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The influence of Sambiloto (*Andrographis paniculate Nees*) leaf extract towards periodontal disease associated with HIV

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Abstract

Background: Necrotizing periodontal disease (NPD) represents a serious and swiftly advancing type of periodontal disease that is frequently found in individuals with compromised immune systems, especially those infected with HIV. The microbial composition associated with periodontal diseases in HIV patients reveals a significant presence of red and orange complex bacteria, including *Tannerella forsythia* and *Fusobacterium nucleatum*. In recent years there has been a growing interest in herbal medicine as treatment. *Andrographis Paniculata Nees*, commonly known as Sambiloto is a medicinal herb widely used worldwide, especially in subtropical regions such as India, Thailand, Vietnam, and China. Sambiloto primarily consists of diterpenoids, flavonoids, and polyphenols. The main diterpenoid present in sambiloto is andrografolid. Andrographolide is the key active component responsible for most of its pharmacological effects. The substances found in the stem and leaves of this plant exhibit anti-inflammatory, antibacterial, and antiviral properties. Recent studies have explored the antiviral properties of Sambiloto, which may be effective against various viruses. Computational analyses have identified bisandrographolide and phytol as promising anti-HIV compounds, showing effectiveness in inhibiting HIV-1 protease.

Purpose: To discuss the influence of sambiloto leaf extract towards HIV patients associated with periodontal disease.

Method: The leaf extract of sambiloto does inhibit bacterial growth within periodontal disease associated with HIV.

Results: The leaf extract of sambiloto has antiviral and antibacterial properties having the ability to inhibit periodontal bacteria within HIV.

Conclusion: The leaf extract of Sambiloto does inhibit bacterial growth within periodontal disease associated with HIV.

Keywords: Sambiloto (*Andrographis paniculate Nees*); HIV; Necrotizing periodontal disease; Bacteria

1. Introduction

Periodontal disease is a common chronic inflammatory condition that affects the gums and the supporting structures of the teeth, often leading to tooth loss and systemic inflammation. [1] Periodontal disease is also defined by the interactions between the host and microorganism, resulting in tissue damage caused by microbial activity and an exaggerated immune response from the host. The disease is also defined by the interactions between the host and microorganisms, resulting in tissue damage caused by microbial activity and an exaggerated immune response from the host. The human immunodeficiency virus (HIV) causes a viral infection that compromises the immune system. This virus is part of the lentivirus family, which is subgroup of retroviruses. HIV has a particular affinity for immune system

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cells. As a result of a compromised immune system cells, it can contribute to the development of periodontal disease and an unusual progression of the condition. Individuals who are HIV-positive are at a heightened risk of developing necrotizing periodontal disease, characterized by severe and rapidly progressing necrotic ulcers in the periodontal tissues. [7] Consequently, it is essential for HIV-positive individuals to uphold proper oral hygiene and to seek reek regular dental care. Individuals infected with HIV often exhibit oral manifestations including necrotizing ulcerative gingivitis (NUG), necrotizing ulcerative periodontitis (NUP), and oral candidiasis. May act as markers for the severity of HIV disease, showing a correlation with reduced CD4+ T- cell counts and heightened viral load. [32] The microbial composition associated with periodontal diseases in HIV patients reveals a significant presence of red and orange complex bacteria, including *Tannerella forsythia* and *Fusobacterium nucleatum*. [33] Antibiotics act as a remedy for bacterial infections by either inhibiting or eradicating bacteria. When used appropriately, they can effectively resolve infection-related problems. Misuse can result in negative consequences, including the emergence of antibiotic resistance. [6] Thus investigating natural antibacterial agents offers a promising alternative to reduce the increase of antibiotic resistance, especially those sourced from plants*. Andrographis Paniculata Nees,* commonly known as Sambiloto is a medicinal herb widely used worldwide, especially in subtropical regions such as India, Thailand, Vietnam, and China. [9] Recent studies have explored the antiviral properties of Sambiloto, which may be effective against various viruses. Computational analyses have identified bisandrographolide and phytol as promising anti-HIV compounds, showing effectiveness in inhibiting HIV-1. [12]

Sambiloto contains the main compounds diterpenoids, flavonoids, and polyphenols. The main diterpenoids, flavonoids, and polyphenols. [24] Due to its antibacterial characteristics, andrographolide can inhibit the quorum sensing activity (expression of virulence factors) of bacteria. Flavonoids can also obstruct the synthesis of the cell wall, which is essential for maintaining cell wall integrity, ultimately leading to cell lysis. [6] Alkaloids inhibit cell respiration and inhibit various bacterial enzymes as DNA intercalators and inhibit bacterial cell topoisomerase enzymes. [27] Meanwhile, saponins can alter the fluidity of the cell membrane. [28] Meanwhile, tannins are capable of disrupting established biofilms, which increases fragility and susceptibility to damage. [9] In the pursuit of developing oral hygiene products designed to prevent oral infections, various Ayurvedic components, including *Andrographis paniculate*, have been assessed for their effectiveness against dental pathogens. Sambiloto (*Andrographis paniculate Nees*) has been investigated in relation to HIV, with oral manifestations serving as crucial indicators of HIV infection; notable examples include Necrotizing Periodontal Disease (NPD).

2. Methods

The type of research used in this study is a literature review with a narrative design, utilizing secondary data obtained from previously published researches. The literature search was carried out using online databases such as PubMed, ScienceDirect, and ResearchGate.

3. Result

3.1. Periodontal Disease Associated with HIV

Periodontal disease, a long-lasting inflammatory condition that impacts the tissues surrounding and supporting the teeth, poses a considerable concern for individuals infected with the human immune immunodeficiency virus (HIV). The connection between HIV and periodontal disease has been thoroughly examined in recent decades because of its clinical and public advance more swiftly and be more severe, adversely affecting their quality of life and oral health. (2) In 2017, the American Academy of Periodontology, in collaboration with the European Federation of Periodontology, devised a new classification of periodontal and peri-implant diseases. In this new classification, periodontitis can be subdivided into three categories: (1) Necrotizing periodontal diseases; (2) Periodontitis; (3) Periodontitis as a manifestation of systemic diseases. [2]

NUP and NUG has now been identified as NPD as the term ‘ulcerative’ is no longer used in classification as ulceration is considered secondary to the gingival necrosis present. [29]

3.2. Necrotizing Periodontitis Disease

Necrotizing Periodontal Disease (NPD) represents one type of periodontitis. The clinical signs of NPD consist of ulcerative and necrotic papillae, gingival margins that are covered with a yellowish-white or grayish film, obstruction and ulceration of the interdental papillae, gingival bleeding (both intentional and spontaneous), gingival discomfort, and unpleasant breath. NPD is categorized as an acute periodontal lesion. Symptoms accompanying NPD may include fever, fatigue, and lymphadenopathy. The causes of NPD are linked to microorganisms, infections, and a weakened

immune response, which can worsen the condition. [17] NPD has three forms: Necrotizing Ulcerative Gingivitis (NUG), Necrotizing Ulcerative Periodontitis (NUP), and Necrotizing Ulcerative Stomatitis (NUS). The primary distinction between NUG and NUP is that NUG does not involve rapid bone loss (osteonecrosis). [34]

3.3. Etiology

The cause of periodontal disease in patients with HIV is linked to an exacerbated inflammatory response resulting from HIV's effect on the immune system. This leads to greater damage to the gums and supporting tissues compared to what is usually observed in non-HIV patients. The compromised immune system, along with the existence of oral bacteria and plaque, fosters a setting where inflammation and tissue destruction progress more rapidly, rendering individuals with HIV more vulnerable to periodontitis. HIV compromises the immune system, resulting in a diminished capacity to combat pathogens. This encompasses the bacteria and microorganisms responsible for periodontal disease. The accumulation of plaque on the teeth and gums is a leading factor in the development of periodontal disease for all individuals. In patients with HIV, this typical bacterial presence may provoke a heightened inflammatory reaction, leading to more significant damage. [18]

3.4. Treatment

Treatment typically involves mechanical debridement in conjunction with antimicrobial therapy. However, mechanical therapy has several limitations and challenges, such as deep pockets, complex pockets, and furcation involvement, among others. As a result, supportive therapy is crucial in periodontal treatment. Supportive therapy may include assessment and evaluation, plaque management, and the administration of antibiotics. Nevertheless, broad-spectrum antibiotics can negatively impact beneficial bacteria, highlighting the need for the development of more targeted agents. Antibiotics act as a remedy for bacterial infections by inhibiting or eradicating bacteria. When used appropriately, they can effectively resolve infection-related problems. On the other hand, misuse can result in negative consequences, including antibiotic resistance. Thus, the investigation of natural antibacterial agents offers a promising alternative to reduce the emergence of antibiotic resistance, especially those sourced from plants. [2]

3.5. Sambiloto (*Andrographis paniculata Nees*)

In recent decades, there has been a significant increase in the resistance of human pathogenic bacteria to current antibiotics and chemotherapeutic agents utilized for conditions such as tooth decay, gingivitis, periodontitis, and fungal infections across different age groups. Recent studies have highlighted the antimicrobial properties of Sambiloto in the fight against oral pathogens. [7] *Andrographis paniculata Nees*, commonly referred to as Sambiloto, is a medicinal herb that is extensively used globally, particularly in subtropical areas like India, Thailand, Vietnam, and China. In Thailand, the Ministry of Public Health has recognized bitter melon as one of the medicinal plants included in the National List of Essential Medicines, which are employed in hospitals and public health services. [9] This recognition is due to Sambiloto's proven effectiveness in addressing a variety of health concerns, including fever, respiratory syndromes, diabetes, skin infections, and numerous viral infections, which can be attributed to its analgesic, antibacterial, antimalarial, antiviral, anti-inflammatory, and immunomodulatory properties. [10] [11] Moreover, the plant contains several key compounds with anti-HIV potential, including andrographolide and its derivatives. Molecular studies show these compounds can inhibit viral processes such as fusion, absorption, and reverse transcription. [12] Sambiloto comprises key compounds such as diterpenoids flavonoids, and polyphenols. The primary diterpenoids, flavonoids, and polyphenols are noteworthy. [24] Andrographolide, due to its antibacterial properties, can inhibit the quorum sensing activity in bacteria. Flavonoids are also capable of obstructing the synthesis of the cell wall, which is crucial for preserving cell wall integrity, ultimately resulting in cell lysis. [16] Alkaloids impede cellular respiration and inhibit various bacterial enzymes, acting as DNA intercalators and blocking bacterial cell topoisomerase enzymes. (26) Additionally, saponins can modify the fluidly of the cell membrane. [28] Tannins, on the other hand can disrupt established biofilms, thereby increasing fragility and vulnerability to damage. [9] In the effort to create oral hygiene products aimed at preventing oral infections, various Ayurvedic components, including *Andrographis paniculata*, have been evaluated for their efficacy against dental pathogens. [7]

4. Discussion

Andrographis paniculata is a Latin name for Sambiloto. This plant thrives in warm regions characterized by tropical and subtropical climates, including areas in Asia, India, Sri Lanka, Java, Pakistan, Indonesia, and Malaysia. [21] *Andrographis paniculata*, a medicinal herb commonly utilized in traditional Asian medicine, has attracted considerable interest due to its various therapeutic benefits. [19] The leaves of this plant are the most frequently employed part, and when boiled, they produce a dark-colored infusion with a distinctly bitter. As an herbal remedy, sambiloto offers a range of beneficial pharmacological properties, including antimalarial, antidiarrheal, antipyretic, and anti-inflammatory effects. [21]

Sambiloto demonstrates a wide range of antimicrobial effects against both gram-positive and gram-positive and gram-negative bacteria, in addition to fungi. [35] Furthermore, sambiloto extract has shown properties that combat inflammation and oxidative stress. [31]

The taxonomy of *Andrographis Paniculata* (Sambiloto) is as follows: [40]

- Botanical Name: *Solanum xanthocarpum*
- Kingdom: *Plantae*
- Subkingdom: Trachebionta
- Division: Magnoliopsida
- Subclass: Asteridae
- Order: Solanales
- Family: Solanaceae
- Genus: *Solanum*

Different parts of plants, such as leaves, fruits, seeds, and bark, are used to treat ailments that impact various bodily systems. [19] Sambiloto features small tubular flowers that emerge from the tips of its stems, displaying a purple and white coloration. The plant comprises bioactive compounds, including andrographolide, which was measured at 2.208% during the vegetative stage [21]. The stem and leaves of *A. Paniculata* are rich in compounds such as diterpenoids and flavonoids, which demonstrate antidiabetic effects by influencing various molecular pathways, including DPP4, PTP1B, α-glucosidase, GLUT, and glucokinase. [36] The entire sambiloto plant, encompassing its flowers and fruits, possesses medicinal properties. Nevertheless, the leaves and stems are the components most frequently utilized in traditional medicine. [21]

A phytochemical analysis was performed to determine the presence of key compounds, such as andrographolide, phenols, tannins, flavonoids, saponins, glycosides, steroids, terpenoids, and alkaloids. These secondary metabolites are recognized for their extensive biological and therapeutic advantages, indicating that this species may have a range of medicinal applications. It is particularly rich in phenols, flavonoids, and alkaloids, showcasing significant antioxidant, antiviral and antimicrobial properties, which include both antibacterial and antifungal activities. [5]

4.1. Andrographolide

The main diterpenoid is andrographolide, which is mostly concentrated in the leaves, at over 2%. Andrographolide can function as an immunomodulator that stimulates the immune system. Andrographolide increases the production of blood mononuclear cells, tumor necrosis factor TNF-α, interferon (IFN)-α, and (IFN)-γ, as well as the activity of macrophage phagocytosis. This indicates that andrographolide can function as an immune system stimulant that can enhance specific and nonspecific immune functions through the induction of NK cells, macrophages, and cytokines. [25] The mechanism of action of andrographolide as an antibacterial and anti-inflammatory agent involves the destruction of bacterial cell membranes, inhibition of DNA transcription, biofilm formation, and quorum sensing. Andrographolide inhibits bacterial quorum sensing activity by reducing LuxS enzyme and autoinducer-2 molecule (AI-2) levels, thereby inhibiting phagocytosis and preventing bacteria from being digested by neutrophils. Andrographolide has been studied for its functions as an antioxidant, anti-inflammatory, anti-adhesion, antibacterial, antiviral, and anti-HIV agent. Andrographolide can prevent the production of reactive oxygen species (ROS) or free radicals by neutrophil cells. [6] The reactions inhibited by andrographolide are neutrophil adhesion and transmigration. In addition, the andrographolide molecule also affects the expression of the Mac-1 gene. Andrographolide can suppress the expression of the Mac-1 gene, which causes a decrease in ROS production by neutrophil cells. As an anti-HIV agent, the compound 2',6'-dichloronicotinoil andrographolide has a mechanism that interferes with the initial events of HIV entry into target cells by interacting with gp120. Specifically, this compound inhibits HIV-1 infection by blocking the interaction of gp120-CD4/CXCR4/CCR5. [25]

4.2. Flavonoids

Flavonoids are organic compounds distinguished by various phenolic structures and abundant in numerous natural sources, including fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine. The health benefits associated with these natural compounds are well-documented, prompting efforts to extract flavonoids for various applications. The seven most prevalent compounds in this category include apigenin, galanin, hesperetin, kaempferol, myricetin, naringenin, and quercetin. Research conducted through in vitro, in vivo, and clinical studies suggests that these flavonoids exhibit significant anti-diabetic, anti-inflammatory, antibacterial, antioxidant, antiviral, cytotoxic, and lipid-lowering properties. Certain flavonoids disrupt the production of peptidoglycan, an essential element of the bacterial

cell wall. By obstructing vital enzymes that play a role in this synthesis, flavonoids compromise the integrity of the cell wall, resulting in cell lysis. [37]

4.3. Alkaloids

Alkaloids can form hydrogen bonds with enzymes, receptors, and proteins. Alkaloids have many pharmacological properties, such as central nervous system stimulants (brusin), anticholinergic agents (atropine), oxytocin and vasoconstrictor activity (ergometrin), and antimalarial activity. The mechanism of action of alkaloids as antibacterial agents is through the inhibition of cell wall synthesis, which causes lysis of the bacterial cell wall, thereby inhibiting bacterial growth and even causing bacterial death [38]. Another antibacterial mechanism of alkaloids is that alkaloid components are known to be DNA intercalators and inhibit bacterial cell topoisomerase enzymes. [27]

4.4. Saponin

Plant saponins are recognized for possessing the highest surfactant properties among all bioactive chemical compounds. When mixed with water, they create a soapy lather, which is the origin of their name “saponins.” Their natural origin renders them eco-friendly, as they are biodegradable and non-toxic, which is crucial for both environmental and health considerations. In addition to their bioactive nature, previous studies have highlighted that saponins exhibit superior physicochemical properties compared to synthetic alternatives. Plants rich in saponins present remarkable physicochemical and biological characteristics, positioning them as a valuable source of natural surfactants for both research and commercial applications. [28] Saponins have the ability to modify the fluidity of the cell membrane, resulting in increased fragility and a higher vulnerability to damage. [9]

4.5. Tannin

The antibacterial properties of tannins stem from their capacity to interact robustly with lipid membranes, which alters their physiochemical characteristics such as fluidity and permeability. Additionally, tannins interact with various proteins, including serum albumin, alpha-synuclein, salivary α-amylase, and bacterial proteins like streptococcus glucosyltransferase, protease, and neuraminidase, leading to their inhibition. [29] Certain tannins have demonstrated the capacity to disrupt established biofilms, potentially by interfering with the extracellular polymeric substances (EPS) that maintain the integrity of the biofilm matrix and by influencing bacterial viability within the biofilm. [39]

5. Conclusion

In conclusion, leaf extract of Sambiloto (*Andrographis Paniculata Nees)* has potential in inhibiting bacterial and viral activity towards periodontal disease associated with HIV.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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