [25]. However, as HIV-infected patients begin to live longer on HAART, issues regarding viral resistance, short and long-term drug toxicities have become important issues. Also, limited access or affordability of biomedical care in some regions around the globe [26] makes patient adherence to ARV a major challenge [27, 28].

Additionally PLWHA that have cancer, autoimmune diseases and arthritis patients have been found to be unresponsive to mainstream therapies. Due to the scarcity of treatment options PLWHA have to look for physiological, psychological and spiritual therapeutic options to soothe the effects and associated complications of the disease [29].

Several reports tend to show that patients who are dissatisfied with the conventional therapies turn to traditional medicines to help combat or gain control over their illness [30]. Moreover some patients uncertain in their choice of treatments end up using both conventional ART therapies and traditional medicines [26]. Indeed, herbal remedies are perceived as good supplements to ART because of their immune-stimulatory properties ability to 'wash toxins' from the body, replace nutrients and improve appetite levels [31]. These traditional medicine forms fall under the broad umbrella of CAM.

**Traditional medicines and CAM**

Traditional medicine is the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses. Traditional medicine that has been adopted by other populations (outside its indigenous culture) is often termed CAM [3, 26].

There is no universally agreed definition for CAM. However, CAM can be defined as a broad domain of resources that encompasses health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the dominant health system of a particular society or culture in a given historical period. CAM includes such resources perceived by their users as associated with positive health outcomes [32]. CAM therapies represent a large collection of products and practices, with current estimates putting the total number of CAM therapies well above several hundred. The US National Centre for Complementary and Alternative Medicine (NCCAM) uses a classification method to group CAM therapies into five distinct categories [32]:

1. Biologically based therapies are compounds that are typically found in nature (e.g., herbal products)
2. Mind-body medicine, which relies on the belief that systems of thought affect bodily functioning (e.g., meditation, t'ai chi, yoga, biofeedback)
3. Manipulative and body-based practices, which involve the movement of specific body parts (e.g., massage based therapies)
4. Energy medicine, which uses energy fields (e.g., bio-electromagnetic therapies)
5. Alternative medical systems, which rely on theories and beliefs that have developed apart from

conventional medical practices (e.g., acupuncture, ayurvedic medicine, homeopathy)

The NCCAM has classified CAM to help understand and group the many divergent CAM therapies [32] and summarised in Table 1.

**Table 1:** Classification of Complementary and Alternative Medicine

| Therapy | Description |
|---|---|
| Acupuncture | Insertion of needles into the skin at special sites, known as points, for therapeutic or preventive purposes |
| Aromatherapy | Use of plant essences for therapeutic purposes, usually with massage |
| Guided imagery | Controlled use of mental images for therapeutic purposes |
| Herbal medicine | Medical use of preparations made from plant material |
| Homeopathy | A therapeutic method, developed by Samuel Hahnemann, often using highly diluted preparations of substances whose effects when administered to healthy subjects in less diluted form correspond to the manifestations of the disorder in the unwell patient |
| Hypnotherapy | Induction of a trance-like state to facilitate relaxation and make use of enhanced suggestibility to effect behavioral changes and treat medical conditions |
| Magnet therapy | Permanent or pulsed magnetic fields applied to head or other parts of body |
| Massage | Manipulation of the soft tissues of the whole body using pressure, friction, and traction |
| Meditation | Diverse range of techniques based on listening to the breath, repeating a mantra, focusing attention to bring about a state of calm |
| Osteopathy | Manipulation of soft tissues and the mobilization/ manipulation of peripheral or spinal joints |
| Reflexology | Manual pressure applied to specific areas of the feet (sometimes hands or ears) that are believed to correspond with other areas or organs of the body to prevent and treat illness |
| Relaxation | Various techniques for eliciting the 'relaxation response' of the autonomic nervous system |
| Spiritual healing | Channeling of 'healing' energy from a healer to a patient to treat an illness |
| T'ai chi | System based on Chinese philosophy and martial arts using specific movements to enhance wellbeing |
| Yoga | A mind-body intervention including gentle stretching, exercises for breath control and meditation |

## Common CAM Therapies Used Among HIV/AIDS Patients

### Chinese herbal medicine (CHM)

CHM is a major aspect of the Traditional Chinese medicine (TCM), one of the oldest medical systems in the world. CHM involve the use of single herb, combination of herbs into herbal formulas and materials arising from mineral and animal sources [33].

Numerous studies have claimed Chinese herbs and herbal formulations to be effective in managing HIV at the immunological as well as symptomatic level. In this line, *Radix astragali*, and *Cordyceps* spp. have been individually reported to enhance T helper lymphocytes and improve the immune system of HIV patients [34]. Alongside, the Chinese herb compound 'ZY-1' has been reported to promote activation and hyperplasia of CD4+ cells in the lymph nodes [35]. Additionally, administration of 'Aining Granule' alongside HAART has been shown to lower the risk for the decrease CD4+ cell counts and had significant improvement of symptoms such as fatigue, anorexia, nausea, diarrhea, skin rash [36].

### Acupuncture, moxibustion and relaxation response techniques

Acupuncture and moxibustion are allied therapies of the TCM except that their stimulation methods are different. Moxibustion uses the heat generated by burning herbal preparations containing *Artemisia vulgaris* to stimulate acupuncture points [37]. Relaxation response techniques include a number of practices such as progressive relaxation, guided imagery, biofeedback, self-hypnosis, and deep breathing exercises which target at producing the body's natural relaxation response, characterised by slower breathing, lower blood pressure, lesser pain and a feeling of calm and well-being [38].Solitarily, acupuncture has been recognised to bring improvements in emotional, mental and peace/spiritual areas in the lives of patients living with HIV [39].

Acupuncture coupled with moxibustion, has been reported to be beneficial for HIV positive patients with peripheral neuropathy through mitigation of the severity of lower limb neuropathic pain and numbness associated with HIV/AIDS [40]. Additionally, combining relaxation response techniques to acupuncture was clinically cited to be significant in ameliorating emotional, functional and global well-being as well as mental health and peace in PLWHA [41].

**Massage**

The reported effects of massage include pain relief, decreased levels of depression, improved blood flow and blood composition, reduced edema, and increased mobility of connective tissue, muscle and the nervous system [18]. It is alongside proposed that via alterations in biochemistry such as reduced cortisol levels, stress level can be reduced leading to an increase in CD4+ and CD8+ cells and in turn the general function of the immune system can be improved [42]. In adjunct, massage has been attributed to have a positive impact on immune function in HIV positive children not receiving ARV [43].

Among traditional lifestyle modifications, yoga has been attested to lower blood pressure in pre-hypertensive HIV infected adults with mild to moderate cardiovascular disease risk factors [44]. It has also been shown that yoga can reduce the amount of hot flashes in HIV positive menopausal women [45]. Yoga alongside t'ai chi and relaxation response techniques have been documented to reduce blood pressure and are claimed to benefit HIV patients with hypertension [46]. Furthermore, mindfulness-based stress reduction which brings together body scan, sitting meditation and yoga specifically Hatha yoga practice, comprising of breathing exercises and simple stretches [47] is claimed to alleviate depression in HIV positive patients [40].

**Ayurveda**

Ayurveda represents one of the most ancient systems of traditional medicine of the world, practiced in India since 5000 BC. It is a holistic approach towards disease management and prevention, health maintenance and longevity promotion through medicinal herbs, minerals, diet, lifestyle and spirituality [48]. Ayurvedic herbalism has reported several herbs and herbal formulation in the limelight as anti-HIV agents. The herbal formulation 'AC II' consisting of *Withania somnifera* rhizome, *Mesua ferrea* (flower buds), Syzygium aromaticum (flower buds), *Elettaria cardamomum* (seeds), *Piper nigrum* (seeds), *Piper longum* (seeds) and *Zingiber officinale* (rhizome) has been demonstrated to exhibit immune-stimulating activity and to delay the onset of symptoms in PLWHA [49].

**Micronutrients**

Selenium, a trace mineral and antioxidant in nature plays an important part in the immune system by stimulating various immune responses. Selenium has been found to increase CD4+ count in HIV/AIDS patients on a nine month basis [50]. The mineral deficiency has been found in HIV positive patients since the virus acts by lowering selenium levels in the body thereby suppressing the immune system to a greater extent [42]. Additionally, vitamin B12 supplementation increases CD4+ cell count and survival time among PLWHA. The scientific community has proved that vitamin C can successfully inhibit replication of the HIV retrovirus and high serum levels of vitamin E has been shown to reduce HIV progression [51].

**Medical marijuana (*Cannabis sativa*)**

Among the 460 known chemicals from the plant species *Cannabis sativa*, the cannabinoids have been the most medicinally valued group due to their potent immune-modulatory and psychoactive properties. Tetrahydrocannabinol one of the cannabinoids has the potential to bind to G protein-coupled cannabinoid receptors in neurones and immune cells thereby inhibiting/stimulating the production of neurotransmitters and cytokines. Indeed, this compound has been given considerable scientific attention as an anti-emetic and appetite stimulant and its synthetic form dronabinol has been developed and marketed to improve appetite and hence cause weight gain in HIV/AIDs patients [52]. Additionally, sensory neuropathy is the most common peripheral nerve disorder among HIV-positive individuals while the most prominent symptom is pain [30]. Smoked cannabis has been shown to have a doubling effect in reducing peripheral pain compared to placebo trials following a five day treatment [53].

**Herbal therapies**

In spite of the increased availability of antiretroviral drugs, the prevalence of traditional herbal therapies used by HIV-infected individuals cannot be contested [30]. Herbal remedies are often sought as a primary intervention for HIV/AIDS as well as HIV-related complications including dermatological disorders, nausea, depression, insomnia, and weakness [54]. Prone to opportunistic infections triggered by fungus and bacteria as a result of immunosuppression, HIV/AIDS patients make extensive use of traditional remedies in the treatment of such infections [55]. Consequently, an exuberant diversity of published material is available on the use of herbal remedies in a number of developing countries, like Asian and Africa. One of the endorsing reasons could be the fact that Sub-Saharan Africa is the most vulnerable and highly targeted region with figures revealing that 1 in 20 adults lives with HIV which globally accounts for 69% of all

PLWHA [56]. The use of herbal remedies is ascending due to traditional beliefs and at times incoherent access to antiretroviral drugs [30]. In addition, the most common reasons buoying patients for using herbs include general well-being, relaxation, less pain and stress, spiritualism, to improve energy level, to supplement dietary intake and to enhance response [55].

A rich diversity of medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in sub-Saharan Africa have been documented as summarised in Table 2 [57]. The most prevalent ones which have been extensively reported and exploited [54] include *Hypoxis hemerocallidea* (African potato) and Sutherlandia. Moreover, *Azadirachta indica, Carissa edulis*, *Ximenia americana* have also been frequently cited medicinal plants used by PLWHA [26]. Aloe sp., *Erythrina abyssinica*, *Sarcocephalus latifolius*, *Psorospermum febrifugum*, *Mangifera indica* and *Warburgia salutaris* were commonly used in Uganda for treating HIV/AIDS and related complications [58]. *Allium sativum, Zingiber officinale, Aloe vera* gel, *Moringa oleifera*, Chinese herbal remedies, 'Stametta' (aloe mixed with vitamins and herbs) and some herbs simply labeled 'Back to Eden' were also commonly used herbal remedies [31].

**Table 2:** Common traditional medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Sub-Saharan Africa

| Species | Family | Traditional uses | Parts used* | Mode of application | References |
|---|---|---|---|---|---|
| *Allium sativum* L. | *Alliaceae* | • Malaria, HIV/AIDS | R | Crushed, chewed Raw | [26] |
| *Aloe* spp. | *Aloaceae* | • Swelling, boils, burns<br>• Fever, hepatitis<br>• Herpes zoster | L<br>L, RB<br>L | Decoction taken orally, applied to affected area | [26, 58- 60] |
| *Azadirachta indica* A. Juss. | *Meliaceae* | • Malaria, skin rashes, HIV/AIDS | L, B | Decoction taken orally, steambath, washing, rubbed on teeth or gums | [26] |
| *Bidens pilosa* L. | *Compositae* | • Stomach ache, oral candidiasis | L | Decoction taken orally | [26, 59] |
| *Carica papaya* L. | *Caricaceae* | • Malaria, gonorrhea<br>• Children's cough, oral candidiasis | L, R<br>L, R | Infusion, decoction taken orally | [26, 59] |
| *Carissa edulis* (Forssk.) Vahl | *Apocynaceae* | • Amebas,gonorrhea,sexually transmitted infections | R | Decoction taken orally | [26, 58] |
| *Cymbopogon citratus* (DC.) Stapf | *Poaceae* | • Headache, purify blood, clean pores | L | Decoction taken orally, Tea | [26] |
| *Dalbergia melanoxylon* Guill.&Perr. | *Papilionaceae* | • Back and joint-aches, oral candidiasis, ulcer boils | L | | [60] |
| *Erythrina abyssinica* DC. | *Papilionaceae* | • Cough | SB, RB, RW | | [58] |
| *Garcinia buchananii* Bak. | *Clusiaceae* | • Cryptococcal meningitis, herpes zoster, herpes simplex, skin rashes, tuberculosis, chronic diarrhoea, | B/R | Drinking,<br>Rubbing | [60] |
| *Garcinia huillensis* Bak. | *Clusiaceae* | • Tuberculosis, chronic diarrhoea, cryptococcal meningitis, herpes zoster, herpes simplex, skin rashes | B, R | | [59] |
| *Harungana madagascariensis* Lam. Ex Poir | *Clusiaceae* | • Chronic diarrhea | L, B | | [59] |
| *Lannea stuhlmannii* Engl. | *Anacardiaceae* | • Herpes zoster, herpes simplex, skin infections | R | Rubbing | [60] |

| | | | | | |
|---|---|---|---|---|---|
| *Mangifera indica* L. | *Anacardiaceae* | • Diarrhea, cough<br>• Tuberculosis | SB, RB<br>L | | [58, 59] |
| *Moringa oleifera* Lam. | *Moringaceae* | • Cold and flu, diarrhea, 'boost' the immune system and reinvigorate the body | L | Tea, cooked as vegetable | [31] |
| *Moringa stenopetala* L. | *Moringaceae* | • Vomiting, diarhoea | | | [60] |
| *Ozoroa insignis* Del. | *Anacardiaceae* | • Skin rashes, tuberculosis, herpes simplex, herpes zoster, cryptococcalmenengitis, oral candidiasis | R | | [59] |
| *Psidium guajava* L. | *Myrtaceae* | • Malaria, diarrhea<br>• Tuberculosis, chronic diarrhoea, coughing | L, F<br>L | Decoction taken orally | [26, 60] |
| *Psorospermum Febrifugum* Spach. | *Clusiaceae* | • Herpes zoster, herpes simplex, cryptococcal meningitis, skin infections. | B, R | | [59] |
| *Sarcocephalus latifolius* (Sm) E.A. Bruce | *Rubiaceae* | • Diarrhea, sexually transmitted diseases | RB, WR | | [58] |
| *Securidaca longipedunculata* Fres. | *Polygalaceae* | • Cryptococcal meningitis, oral candidiasis, coughing | L/R, B | | [60] |
| *Warburgia salutaris* (Bertol.f.) Chiov. | *Canellaceae* | • Cough | SB | | [58] |
| *Ximenia americana* L. | *Olacaceae* | • Boils, skin rashes | R, L, F | Decoction taken orally, steam bath, chewed raw | [26] |
| *Zingiber officinale* Roscoe | *Zingiberaceae* | • Malaria, sore throat | R | Chewed raw, decoction taken orally | [26] |

L, leaves; RB, root bark; SB, stem bark; R, root; B, bark; Fruit, F; WR, whole root; RW, root wood

## Documented Evidence of Medicinal Plants against HIV/AIDS

### α-Zam

α-Zam, a herbal blend comprising of 60% *Nigella sativa* and 40% fresh pure honey was tested in 6 HIV-positive patients in Nigeria. This clinical study demonstrated that the concoction consisting of a rich panoply of phytoconstituents including saponins, tannins, cardenolides, alkaloids and anthraquinones; elevated CD4+ count, lessen viral load of HIV-RNA notably from an average of 423,000 copies/ml to quite insignificant amounts (≤50 copies/ml) in all HIV patients. This consequently resulted in the remarkable disappearance of various symptoms and signs associated with HIV infection, for instance, diarrhea, fever, cough, oral thrush, and skin rashes within 3 weeks [61].

### *Azadirachta indica*

*In vitro* studies using *Azadirachta indica* leaf extract interfered with HIV-1 replication in C8166 CD4+ cells by predominantly suppressing the activity of HIV-1 reverse transcriptase and consequently diminishing HIV p24 antigen concentration. Additionally, *ex vivo* studies using the extract was successful in down-regulating specific immune activation markers which could have beneficial immunomodulation effects in HIV-infected patients [62].

Moreover, Praneem, a polyherbal formulation consisting of purified extracts of *Azadirachta indica* was investigated in 20 eligible uninfected women and entailed intra-vaginal administration of the tablet for 14 days consecutive days. Since no predominantly serious adverse effects were detected Praneem was validated as safe for use once daily by intra-vaginal route for 14 consecutive days in

sexually active HIV-uninfected women however phase II trials should be undertaken for further assertion [63].

***Camellia sinensis***

Green tea prepared from *Camellia sinensis* has been associated with positive health benefits for a number of years. A number of chemical substances known as flavonoids form an integral part of tea and have been found to have antibacterial, antitumour and antiviral effects. Concerning the mechanism of inhibition, one plausible explanation might be due to a significant boost in immune response via an increase in γ-δ lymphocytes and in turn of γ-interferon recorded following intake of 4-5 cups of black tea for 4 weeks *in vivo*. Additionally, the polyphenolic content from tea extract, particularly (−)-epigallocatechin-3-gallate (EGCG) and (−)-epicatechin-3-gallate have been well documented to be effective antimicrobial agents by disrupting the cytoplasmic membrane of various microbial strains. Interestingly, *in vitro* studies have shown the main flavonoid in green tea, (EGCG), can prevent HIV from binding to CD4+ cells by 40% at minimum concentrations. Based on these findings, two to three cups of green tea can be expected to reduce HIV binding by a factor of ten to twenty folds [42]. EGCG can also inhibit semen-derived enhancer of virus infection activity and abrogates semen-mediated enhancement of HIV-1 infection [64].

**Honey**

Natural honey highly acclaimed since years particularly for its antimicrobial potency, has multifarious therapeutic applications and accordingly its use against HIV has been investigated.

Researchers round the globe have worked both in-vitro and *in vivo* to unveil the unknown benefits of the inestimable attributes of honey as well as its applications. Blessed by these varying colourful colloids, it has set templates since prehistoric times and is still being exploited for its tremendous antimicrobial benefits. This substance has been used in folk medicine since ancient times. The different biological, chemical and physical properties of honey have revealed several claims through different techniques.

Scientific evidence from a case study report conducted on a 30 year-old HIV positive Iranian who had never received prior treatment by administering 80g natural honey daily for three months period; revealed elevated levels of CD4+, CD8+, red blood cells and specific white blood cells. Consequently, this finding suggested that natural raw honey may seemingly boost the immune system function in HIV positive patients but it warrants the need for further clinical trials in patients [65].

***Hypoxis hemerocallidea***

*Hypoxis hemerocallidea*, commonly known as African potato possesses potent biologically active phytoconstituents such as hypoxoside (active form = rooperol) and stigmastanol and is being actively used by patients with HIV/AIDS as an immunostimulant. A daily dose of 2,400 mg of raw plant is claimed to be therapeutically effective. There is some indirect evidence that sterols and sterolins, found in the root of *Hypoxis*, have the potential to enhance immunity [54].

***Humulus lupulus***

Xanthohumol, prenylchacone flavonoid, is a natural product with multi-biofunctions purified from Hops (*Humulus lupulus*). Xanthohumol inhibits HIV-1 induced cytopathic effects, the production of viral p24 antigen and reverse transcriptase at non-cytotoxic concentration. It also inhibits HIV-1 replication in peripheral blood mononuclear cells (PBMC) [66].

***Panax ginseng***

The root extract of *Panax ginseng* has been of medicinal importance to the Chinese population for now more than 2000 years. In healthy humans the regular ginseng dosing has the potential to induce the body's immune function. Targeting neutrophils, CD4+ cells and natural killer cells are some of the various epitomes of pathways via which ginseng exert its beneficial immunomodulatory effects. Due to its inherent capacity of boosting the immune system ginseng has been actively used by PLWHA throughout the years. The administration of 5.4 mg of ginseng daily for 6 months to HIV-1 patients has been shown to maintain and or increase the level of their CD4+ cell counts. Along the concomitant administration of ginseng with zidovudine (ZDV) can also decrease the virus resistance to the drug. Interestingly, PLWHA relying only on Korean red ginseng have been able to maintain their CD4+ count up to 8 years [67].

**Extracts from *Lamiaceae* family**

Extracts from lemon balm (*Melissa officinalis* L.), peppermint (*Mentha piperita* L.), and sage (*Salvia officinalis* L.) have been reported to exhibit a high and concentration-dependent activity against the infection of HIV-1 in T-cell lines, primary macrophages, and in *ex vivo* tonsil histocultures.

Mechanistically, extract exposure of free virions potently and rapidly inhibited infection, while exposure of surface-bound virions or target cells alone had virtually no antiviral effect. In line with this observation, a virion-fusion assay demonstrated that HIV-1 entry was drastically impaired following treatment of particles with *Lamiaceae* extracts, and the magnitude of this effect at the early stage of infection correlated with the inhibitory potency on HIV-1 replication. Extracts were active against virions carrying diverse envelopes (X4 and R5 HIV-1, vesicular stomatitis virus, ecotropic murine leukemia virus), but not against a non-enveloped adenovirus. Moreover, sucrose-density equilibrium gradient analyses disclosed a marked increase of virion density [68-69].

***Mangifera indica***

Mangiferin, a major C-glucosylxanthone isolated from *Mangifera indica* extracts essentially demonstrated anti-protease activity by targeting HIV-1 protease and also hindered HIV-1IIIB induced syncytium formation at non-cytotoxic dose-dependent concentrations [70]. Another study revealed that *M. indica* stem bark extract prolonged T-cell lymphocytes survival by counteracting T-cell activation. It also demonstrated that *M. indica* extract reduced anti-CD3-induced accumulation of reactive oxygen species (ROS) and intracellular free $Ca^{2+}$ and accordingly down-regulated CD95L mRNA expression and CD95-mediated activation-induced cell death (AICD). Since both upregulation of CD95 ligand expression and enhancement of AICD are important underlying features of AIDS, this finding suggests that *M. indica* may have positive implications on the immune system of HIV/AIDS individuals [71].

***Momordica charantia***

*Momordica charantia* commonly known as bittergourd [72] contains anti-HIV proteins namely alpha- and beta momorcharin in its seeds, fruits and leaves. These phytochemicals alongside MAP-30 (*Momordica* Anti-HIV Protein) -a chemical analog of alpha- and beta momorcharin [73] - have been reported to inhibit infection and growth of the HIV virus [74]. MAP-30 can also activate natural killer cells, interfere with the ability of HIV viruses to divide and spread [75]. Further, MAP-30 has been established non-toxic to normal cells [76] and has improved the efficacy of anti-HIV therapy when used in combination with other anti-viral drugs. Besides, *Momordica charantia* has shown ability to counteract HAART associated hyperlipidemia in rats fed a high-fat diet [73].

**Propolis**

Propolis, the resinous substance converted by bees' enzymes following its recovery from bud and exudates of plants, is well-known predominantly for its immunomodulatory effects [77]. Propolis was found to possess anti-HIV-1 activity at a concentration of 66.6 µg/ml with maximal inhibition of 85 and 98% respectively on CD4+ and microglial cell cultures. The presumable mechanism of propolis in CD4+ lymphocytes was deduced to involve to a certain extent suppression of viral entry [78].

***Citrus* spp**

Two limonoids, limonin and nomilin, inhibits the HIV-1 replication in a dose-dependent manner as well as the production of HIV-p24 antigen. Moreover, these compounds were able to inhibit the HIV-1 replication even in infected macrophages/monocytes. As regards the mechanism of action, limonin and nomilin inhibits *in vitro* HIV-1 protease activity [79].

***Punica granatum***

One among the optimistic prevention strategies for HIV/AIDS encompasses microbicide formulations which are particularly topical formulations designed to block HIV-1 infection, and they can additionally block virus transmission when applied vaginally (and possibly rectally) before intercourse. Accordingly, following its adsorption on corn starch, HIV-1 entry inhibitors from *Punica granatum* (pomegranate) juice form a complex which blocks the virus binding to CD4+ and CXCR4/CCR5. This potential anti-HIV-1 microbicide from *Punica granatum* can be regarded as a low-cost, safe and readily available source [80]. Indeed, *Punica granatum* is rich source of polyphenols and tannins which is claimed to account for its potent antioxidant and anti-inflammatory activities [81].

***Sutherlandia frutescens***

Scientific evidence relating to the mechanism by which *Sutherlandia* acts on the immune system is scant. L-canavanine, an arginine analogue from *Sutherlandia* is claimed to have anti-viral activity against a number of viruses including HIV. The recommended therapeutic dose of *Sutherlandia* in humans is 9 mg/kg/day. The antioxidant potential of *Sutherlandia frutescens* from hot water extracts was found to possess superoxide as well as hydrogen

peroxide scavenging activities which could account for anti-inflammatory properties [54].

***Terminalia chebula***

Gallic acid and galloyl glucoses from *T. chebula* fruits are claimed to inhibit HIV-1 integrase activity [64]. Alongside, the methanolic and aqueous extracts of *T. chebula* have had significant inhibitory activity with half maximal inhibitory concentration ($IC_{50}$) ≤5 µg/mL on HIV-1 reverse transcriptase [82]. *T. chebula* fruits contain other phenolic acids such as ellagic acid and chebulic acid which act as HIV-1 protease inhibitors [83].

**Abortion of viral cell to CD4+ cell fusion by plant metabolites**

Following entry within the human body, attachment of the HIV virus arises due to binding of glycoprotein (gp-120) found on the viral coat to CD4+ receptors on host cells. Various natural products have been postulated for inhibition of this binding and indeed they have the potential to reduce the infectivity of HIV.

*Detarium microcarpum* Guill. and Perr. is an African tree belonging to the family, *Caesalpiniaceae*. The tree height reaches up to 15 m and it can reach 25 m in moist areas. It contains the flavonoid epicatechin-3-*0*-gallate which prevents the attachment of gp-120 to CD4+ cell receptors. It is also known to be an inhibitor of HIV-reverse transcriptase.

Heparin, carrageenan and dextran sulphate forming part of the various algeal species polysaccharides belonging to the Gigartaceae and Solieracaceae family can inhibit HIV replication *in vitro* by blocking the absorption of virus particles to cells through a selective action. Additionally, blue green algae harness the protein Cynovirin-N which irreversibly inactivates HIV aborting cell to cell fusion and infection to HIV.

*Castanospermum austral* A. Cunn. belonging to the *Fabaceae* family of plant contains the sugar alkaloid castanospermine which has the potential to impair the binding between CD4+ and gp-120 hence interfering with glycoprotein synthesis. *In vitro*, castanospermine when used in combination with zidovudine potentiates the action of the antiviral drug without any risk of toxicity [84].

**Inhibition of HIV reverse transcriptase and replication**

After penetration of HIV into CD4+ cells HIV reverse transcriptase transcribes the single stranded RNA into double strands. *Oenothera erythrosepala* Borbas belonging to the *Onagraceae* family contains the macrocyclic ellagitannin such as oenothin B that inhibits HIV absorption and transcription. *Ipomoea cairica* (Linn.) sweet from the *convolvulaceae* family of plants bear lignanolides which are important inhibitors of HIV replication.

*Calophyllum lanigerum* Miq. from the clusiaceae family contains calanolide A, a coumarin derivative which is a potent inhibitor DNA polymerase activity of HIV reverse transcriptase. The Chinese herbal medicine *Scutellaria baicalensis* Georgi containing baicalein and baicalin are important inhibitors of HIV infectivity and replication.

*Papaver somniferum* Linn. contains the alkaloid papaverine has been shown to inhibit HIV replication *in vitro*. *Rosa woodsii* Lindl. leaves, *Prosopis glandulosa* Torr. leaves and twigs and the whole plants *Phoradendron juniperinum* A. Gray, *Hyptis capitata* Jacq. produce oleanolic acid which is an active anti-HIV principle. *Lomatium suksdorfii* and *Angelica morii* Hayata produce the secondary metabolite suksdorfin which is a pyranocoumarin derivative that is active in inhibiting HIV replication [84].

**Side-Effects Associated with CAM**

Concurrent use of natural health products such as vitamins, nutrients and herbal remedies with ARV is widespread among HIV-infected patients and the most common and fastest growing CAM modality is herbal medicine [85]. Indeed, the concomitant use of herbs with conventional drugs regimens without medical supervision is a common practice among HIV/AIDS patients and which can be potentially dangerous. Herbs contain a diversity of constituents that act as substrates for conventional drug targets. Herb-drug interactions arise whenever herbal constituents induce or inhibit enzymes or transporters on which conventional drugs act [86].

Limited studies have probed for pharmacokinetic and pharmacodynamics interactions that may arise whenever the use of herbs and conventional drugs are combined. However some studies have shown that the concomitant use of herbs and ARV alter various pharmacokinetic endpoints such as area under the curve, time to maximum plasma concentration, peak plasma concentration, trough concentration, clearance, volume of distribution and half-life. These alterations result in toxicity, more severe adverse effects, sub-therapeutic drug concentrations, HIV resistance and treatment failure. The risk of interaction increases as the number of co-administered drugs increases [87]. Most

antiretrovirals are metabolized via the CYP3A4 and P-glycoprotein systems. Dietary supplements that induce these systems may decrease serum levels of the antiretrovirals.

A number of herbal medicines have been shown to interact with ARV when taken concomitantly. The African potato (*Hypoxis hemerocallidea*) and Sutherlandia have been shown to inhibit ARV metabolism and transport. Additionally, recent studies have demonstrated that commonly used dietary supplements can impact on ARV effectiveness. The antidepressant St. John's Wort (*Hypericum perforatum*) has been shown to lower plasma concentrations of saquinavir and indinavir respectively consequently leading to treatment failure and resistance to ARV regimens [88]. Garlic supplements (*Allium sativum*) used by HIV/AIDS patients to control the rise in cholesterol levels caused by protease inhibitors. Enthrallingly, garlic and protease inhibitors share the same CYP 450 enzyme metabolic pathway and have been shown to lower plasma concentrations of saquinavir by at least 50% [89]. Milk thistle, *Echinacea* species, and goldenseal inhibit CYP450 enzymes *in vitro*, but not to a clinically relevant effect [90].

Vitamins, an integral part of food, are also taken by HIV/AIDS patients in an attempt to boost the immune system [91] and have been shown to impede on ARV plasma concentration. Vitamin C has been shown to significantly affect the regulation of several of the key CYP enzymes, which include isoforms of CYP, family 3, and subfamily A (CYP3A). It has been observed that the steady-state plasma concentrations of indinavir is reduced up to 20% in HIV/AIDS patients receiving high daily doses of vitamin C ranging from 800 to 1000 mg [92].

Bone problems resulting from nutritional deficiency and/or drug interactions contribute to make vitamin D a nutrient of concern in the context of HIV. 1,α-25-dihydroxyvitamin D3 a derivative of vitamin D regulates the genes responsible for the production of enzymes (including CYP3A4) that are responsible for detoxification in the intestine. Induction of genes that amplify production drug-metabolizing enzymes by vitamin D do not promote its supplementation in HIV/AIDS patients following ART drug regimens has potentials to negatively impact on the treatment's safety and efficacy [93].

## CONCLUSION

The introduction of HAART has significantly reduced AIDS related morbidity and mortality. Although the quality of life of those infected has been improved, patients continue to experience physical and emotional discomforts due to the infection and the treatment. The failure of conventional therapies has compelled patients to seek relief through the use of CAM despite accepting certain levels of uncertainty in the hope to assuage their suffering. Many CAM therapies have been shown to have beneficial effects in HIV/AIDS patients and most act by boosting the immune system and increasing the number of CD4+ cells. Additionally, CAM therapies are employed by HIV patients both on and off ARV. Harmful interactions may arise due to the concomitant use of ARV and CAM of which most patients are ignorant. It therefore remains the clinicians' obligation to inquire about CAM use when assessing, treating, and monitoring patients to ensure the effective use of conventional medicine alongside preventing drug toxicity, treatment failure and ARV resistance.

## REFERENCES


1. Oti SO, Mutua M, Mgomella GS, Egondi T, Ezeh A, Kyobutungi C. HIV mortality in urban slums of Nairobi, Kenya 2003–2010: a period effect analysis. BMC Public Health. 2013; 13:588.
2. WHO. HIV/AIDS. Fact sheet number 360, 2013.
3. Hardon A, Desclaux A, Egrot M, Simon E, Micollier E, Kyakuwa M. Alternative medicines for AIDS in resource-poor settings: Insights from exploratory anthropological studies in Asia and Africa. J Ethnobiol Ethnomed. 2008; 4:16.
4. De Visser R, Grierson J. Use of alternative therapies by people living with HIV/AIDS in Australia. AIDS Care. 2002; 14(5):599-606.
5. Prosperi MC, Fabbiani M, Fanti I, Zaccarelli M, Colafigli M, Mondi A, et al. Predictors of first-line antiretroviral therapy discontinuation due to drug-related adverse events in HIV-infected patients: a retrospective cohort study. BMC Infect Dis. 2012; 12:296.
6. Bodeker G, Carter G, Burford G, Dvorak-Little M. HIV/AIDS: Traditional Systems of Health Care in the Management of a Global Epidemic. J Altern Complement Med. 2006; 12(6):563-76.
7. Des Jarlais DC, Pinkerton S, Hagan H, Guardino V, Feelemyer J, Cooper H, et al. 30 Years on Selected Issues in the Prevention of HIV among Persons Who Inject Drugs. Adv Prev Med. 2013; 2013:346372.
8. Nyamathi A, Singh VP, Lowe A, Khurana A, Taneja D, George S, et al. Knowledge and Attitudes about HIV/AIDS among Homoeopathic Practitioners and Educators in India. Evid Based Complement Alternat Med. 2008; 5(2): 221-5.
9. Kessler RC, Davis RB, Foster DF, Van Rompay MI, Walters EE, Wilkey SA, et al. Long-term trends in the use of complementary and alternative medical therapies in the United States. Ann Intern Med. 2001; 135(4): 262-8.
10. Shah M. Use of complementary and alternative medicine by HIV/AIDS patients. GUJHS. 2004; 1(3).

11. Owen-Smith A, Diclemente R, Wingood G. Complementary and alternative medicine use decreases adherence to HAART in HIV-positive women. AIDS Care. 2007; 19(5):589-93.
12. Peltzer K, Preez NFD, Ramlagan S, Fomundam H, Anderson J, Chanetsa L. Antiretrovirals and the use of traditional, complementary and alternative medicine by HIV patients in Kwazulu-Natal, South Africa: A Longitudinal Study. Afr J Tradit Complement Altern Med. 2011; 8(4):337-45.
13. Hasan SS, Keong C, Choong CLK, Ahmed SI, Ahmadi K, Anwar M. Reasons, perceived efficacy, and factors associated with complementary and alternative medicine use among Malaysian patients with HIV/AIDS. J Altern Complement Med. 2010; 16(11):1171-6.
14. Adler M. ABC of AIDS. 5th ed. BMJ Publishing, London, 2001. p.1.
15. Barasa SS. True story about HIV: theory of viral sequestration and reserve infection. HIV AIDS (Auckl). 2011; 3:125-33.)
16. WHO. HIV/AIDS. Online Q&A. 2013.
17. Lungren JD, Babiker AG, Gordin FM, Borges AH, Neaton JD. When to start antiretroviral therapy: the need for an evidence base during early HIV infection. BMC Medicine. 2013; 11:148.
18. Hillier SL, Louw Q, Morris L, Uwimana J, Statham S. Massage therapy for people living with HIV/AIDS. Cochrane Database Syst Rev. 2010; (1):CD007502.
19. WHO. Interim WHO clinical staging of HIV/AIDS and HIV/AIDS case definitions for surveillance. 2005.
20. Weinberg JL, Kovarik CL. The WHO clinical staging system for HIV/AIDS. Virtual Mentor. 2010; 12(3):202-6.
21. UNAIDS. Fast facts about HIV. 2008.
22. Miller S. Mechanisms of action of antiretroviral agents. SAJHIVMED. 2002; 3(2):16-17.
23. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013.
24. Wilkin TJ, Gulick RM. When to start antiretroviral therapy? Clin Infect Dis. 2008; 47(12): 1580-6.
25. Bryntesson F. The life cycle of the Human Immunodeficiency Virus: a useful tool for teaching scientific and new church principles in the biology classroom. The new philosophy. 2009; 761-90.
26. Nagata JM, Jew AR, Kimeu JM, Salmen CR, Bukusi EA, Cohen, CR. Medical pluralism on Mfangano Island. Use of medicinal plants among persons living with HIV/AIDS in Suba District, Kenya. J Ethnopharmacol. 2011; 135(2):501-9.
27. Max B, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. Clin Infect Dis. 2000; 30 Suppl 2:S96-116.
28. Hsiao A, Wong MD, Kanouse DE, Collins RL, Liu H, Andersen RM, et al. Complementary and alternative medicine use and substitution for conventional therapy for HIV- Infected patients. J Acquir Immune Defic Syndr. 2003; 33(2):157-65.
29. Burg MA, Uphold CR, Findley K, Reid K. Complementary and alternative medicine use among HIV-infected patients attending three outpatient clinics in the South-eastern United States. Int J STD AIDS. 2005; 16(2): 112-6.
30. Bepe N, Madanhi N, Mudzviti T, Gavi S, Maponga CC, Morse GD. The impact of herbal remedies on adverse effects and quality of life in HIV-infected individuals on antiretroviral therapy. J Infect Dev Ctries. 2011; 5(1):48-53.
31. Musheke M, Bond V, Merten S. Self-care practices and experiences of people living with HIV not receiving antiretroviral therapy in an urban community of Lusaka, Zambia: implications for HIV treatment programmes. AIDS Res Ther. 2013; 10(1):12.
32. National Center for Complementary and Alternative Medicine. Complementary, Alternative, or Integrative Health: What's In a Name? 2008.
33. Yeung WF, Chung KF, Poon MMK, Ho FYY, Zhang SP, Zhang ZJ et al. Chinese herbal medicine for insomnia: A systematic review of randomized controlled trials. Sleep Med Rev. 2012; 16(6):497-507.
34. Wang J, Zou W, Liu Y, Xu L, Lu F, Wang Y et al. Assessing the effect of traditional Chinese medicine on CD4+ lymphocyte count of 807 HIV/AIDS cases. Journal of Biomedical Science and Engineering. 2010; 3(9): 833-6.
35. Wang J, Zou W, Liu Y. Use of traditional Chinese medicine in HIV/AIDS in China. JBiSE. 2010; 3: 828-31.
36. Zou W, Liu Y, Wang J, Li H, Liao X. Traditional Chinese herbal medicines for treating HIV infections and AIDS. Evid Based Complement Alternat Med. 2012; 2012:950757.
37. Park JE, Sul JU, Kang K, Shin BC, Hong KE, Choi SM. The effectiveness of moxibustion for the treatment of functional constipation: a randomized, sham-controlled, patient blinded, pilot clinical trial. BMC Complement Altern Med. 2011; 11:124.
38. National Center for Complementary and Alternative Medicine. Relaxation techniques for Health: An Introduction. 2013.
39. Relf MV, Eisbach S, Okine KN, Ward T. Evidence-Based clinical practice guidelines for managing depression in persons living with HIV. J Assoc Nurses AIDS Care. 2013; 24(1 Suppl):S15-28.
40. Anastasi JK, Chang M. Treatment of Human Immunodeficiency Virus (HIV) associated neuropathy with acupuncture and moxibustion. Australian Journal of Acupuncture and Chinese Medicine. 2010; 5(2):37-40.
41. Robertshawe P. Acupuncture review combined effect of relaxation response and acupuncture on patients with HIV. J Aust Tradit Med Soc. 2009; 15(1):19.
42. Palmer R. Use of complementary therapies to treat patients with HIV/AIDS. Nurs Stand. 2008; 22(50):35-41.
43. Shor-Posner G, Miguez M-J, Hernandez-Reif M, Perez-Then E, Fletcher M. Massage treatment in HIV-1 infected Dominican children: a preliminary report on the efficacy of massage therapy to preserve the immune system in children without antiretroviral medication. J Altern Complement Med. 2004; 10(6):1093-5.
44. Cade WT, Reeds DN, Mondy KE, Overton ET, Grassino J, Tucker S, et al. Yoga lifestyle intervention reduces blood pressure in HIV-infected adults with cardiovascular disease risk factors. HIV Med. 2010; 11(6):379-88.
45. McPheeters C, Gregg J. Treatment options for hot flashes in the HIV-Positive menopausal patient. JNP. 2013; 9(3):166-71.
46. Balt CA. Hypertension and HIV Infection. J Assoc Nurses AIDS Care. 2013; 24(1 Suppl):S127-34.
47. Chiesa A, Serretti A. Mindfulness-based stress reduction for stress management in healthy people: A review and meta-analysis. J Altern Complement Med. 2009; 15(5):593-600.
48. Mukherjee PK, Nema NK, Venkatesh P, Debnath PK. Changing scenario for promotion and development of Ayurveda-way forward. J Ethnopharmacol. 2012; 143(2):424-34.
49. Tharakan ST, Kuttan G, Kuttan R, Kesavan M, Austin SR, Rajagopalan K. Immunostimulatory action of AC II- an Ayurvedic formulation useful in HIV. Indian J Exp Biol. 2008; 46(1):47-51.
50. Hurwitz BE, Klaus JR, Llabre MM, Gonzalez A, Lawrence PJ, Maher KJ, et al. Suppression of Human Immunodeficiency Virus Type 1 viral load with selenium supplementation: A

randomized controlled trial. Arch Intern Med. 2007; 167(2):148-54.

51. Oguntibeju OO, van den Heever WMJ, Van Schalkwyk FE. The Interrelationship between Nutrition and theImmune System in HIV Infection: a Review. Pak J Biol Sci. 2007; 10(24):4327-38.
52. Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev. 2013; 4:CD005175.
53. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo controlled trial. Neurology. 2007; 68(7):515-21.
54. Mills E, Cooper C, Seely D, Kanfer I. African herbal medicines in the treatment of HIV: Hypoxis and Sutherlandia. An overview of evidence and pharmacology. Nutr J. 2005; 4:19.
55. Orisatoki RO, Oguntibeju OO. The role of Herbal Medicine use in HIV/AIDS treatment. Arch Microbiol. 2010; 3(1):3.
56. Global fact sheet. Geneva. UNAIDS. 2012.
57. Peltzer K, Preez NF, Ramlagan S, Fomundam H, Anderson J, Chanetsa L. Antiretrovirals and the use of traditional, complementary and Alternative medicine by HIV patients in kwazulunatal, South Africa: a longitudinal study. Afr J Tradit Complement Altern Med. 2011; 8(4):337-45.
58. Lamorde M, Tabuti JRS, Obua C, Kukunda-Byobona C, Lanyerod H, Byakika-Kibwika P, et al. Medicinal plants used by traditional medicine practitioners for the treatment of HIV/AIDS and related conditions in Uganda. J Ethnopharmacol. 2010; 130(1):43-53.
59. Kisangau DP, Lyaruu HVM, Hosea KM, Joseph CC. Use of traditional medicines in the management of HIV/AIDS opportunistic infections in Tanzania: a case in the Bukoba rural district. J Ethnobiol Ethnomed. 2007; 3:29.
60. Chinsembu KC, Hedimbi M. An ethnobotanical survey of plants used to manage HIV/AIDS opportunistic infections in Katima Mulilo, Caprivi region, Namibia. J Ethnobiol Ethnomed. 2010; 6:25.
61. Onifade AA, Jewell AP, Ajadi TA, Rahamon SK, Ogunrin OO. Effectiveness of a herbal remedy in six HIV patients in Nigeria. Journal of herbal medicine. 2013; 3(3):99-103.
62. Awah FM, Uzoegwu PN, Ifeonu P. In vitro anti-HIV and immunomodulatory potentials of Azadirachta indica (Meliaceae) leaf extract. Afr J Pharm Pharmacol. 2011; 5(2):1353-9.
63. Joshi SN, Katti U, Godbole S, Bharucha K, Kumar KB, Kulkarni S, et al. Phase I safety study of Praneem polyherbal vaginal tablet use among HIV-uninfected women in Pune, India. Trans R Soc Trop Med Hyg. 2005; 99(10):769-74.
64. Chinsembu KC, Hedimbi M. Ethnomedicinal plants and other natural products with anti-HIV active compounds and their putative modes of action. Int J Biotechnol Mol Biol Res. 2010; 1(6):74-91.
65. Heidari A, Zia Sheikholeslam N, Amiri GH, Afsahi SH, Sarahroodi S. Has the natural raw honey any effect on HIV infection? IJPRBS. 2012; 1(5):205-10.
66. Wang Q, Ding ZH, Liu JK, Zheng YT. Xanthohumol, a novel anti- HIV-1 agent purified from hops Humulus lupulus. Antiviral Res. 2004; 64(3):189-94.
67. Sung H, Kang SM, Lee MS, Kim TG, Cho YK. Korean red ginseng slows depletion of CD4 T Cells in Human Immunodeficiency Virus type 1-infected patients. Clin Diagn Lab Immunol. 2005; 12(4):497-501.
68. Geuenich S, Goffinet C, Venzke S, Nolkemper S, Baumann I, Plinkert P et al. Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density. Retrovirology. 2008; 5:27.
69. Chinsembu KC, Hedimbi M. Ethnomedicinal plants and other natural products with anti-HIV active compounds and their putative modes of action. Int J Biotechnol Mol Biol Res. 2010; 1(6):74-91.
70. Wang RR, Gao YD, Ma CH, Zhang XJ, Huang CG, Huang JF, et al. Mangiferin, an Anti-HIV-1 Agent targeting protease and effective against resistant strains. Molecules. 2011; 16(5):4264-77.
71. Hernandez P, Delgado R, Walczak H. Mangifera indica L. extract protects T cells from activation-induced cell death. Int Immunopharmacol. 2006; 6(9):1496-505.
72. Paul A, Raychaudhuri SS. Medicinal uses and molecular identification of two Momordica charantia varieties –a review. eJBio. 2010; 6(2):43-51.
73. Trivedi RV, Wadher KJ, Taksande JB, Mahore JG, Umekar MJ. Momordica charantia: A natural and safe approach for the treatment of HIV infection. Int J Pharm Tech Res. 2011; 3(3):1660-66.
74. No authors listed. Monograph: Momordica charantia (Bitter melon). Altern Med Rev. 2007; 12(4):360-3.
75. Kumar DS, Sharathnath KV, Yogeswaran P, Harani A, Sudhakar K, Sudha P et al. A medicinal potency of Momordica charantia. Int J Pharm Sci Rev Res. 2010; 1(2):95-100.
76. Chen Q, Chan LL, Li ET. Bitter Melon (Momordica charantia) reduces adiposity, lowers serum insulin and normalizes glucose tolerance in rats fed a high fat diet. J Nutr. 2003; 133(4):1088-93.
77. Sforcin JM. Propolis and the immune system: a review. J Ethnopharmacol. 2007; 113(1):1-14.
78. Gekker G, Hu S, Spivak M, Lokensgard JR, Peterson PK. Anti-HIV-1 activity of propolis in CD4+ lymphocyte and microglial cell cultures. J Ethnopharmacol. 2005; 102(2):158-63.
79. Battinelli L, Mengoni F, Lichtner M, Mazzanti G, Saija A, Mastroianni CM, et al. Effect of limonin and nomilin on HIV-1 replication on infected human mononuclear cells. Planta Med. 2003; 69(10): 910-3.
80. Neurath AR, Strick N, Li YY, Debnath AK. Punica granatum (Pomegranate) juice provides an HIV-1 entry inhibitor and candidate topical microbicide. BMC Infectious Dis. 2004; 4:41.
81. Al-Mathal EM, Alsalem AM. Pomegranate (Punica granatum) peel is effective in a murine model of experimental Cryptosporidium parvum. Exp Parasitol. 2012; 131(3):350-57.
82. Bag A, Bhattacharyya SK, Chattopadhyay RR, Rashid RA. The development of Terminalia chebula Retz. (Combretaceae) in clinical research. Asian Pac J Trop Biomed. 2013; 3(3):244-52.
83. Choudhari AB, Rangari VD, Darvekar VM. Formulation development for treatment and management of HIV-AIDS. Int J Pharm Pharm Sci. 2011; 3(1):105-8.
84. Sharma PC, Sharma OP, Vasudeva N, Mishra DN, Singh SK. Anti-HIV substances of natural origin: an updated account. NPR. 2005; 70-78.
85. Lee LS, Andrade AS, Flexner C. Interactions between natural health products and antiretroviral drugs: pharmacokinetic and pharmacodynamic Effects. Clin Infect Dis. 2006; 43(8):1052-9.
86. Moltó J, Valle M, Miranda C, Cedeño S, Negredo E, Clotet B. Herb-Drug Interaction between Echinacea purpurea and Etravirine in HIV-Infected Patients. Antimicrob Agents Chemother. 2012; 56(10):5328-5331.
87. Fasinu PS, Bouic PJ, Rosenkranz B. An overview of the evidence and mechanisms of herb–drug interactions. Front Pharmacol. 2012; 3:69.

88. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's Wort. Lancet. 2000. 355(9203):547-8.
89. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. Clin Infect Dis. 2002; 34(2):234-8.
90. Gardiner P, Phillips R, Shaughnessy AF. Herbal and Dietary Supplement–Drug Interactions in Patients with Chronic Illnesses. Am Fam Physician. 2008; 77(1):73-8.
91. Standish LJ, Greene KB, Bain S, Reeves C, Sanders F, Wines RC, et al. Alternative medicine use in HIV-positive men and women: demographics, utilisation patterns and health status. AIDS Care. 2001; 13(2):197-208.
92. Slain D, Amsden JR, Khakoo Ra, Fisher MA, Lalka D, Hobbs GR. Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. Pharmacotherapy. 2005; 25(2):165-70.
93. Raiten DJ. Nutrition and pharmacology: general principles and implications for HIV. Am J Clin Nutr. 2011; 94(6):1697S-1702S.