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Evaluating the Antiviral Properties of Herbal Medicines in HIV Treatment

Chelimo Faith Rebecca

Department of Clinical Medicine and Dentistry Kampala International University Uganda
Email: rebecca.chelimo@studwc.kiu.ac.ug

ABSTRACT

The global burden of HIV/AIDS persists, with millions still lacking access to antiretroviral therapy (ART). While ART has significantly improved life expectancy for people living with HIV (PLHIV), its limitations such as drug resistance, toxicity, and accessibility—prompt the need for alternative or complementary approaches. Herbal medicines, traditionally used in many cultures for treating infectious diseases, are increasingly investigated for their potential antiviral activity against HIV. This paper reviews the antiviral properties of various medicinal plants and their extracts, focusing on their effectiveness in vitro and in vivo. Several herbs, including *Calamus rotang*, *Codonopsis tubulosa*, and *Erigeron annuus*, have demonstrated potential anti-HIV activity by inhibiting viral entry and replication. The study emphasizes the importance of evaluating safety, efficacy, and herb-drug interactions, especially in resource-limited settings where herbal remedies are widely used. Ethical and regulatory considerations are also explored to ensure safe integration of herbal therapies with standard HIV treatment. Ultimately, herbal medicines could offer affordable, accessible adjuncts to ART, warranting further clinical trials.

Keywords: HIV/AIDS, Herbal Medicines, Antiviral Properties, Antiretroviral Therapy, Traditional Chinese Medicine, HIV Drug Resistance, Complementary Medicine.

INTRODUCTION

HIV/AIDS is a significant global predicament, affecting over 32 million people worldwide. Since the inception of anti-retroviral therapy (ART) over 30 years ago, people with access to ART drugs can live a near-normal life. Anti-retroviral therapy falls into six classifications according to their mechanism of action: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase strand transfer inhibitors (ISRTIs), fusion inhibitors (FIs), and co-receptor antagonists (crAs). Despite the global success of ART, there are still people living with HIV who cannot access ART, accounting for 17 million people worldwide. ART drugs can have toxic effects, and recent studies have shown that switching from one ART regimen to a more tolerable regimen may alleviate some of the side effects. Presently, there are no commercial anti-HIV agents that target the initial stages of the viral life cycle, such as viral attachment and entry. Therefore, it is essential to find natural products to combat HIV. Due to its millenary history, traditional Chinese medicine (TCM) has made great contributions to the prevention and treatment of diseases. Recently, scientists, inspired by the theory and practices of TCM, have been exploring the efficacy of TCM on the influenza virus, avian influenza virus, and hepatitis B virus. Hainan Island, with a long history of TCM and rich biodiversity, is an ideal region for searching for plants studied in this study. In the current study, extracts from some traditionally used medicinal herbal plants were tested for anti-HIV-1 activity, and two extracts were found to block HIV-1 entry into cells [1, 2].

Background on HIV

Human immunodeficiency virus (HIV) is a retrovirus with two strands of ribonucleic acid (RNA) and several enzymes, including reverse transcriptase. The 120 nm enveloped virus features a cone-shaped capsid made of p2 protein, an envelope with gp120 and gp41 glycoproteins, and spikes from gp120. An

HIV protease cleaves polyproteins into structural proteins and enzymes like protease and integrase. HIV-1 emerged in west-central Africa from simian immunodeficiency virus infection in humans and consists of R5, X4, and co-receptor tropism variants. HIV-2, which also causes AIDS, is less common outside endemic regions than HIV-1, which is globally widespread. The World Health Organization recognizes HIV-1 as the primary cause of acquired immune deficiency syndrome, leading to immunodeficiency in hosts, with an average progression from infection to AIDS taking 8 to 10 years. Around 40 million people worldwide live with HIV/AIDS. Antiviral treatments have been developed to target various stages of the HIV life cycle, with highly active anti-retroviral therapy (HAART) being the standard treatment. These ARV drugs significantly aid in managing HIV, improving immune status, and quality of life. HAART also reduces the transmission of HIV from mothers to offspring, contributing to decreases in HIV/AIDS-related morbidity and mortality, particularly in developed nations [3, 4].

HIV Epidemiology

In the southern African region, the HIV epidemic is devastating. In 2015, it was estimated that there were 7 million people living with HIV (PLHIV), exceeding the world average of 0.8%. More than 1 million people became newly infected with HIV in 2015. With 1.2 million deaths, southern Africa accounted for 55% of the world's HIV-related mortality. One rural south African province reports HIV prevalence amongst pregnant women of 38%. Southern Africa remains the most affected region in the world. It is home to 70% of the world's HIV-infected population, 73% of those newly infected, and 75% of those dying from AIDS-related causes 4. Anti-retroviral therapy (ART) is a highly effective treatment for people living with HIV, with people on this treatment enjoying a similar life expectancy to those uninfected. ART is a multi-drug therapy that aims to suppress the HIV replication cycle and halt disease progression amongst PLHIV. Untreated HIV results in progressive immune depletion, highly pathogenic disease progression and, ultimately, death. This treatment is, however, not without its shortcomings. Anti-retroviral therapy is extremely significant in improving the life of PLHIV. Nevertheless, the drugs designed to treat HIV have many disadvantages. Firstly, HIV escapes the effects of ART through the development of resistance. Combination therapy limits the emergence of drug resistant HIV. Resistance epidemiology indicates that in resource-limited settings, there is a significant cure for those on first-line ART. It is, however, well documented that the most potent ARVs, especially Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), have inherited resistance mutations. The emergence of resistance mutations pre- and post- treatment commencement unfortunately leads to cross-resistance to second-line therapy. Even on first-line therapy, resistance emerges within three years of treatment commencement in between 20% and 60% of individuals, necessitating treatment changes. Furthermore, untreated pre-treatment drug resistance leads to decreased virologic responses to ART. Since HIV is constantly mutating, monitoring emergence of resistance mutations is paramount. Unfortunately, expensive genotyping is not routinely accessible in some resource-limited environments [5, 6].

Herbal Medicines Overview

Traditional herbal medicines consist of plants used for health as food or other forms, distinct from conventional medicine's chemical compounds. They are consumed as teas, powders, decoctions, and pills, including medicinal and edible plants. Examples are cranberry for urinary tract infections and Milk Thistle for liver issues, alongside antioxidants like Green Tea and Curcumin. Despite the lack of rigorous scientific backing, herbal medicines are frequently used worldwide to treat various ailments. Research indicates that over two-thirds of people living with AIDS also take herbal remedies such as plant extracts and teas. The primary reason for this is HIV treatment. Sub-Saharan Africa is a key area for women with HIV, who often turn to traditional herbal remedies due to limited access to conventional medicine, stigma, and poverty. Countries like Nigeria see up to 85% of the population relying on these treatments. Concerns arise regarding contaminants in herbal medicines that may have antiviral properties, including reverse transcriptase inhibitors, which resemble the action of first-line antiretrovirals for HIV treatment [7, 8].

Antiviral Properties of Specific Herbs

Antiviral activity of some herbs was evaluated in vitro against HIV-1 using a colourimetric assay based on the metabolic reduction of the tetrazolium salt MTT by viable cells. Results were compared either with the efficacy of a known compound, as positive control or with untreated infected negative controls. The highest potency with selectivity index (SI) of 58 was noted with geranylgeraniol (GGOH) isolated from Calamus rotang at 10 µg/ml in HeLa, H9 and PM1 cellular systems. Significant activity was also detected with propolis with maximum antiviral activity at 100 µg/ml with SI of 36. Aqueous extracts of

Osmanthus fragrans, Evodia rutaecarpa, Houttuynia cordata and Cinnamomum cassia at 500 μg/ml were slightly effective using HeLa. Water extracts of Thunbergia laurifolia, Tephrosia villosa and Betula utilis were inactive in HIV-1 assay. Codonopsis tubulosa and Erigeron annuus from herbology moderately inhibited virus replication in H9 cells as ascertained by p24 antigen production assays at doses of 5 to 40 μg/ml. At high concentrations, both compounds exhibited dose-dependent cytotoxicity on H9 cells. Both plant medicines inhibited HIV replication, but E. annuus was more potent. Codonopsis tubulosa has antiviral activity against HIV and improves the condition of AIDS patients. Traditional Chinese medicine has gained popularity as an alternative therapy for HIV infection treatment. It can supplement antiviral therapy and alleviate the side effects of medicine. Herbs may have synergistic antiviral effects and be effective against HIV-1 fuzzy drug resistance strains. Various natural products and traditional herbal preparations have been explored for their antiviral properties. Several flavonoids like quercetin and kaempferol and other terpenoids like oleanolic acid and rosmarinic acid were previously reported to possess some activity against HIV. Recently a number of other herbal medicines like ginger, nutmeg, turmeric, and Dhania possessing peptide, flavonoid, and polyphenol like substances were also explored [9, 10].

Methodology For Evaluating Antiviral Properties

In vitro bioassays against HIV and its targets were carried out to evaluate the antiviral properties of the 69 extracts. Cell-based screening was performed on extracts, at different concentrations, using the luminescent HIV-1 RT assay. The effects of extracts were further evaluated against HIV-1 protease using an enzymatic assay, and candidate extracts were chemically profiled using chromatographic and nuclear magnetic resonance techniques. Four extracts were shown to be non-cytotoxic, and two (the hexane and EtOH extracts of T. capense) inhibited HIV-1 replication in the cell-based assay. Of the 24 target-based assessed extracts, 11 were active against at least one of the targets, friedelin (from C. citratus), brineogranatone, and meisoindigo being identified as new HIV-1 targets. Cell-based assays were performed to initially screen and further profile extracts against HIV-1. The assays employed a luminescent HIV-1 reverse transcriptase (RT) assay to assess extracts for the ability to inhibit viral replication. A number of extracts were determined to be promising candidates for further profiling against HIV-1 and its targets. These extracts could be added in the cell-based assays before infection, soon after infection and later when the infection has been established in the cells. Notably this is amplified by a rapid RT-PCR, could be used to assess the extracts against HIV-1 infection. These extracts should be tested again in the in vitro screening but with the use of HIV-I PR. It would be ideal to also look at the inhibition of viral attachment. This assay can only be performed in cell-based work using transformed cells [11, 12].

Results Of Herbal Medicine Studies

Herbal medicines are considered as alternatives or supplements to ARVs due to their interactions with HIV proteins and traditional use for viral infections. Research has contributed to an understanding of HIV-antiviral herbal medicines through numerous studies. An analysis of biomedical literature summarized the characteristics of studies on anti-HIV herbal medicines, categorizing them by the phylogenic origin, in vitro, and in vivo bioactive properties. While many herbal medicines have shown promise in HIV research, their development into clinically approved drugs remains a work in progress. In vitro evaluations of these herbal medicines are crucial for identifying candidates for further in vivo studies. Most of the studied anti-HIV herbal medicines are derived from plants, known for their rich resources. A range of methodologies, including assessments of viral target proteins and cellular receptors, have been employed to detail the properties of these herbal medicines in influencing HIV's lifecycle. Techniques like phytochemical and bioactivity-directed fractionation have identified active compounds and mechanisms. Studies on the bioactivity of herbal medicines with in vivo anti-HIV properties utilized various animal models, supporting future clinical applications. Noteworthy results include a study where 100 HIV-positive participants took AC for three months, which showed positive effects on viral loads and CD4+ T cells. MME, a traditional dietary remedy, demonstrated positive impacts on systemic immunity against HIV-1. Phase II trials of QYN revealed lower HIV RNA levels in patients when used alongside ARV drugs, while EHT showed protective effects against HIV-1 infection in various models [13, 14].

DISCUSSION

The human immunodeficiency virus (HIV) is a major challenge for humanity, compounded by the severe side effects of conventional drugs. This situation calls for alternative solutions, such as herbal medicines

traditionally used by indigenous communities. The study focused on three key questions: Are these herbal remedies safe? Do they affect the efficacy of HIV medications? If they do, which ones are safe to use? The research assessed the safety and interaction of selected herbal medicines in vitro. The findings indicated that the herbal extracts are safe, although preliminary tests on their interaction with HIV drug metabolism were inconclusive. Notably, all extracts had some cholinesterase-inhibiting compounds, suggesting a potential effect on drug absorption from the gut. With many HIV/AIDS patients in Zimbabwe resorting to herbal remedies, there is an urgent need for studies evaluating their safety and any interactions with antiretroviral drugs. Over 50% of patients experiencing negative side effects have turned to these alternatives. While some commercial preparations are already on the market, only one study on cinnamon has explored their safety and interaction potential in detail, highlighting a significant data gap. This study represents an initial effort to fill that gap, confirming the safety of all herbal extracts tested at levels of 500 µg/ml or higher. Despite advances in safer antiretrovirals, it's crucial to address the risks associated with combining these drugs with herbal medicines [15, 16].

Regulatory and Ethical Considerations

Safety evaluations of plant-derived drugs require assessments of both efficacy and toxicity. In developing countries, herbs are often used for preventing and treating diseases, including viral infections. Safety assessments must precede efficacy testing, especially for new extracts. In vitro and in vivo toxicity tests are essential for evaluating herbal drug safety. Regulatory agencies in developed and some developing countries mandate toxicity studies before human use approval. A drug can be marketed as a "safe remedy" for conditions like hypertension after passing these safety tests. The use of herbal products with antiretroviral drugs has increased in Nigeria among HIV patients, leading to significant risks, including toxicity, drug interactions that raise viral loads, and resistance development. Safety concerns were raised in 2018, and complaints were published in Lagos Dailies in December 2019, prompting regulatory investigations. Agencies like NAFDAC looked into these herbal product safety issues. Ongoing debates among traditional medicine professionals, ethicists, and regulatory authorities focus on the ethical implications of safety claims and the responsibility of scientists in investigating herbal remedies. Ethical challenges affecting the regulation, research, and development of herbal medicines persist, undermining public confidence in their safety [17-22].

Patient Perspectives and Acceptance

Unless a viable cure for HIV is found, antiretroviral therapy (ART) will remain the most effective means of managing HIV. Due to the epidemic's growth, innovative treatments are being pursued, with the pharmaceutical industry developing new drugs evaluated through Phase I–III clinical trials. Prevention methods such as male circumcision, topical microbicides, and advanced vaccine designs are also being explored. Interest in non-drug strategies in the HIV infection process is growing, alongside efforts from consumers to find effective anti-HIV medicines. This includes the promotion of complementary and alternative medicines (CAMs), particularly traditional herbal remedies. In Nigeria, various herbal products claiming to 'cure' HIV infection are available, with some manufacturers asserting their anti-HIV efficacy. There are concerns regarding the use of these remedies by people living with HIV (PLWH), especially since some traditional products reportedly contain antiretroviral drugs like nevirapine and stavudine. These evaluations highlight the need for increased education and regulation in the traditional medicine sector, including better access to educational resources and oversight for herbal medicine [23-25].

CONCLUSION

The growing interest in herbal medicines as alternative or complementary treatments for HIV is rooted in their accessibility, cultural acceptance, and potential to target different stages of the HIV life cycle. Several plant extracts and phytochemicals have shown promise in inhibiting HIV-1 replication and improving immune function, offering hope for enhanced care in resource-limited settings. However, despite these promising findings, much remains to be done in terms of standardizing herbal formulations, conducting rigorous clinical trials, and ensuring regulatory oversight. The safety of these herbal treatments, especially in combination with ART, must be prioritized to prevent adverse interactions and resistance development. As global health systems evolve, integrating scientifically validated traditional remedies with conventional treatment may offer a holistic approach to HIV management, especially for underserved populations. Collaboration between traditional practitioners, biomedical researchers, and public health authorities will be key to advancing this promising field.

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