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The Role of Medicinal Plants in Mitigating HIV-Related Inflammation

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ABSTRACT

Despite the transformative role of antiretroviral therapy (ART) in managing HIV, chronic inflammation persists in people living with HIV (PLWH), contributing to immune exhaustion and the development of non-AIDS comorbidities. Persistent immune activation marked by elevated pro-inflammatory cytokines and T-cell exhaustion markers such as PD-1 and CD69—continues to drive pathogenesis, even in individuals with suppressed viral loads. Medicinal plants, long used in traditional health systems, offer bioactive compounds with significant immunomodulatory and anti-inflammatory potential. This paper investigates the role of selected medicinal plants in modulating HIV-related inflammation, especially their effects on CD4+ T-cell activation and exhaustion in ex vivo and cytokine-induced models. Promising candidates, including *Azadirachta indica*, *Ginkgolide A*, and *epicatechin gallate*, demonstrated potent downregulation of activation and exhaustion markers in peripheral blood mononuclear cells (PBMCs). These findings suggest that anti-inflammatory phytochemicals could serve as adjunctive therapies to ART, especially in resource-limited settings, by improving immune profiles and reducing systemic inflammation. The integration of traditional knowledge with biomedical research presents a vital path toward complementary HIV treatment strategies.

Keywords: HIV-related inflammation, Medicinal plants, CD4+ T-cell activation, Immune exhaustion, Peripheral blood mononuclear cells (PBMCs), Azadirachta indica, Anti-inflammatory phytochemicals.

INTRODUCTION

Human immunodeficiency virus (HIV) is a lentivirus that primarily infects immune cells, potentially leading to acquired immunodeficiency syndrome (AIDS). Advancements in antiretroviral therapy (ART) have significantly enhanced the quality of life for people living with HIV (PLWH), yet they remain immune compromised and face chronic inflammation, contributing to noncommunicable diseases such as diabetes and inflammatory bowel diseases. This health burden affects PLWH's productivity and well-being, highlighting the need for improved management of HIV-1 associated inflammation. Medicinal plants with anti-inflammatory effects are promising candidates for HIV treatment. Chronic inflammation in HIV-1 is associated with chronic immune system activation and exhaustion, characterized by increased CD69 activation and PD-L1 markers in pre-activated CD4+ T effector memory cells. Interventions limiting immune-cell activation and exhaustion may enhance disease outcomes, offering avenues for better HIV-1 therapy. This study evaluates the efficacy of various medicinal plants to reduce HIV-1 related CD4+ T-cell activation and exhaustion in two inflammation models. Substances that downregulated activation/exhaustion markers were tested in primary peripheral blood mononuclear cells (PBMCs) under cytokine exposure. Additionally, a 24-hour exposure of ex vivo HIV-1-negative PBMCs to these substances assessed effects on TCR-independent activation, exhaustion, and viability. Several promising candidates emerged, particularly A. indica ethanolic extracts, which robustly down-regulated activation/exhaustion markers. Ginkgolide A, epicatechin gallate, and N-phenyl-1,2-ethanediamine selectively limited these markers post-cytokine exposure, with Ginkgolide A showing weak capacity to

curb TCR-independent activation. These results underscore the potential of anti-inflammatory medicinal plants in managing HIV for PLWH unresponsive to ART [1, 2].

Understanding HIV and Inflammation

HIV is a retrovirus responsible for more than 500 000 deaths each year worldwide. HIV infection leads to increased transcription of pro-inflammatory cytokines and chemokines, resulting in chronic immune activation and inflammation. Acute HIV infection is characterized by depletion of CD4+ T helper cells, leading to HIV-associated morbidity and mortality. Mechanisms underlying dysregulated immune activation may stem from the inherent characteristics of the virus and the impact of inflammation on long-term virological control of infection. HIV-infected individuals are susceptible to co-infections with other viruses, such as cytomegalovirus and human herpes virus-8. Both co-infections may facilitate greater disruption of cytokine-mediated mediators than HIV alone, thus fuelling persistent immune activation. Longevity and sustained viral control in elite controllers has been confounded by ongoing lymphatic site inflammation and tissue damage, presumably driven by the effects of cumulative immune activation. Treatment with ART does not fully restore immune homeostasis within gut tissues of chronically-infected individuals, perpetuating gut-associated inflammation. Strategies to reduce inflammation at immune tissues could thus help to enhance durable viral control and limit ongoing pathology. Cytomagnetic reduction in immune activation has clear benefit for positive outcomes in 2-node adjunctive treatment in addition to standard ART. Each intervention has shown efficacy in reducing immune activation, including mechanistic CD4-Tfh benefitting virus controlling traits of bacteria. Cases indicate that once daily low-dose regimen of chloroquine, in addition to standard ART, resulted in persistent reduction of immune activation and increases in CD4+ T lymphocyte counts. Chloroquine treatment improved immune profiles, which were sustained for upwards of 120 days post-elevation. Increased expression of CD8+ Tfh [3, 4].

HIV Pathophysiology

Human immunodeficiency virus (HIV) is the etiological agent for acquired immune deficiency syndrome (AIDS), an infectious disease that is characterized by progressive depletion of CD4+ T helper (Th) lymphocytes. AIDS-related morbidity and mortality are primarily due to opportunistic infections, malignancies, and neurocognitive disorders. HIV directly impairs CD4+ T-cell functions and indirectly causes immune aberrancies such as chronic activation and exhaustion, polyfunctional T-cell loss, and changes in T-cell phenotype or migratory patterns. Individuals on life-prolonging antiretroviral therapy (ART) have better gains in CD4+ T-cell counts and immune restoration than patients who are ART-naive. However, even with effective therapy, some people living with HIV (PLWH) have persistently low CD4+ T-cell counts and poor immune functions. Late ART initiation is linked to progressively severe immunodeficiency and chronic HIV pathobiology such as chronic T-cell activation and exhaustion, and intrinsic CD4 loss within tissues. Evidently, HIV-1 infection is not only an immediate risk for AIDS but it also promotes CD4+Th loss. Th depletion and associated immune deficiencies are hallmarks of HIV pathogenesis. Vulnerable immune system is the common outcome of AIDS progression in all regions of the world.HIV-1 predominantly infects CD4+ T lymphocytes and skews diverse cellular pathways to favor its replication. The resulting immune perturbations include early depletion of proliferating Th cells, late progressive loss of resting naïve cells, chronic inflammatory environment, chronic T-cell activation background, HIV-specific T-cell functional impairment, and major upregulation of immune checkpoint molecules. Shortly after HIV-1 transmission, the virus gets access to intestinal CD4+ T lymphocytes, which are subjected to massive productive viral replication. Intestinal infection is associated with early depletion of Th cells in the gut-associated lymphoid tissue. Gut CD4+ T-cell depletion occurs during the chronic phase of infection in lymphoid tissues and blood. Depletion of gut-resident Th cells is coupled with damage of the gut epithelium and on-going intestinal inflammation. The initial loss of gut CD4+ T cells profoundly alters homeostasis and circulation of subsequent lymphoid and mucosal immune cells, leading to systemic immune aberrancies. Consequently, chronic activation of Th cells occurs in both lymphoid and peripheral tissues of individuals on ART [5, 6].

Inflammatory Responses in HIV

Human immunodeficiency virus (HIV) infects the CD4+ T cells in the gut-associated lymphoid tissue (GALT) leading to gut epithelium damage and chronic immune activation. This is characterized by increased production of pro-inflammatory cytokines among which are IL-6, IL-1β, TNFα, MIP-1α, MIP-1β, and systemic immune activation, increased levels of sCD14, sCD163, CCR2, IL-6, TNFα, and microbial translocation. Despite the known benefits of anti-retroviral therapy (ART) in controlling viral replication, situations where the best virologic and immunologic response is not achievable still exist.

PLWH in ART logarithmically deplete CD4+ T cell counts as soon as 3 months on ART with increased frequencies of activated, PD-1hi, and inflammatory HLA-DR+CD4+ T cell populations compared to before ART. This uncontrolled immune activation drives concurrent increase in the levels of immune activation and inflammation biomarkers, suggesting that undetectable HIV-1 viral load is not sufficient to normalize the immune system. Compared to the rest of the world, untreated PLWH in SSA have a higher CD4+ T cell activation levels due to a larger burden of endemic pathogens that constantly activate the immune system and lead to progression of HIV disease. Activation of lymphocyte populations is crucial for maintaining a robust immune response against pathogens. However, when left unchecked, this immune responsiveness leads to chronic immune activation and is claimed to cause many immune-related non-AIDS events. With ART, hyper-activation of the immune system is not curbed; thus, the transition from the classic immunodeficiency spectrum of HIV disease to the new chronic progression spectrum is observed primarily in HIC. Chronic immune activation has been suggested to drive ensuing HIV disease, leading to early ART initiation (<6 months post-infection) as a preventive measure against progression of co-morbidities. However, ART does not halt but arguably enhances systemic immune activation in chronic HIV-1 infection. Compounds have been identified as modulating CD4+ T cell responsiveness. An ethanolic extract from A. indica leaf has been shown to down-regulate CD4+ T-cell activation by limiting the PFU of HIV-1, suggesting a potential application in herbal therapy for the management of HIV disease [7, 8].

Impact of Inflammation on HIV Progression

Inflammation is a normal immune response that helps fight infections and maintain health. However, uncontrolled inflammation can lead to harmful processes over time. In HIV-infection, consequences such as CD4+ T-cell depletion and chronic inflammation arise from factors like cytokine dysregulation and gut dysbiosis, resulting in what is known as HIV-associated inflammation. The infection begins with an acute phase where the virus spreads, particularly in the gut, followed by an immune response that reduces viral load but fails to eliminate the virus, resulting in chronic infection. This phase is marked by heightened immune activation and rapid turnover of immune cells, which the bone marrow struggles to replace, leading to chronic activation and a pool of non-functional cells. Early initiation of antiretroviral therapy (ART) can prevent T-cell activation and disease progression, suggesting that timely intervention in at-risk populations may significantly reduce HIV incidences. Chronic HIV is accompanied by persistent inflammation, with a gradual depletion of CD4+ T-cells, macrophages, and dendritic cells, compromising effective immune responses. This results in a shift towards a less functional B-cell response, which inadequately addresses the HIV reservoir. CD8+ T-cells become exhausted, showing decreased functionality and capacity to produce antiviral compounds, with markers such as PD-1 and Tim-3 increasing in exhausted antigen-specific CD8+ T-cells during natural and spontaneous resolution in the SIV macaque model [9, 10].

Medicinal Plants: An Overview

Medicinal plants are widely used in developing countries to treat various ailments, with fitoterapia being important in traditional medicine. Herbology includes the preparation and administration of plant-based remedies and is a form of healthcare practiced by traditional healers. Herbal medicine and dietary supplements are increasingly popular as complementary medicines in developed countries. Ethnopharmacological studies document traditional medicinal plants, and the challenging task is to validate this information through anticancer and antimicrobial activity screening. PAS has recently conducted studies on South African traditional medicinal plants used as anti-cancer agents, leading to the further screening of selected plants as potential antiviral agents. Antiviral activity has also been screened against other viruses, including HIV. Acquired immunodeficiency syndrome (AIDS) is a lethal disease caused by the human immunodeficiency virus (HIV). HIV becomes latent after infecting a lymphocyte and remains dormant during this period, causing no observable effects. However, massive replication of the virus occurs after several years. Infection leads to the death of T4 cells, resulting in a breakdown of the immune system and the destruction of the immunocompetent cells needed for specific immunity. HIV infection is treated using a battery of anti-HIV drugs referred to as highly active antiretroviral therapy (HAART). While these drugs are successful and help maintain the health of the infected individual, they cannot eliminate the virus from the body and thus may lead to the development of drug-resistant mutations. Drug-resistant viral mutations develop because of treatment failure in some patients. Pharmacoeconomic studies showed that HAART therapy may be associated with increased drug

expenditure for the patient on treatment. These studies show that plants traditionally used as anti-HIV agents warranted further attention [11, 12].

Mechanisms of Action of Medicinal Plants

Despite extensive efforts to combat the HIV/AIDS pandemic, millions of people suffer the shame, isolation, and stigma of living with HIV/AIDS. The enormous energetic demand of viral replication leads to the exhaustion of intracellular resources, overwhelming the metabolic and oxidative balancing capacity of host cells. The evidence is unequivocal: HIV infection ignites a cascade of inflammatory processes-leading to aberrant accumulation of dysfunctional macrophages and lymphocytes, a loss of non-infected T-cells, and a plethora of diseases correlated with persistent inflammation. All these processes stepwise facilitate the genesis of opportunistic invasions, central nervous system ravage, cancer development, and degenerative diseases such as cardiovascular disorders. Hence, targeting inflammation is a promising strategy for the prevention and treatment of HIV-associated comorbidities. A wealth of data points to a disproportionately high prevalence of HIV-1 infected individuals and HIV-1-associated disease burden in developing countries, particularly sub-Saharan Africa. Plants have evolved an enormous structural diversity for large secondary metabolite networks, including flavonoids such as quercetin, isoflavonoids such as genistein, catechins such as epigallocatechin-3-gallate, phenolic acids such as rosmarinic acid, alkaloids such as anthranilic acid, essential oils such as eugenol, terpenoids such as curcumin, coumarins such as umbelliferone, and polyunsaturated fatty acids such as α-linolenic acid. Pharmacological studies during the last century have led to the identification of many therapeutic regimes from medicinal plants for diverse disorders. Era after era, plants have provided novel drugs for clinically unmet needs and novel chemotherapeutics, thereby reshaping the treatment landscape. Numerous herbal medicines with anti-HIV activity have been reported, with a dearth of data on toxicity, active compounds and scientific underpinning behind drug delivery. In view of the devastating HIV/AIDS pandemic in many AIDS-affected regions, targeting HIV and HIV-associated diseases is of utmost clinical importance [13, 14].

Key Medicinal Plants for HIV-Related Inflammation

Medicinal plants have significant potential to aid people living with human immunodeficiency virus (HIV) in resource-limited settings. People living with HIV (PLWH) resort to herbal therapy for alternative treatment when antiretroviral therapy (ART) is not available, ineffective, or expensive. An ethnomedicinal survey conducted in Uganda on plants used in the treatment of HIV/AIDS and related infections provided a library of 54 plant species. A literature review on the secondary metabolites of the selected plants revealed several bioactive compounds with reported immunomodulatory and HIV-1 inhibitory activities with potential for therapeutic use against HIV-1. These plant species can be a useful source of bioactive compounds for the development of anti-HIV-1 drugs with reduced side effects. Potential candidates include Acanthosicyos horridus, Aloe ferox, Aloe marlothii, Azadirachta indica, Calpurnia aurea, Cassia fistula, Combretum caledonianum, Erythrina abyssinica, Euphorbia hirta, Ficus mucuso, Hypoestes aceptuosa, Lannea schweinfurthi, Lippia javanica, Moringa oleifera, Parinari curatellifolia, Pericopsis angolensis, Securinega virosa, Siphonochilus aethiopicus, Sutherlandia frutescens, Syzygium guineense, Tetrapleura tetraptera, and Warburgia salutaris. Ethnobotanical investigations have demonstrated that traditional medicine beliefs and practices have a rich history predating colonial times in southern Africa. Medicinal plant use continues to be important in southern Africa, particularly in remote rural areas where conventional health care is inaccessible or not trusted. The leaves, roots, or stems of plants are traditionally processed via herbal infusions, decoctions, tinctures, and powder or tablets. Other forms of preparation include the use of aromatic plant species for fumigation against pathogenic microorganisms. Traditional medical practitioners are valued for their knowledge and played an integral part in initiating the first anti-HIV drug development in the mid-1980s and addressing the HIV/AIDS epidemic. In southern Africa, 88 plants have reported use in treating HIV/AIDS symptoms. Of these species, a quarter are widely used, 15 were received from Botswana, and 23 from South Africa. Herbal plants that experienced increased popularity include Aloe species, Waltheria indica, Sparattosperma celosioides, and Vernonia amygdalina. Herbalists increasingly promote Morus nigra, Parinari curatellifolia, and Senna obtusifolia for HIV-related symptoms. HIV is the causative virus of acquired immunodeficiency syndrome (AIDS). Patients infected with HIV are diagnosed as having AIDS when the CD4+ T-cell count drops below 200 cells/mm3, when opportunistic infections occur, or both. There are 36.7 million people living with HIV worldwide, 2.1 million of whom are members of this group succumbing to HIV-related illnesses every year [15, 16].

Clinical Studies and Evidence

HIV/AIDS remains a devastating pandemic, mainly affecting those in developing nations where poverty and limited access to treatment exacerbate the problem. HIV-1 is the most common type, primarily targeting CD4+ T cells, with other cells like macrophages presenting the virus to these T cells. The virus's entry and reverse transcription are aided by proteins encoded in the HIV genome. Across five tribal groups, the condition known as Hondhoro was frequently cited, characterized by malaise, lack of strength, and various physical symptoms, including pain in multiple areas and skin issues. Antiretroviral therapy (ART) has significantly improved life quality for HIV-positive individuals, yet in resource-limited settings, access to ART is restricted. Cultural factors and inadequate healthcare have prompted reliance on herbal remedies for treatment. Research is necessary to explore the immune-boosting potential of medicinal plants in managing HIV. The infection primarily targets CD4+ T cells and alters cellular processes to promote its replication, with chronic immune activation stemming from responses to gut bacteria. The study included predominantly female participants, revealing how socio-economic factors affect their choice of complementary and alternative medicines (CAMs). The usage of various plant species, administration methods, and frequency of CAMs for managing HIV-related symptoms varied by tribal group, with most using them daily or weekly [17, 18].

Challenges and Limitations

There is no doubt that the culture and accepted forms of healing change and grow, leaving behind former traditions. This is a necessity in life. However, it is often feared that indigenous knowledge systems and forms of healing will become lost forever, and their place taken by Western systems. This undesirable scenario is one of the major threats to indigenous peoples' rights, custom, health, and well-being. This is especially true in rural Africa, where contemporary socio-political and economic circumstances threaten to completely erase the memory of centuries of experience and accumulative knowledge. Medicinal plants are an important part of this heritage, and their immediate collation and conservation is a top priority. Until this is done, on-the-ground efforts should be embraced across cultures to protect and enhance the survival of indigenous medications. The worries and circumstances presented above are certainly relevant in the case of southern Africa, specifically Tanzania. Through formal industry, there is the threat that national and community health will be dictated by foreign powers focusing little on community welfare or tradition. The value of this knowledge should be explicitly defined and delineated so that informed decisions are made regarding its future protection and enhancement. Historically, however, there is often a strong recognition of indigenous knowledge, aroma, and medicinal plant remedies through which community health has been maintained. This is a viable system but is presently under threat as major, urban-centre globalization focuses almost exclusively on Western medicine. Little research is being done into the collation, conservation, and elaboration of this traditional knowledge and its remedies to promote their protection and enhance their use. There is widespread recognition that a cure for HIV/AIDS-related opportunistic infects is highly sought after. Towards this goal, many tropical plants known to the rural community have been investigated, but there is little acquaintance of the agglomeration of knowledge and use of plants for HIV/AIDS care by traditional healers [19, 20].

Future Directions in Research

Since the discovery of HIV in 1983, research has aimed to eradicate this virus responsible for the global AIDS pandemic. Despite the effectiveness of highly active anti-retroviral therapy (HAART) in preventing AIDS, finding a complete HIV cure remains challenging. Host cellular factors involved in HIV replication serve as potential therapeutic targets. New insights from recent studies highlight that astrocytic and microglial cells contribute to latent infections and persistent HIV reservoirs. Neurocognitive impairment and cough due to opportunistic infections can occur in HIV-infected individuals. There is a growing interest in phytochemicals as treatments for HIV-related neurocognitive disorders (HAND). Non-toxic therapeutics that inhibit HIV replication are essential. Certain phenolic compounds can block HIV's binding to CD4, its primary receptor. For instance, epigallocatechin gallate (EGCG), found in green tea, inhibits HIV entry by binding to viral glycoproteins. The roles of various cellular factors in HIV entry are established, yet the medicinal potential of natural products impacting these factors remains largely uninvestigated. Notably, promising medicinal plants like curcuma, Tulsi, and ginger have not been assessed for their anti-HIV properties. Advances in extract preparation and in vitro assays can improve the identification of new anti-HIV agents. Phylogenetic studies of enzymes in the HIV life cycle combined with plant screenings may reveal effective treatments. Additionally, exploring epigenetic targets that regulate factors in the HIV life cycle could uncover new therapeutic strategies. Indigenous knowledge of

medicinal plants may offer insights for discovering new bioactive substances aimed at treating HIV and associated inflammatory disorders while creating potent HAART with reduced toxicity [21-26].

CONCLUSION

Medicinal plants offer a promising complementary strategy for managing HIV-associated chronic inflammation, a persistent challenge in the ART era. Evidence from preclinical studies reveals that certain plant-derived compounds, such as those from *Azadirachta indica* and *Ginkgolide A*, can effectively downregulate inflammatory and exhaustion markers on CD4+ T-cells. This immunomodulatory activity underscores the therapeutic potential of phytochemicals in reducing the burden of chronic immune activation and related comorbidities. As HIV remains a global health issue, particularly in sub-Saharan Africa where traditional medicine plays a vital role, integrating validated herbal therapies into mainstream treatment could improve outcomes for PLWH. However, this integration requires rigorous clinical validation, toxicity profiling, and standardization to ensure safety and efficacy. Conservation of ethnobotanical knowledge and support for biocultural diversity are also crucial for safeguarding these plant-based health resources.

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