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Plant-Based Antimicrobials: A New Hope for Treating Diarrhea in HIV Patients

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ABSTRACT

HIV-associated diarrhea (HAD) remains a persistent and under-addressed complication among individuals living with HIV, significantly impacting quality of life, treatment adherence, and overall immune function. Although antiretroviral therapy (ART) has transformed HIV from a fatal disease to a manageable chronic condition, gastrointestinal disturbances—particularly diarrhea—continue to affect a substantial portion of patients, with limited effective therapeutic options. This paper explores the potential of plant-based antimicrobials (PBAs) as alternative or adjunctive treatments for diarrhea in HIV-infected individuals. Drawing from ethnomedicinal practices and modern scientific evidence, PBAs such as curcumin, ginger, and tannin-rich plants like *Cudrania tricuspidata* demonstrate promising antimicrobial, anti-inflammatory, and microbiota-modulating effects. Preclinical studies using rodent models and early-phase clinical trials support the efficacy of these compounds in alleviating diarrhea and restoring gut homeostasis. The incorporation of PBAs into HIV care protocols, especially in resource-limited settings, offers a low-cost, culturally accepted, and potentially safer option to improve patient outcomes. Continued interdisciplinary research is essential to optimize dosage, elucidate mechanisms of action, and ensure the safety and efficacy of PBAs in the context of HIV-associated diarrhea.

Keywords: HIV-associated diarrhea, Plant-based antimicrobials, Gut microbiota modulation, Antiretroviral therapy (ART), Phytochemicals, Curcumin, Traditional medicine.

INTRODUCTION

The World Health Organization emphasizes the need for increased focus on HIV-associated diarrhea (HAD) as a critical global health issue. HAD often has non-infectious origins and may contribute to low-grade enteropathy, impacting premature mortality and immune dysfunction. Research on non-infective diarrhea mechanisms includes microbial dysbiosis and mucosal transporters. The use of plant-based antimicrobials (PBAs) in a tested proprietary formula (M) could alleviate DSS-induced diarrhea in C57Bl/6 rodents. PBAs, derived from plant sources like fruits and spices, may serve as alternatives to combat diarrhea from enteritis and aid in HIV enteropathy treatment through probiotics and prebiotics. This is particularly beneficial for economically disadvantaged populations with limited healthcare access. To test the efficacy of a PBA supplement (M) against DSS-induced diarrhea, C57Bl/6 mice were treated with either DSS or water and given the supplement or a control diet. Metabolic responses (body mass, hydration, rectal temperature) were monitored, and fecal samples were collected for analysis of composition and microbial profiling. The supplement led to increased body mass, reduced weight loss, and altered gut microbiota, indicating a protective effect against diarrhea through microbiome modulation. Further studies are warranted to explore this potential [1, 2].

Understanding Diarrhea in HIV Patients

Diarrhea is the frequent passage of loose or watery stools, and in HIV patients, while it is seldom carelessly spoken about, it can nevertheless lead to mounting anguish, isolation, and deep embarrassment. HIV patients living with diarrhea often stop going out or meeting their friends; at times they cramp up in their seats while trying to catch a bus, fearing catastrophic embarrassment. They may spend painful

seconds at public consumption toilets, desperately striving to hold large liquid stools inside while trying to decide the best way to complete their daily activities, be it work, meetings, or family gatherings. In HIV patients, secretive diarrhea is often the last straw. This concern is aggravated by blood, which can lead to a doctor's visit, and additionally by incontinence, in which cases an unplanned trip is taken to the bathroom. Mild infectious causes or changing diet can often be normalized, but when occasions become several weeks long and stool is oily, bile-stained, and loose, a medical assessment should follow. Antiretroviral therapy is essential in treating all HIV-infected individuals—those in discordant couples, those with stage 1 disease or a CD4 count below 350 cells/μL will start therapy irrespective of their stage. Thus, the numbers of HIV patients needing care and treatment are growing immeasurably. Concurrently, due to therapy, the mortality rates have greatly fallen, and the epidemiology of HIV disease has changed: the incidence of looser stools in HIV patients still has to be properly studied. Management of HIV patients experiencing loose stools has to be studied: loose stools in newly diagnosed HIV patients in self-referred patients were studied regarding clinical and laboratory parameters. A need for a scoring system based on clinical parameters that should assist rural health care providers in HIV care programs, especially in resource-poor countries, was both felt and developed earlier. Nonetheless, HIV patients undergoing therapy in general have care providers professionally managing therapy, and routine stool examination in patients on therapy is neither done nor sought by practitioners in the clinic setting [3, 4].

Current Treatment Options

Individuals infected with the human immunodeficiency virus (HIV) experience a number of symptoms, including gastrointestinal disorders such as diarrhea. This is especially true among those being treated with antiretroviral therapy (ART) medications, particularly protease inhibitors (PIs). The multitude of possible causes of diarrhea can complicate its evaluation, and various treatments are available based upon the likely cause. ART medications are typically the first agents considered, but a variety of alternative or adjunctive therapeutic options are available, from both Western medicine and traditional healing perspectives. Diarrhea has been historically recognized as one of the most common clinical signs of advanced HIV infection. Prior to the availability of potent antiretroviral treatment (ARV), its prevalence had been demonstrated to be as high as 80% or more among AIDS patients. Fortunately, with the advent of highly active antiretroviral therapy (HAART), a significant reduction in the incidence of diarrhea was seen. However, even today, antiretroviral therapy agents can elicit a range of adverse symptoms and events, including diarrhea. Among HIV patients on HAART medication, the reported prevalence of diarrhea remains between 25% and 55%. Whenever diarrhea is present, an accurate diagnosis is essential to guide the selection of treatment options and, ideally, to remove or prevent future exposure to an underlying cause. The concurrent use of multiple ARV medications has undoubtedly improved the safety, efficacy, and tolerability of HIV regimens. That said, numerous anti-HIV agents (particularly PIs) themselves have been associated with adverse events that may prompt discontinuation of treatment, leading to a deterioration of immune status and subsequent increase in susceptibility to opportunistic infections. Diarrhea has been a particular concern with the PIs, with the most frequently implicated agents being ritonavir, nelfinavir, and indinavir. In the most severe cases, the condition may progress to dehydration and loss of hydration-related electrolytes, thereby threatening the patient's life [5, 6].

Introduction To Plant-Based Antimicrobials

Diarrhea remains a world food safety concern. A critical assessment revealed that it is the second major cause of mortality in children under the age of 5. In 2009, it was confirmed that diarrhea is responsible for the deaths of 1.5 million children annually, with 4 out of 5 of these deaths occurring in the developing world. Annually, an estimated 3 to 5 billion episodes of diarrhea occur in children below 5 years, with about 1 billion diarrhea-associated illnesses in adults. For example, the most recent estimates indicate that diarrhea is the leading food-borne pathogen in Ethiopia, with the country accounting for around 27% of the number of deaths from this cause. In Mozambique, 200,000 episodes of diarrhea and 1620 deaths per year have been reported. In theory, patients who experience severe dehydration should be treated with drip infusion of physiological saline, however, patients are usually given homemade beverages, and thus only mild dehydration is treated. Almost every family is affected by diarrhea in Mozambique, and patients are treated with traditional medicines or home ingredients. It is conceivable that this mass is a breeding ground for resistant bacteria. As the bacteria responsible for diarrhea are known and their susceptibility to already commercially available antibiotics established, there is good reason to seek the effectiveness of these already publicly known extracts at much cheaper prices. Laboratory investigations have previously been conducted on the antimicrobial effects of plant extracts against gram-positive and gram-negative bacteria. Similar research on the antimicrobial activity of several ethnomedicinal plants

against bacterial pathogens was conducted elsewhere, too. Now it is of interest to determine whether and how the extract selected based on these ethnomedical reports would perform in vitro for its activity against selected bacterial diarrhea cases. As such, a preliminary antimicrobial screening of selected extracts against eight known gram-positive and gram-negative bacteria was conducted. It was further investigated to determine which bacterial pathogens the extract was effective against, the active compounds, the mechanism of action, the extraction and purification methods, and finally, the plant species might be identified as a potential source of lead antibiotic compounds [7, 8].

Mechanisms of Action

Diarrhea is a leading cause of morbidity worldwide, including in HIV-infected patients. Among the multiple causes of diarrhea in HIV+ patients, those associated with HIV itself and compatible with intestinal and systemic inflammation are the most prevalent causes. Concomitant infections such as rotavirus or enteroinvasive pathogenic Escherichia coli are common and intractable causes of HIV-associated diarrhea. In HIV+ patients, alterations of gut microbiome and immune activation increase the risk of extra-intestinal infections. These gut disorders lead to HIV-associated obesity, fatty liver, and metabolic diseases. On the contrary, diarrhea is very unlikely in HIV-negative patients infected by enteric virus or pathogenic E. coli, indicating that pre-existing immune disruption is a crucial requirement for the elicitation of infectious diarrhea. These insights indicate that efforts aimed at restoring a hemostatic gut immune environment should be explored as new approaches for secondary prevention of diarrhea in HIV+ patients. As an alternative, enteric lactobacilli suspensions showed limited effects as probiotic therapies against HIV-associated diarrhea. The health benefits of plant-derived food bioactive compounds and phytochemicals are well-characterized, including fruit polyphenols, curcumin, resveratrol, flavonoids, and plant polysaccharides. From the screening of food plants, Cudrania tricuspidata has been identified as a rich source of potentially bioactive tannins that epigenetically up-regulate the expression of interleukin-8 pro-inflammatory mediator gene and antimicrobial peptide-encoding genes such as human beta-defensins. Mechanism studies further revealed that these effects are mediated through direct epigenetic regulation mediated by C. tricuspidata tannins treatment, leading to modulation of gut microbes toward enhancing the abundance of Lactobacillus and Lactococcus that contribute to the regulation of enter immunoglobulin A and IL-8 secretion. C. tricuspidata tannins might serve as a new hope for the treatment of diarrhea in HIV+ patients by restoring gut homeostasis [9, 10].

Key Plant-Based Antimicrobials

The severity of the AIDS epidemic in Africa is currently increased by opportunistic illnesses such as appendicitis, certain infections of the nervous system and the eye, and especially pancreatitis. Of all the opportunistic infections that occur in HIV positive patients, diarrhea appears to be a particularly troublesome side effect of HIV/AIDS infection and highly active antiretroviral therapy (HAART). Worldwide, HIV and AIDS estimates indicate that 36.9 million people were living with HIV at the end of 2014, of whom 2.6 million (7%) were children aged 15 years or younger. 19 million (53%) of the 36 million people living with HIV have yet to be diagnosed, making them unaware of their HIV positive status and meaning that they cannot take advantage of the life-saving drugs that are available. In South Africa, the prevalence of HIV is estimated at 4 million people, with about 3.6 million (90% of those who are HIV infected) being on HAART. Epidemiological studies indicate that western non-coliform bacteria are the most prevalent and most important enteropathogens in HIV infected people. Therapies based on natural products have become an important area of focus in medical research because of microbial resistance to synthetic medicines. Different ethnomedicinal surveys of plants used in treating diarrhea have been carried out in many countries. The aim of the present paper is to review the bioactive principles of plants used as traditional medicines to treat diarrhea, with emphasis on those that have undergone scientific evaluation. Antimicrobial phytochemicals are briefly discussed as useful modes for the treatment of enteropathogenic diarrhea. Diarrhea, an intestinal condition that is characterized by an increase in stool weight (200 g/day), frequency (3/4 times a day), or liquidity, is one of the most commonly reported ailments. It is a global problem that affects millions of children and adults, especially in developing countries. Non-infectious causes of diarrhea include those of neurogenic origin, such as irritable bowel syndrome, neuroendocrine tumors, and the dumping syndrome. But infectious diarrhea due to exposure to bacteria, viruses, protozoa, and other parasites is the main cause of morbidity and mortality [11, 12].

Clinical Studies and Evidence

In a clinical study, the efficacy of a novel curcumin formulation, methoxy (O-methyl) curcumin powder, was tested alongside a germanium-based formula in three HIV-positive patients with chronic diarrhea and drug-resistant infections. Both ARV-naive patients and one with infections tolerated the curcumin

well, experiencing no significant side effects. Dosage began with two capsules of curcumin twice daily with food; if severe loose stools occurred, the dosage was halved until improvement was noted, after which it was gradually increased. The germanium powder was administered simultaneously with similar dosage adjustments. After 10 days, all patients reported improvements in stool frequency, less volume, and consistency. Patient 1 saw significant changes after two days, experiencing more solid stools and reduced frequency. However, he faced stomach upset, nausea, and temporary loss of appetite that lasted four days due to mild diarrhea, but overall, curcumin was continued with a gradual increase in dosage. By the end of one month, he reported lasting improvements, going three to five days without bowel movements and a notable decline in diarrhea frequency. Follow-ups revealed no opportunistic infections, and the immune response was restored, though he continues taking curcumin for its anti-inflammatory properties. This study suggests that integrating curcumin, probiotics, and dietary amendments may effectively manage diarrhea in HIV patients, warranting further research for confirmation [13, 14].

Safety and Efficacy

Research on the antimicrobial and toxicity potential of B. axillaries leaves focuses on treating diarrhea in HIV patients. In vitro studies assessed the leaves against ten bacteria and three fungi species, finding significant antimicrobial activity against ten clinical strains, notably Enterobacter spp and Streptococcus faecalis, indicating its therapeutic potential for AIDS-related diarrhea. The extract showed activity against certain fungi, with minimal toxicity observed in rats. Current work includes bioactivity-guided fractionation to isolate effective secondary metabolites and constituent's toxic to pathogens, aiming for plant-derived antibiotic alternatives. Additionally, further studies will explore the structure-activity relationship of the metabolites, toxicity in fish and birds, and identify constituents effective against agricultural pests. These investigations are critical to understanding the mechanism of action and safety profile of B. axillaries, prompted by the rising cases of diarrhea among HIV-infected individuals. Known for its antidiarrheal properties, this plant's traditional use motivates research validating its antimicrobial and toxicity properties. Despite some prior studies, there is limited knowledge about B. axillaries' effectiveness against selected pathogens, highlighting the need for research on methanol and aqueous extracts of this plant [15, 16].

Integration Into HIV Care

The outcomes of HIV have significantly improved due to advances in antiretroviral therapy (ART); however, gastrointestinal issues, particularly diarrhea, are often overlooked, complicating patient management. The severity and duration of diarrhea adversely affect quality of life (QoL) and adherence to ART. Diarrhea in HIV patients can stem from both HIV-related and unrelated factors. In cases of early or moderate immune deficiency, complications from HIV-associated diarrhea may outweigh the benefits of combination antiretroviral therapy (cART). Effective monitoring and management of adverse effects (AEs) are crucial for maintaining treatment compliance and ensuring therapeutic success. To enhance cART management in HIV-infected individuals, increased awareness of adverse effects and a deeper understanding of diarrhea's natural history are essential. Diarrhea poses a significant challenge for HIV-positive individuals, often leading to decreased QoL and poor adherence to treatment. Understanding the pathophysiology of diarrhea in these patients involves examining how HIV affects the gastrointestinal tract and its interactions with the immune and autonomic nervous systems. HIV primarily infects lymphoid tissue in the gut, resulting in immune activation that may disrupt the gut barrier. Furthermore, HIV can damage autonomic nerves in the intestine, causing accelerated transit times. Although switching ART regimens is possible, patients may experience diminished QoL post-switch. It is advisable to manage mild to moderate AEs before making any changes to a stable ART regimen. Addressing noninfectious symptoms and diarrhea involves careful dietary practices, modifications to cART, and pharmacologic treatments. The intersection of virulence factors with the host environment can lead to bacterial overgrowth and related health issues. In HIV cases, both the immune system and gut microbiome are impacted, leading to mucosal atrophy and loss of gut-associated lymphoid tissue, allowing bacterial translocation into circulation, which activates the innate immune system and fosters chronic inflammation [17, 18].

Future Directions in Research

Future directions in the research of Diarrhea in HIV Patients are paramount, given the high prevalence and severe consequences in this population. Promoting dietary management research will hopefully expand the treatment options available in resource-limited countries. Through education, traditional and complementary interventions could potentially give this vulnerable population a high-quality treatment option with low side effects compared to other alternatives. Research should focus on traditional and

complementary approaches to treat drug-resistant pathogens, delivered through diet. A traditional fermented milk product, or certain botanicals, could be tested quantitatively to address these needs in a targeted way. Plant botanicals with anti-retroviral, antioxidant, and anti-infection activities are immensely important for mitigating some co-morbidities. Identifying, preserving, and extracting active principles could hold the key to new therapeutic candidates and improve the quality of life of HIV patients. Additionally, selecting herbal plants based on this capacity could also be a worthwhile avenue of research. With the proven anti-retroviral conditions and an anti-diarrheal activity, curcumin from turmeric has enormous potential for future research. Anti-infective tests could be performed on staple foods that contain curcumin to approach an idea of the level needed. Another plant with the most promising anti-diarrheal activities is ginger. Co-harvesting and co-using turmeric and ginger could be advantageous to both shorten selection times and improve low immune conditions in HIV patients [19-23].

Challenges and Considerations

Diarrhea is a common event in HIV patients receiving ART and is a detrimental outcome affecting the malabsorption of crucial nutrients and drugs. The incidence and type of diarrhea associated with HIV infection—and/or ART—widely vary from one setting to another. Diarrhea screening and management in HIV clinics and facilities have been sub-optimal in settings where care is needed the most. There is ample evidence that diarrhea-related HIV patient loss to care is associated with far-reaching effects on clinical and epidemiological outcomes, which include treatment failure, resurgence in morbidity and mortality, as well as treatment resistance. Resource, capacity, and structural challenges complicating diarrhea management have been well characterized; however, the extra burden posed by the coronavirus disease 2019 pandemic and its aftermath is looming to present a new challenge for the management of diarrhea in HIV care settings. The role of local collaborations between health care providers, caregivers, pharmacy distributors, local AIDS associations, and civil societies in managing ART-related diarrhea cases is proposed to enhance the current response to HTS, as supported by local community testimonials. Diarrhea in HIV patients is a complex and multi-faceted event whose link to ART adherence is largely indirect and influenced by current factors and future challenges. Diarrhea in HIV patients is modifiable with the potential to ameliorate care, ART adherence, and ART-implicated loss to care. Once approaches to management have been better cataloged, a setting-specific protocol can be developed and validated. Ultimately, this will allow more effective management and improved related health and population outcomes for HIV patients beginning ART in Botswana. Understanding the multi-faceted nature of ART-related diarrhea is crucial in devising a suitable response. Further mounting evidence attesting to the food safety risks in rural Botswana can be leveraged to propose necessary interventions in the food supply chain [24-27].

CONCLUSION

The persistent burden of diarrhea among HIV-infected individuals, despite advancements in ART, highlights a pressing need for alternative, complementary therapeutic strategies. Plant-based antimicrobials emerge as a promising solution, offering multifaceted benefits ranging from antimicrobial and anti-inflammatory activity to microbiota modulation and gut barrier restoration. Evidence from traditional medicine and scientific studies converges to validate the potential of natural compounds such as curcumin, ginger, and tannin-rich plants. Integrating these compounds into HIV care, especially in settings where conventional medicine may be unaffordable or inaccessible, can significantly enhance quality of life and treatment adherence. However, rigorous clinical trials and standardized protocols are needed to fully establish their safety, efficacy, and role within modern HIV treatment regimens. As research progresses, PBAs could transition from supplemental remedies to central pillars in the comprehensive management of HIV-associated diarrhea.

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