

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Review On Potential Of Medicinal Plants To Treat HIV/AIDS.

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ABSTRACT

Since the identification of the AIDS causal agent in the 1980s, scientists have been working to find medicines to treat this terrible and fatal illness. Although the discovery of antiretroviral therapy (ARTs) revolutionized medication research for the treatment of AIDS, safety concerns have prompted a quest for novel medicines that not only suppress virus replication but also rebuild the immune system. The declining efficacy of several synthetic medications, as well as the growing number of contraindications to their use, has brought medicinal plant use back into the spotlight. Thus, research into phytotherapy (treatment by medicinal plants) for the treatment of HIV/AIDS may produce a high return in terms of prospective sources of medicinal plants that play critical roles in disease prevention, treatment, and their promotion and usage are compatible with all existing disease preventive techniques. The purpose of this study is to explore the potential of Medicinal Plants to treat HIV/AIDS by various original articles and case study/reports.

Keywords: HIV/AIDS , Medicinal Plants , Phytotherapy , Opportunistic Infection , Chemokine receptors , CD4+ Cells , Extracts.

<https://doi.org/10.33887/rjpbcs/2022.13.1.28>

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INTRODUCTION

According to the World Health Organization, the human immunodeficiency virus (HIV) has infected over 75 million individuals worldwide, with roughly 37 million still alive and living with the illness [1,2]. 26 million of these patients are currently projected to live in Africa, 3.3 million in the Americas, 3.5 million in Southeast Asia, 2.4 million in Europe, 360,000 in the eastern Mediterranean, and 1.5 million in the western Pacific [2]. According to 2016 data, there were around two million new HIV infections and up to one million deaths as a result of the disease [2]. Importantly, these annual figures are significantly lower, as the number of newly infected individuals has decreased by 35% since 2000, and the fatality rate has decreased by nearly 50%.[2].

Pathophysiology of HIV/AIDS: The HIV virus is a retrovirus that can integrate a DNA copy of the viral genome into the host cell's DNA. T lymphocytes (activated T lymphocytes are favoured targets), monocytes, macrophages, and dendritic cells all have receptors on their surfaces that allow the virus to enter the cell. HIV-1 interacts to the chemokine receptor 5 or the CXCR4 chemokine receptor 4 via interactions with the envelope proteins to gain access into the host cell. Single-stranded RNA is reverse transcribed into HIV DNA and then incorporated into the host DNA after fusion and uncoating [1,3].

- **Pathogenesis :** This virus infects CD4+ cells and the CCR5 or CXCR4 chemokine receptor. The presence of infection in CD4+ cells shows that the patient's immune system is impaired. In 1996, a cohort study found that the viral load in the plasma could predict the course of HIV infection within 6 to 12 months, and that at this point, the CD4+ count verified the disease severity. During the early stages of infection, more than half of the CD4+ cells decline. When the number of these cells falls, the disease advances from acute to chronic. CD4+ T lymphocytes are reduced in the gut during HIV infection, and helper cells generate interleukins to keep the mucosal barrier intact.[3]

Diagnosis of HIV/AIDS ; The HIV virus is commonly detected in the blood as viral RNA load, and infection is accompanied by an acute symptomatic period that includes fever, general malaise, lymphadenopathy, rash, and myalgias, although catastrophic complications such as meningitis have also been observed.[3,4] The plasma levels of HIV RNA are at their highest during acute infection, and the severity of symptoms is linked to the level of viral load. Both viral replication and pathogenicity are thought to be determined by viral properties and viral load. As a result, clinical outcomes and illness progression are influenced by the virus genotype as well as the host.[4]

Medicinal plants used to treat HIV/AIDS ; Drugs derived from natural resources, such as medicinal plants, have remained the treatment of choice for a variety of infectious and non-infectious disorders. It has been widely reported that medicinal plants are being utilised to treat HIV/AIDS with low or no negative effects. Because herbs are a possible source of antioxidants and nutraceuticals components, they not only alter viral particle replication but also serve as immunomodulators and immune stimulants. In the literature, a variety of plants with anti-HIV activity have been described.

Vernonia amygdalina: Vernonia amygdalina is a shrub that has traditionally been used as an HIV/AIDS treatment. It is a member of the Asteraceae family and is known as Bitter Leaf due to its bitter flavour. Vernonia amygdalina is a plant with nutritional and health benefits. The effects of Vernonia amygdalina leaf extract on HIV patients and those on antiretroviral therapy have been studied. For a four-month period, aqueous extracts of fresh leaves of V. amygdalina were combined with ART to assess the effect of herbs on CD4+ cell count. The CD4 count was shown to be higher in patients who utilised the leaf extract or supplements in the trial. The CD4 count increased in those who took both supplements and leaf extract. CD4 cell count was observed to be higher in the experimental group than in the control group. Furthermore, these patients heal from skin rashes. The leaves of V. amygdalina are utilised in HIV care because they have an immunological effect on HIV patients. The CD4 count is proportional to the white blood cell count. In the HIV phase, CD4 cells decreased to a low level, unable to compete with infections. Fresh bitter leaf leaves are beneficial in the treatment of AIDS patients' recurrent fevers, headaches, and joint pain. V. amygdalina is sometimes used as a food supplement.[6]

Rheum Species: Rheum palmatum L. and Rheum officinale Baill extracts have been discovered to possess phytochemical components that selectively decrease HIV replication. Esposito et al. (2016) identified and examined the anti-HIV efficacy of anthraquinone derivatives on the activities of HIV-1 RT-associated DNA Polymerase (RDDP) and Ribonuclease H in biochemical experiments (RNase H). The researchers next looked at anti-HIV signals including HIV-1 mutant RTs, integrase (IN), and viral replication to determine if

there were any new therapeutic alternatives. According to the findings, *R. palmatum* L. and *R. officinale* Baill extracts decrease HIV-1 RT-associated RNase H function. Furthermore, the phytoconstituents Sennoside A and B were found to be responsible for suppressing both RDDP and RNase H RT-related actions. Sennoside A's antiviral action is mediated by two RT binding sites, according to further research. Furthermore, cell-based investigation demonstrated that Sennoside A inhibits HIV-1 replication, and in vitro tests revealed that this phytochemical inhibits HIV-1 IN activity. At the period of viral DNA creation, the principal target for Sennoside A was the viral transcription process.[7]

Trigonostem xyphophylloides and Vatica astrotricha: Two traditional Chinese medicinal plants, *Trigonostem xyphophylloides* (TXE) and *Vatica astrotricha* (VAD) extracts, were studied to see if they had any inhibitory effects on HIV-1. The results showed that both extracts considerably slowed HIV-1 replication and syncytia formation in CD4+ Jurkat cells, with minimal side effects on host immune cell multiplication and survival. *T. xyphophylloides* and *V. astrotricha* extracts also had no inhibitory effects on the HIV-1 RT enzyme, according to studies. TXE and VAD extracts both inhibited HIV multiplication and entrance into target cells, indicating that they had anti-HIV potential. Molecular studies have demonstrated that phytochemical ingredients impede HIV-1 interaction with target cells, i.e., the interaction between gp120 and CD4/CCR5 or gp120 and CD4/CXCR4, implying that these two extracts could be developed as HIV-1 entry blockers. [8].

Medicinal plants and Secondary metabolites having Anti – HIV activity ; Many anti-HIV-1 compounds have been reported to suppress HIV at nearly all phases of the viral life cycle after being screened and isolated from natural sources. Alkaloids, sulfated polysaccharides, polyphenolics, flavonoids, coumarins, phenolics, tannins, triterpenes, lectins, phloroglucinols, lactones, iridoids, depsidones, O-caffeoyl derivatives, lignans, ribosome inactivating proteins, saponins, xanthone, naphthodianthrones, photosensitisers, phospholipids, quinones and peptides . [9] The anti-HIV activities of extracts from some medicinal plants have been reviewed.

Artemisia annua L. (Asteraceae): Using proven cellular systems, the anti-HIV activity of a tea infusion made from the Chinese medicinal plant *Artemisia annua* L. was investigated. *Artemisia annua* tea infusions were shown to be very active, with IC₅₀ values as low as 2.0 g/mL. Furthermore, at 25 g/mL, artemisinin was shown to be inactive, while the related species *Artemisia afra* (which does not contain artemisinin) showed a similar degree of activity.[10]

Astragalus membranaceus Bunge (Fabaceae): *Astragalus membranaceus* is a well-known immunostimulant in Chinese traditional medicine. *Astragalus* extracts have been shown to restore or enhance local graft versus host rejection in immune-suppressed and immune-competent human patients. In HIV-positive patients, these extracts improved symptomology. These findings show that *Astragalus* extracts are safe, however mutagenicity has yet to be determined.[11]

Calendula officinalis L. (Asteraceae): *Calendula officinalis* flowers are used in ointments in India to heal wounds, herpes, ulcers, frostbite, skin damage, scars, and blood purification. In ancient medicine, infusions made from the leaves were used to treat varicose veins. In an in vitro (3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide)(MTT)/tetrazolium-based test, a dichloromethane-methanol (1:1) extract of *Calendula officinalis* flowers showed strong anti-HIV activity. At a concentration of 1000 g/mL, this activity was attributed to inhibition of HIV-1-RT as well as suppression of HIV-mediated fusion at 500 g/mL.[12]

The capacity of organic and aqueous extracts of dried flowers from *Calendula officinalis* to inhibit the human immunodeficiency virus type 1 (HIV-1) replication was investigated. In an in vitro MTT tetrazolium-based assay, both extracts were relatively harmless to human lymphocytic Molt-4 cells, but only the organic one displayed strong anti-HIV activity. Furthermore, uninfected Molt-4 cells were totally protected for up to 24 hours in the presence of the organic extract (500 µg/mL) against fusion and subsequent death caused by cocultivation with persistently infected U-937/HIV-1 cells. It was also shown that an organic extract from *Calendula officinalis* flowers reduced HIV-1 reverse transcription (RT) activity in a dose- and time-dependent manner. In a cell-free setting, a 30 minute administration of partly purified enzyme resulted in an RT inhibition of 85%. These findings indicated that an organic extract of *Calendula officinalis* flowers have anti-HIV characteristics that could be useful in the treatment of HIV.[13]

Clinical studies on treatment of HIV/AIDS by Medicinal Plants ; Several clinical studies are conducted to examine the effect of medicinal plants on HIV/AIDS. Several studies are reviewed and concluded in this article.

Studies of Chinese medicine : Although the human immunodeficiency virus (HIV) was initially detected in China in 1985, it was not until the outbreak among former plasma donors in central China that the full extent of the virus's spread became apparent. During the early to mid-1990s, poor rural farmers supplied plasma to unscrupulous collectors in filthy conditions, resulting in incalculable numbers of illnesses.[14]

- Methods ; Randomised controlled trials (RCTs).
- Results ; Key data from these studies are summarized in Figure 1 and 2 [15–22]. Eleven different kinds of Chinese medicines in a total of 998 patients with HIV infection or AIDS were tested. A placebo procedure was employed in all 11 trials. All of the included trials adopted a two-arm parallel group design [15–22].

Study (country)	Design	Participants (n)	Treatment	Control	Outcome measures	Main findings
Burack et al. 1996 (US) [13]	Parallel, two arms, Double-blind trial	Symptomatic patients infected with HIV with decreased CD4 cells (30)	Chinese herbal preparation (IGM-1) for 12 weeks	Placebo	Symptoms, CD4 cell counts, quality of life, adverse effects	Overall life satisfaction improved in patients treated with herbs, no difference in CD4 count and symptom severity
Sangkitporn et al. 2005 (Thailand) [14]	Multicentre, double-blind, placebo-controlled trial	Adults with HIV-1 infection (60)	Chinese herbal compound (SH) plus ZDV and ddC for 24 weeks	Placebo plus ZDV and ddC for 24 weeks	HIV RNA, CD4 counts, adverse effects	Significant decrease in HIV RNA levels in SH group than placebo without serious adverse events
Shi and Peng 2003 (China) [15]	Parallel, two arms, Double-blind trial	Adult patients infected with HIV and AIDS (36)	Qiankunng (extracts from 14 herbs) for 7 months	Placebo	CD4 cell counts, viral loads, adverse effects	Significant decrease in HIV RNA levels in herb group than placebo. Use of herbs was related to gastroenterological adverse effects.
Wang et al. 2006 (China) [16]	Parallel, double-blind, placebo-controlled trial	Patients infected with HIV and AIDS (72)	Chinese herbal preparation ZY-4 for 6 months	Placebo	CD4 cell counts, viral loads, symptom, body weight, adverse effects	Significant increase of CD4 counts in ZY-4, but not significant difference on symptoms, weight or viral load between groups

Figure 1 Key Data obtained by studies

Weber et al. 1999 (Switzerland) [17]	Parallel, two arms, Double-blind trial	Adults infected with HIV with decreased CD4 cells (68)	Chinese herbs (35 herbs) for 6 months	Placebo	AIDS event, CD4 cell counts, viral load, quality of life, adverse effects	No positive findings for the outcome and herbs associated with adverse effects
Wang et al. 2008 (China) [18]	Parallel, two arms, placebo-controlled Double-blind trial	adults infected with HIV, received HAART therapy for 0.5–1 year (100)	Chinese herbal preparation Aining Granule (AG) plus d4T, ddi and NVP for 11 months	placebo plus d4T, ddi and NVP for 11 months	Symptoms, CD4 cell counts, viral loads, CD8, IL-2, IL-4, IFN- γ , adverse effects	Significant decrease of CD4 counts in placebo group, improvement of symptoms of anephthymia, diarrhea and nausea, but not significant difference on viral load, CD8, IL-2,4 between groups
Jiang et al. 2009 (China) [19]	Parallel, two arms, controlled open label trial	Patients who are HIV infection and AIDS with oral candidiasis symptoms (80)	Chinese herbal preparation XiaoMi Granule (XMG) plus Nystatin for external use for 2 weeks	Nystatin for 2 weeks	Symptoms of oral candidiasis, adverse effects	Significant improvement of symptoms of oral candidiasis in herb group, no adverse event was found
Jiang et al. 2011 (China) [20]	Parallel, double-blind, double dummy trial	Patients who are HIV infection and AIDS with leukopenia symptoms (116)	Chinese herbal preparation Jingyuankang Capsule (JC) plus AZT, ddi, NVP and analogue Leucogen Tablets for 6 months	Leucogen Tablets plus AZT, ddi, NVP and analogue JC	Peripheral leukocytes, adverse effects	Significant increase of peripheral leukocytes without serious adverse events

Figure 1: Key Data obtained by studies

- 1) **Study performed in USA** ; Paice et. al 1996 performed a study in USA regarding the effects of medicinal plants against HIV/AIDS. They used A natural substance derived from chili peppers of the Solanaceae family in a form of commercially available cream (containing 0.075% of capsaicin) produced by Zostrix-HP; Gen-Derm Corporation, Lincolnshire, IL, USA.[23]

Table 1: Study performed by Burack et. Al

Methods	Multicentre, randomised, double-blind, placebo-controlled trial. Generation of allocation sequence: unclear. Double blind: stated but no information about who were blinded. Withdrawal/dropouts: 12 participants (46%) dropped out before the end of 4 weeks period. Intention to treat analyses: no
Participants	Study country: USA. Setting: two hospital-based inpatients and outpatients. 26 participants with HIV-related DSPN (distal symmetrical peripheral neuropathy) (15 in capsaicin group and 11 in placebo group). Diagnostic criteria not described.
Interventions	Experiment: Capsaicin (chili peppers of the Solanaceae) cream (0.075%), topical use, 4 times daily for 4 weeks; Control: Placebo (only vehicle of the cream), topically 4 times daily for 4 weeks Co-intervention: usual analgesic therapy in both arms.
Outcomes	Pain intensity, pain relief, sensory perception, quality of life, mood and function
Notes	Containers were used for tested drug or placebo.

Study performed in france : The study was performed by Durant et.al 1997 using a preparation of Boxwood (*Buxus sempervirens* L.), a plant listed in the French Pharmacopoeia.[24]

Table 2: Study performed by Durant et. Al

Methods	Randomised, double-blind, placebo-controlled trial. Generation of allocation sequence: unclear. Double blind: not specified. Withdrawal/dropouts: not reported. Intention to treat analyses: yes.
Participants	Study country: France. Setting: hospitals. 43 asymptomatic HIV positive patients with CD4 cell counts between 25 and 50 millions per litre (22 in SPV30 (990 mg/day) group, and 21 in placebo group). Diagnostic criteria not described.
Interventions	Experiment: SPV30 (<i>Buxus sempervirens</i> L. preparations), two capsules (165 mg each) every eight hours daily (990 mg/d), for 30 weeks Control: Placebo, two capsules every eight hours, for 30 weeks.
Outcomes	AIDS related complex; CD4 cell count , and adverse events.
Notes	Raw data were not available from the abstract.

CONCLUSIONS

After studying and reviewing many authors around the world this paper can be concluded as The medicinal plants having anti-viral activities can be used to treat the HIV/AIDS infection .However the point can be also noted that the medicinal plants originated in China is used widely.

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