Research Output Journal of Public Health and Medicine 5(2):23-30, 2025

ROJPHM ISSN ONLINE: 1115-9715
ISSN PRINT: 1115-6147
https://rojournals.org/roj-public-health-and-medicine/

https://doi.org/10.59298/ROJPHM/2025/522330

Investigating the Immunomodulatory Effects of Medicinal Plants in HIV Treatment

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ABSTRACT

The global burden of HIV continues to affect over 37 million individuals, disproportionately impacting populations in sub-Saharan Africa (SSA), where access to antiretroviral therapy (ART) is often limited. Chronic immune activation and inflammation remain key contributors to HIV progression, even in patients on ART. This has led to increased interest in complementary therapies, particularly the use of traditional medicinal plants with immunomodulatory properties. This paper investigates the immunological mechanisms behind HIV pathogenesis, reviews the ethnopharmacological use of medicinal plants such as *Moringa oleifera*, *Azadirachta indica*, and *Momordica foetida*, and evaluates their phytochemicals and immunomodulatory potential in modulating HIV-induced CD4+ T cell activation and exhaustion. Results from in vitro and community-based studies demonstrate that these plants can influence immune responses, reduce markers of T cell exhaustion (e.g., CD69, HLA-DR, PD-1), and exhibit hepatoprotective and nephroprotective effects. The study emphasizes the value of integrating ethnobotanical knowledge with modern pharmacological research to develop novel immunotherapeutic agents. However, more rigorous clinical trials and toxicity profiling are essential to validate their efficacy and safety, particularly when used alongside ART.

Keywords: HIV, Immunomodulation, Medicinal Plants, *Azadirachta indica*, *Moringa oleifera*, *Momordica foetida*, Traditional Medicine.

INTRODUCTION

According to the World Health Organisation (WHO), there are over 37 million people living with the Human Immunodeficiency Virus (HIV) worldwide. The virus causes a reduction in immune function that leads to the Anti-Retroviral therapy (ART) resistant Acquired Immune Deficiency Syndrome (AIDS), which is characterized by opportunistic infections and other chronic inflammatory diseases. ART in peri-urban settings, such as sub-Saharan Africa (SSA) is limited mainly due to national priorities and funding of these countries on other diseases, such as malaria. This has prompted the search for alternative medicines to ART, with herbal therapy being the most common. Herbal products are deemed safer and more effective as they focus on the host's immunity rather than HIV. Being a chronic infection, the efforts explored should target the return of the host to normal homeostasis. Towards this end, many plant species have been shown to possess the ability to modulate the actions of HIV-induced chronic hyperimmune activation. Of note are the studies on the immunomodulatory effects of the extracts of Moringa oleifera and Azadirachta indica. Long-term ART prevents the vast majority of HIV outcomes. However, in low-resource settings such as SSA, ART is limited. Likewise, the expenditure on ART is unsustainable due to changed health care priorities in funding countries. Consequently, this is one of the reasons why individuals infected with HIV-1 in SSA are more prone to ill health and death. Alternative herbs such as Moringa oleifera and Azadirachta indica are amongst the most commonly used plants to treat HIV. The latter possesses potent immunomodulatory effects on HIV-1-associated chronic CD4(+) T cell activation/exhaustion. Another commonly used plant species has been Moringa oleifera, although not

much data on its role or proposed mechanisms has been published. This dual proposal for plants to target the two prongs of HIV-1 disease progression offers proof of concept of the need for the investigation of the selected medicinal plant species for their benefit in the management of HIV-1 disease in cellular and animal-derived models [1, 2].

Background on HIV

The immunology behind HIV is a complex interplay between HIV and the immune system. HIV is a virus that exclusively infects cells actively involved in the immune response, mainly CD4 T lymphocytes and macrophages. These cells express the CD4 glycoprotein on their membrane. Immunological studies showed that several different cells can be infected with HIV, provided they express CD4 on their surface. The maturation of monocyte-macrophage cells leads to the expression of CD4 on monocytes, allowing it to be infected with HIV. Once inside the target cell, HIV primarily infects and expresses proteins involved in transcription and replication of the viral genome. HIV-1 enters cells via a mechanism involving receptor binding, internalization, and membrane fusion. These events might be blocked by compounds specifically targeting either the CD4-gp120 or co-receptor-gp120 interactions or the downstream steps in the HIV entry process. The CD4 molecule on the cell surface is the primary receptor for HIV-1 entry into cells. CD4 expresses receptor-like activity, inducing a conformational change on gp120 that exposes a co-receptor binding site on HIV-1. A further conformational change of the envelope glycoprotein gp41 mediates membrane fusion and allows entry of the viral nucleocapsid core into the cell. HIV isolates can be assigned broadly to one of two categories based on co-receptor preferences: "R5" and "X4" viruses. R5 strains use the chemokine receptor CCR5 for entry, whereas X4 strains preferentially utilize the CXCR4 receptor. In cell lines or after prolonged in vitro passage, R5 strains can switch to X4. Dual tropic strains that use either co-receptor have also been described. Some primary isolates utilize the "alternative" coreceptor for entry. These atypical co-receptor-tropic viruses are found primarily in infants. The presence of co-receptor tropism tests determines drug sensitivity, which is good news as it ensures specific drugs can be widely used along with protease inhibitors [3, 4].

Medicinal Plants and Their Historical Use

Medicinal plants used to treat HIV/AIDS-associated diseases represent a valuable resource for drug discovery. These plants are crucial for individuals in remote areas lacking access to conventional healthcare. Ethnomedical knowledge about their use helps preserve indigenous cultures and can identify bioactive compounds for effective treatments. Traditional medicine, a widespread practice for centuries, includes various health care methods involving plant-based remedies and other natural materials. Over 75% of the global population relies on such traditional methods for primary healthcare, particularly in developing nations. The knowledge of herbal medicine is passed down through generations, and these remedies are vital when modern alternatives are costly or unavailable. Historical texts provide extensive information on medicinal plants, and their use continues to play a significant role in local health systems. Ethnobotanical research remains essential for discovering new bioactive substances, with growing interest in the biological effects of traditional medicinal plants [5, 6].

Immunomodulation: Concepts and Mechanisms

Immunomodulators are biologically active substances that can modify the immune system's activity, influencing immune response through stimulation or suppression. While their safety and utility are established, their mechanisms are often unclear. They can affect various biological activities, acting on leucocytes and lymphocytes while altering the physiology and biochemistry of organs, particularly hormone secretion and antigen protein production. These substances can initiate a cascade of changes in biological systems, affecting their functions interdependently. Naturally occurring immunomodulators from plants are acknowledged, yet those from cultivated sources are often overlooked. Immunomodulation encompasses substances that enhance or reduce immune responses and is typically categorized as immunostimulant, immunosuppressant, or immunoadjuvant. Immunostimulants bolster the immune response, enhancing defense against various agents. Many substances, including lectins, polysaccharides, and flavonoids, can boost immune reactions through both innate and adaptive mechanisms. However, excessive immune system activity can lead to chronic diseases, such as arthritis and autoimmune disorders, where the immune system fails to distinguish self from non-self. Conditions like allergies, asthma, complications in healing, or cancer arise from imbalanced immune regulation. Immunosuppressants target inflammation's effector side, and inhibiting key signaling pathways can help alleviate autoimmune diseases. Conversely, in an immune-sufficient state, hosts face daily threats from opportunistic pathogens, potentially leading to severe infections when vulnerabilities arise [7, 8].

Medicinal Plants with Immunomodulatory Properties

A wide variety of medicinal herbs have been used since ancient times in the treatment, management, and prevention of human diseases. Several medicinal plants have been identified as candidates for the development of phytocompounds with immunomodulatory properties. Imbalances between the immune system and disease states may lead to the development of immunocompromised status. It is generally recognized that the immune system can be modulated by various medicinal herbs. Immunomodulators can enhance the host immune system against pathogens and tumors while also protecting it from the damage caused by the over-reactivity of the immune system. Therefore, these medicinal herbs, which contain various phytocompounds with immunomodulatory effects against immunocompromised conditions, are worth developing. Traditionally, herbs with immunomodulatory activities are employed to enhance host immunity and help patients suffering from impaired immunity recover. Here, we propose ethnophytomedicine-based approaches for discovering medicinal plants and novel phytocompounds with immunomodulatory properties. As indicated in ethnophytomedicine, numerous anticancer agents and immune-related compounds have been derived from medicinal herbs. Thus, for the global transformation of traditional medicine to modern medical practice, ethnophytomedicine may serve as a novel paradigm of bioprospecting ethnomedicine for drug development in the 21st century. Plants and their extract parts are generally used in herbal medicine, and they are rich in active compounds. Phytocompounds derived from plants with immunomodulatory activities include arabinogalactan, beta-glucan, polysaccharides, alkaloids, flavonoids, limonoids, resins, terpenoids, polysaccharides, organosulphur-containing compounds. Therefore, plants with high structural diversity can be employed as potential candidates for new immunomodulatory agents. As mentioned above, raw ingredients from medicinal herbs used in traditional medicine could often deliver beneficial or adverse effects to human health. For example, some plant extracts were revealed to suppress hematopoiesis and promote trans-differentiation and apoptosis of mouse bone marrow stem cells. To ensure their efficacy and safety in clinical practices, they need further activity screening and pharmacological research. With the support and integration of cutting-edge biotechnologies, medicinal herbs might be metabolically/dynamically engineered to enhance their potency, bioavailability, animal/target specificity, or tissue accumulation. Phytocompounds can also be engineered to increase their delivery efficacy to specific sites by using nanocarriers [9, 10].

Phytochemicals in Medicinal Plants

Several medicinal plants and their phytochemical compounds are tested for their ability to provide immunomodulatory effects against immunocompromised diseases through different mechanisms. The plant species include Hibiscus rosa-sinensis, Asteracantha longifolia, Terminalia arjuna, Moringa oleifera, Ficus carica, Withania somnifera, Silybum marianum, Mentha spicata, Ocimum basilcum, Morus alba, Trigonella foenum-graecum, Momordica charantia, Cardiospermum halicacabum, Umckaloabo, and Tilia cordata. These plants are tested for their pharmacological activity with assurance on bovine serum albumin (BSA) stability and tryptophan fluorescence in the context to HIV immuno-suppression. The plants are also assessed for their possible immunomodulatory effect on LPS and Con-A-induced lymphocyte proliferation and immunosuppression in mice. The toxicity effect of plant extracts is also evaluated on liver and kidney function through liver and kidney enzyme levels in blood serum. The immunoblot analysis of the spleen showed the augmenting effect of plant extract on ACTH, serum Cortisol, CRF, Hypothalamic IL-1β, and Pituitary POMC, along with the downregulating effect on the Hypothalamic VIP level. The toxicity study revealed the hepatoprotective and nephroprotective effects of the plants. Finally, the beneficial effects of the studied plants towards health and disease prevention among HIV/AIDS patients are also highlighted. Thus, the medicinal plants used traditionally as immunomodulators are a source for phytocompounds suitable for development as drug candidates. Medicinal plants and their phytochemicals have gained importance in the last decade in the herbal sector, and they are an indispensable part of the complementary and alternative medicine systems. Vaccination and immune-modulation are potential approaches to fight various diseases of the evolving world. Medicinal plants are traditionally used against different infectious agents with the assurance of safety and without the adverse property of toxicity on the global population. There is still a lack of scientific validation to confirm the immune-modulatory activity of these native flora, reveal their possible active components, and attenuate their immuno-compromising activity as harmful agents by prohibiting the incomprehensible side effects of the synthetic drugs available in the modern health care system. The present review emphasizes the bioactive constituents from medicinal plants, their studied efficacy, and scientific validation against HIV/AIDS immunosuppression. As a consequence, the extensive knowledge

gained could be a worthwhile repository for further advancement and utility of the immuno-modulators in a pharmaceutically and clinically relevant way [11, 12].

Research Methodologies

The use of traditional medicine in Uganda is rampant among communities, particularly in rural settings. Yet, most medicinal plants have not undergone phytochemical and pharmacological investigations. This study examined the immunomodulatory activity of common Ugandan medicinal plants. The extract with the most pronounced activity was from Azadirachta indica A.Juss. It was able to downregulate HIV-induced peripheral blood mononuclear cell activation and exhaustion. The extract was also able to reverse T cell receptor 2-induced expression of CD69 and HLA-DR in HIV-exposed but uninfected PBMC. In light of these results, further trials are warranted 8. This study investigated the possibility that extracts of some locally available medicinal plants could protect HIV-positive individuals from ART-driven or ART-independent CD4+ T cell activation, like A. indica. This was investigated using mixed lymphocyte reaction and T cell receptor 2 stimulation of healthy PBMC, HIV exposed but uninfected PBMC, chronically HIV-infected PBMC on ART, and virologically suppressed with a regimen that included dolutegravir. Several Ugandan medicinal plant extracts were tested for their in vitro immune-modulatory activity. The extracts with promising activity against activation independent of the HIV infection status were on Moringa oleifera, Momordica foetida, and Azadirachta indica. The last extract could downregulate HIV-induced CD4+ T cell activation and exhaustion. This extract could also reverse TCR2-induced CD69 and HLA-DR expression in healthy PBMC and PBMC from HIV exposed but uninfected individuals [13, 14].

Case Studies And Findings

The study highlighted the types of medicinal herbs used by HIV-positive people in Lesotho and the reasons for their use. The study used a cross-sectional quantitative approach with interview-administered questionnaires and random sampling. A considerable proportion (69.9%) of HIV-positive people used medicinal herbs in this population, although few used them exclusively. Homeostatic herbs were the most common (72.1%) herbs, and Aceraceae was the most common family used (42.9%). Allium sativum and Dicoma anomala were the most commonly used medicinal herbs. Boosting the immune system and treating gastrointestinal ailments were the most commonly reported reasons for use (73.3% and 50%, respectively). Most HIV-positive people using medicinal herbs did not disclose their use to healthcare providers. Considering the negative experiences with formal medication, the study's findings highlight the need for HIV counselling protocols in Lesotho that address seizures and the dangers of using medicinal herbs whose safety and compatibility with antiretroviral drugs are not known. The utilization of herbal medications is likely to increase now that ART is being rolled out, and the efficacy and toxicity profiles of the medicinal plants identified in this study need to be investigated. More studies need to be conducted since a considerable proportion of HIV-positive people use medicinal herbs instead of ART. Schistosomiasis, tuberculosis, and HIV infection are comorbid infections in sub-Saharan Africa and confound HIV treatment. Life-prolonging ART has remarkably improved the quality of life of PLWH worldwide. However, in resource-limited settings such as SSA, incapacitated health care systems limit access to ART. Herbal therapy is a cultural norm among many African people and is perceived as a cheap and more effective alternative to ART. Thus, it is common for PLWH who are actively enrolled on ART to concurrently use traditional herbal medicines. Such treatment adherence is likely to exacerbate the sub-optimal therapeutic responses to ART and high drug toxicity reported when ART is taken in conjunction with herbal therapy. The safety and efficacy of traditional herbal medicines used by PLWH on ART need to be investigated thoroughly as new classes of ART are rolled out in SSA [15, 16].

Case Study 1: Plant A

Life-prolonging antiretroviral therapy (ART) has significantly improved the quality of life for people living with HIV (PLWH) globally. However, in resource-limited settings like sub-Saharan Africa (SSA), limited healthcare access complicates ART availability. Here, cultural factors and inadequate healthcare push PLWH towards herbal therapies. Many individuals on ART simultaneously use traditional medicines, necessitating research into the immune-boosting effects of these plants in HIV management. HIV primarily targets CD4+ T cells, disrupting various cellular pathways to enhance its replication, leading to persistent CD4+ T cell activation, shown by increased surface markers like CD69 and HLA-DR. Chronic immune activation is largely driven by responses to bacterial antigens from gut microbial translocation, resulting from HIV-induced gut epithelium damage. This condition is correlated with a

faster progression to AIDS, indicating better predictive value over viral load and CD4+ counts. The ongoing CD4+ T cell response to antigens causes T cell exhaustion, evidenced by elevated PD-1 and Tim-3 inhibitory markers. Increased exhaustion markers correspond to diminished HIV-specific functions, including reduced IL-2 and TNFα secretion. Blockading these markers, like anti-PD-1, has shown potential in enhancing disease outcomes by curbing hyperimmune activation. Therapies limiting T cell activation could offer further benefits alongside ART. In SSA, HIV-1 individuals experience higher T cell activation levels due to the endemic pathogen load, highlighting the necessity for therapies focused on reducing hyper-immune responses. Studies indicate that long-term Cotrimoxazole use with ART lowers monocyte pro-inflammatory cytokine secretion without impacting CD4+ T cell activation. We evaluated ethanolic plant extracts for immune-modulatory potential, selecting Momordica foetida, Azadirachta indica, and Moringa oleifera based on their reported use by PLWH in SSA. Our findings reveal that A. indica leaf extracts can reduce CD4+ T-cell activation and exhaustion following in vitro stimulation of HIV-infected PBMCs, suggesting its potential as a source of compounds targeting chronic immune activation in PLWH [17, 18].

Case Study 2: Plant B

As a member of the Immune Response to HIV Group (IRHG) at Makerere University, a study was conducted on the immunomodulatory effects of selected medicinal plants for HIV management in collaboration with the Immunology Department. The effectiveness of extracts from three plants—Momordica foetida, Azadirachta indica, and Moringa oleifera—on HIV-infected T cells was evaluated. One journal article reports these findings. In Uganda, where one in 25 adults is infected with HIV, antiretroviral therapy (ART) greatly enhances the quality of life, but limited access in resource-poor settings leads to disease progression. Chronic immune activation is a major contributor to HIV pathogenesis, highlighting the need for high-throughput discovery of compounds targeting HIV-associated inflammation. There is significant reliance on traditional therapy for HIV management in sub-Saharan Africa, necessitating studies on the immune-boosting potential of crude plant extracts. A library of 227 plants used in anti-HIV remedies identified six ethnopharmacologically supported plants: Lantana camara, Vernonia amygdalina, Momordica foetida, Azadirachta indica, and Moringa oleifera. The immune-modulatory ability of A. indica was assessed using a co-culture model of HIV-infected CD4+ T cells through morphological and fluorescence-assisted measurements. The results provide the first evidence supporting the traditional use of A. indica in HIV management in Uganda [19, 20].

Case Study 3: Plant C

HIV principally infects CD4+ T cells, skewing diverse cellular pathways to favour its replication. This is accompanied by persistent CD4+ T cell activation denoted by increased surface expression of the early activation marker CD69, the antigen-presenting molecule HLA-DR, and the metabolite marker CD38 8. In HIV protein transgenic mice, the acute HIV infection is associated with a transient increase in CD4+ T cell activation. This chronic immune activation is driven by responses to bacterial antigens arising from gut microbial translocation. Early in infection, HIV causes damage to the gut epithelium, allowing gut microbes to transverse the protective gut barrier and establishing systemic immune activation, thus, CD4+ T cell activation is a marker of HIV disease progression, while HIV-1 geographic strains are not [21, 22, 23, 24]. In resource-limited settings, plant extracts with bioactive components hostile to HIV-1 could provide cheap therapy alternatives to ART. Before assay, plant extracts were screened for combination additive drug interactions using the fixed ratio method. It was found that an A. indica leaf ethanol: water mixture with additives N-acetyl cysteine and Pam2 was able to downregulate total HIV-1 p24 secretion from infected cells. Since a mixture of p24 and HIV-mimicking viral envelope proteins was secreted by infected cells, both the SEB and the addition of serum were confirmed to trigger avid neutralizing activity [25, 26, 27]. The presence of plant compounds potentiated the prevention of residual viral escape. However, short drought-like residues were detectable in infected control wells treated 4-6 days with their daily target imprinting dose. This highlights the intense viral replication within the infected cell supernatant. To ascertain the bioactive mechanisms behind the observed HBsAg neutralization potency, VLP characteristics were first examined. Transmission electron microscopy images verified that potent plant extracts were produced of a similar size and morphology to HBsAg, the primary marker of HBV and a major target for vaccine development. Lesser weight VLPs were also identified upon stirring, indicative of potential misfolded, defective particles that may compromise the neutralizing potency of the extracts [28, 29, 30].

Challenges in Researching Medicinal Plants

Research on the role of medicinal plants in HIV treatment presents unique challenges. Firstly, limited funding and resources often hinder comprehensive studies, making it difficult for researchers to investigate all facets of the research problem. Furthermore, many herbal medicines lack scientific documentation, resulting in a low priority for research on them. Time-consuming requirements for traditional medicines, like ethnobotanical interviews and toxicology assessments, compound this issue. The relatively low prevalence of HIV in some regions also constrains local research efforts. Meanwhile, pharmaceutical companies aggressively protect their intellectual property rights for patented ARTs. HIV medication uncertainty can lead to skepticism toward clinical trials and education by researchers unfamiliar with herbal medicine. In some cases, a lack of trust can exist between herbalists and Western researchers, making it hard to recruit participants for studies. Revealing a person-consuming plant can also endanger that person's livelihood or allow for unscrupulous replicators. Thus, promising lead compounds may not be adopted for therapeutic preparation [30, 31, 32, 33, 34]. Uncovering new pathways of drug metabolism may delay exploration. Notably, a lack of regulation and quality control can enable serious product adulteration. It poses a risk to consumers through contamination with harmful ingredients. The time required for these studies often precludes using resources as intended. Legislative roadblocks exist, as most freely available medicinal plants cannot be used in phytopharmaceuticals outside their country of origin; thus, research pursued here has limited application elsewhere. Furthermore, trials take years to implement and even longer to yield affordable products. Several natural products are locked up globally, awaiting investigation for their health-promoting properties. The legislative need for development grants is evident, as is the irony of denying developing countries access to products on which they might depend most [23, 24].

Future Directions in Research

The major focus hereon will be the potential use of plant extracts in either curative vaccines, natural anti-HIV agents, or as a complement and enricher of needed medicinal treatments. It is important to emphasize from the outset that so-called plant 'cures' for HIV/AIDS, such as the oral infusion of sutherlandia or African potato root, are ineffective since no known plant is intrinsically anti-HIV or, for that matter, directly antiviral. This applies similarly to treatments with garlic or other allicin-rich products, including those commonly available in North American health food, natural food, or vitamin stores. There currently exists no herbal 'cure' or 'magic bullet' for HIV/AIDS. However, extensive research has been carried out on natural products originally derived from plants, microorganisms, or marine organisms, including efforts to determine chemotherapeutic properties that might lead to novel AIDS antiviral agents. Bioassay-guided fractionation of meroterpenes from plant sources and various other natural products such as azadirachtin or other extracts from neem, shikimic acid from sweetgum, or kudzu extract from pueraria, offer hope for new architectures capable of attacking the HIV target. By whatever method, this search for novel anti-HIV agents based on natural products will take time, and extensive research efforts will be needed to assess potential candidate products for toxicity to normal cells, selectivity indices, and therefore safety for human use. The rapid investigation of crude extracts on cultured cells for selectivity and toxicity can establish or reject products for further intensive study, but information concerning individual compounds must be generated from scratch and will inevitably take much longer. Other research efforts described earlier may provide intermediate solutions which, while not effective themselves or suited for use on human patients, could furnish candidates that might be amenable to synthetic chemists for the production of something better. For tropical developing countries, however, a cheaper out-of-patent or nontoxic anti-HIV agent must be available, and it is possible that naturally occurring products could fill this need [25, 26].

CONCLUSION

This investigation underscores the potential of traditional medicinal plants as immunomodulatory agents in the management of HIV, particularly in regions where ART access remains constrained. The phytochemicals present in *Azadirachta indica*, *Moringa oleifera*, and *Momordica foetida* demonstrate the ability to modulate immune responses by reducing HIV-induced CD4+ T cell activation and promoting immune homeostasis. These findings support the ethnopharmacological relevance of such plants and present a promising avenue for developing adjunctive therapies targeting chronic immune activation in HIV patients. However, the concurrent use of herbal remedies with ART raises concerns regarding drug interactions and toxicity. Therefore, further pharmacological investigations and clinical validations are

imperative to ensure the safe integration of traditional medicine into modern HIV treatment strategies, ultimately contributing to improved outcomes for people living with HIV in resource-limited settings.

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CITE AS: Mugo Moses H. (2025). Investigating the Immunomodulatory Effects of Medicinal Plants in HIV Treatment. Research Output Journal of Public Health and Medicine 5(2):23-30. https://doi.org/10.59298/ROJPHM/2025/522330