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### WHAT HAPPENS IF THE BROMELAIN IN *Ananas comosus* L. Merr. GIVEN TO PEOPLE LIVING WITH HIV/AIDS (PLWHA) ? : A REVIEW

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#### ABSTRACT

**Background:** Human immunodeficiency virus /Acquired immunodeficiency syndrome (HIV/AIDS) is a global problem that requires serious treatment. Antiretroviral therapy (ART) has the potential to cause side effects and drug resistance for people living with HIV/AIDS (PLWHA). Alternative therapies using combination of bromelain and ART to maintain and improve immunity of PLWHA. The objective of the study was to describe the potential of bromelain in pineapple (*Ananas comosus* (L.) Merr) to increase the immune system of people living with HIV/AIDS.

**Methodology:** The research method used a systematic literature review. The literature that this study used was search through in the Science Direct and Google Scholar database. The article search used the keyword *Ananas comosus* (L.) Merr, HIV/AIDS healing pathway or bromelain enzyme healing pathway HIV/AIDS and Pineapple "bromelain enzyme" for HIV/AIDS. Obtained 4 articles from 219 articles published between 2010 until 2019. The article used in this study written in English and Indonesian.

**Results:** The results showed that the bromelain enzyme in pineapple have proteolytic properties that can destroy the protein layers of the HIV viruses. The other benefit are immunomodulators that can increase the immune system of PLWHA by increasing CD4 counts or maintaining the stability of the CD4 count and reducing viral load levels even undetectable.

**Conclusion:** The conclusion of this study is bromelain in pineapple can be used as an alternative cure for PLWHA which do not have side effect and can destroy the HIV virus protein layer and increasing the immune system of PLWHA as well.

**Keywords:** bromelain against PLWHA, *Ananas comosus* (L.) Merr. immune system of PLWHA

#### INTRODUCTION

Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) is a collection of signs and symptoms of disease that arise from damage to the human immune system due to retroviruses called the HIV virus [1]. The HIV virus attacks and damages CD4 cells, causing a person susceptible to various infections, this is because the body loses its ability to fight an illness or infection. A person infected with HIV can develop into AIDS if the CD4 cell count is below 200 cells/mm and has opportunistic infection [2].

The World Health Organization (WHO) states that in 2017 the number of HIV sufferers globally was 36.9 million, consisting of 35.1 million adults and 1.8 million children (15 years). The new global HIV infection in 2017 of 1.8 million is still far from the target of the United Nations (Fast-track Program), that the target for 2020 is the reduction of new HIV infections to less than 500.000 people [3]. While

deaths from AIDS in 2017 globally amounted to 940,000 people consisting of 830,000 adults and 110,000 children (<15 years). Whereas the number of deaths from AIDS in 2017 in Asia and the Pacific is 170,000 people [1]. This condition is a serious challenge to achieve the goals of the Sustainable Development Goals (SDGs) in 2030. One of the SDGs goals is to end the AIDS epidemic as a public health threat in 2030 [3].

Until now, the most effective treatment for people with HIV/AIDS (PLWHA) is by antiretroviral therapy. Antiretroviral therapy in people with PLWHA functions to increase immunity and check the amount of viral load. Antiretroviral treatment has succeeded in turning HIV infection from critical illness and terminals into chronic diseases thereby reducing HIV-related morbidity and mortality [4]. The results of a trial conducted in 2011 that if an HIV-positive person adheres to taking ART can reduce the risk of transmission of the virus to with 96% to uninfected sexual partners. WHO recommends ART therapy for all people living with HIV, this is because doing ART therapy early can significantly reduce HIV transmission [1]. However, ART must be consumed for life and has the potential to cause serious side effects such as drug resistance, neurotoxicity, changes in lipid metabolism and protein [4]. Therefore, efforts are needed to find complementary treatments [5].

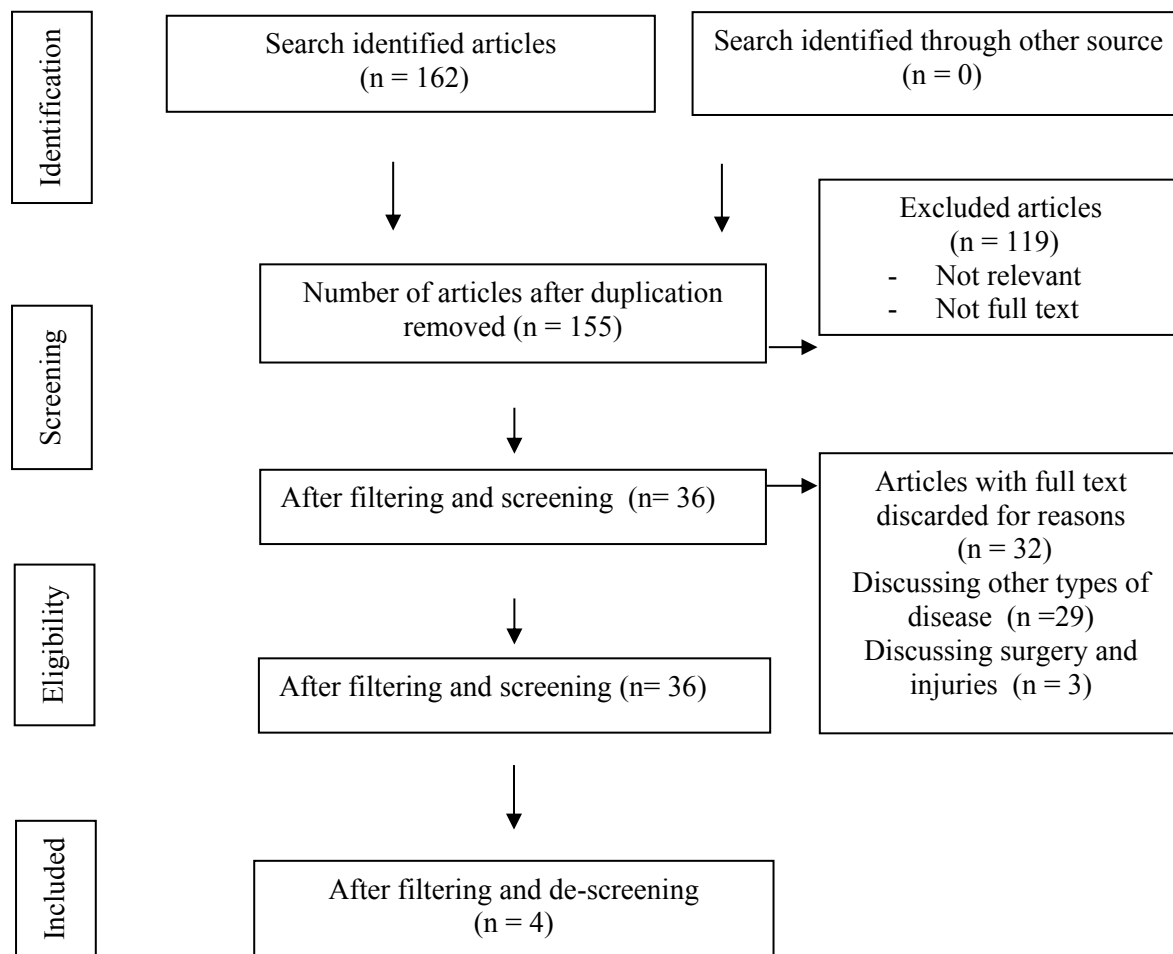
Research efforts have been carried out by researchers to find effective treatments, to prevent and treat HIV / AIDS. The research conducted by Yonathan A.S. et al (2011) that pineapple juice containing the enzyme bromelain turned out to have great potential as an alternative to herbal medicine, to reduce the pain of patients with HIV/AIDS [6]. Research conducted by Maruli, et al. (2015) shows that administration of bromelain in HIV AIDS patients has an impact on progress in increasing CD4 levels in just 2-3 months [7].

Bromelain has been used for a long time in the medical world as a therapy and supplement agent, and has immunomodulatory functions [8]. A preliminary research study has been conducted to find out the benefits of bromelain as a protease enzyme that can be used as an anti-HIV virus [4]. HIV viruses have genetic material (RNA) surrounded by protein capsules, or capsid [5]. HIV attacks in human is host cells called cells CD4. CD4 cells are categorized as T cell lymphocytes which function to protect the body from foreign substances. All living cells have an outer membrane consisting of lipid bilayers and several receptors. CD4 cells have primary receptors d CD4 + and co receptor is called CC chemokine receptors 5 (CCR5) and CXC chemokine 4 receptors (CXCR4) [2]. Bromelain as a protease can destroy the glycoprotein structure HIV cell membrane. Destruction of proteins surrounding the HIV virus is useful to prevent the attachment of HIV particles to receptor cells (CCR5 & CXCR4), so HIV virus RNA is blocked at the entrance and viral proliferation can be suppressed [4].

The literature review aims to determine the potential of bromelain in pineapple against immune system PLWHA.

## **METHODS**

The research method used is a systematic literature review, which collects identifying, assessing and interpreting all findings in research on the potential for bromelain content in pineapple against the immune system of PLWHA. Searching for literature through the Google Scholar and Science Direct databases, uses the keywords "HIV / AIDS ananas comosus healing pathway or bromelain enzyme healing pathway HV / AIDS" and Pineapple "bromelain enzyme" for HIV / AIDS. There were 4 articles from 219 articles published between 2009-2019, which discussed the potential of bromelain in pineapple against the immune system of PLWHA. Articles used in this literary review use English and Indonesian



## RESULTS

Table 1. Summarize Papers

No	Title	Author	Result
1	Bromelain enzyme in fresh pineapple juice as a healing pathway for HIV/AIDS	Pandjaitan M, Nugraha T, Pamudja KH (2014)	The study shows that serum HIV-positive in humans when bromelain is added to different concentrations (4 hours, 37C) then this serum is the examined using HIV I and 2 Mono <sup>TM</sup> tests. The results of both tests show negative results on bromelain concentration >10 mg/ml (specific activity 5.88 U/mg).
2	Alternative Therapy for Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome Patients Using Pineapple Juice	M Pandjaitan, M Tjandra, T Aswani, F Ughi, T Permana MP (2015)	The study showing giving pineapple juice for a period of 10-12 weeks in 13 PLWHA patients increased CD4 + numbers in 4 patients after 5 weeks of giving pineapple juice. However, 9 patients decrease in CD4 cell count. Then 10 weeks later 5 patients had an increase in CD4 cell count, and at week sixteen 4 patients had an increase in CD4 + count. Besides giving pineapple juice can reduce the amount of viral load in patients with HIV/AIDS. This was demonstrated after 10 weeks of administration of 3 patients showing a reduced viral load compared

No	Title	Author	Result
			to before administration. After the 16th week, there were 4 patients who experienced a decrease in viral load.
3	Bromelain Enzyme from Pineapple Fruit as an Antiviral Agent Against HIV, Hepatitis C and Human Papilloma Virus	Pandjaitan M, Nugraha T, et al (2018)	The study showing giving 2 glasses of fresh pineapple juice/day to 7 HIV patients for 4 months could substantially increase the amount CD4 and three of them reached a normal CD4 number. In the follow-up study there were 13 respondents consisting of 12 PLWHA patients, and 1 patient as control with the intervention of giving pineapple juice 2 glass/day for 16 weeks. After 16 weeks, the results showed that 1 patient (control) showed that the number of viral loads decreased from the initial number, but still within normal limits, and the viral load was undetectable. Where as 12 patients with HIV/AIDS 4 of them had an increase in CD4 cell count, 3 of these were undetectable viral loads and 1 patient had a decreased number of viral loads. Furthermore, 6 PLWHA patients experienced a decrease in CD4 cell count, 5 of these viral loads were not detected, 1 of them had an increased viral load. In addition, in this follow-up study 2 respondents were CD4 counts after administration of pineapple juice, the CD4 cell count is not checked, but 1 of them is undetectable and the first one has increased viral load.
4	Effectiveness of Pineapple and Papaya Juice as Side ARV in Improving CD4 Levels	Puspa Wardhani and Nurbani (2016)	There were significant differences in the difference between CD4 counts before and after between treatment groups and groups with p-value of 0.014. In the intervention group there were significant differences in CD4 levels before and after administration of pineapple juice and papaya juice in the intervention group with a p value of 0.016. Whereas in the control group there was no significant difference when given ART. The results showed that the CD4 cell count before and after the intervention was based on the 0.05 p value

Results and literature searches using keywords that have been identified by 162 articles. After duplication checks were made, to obtain 155 access points the screening and screening of selections based on the type of articles relevant to the text were covered by 36 articles. 29 articles discussed about other diseases such as cardiovascular, cancer and diabetes. While the other 3 articles were surgery. There were obtained 4 articles that discussed the potential of bromelain contained in pineapple/*Ananas comosus L.(Merr)*. as an alternative cure in PLWHA. Some studies have been carried out in vitro and directly in humans to examine the potential for immune to PLWHA related to CD4 counts and levels of viral load.

The result of a study conducted by Maruli in 2014 on the effectiveness of fresh pineapple juice containing bromelain encimens were tested in clinical studies effective treatment for PLWHA The study shows that serum HIV-positive in humans when bromelain is added to different concentrations (4 hours, 37C) then this serum is then examined using HIV I and 2 Mono<sup>TM</sup> tests. The results of both tests show negative results on bromelain concentration >10 mg/ml (specific activity 5.88 U/mg) [8].

The results of a study conducted by Maruli in 2015 showed that, giving pineapple juice for a period of 10-12 weeks in 13 PLWHA patients increased CD4 + numbers in 4 patients after 5 weeks of giving pineapple juice. However, 9 patients experienced a decrease in CD4 cell count. Then 10 weeks later 5 patients had an increase in CD4 cell count, and at week sixteen 4 patients had an increase in CD4 + count. Besides giving pineapple juice can reduce the amount of viral load in patients with HIV/AIDS. This was demonstrated after 10 weeks of administration of 3 patients showing a reduced viral load compared to before administration. After the 16th week, there were 4 patients who experienced a decrease in viral load [7].

Furthermore, the results of the study by Maruli in 2018 regarding bromelain contained in pineapple as an anti-viral agent for HIV, Hepatitis C and Human Papilloma Virus, showed that giving 2 glasses of fresh pineapple juice/day to 7 HIV patients for 4 months could substantially increase the amount CD4 and three of them reached a normal CD4 number. In the follow-up study there were 13 respondents consisting of 12 PLWHA patients, and 1 patient as control with the intervention of giving pineapple juice 2 glass/day for 16 weeks. After 16 weeks, the results showed that 1 patient (control) showed that the number of viral loads decreased from the initial number, but still within normal limits, and the viral load was undetectable. Where as 12 patients with HIV/AIDS 4 of them had an increase in CD4 cell count, 3 of these were undetectable viral loads and 1 patient had a decreased number of viral loads. Furthermore, 6 PLWHA patients experienced a decrease in CD4 cell count, 5 of these viral loads were not detected, 1 of them had an increased viral load. In addition, in this follow-up study 2 respondents were CD4 counts after administration of pineapple juice, the CD4 cell count is not checked, but 1 of them is undetectable and the first one has increased viral load [9].

Research conducted by Puspa Wardhani and Nurbani (2016) in Singkawang region, West Kalimantan, about the effectiveness of administration pineapple juice and papaya juice as complementary herbal therapies to increase and maintain CD4 counts in people with HIV / AIDS by providing pineapple juice and papaya juice + ART in the intervention group totaling 10 people living with HIV and the control group consisting of 10 people living with HIV there were differences in CD4 counts between intervention groups and the control group before giving pineapple juice and papaya this was based on a P-value of 0.05. However, there were significant differences in the difference between CD4 counts before and after between treatment groups and groups with p-value of 0.014. In the intervention group there were significant differences in CD4 levels before and after administration of pineapple juice and papaya juice in the intervention group with a p value of 0.016. Whereas in the control group there was no significant difference when given ART. The results showed that the CD4 cell count before and after the intervention was based on the 0.05 p value [10].

## **DISCUSSION**

HIV infection is recognized as one of the biggest challenges in the world faced by mankind in this century related to antiretroviral therapy (ART). However, antiretroviral therapy can cause side effects and resistance to the drug, so that it affects the adherence of HIV / AIDS patients to taking ART therapy [11].

World Health Organization (WHO) mention that treatment using herbal ingredients has been used throughout the world to treat various diseases. There are several herbal medicines that are used as complementary therapies in people with HIV AIDS in several countries in the world. Herbs are herbal ingredients and herbal products that contain active ingredients from plants, or plant ingredients, or combinations that can be used to treat various diseases throughout the world [12]. It is estimated that 80% of people in Africa use herbal medicines to treat various diseases. Herbal therapy is used as complementary medicine or alternative medicine even for conventional medicine in treating various types of diseases. Nigeria is one of the countries in the world that uses herbal medicine in the treatment of HIV. The study conducted in Lagos, Nigeria showed that 8.2% of respondents (people with

HIV/AIDS) used herbal medicine as a complementary therapy in addition to consuming antiretroviral drugs [13].

Ananas Comosus (L.) Merr or Pineapple is one of the plants that has potential for health. It is a family of Bromeliaceae, which is a popular fruit plant in the world. First discovered by Columbus in 1493 on a Gouisure called nana "anas, pineapple is used as a traditional medicine to cure various diseases by native Central and South Amerans. Whereas in Indonesia it is known as pineapple. Pineapple is a tropical fruit that can be consumed directly (fresh fruit) or juice or cooked Indonesia is one of the producers of pineapple in the world, so bush pineapple is once found in Indonesia According to the United States National Library of Agriculture literature that pineapple contains bromelain which is a bromelain proteolytic enzyme can help the protein contamination process by breaking down protein into amino acids pineapple [14]. The other benefit as immunomodulator [15]. Therefore, the use of pineapple is greatly needed because it has efficacy for health. Apart from that it scientifically has minimal side effects and is more economical because it is easily obtained in Indonesia.

Results of the study of Maruli in 2014 deal with the effectiveness of pineapple juice fresh containing bromelain enzymes tested in clinical studies as an alternative treatment for PLWHA The results of this study showed that serum HIV-positive in humans when bromelain was added at different concentrations (4 hours, 37 C) then this serum was then examined using HIV tests 1 and 2 Mono TM test. The results of both tests showed negative results at bromelain concentrations of 10 mg / ml (specific activity 5.88 U / mg) [8]. The result of this study is in line with what was stated by Phyllis A. Balch in 2002, that bromelain is a proteolytic enzyme that can be used as an alternative treatment of chronic conditions such as cancer, diabetes and HIV/AIDS. In this case bromelain serves to inhibit the replication of the protease enzyme. Phyllis A. Balch. in his book that bromelain is useful for inhibiting protease, an enzyme that is the result of replication of the HIV virus. Conducted by scientists at the "Sloan Kettering" cancer center in New York that bromelain can dissolve cellular adhesion molecules that allow HIV to attach to the exposure of uninfected T cells, and increase production of reduced integrin compounds when HIV attacks cells in the central nervous system [16]. Besides that bromelain can destroy the structure of glycoproteins on the outer membrane v HIV virus With the destruction of these protective proteins the attachment of HIV particles to host receptors (CCRS & CXCR4) can be prevented, so blocking occurs in the entrance of viral RNA and proliferation of suppressed virus particles [19].

Furthermore bromelain is a proteolytic enzyme that has been recommended as adjuvant therapy in treatment of viral diseases [17]. In addition, bromelain also has the potential as an undeniable immunomodulator and has been proven in an invitro study. This is demonstrated by modulating adhesion molecules on the surface of T cells, macrophages and NK (natural killer) cells and triggering secretion of IL.-1B, IL-6 and TNFa by 11S blood mononuclear cells) [15]. Bromelain contained in stems and fruit pineapple can be used as an alternative therapy for healing in people with HIV by drinking 250-500 mg (bromelain in tablet form) twice a day between meal times which are useful as alani inhibitors of proteases. Whereas in patients with AIDS, by taking 250-500 mg (bromelain in tablet form) twice a day between meals. However, when you consume bromelain tablets, they cause an allergic reaction, so you can use it stopped. This is based on reports that there were 3 AIDS sufferers who experienced allergies after consuming the bromelain tablet [16].

The results of the research conducted by Maruli 2015 showed that, giving pineapple juice for a period of 10-12 weeks in 13 PLHIV patients increased the CD4 + number in 4 patients after 5 weeks of giving pineapple juice. However, 9 patients experienced a decrease in CD4 cell count. Next 10 weeks later the patient had an increase in CD4 cell count, and in the sixth week 4 patients had an increase in the number of CDs) 4+. Besides giving pineapple juice can reduce the amount of viral load in patients with HIV / AIDS. This was demonstrated after 10 weeks of administration of 3 patients showing a reduced viral load compared to before administration. After the 16th week, there were 4 patients who experienced a decrease in viral load [7]. Furthermore, the results of the study of Maruli in 2015 about bromelain contained in pineapple as an anti-viral HIV agent, Hepatitis C and Human Papilloma Virus, showed that

the provision of fresh pineapple juice 2 cups / day in 7 HIV patients for 4 months could substantially increase CD4 cell counts and three of them reached a normal CD4 cell count. In the follow-up study there were 13 respondents consisting of 12 ODHA patients, and 1 patient as a control with the intervention of giving 2 glasses of pineapple juice / day for 16 weeks. After 16 weeks, the results showed that 1 patient (control) showed that the number of viral loads decreased from the initial number, but still within normal limits, and the viral load was undetectable. Whereas 12 patients with HIV / AIDS 4 of them had an increase in CD4 cell count, 3 of these were undetectable viral loads and 1 patient had a decreased number of viral loads. Furthermore, 6 PLHIV patients experienced a decrease in CD4 cell count, 5 of these undetectable viral loads, 1 of which had an increase in viral load. In addition, in this follow-up study 2 respondents of CD4 cell count after administration of pineapple juice were not examined for CD4 counts, but 1 of them had an undetectable viral load and one had an increase in the number of viral loads [9].

The results of the study of Maruli in 2015 and 2018 are that the results of the study of Maruli in 2011, that administration of 40 mg / ml bromelain can destroy the HIV virus after 4 hours of administration, test results with diagnostic standards, rapid tests and ELISA, and further tests showed negative results .ile giving bromelain 40mg / ml after 2 hours of the results of diagnostic standards, rapid test and can show negative results, but the follow-up test showed positive antigen. Furthermore, giving bromelain 40 mg / ml bromelain + lipase 10 mg / ml, can also destroy the HIV virus after 2 hours and 4 hours of administration. This is the result of tests that show negative results on diagnostic standards, rapid tests and tests and follow-up test [6].

Bromelain enzyme contain in stem and pineapple fruit have a proteolytic ability 80% [14]. Other research results state that one of the common conditions treatments for HIV sufferers are to provide protease inhibitors (PI). PI is useful to inhibit or deactivate proteases from the HIV virus, besides PI has no effect on any other protease in the body. It should be noted that viruses also produce protease enzymes that are harmful to the human body so that the human body reacts directly by activating inhibitor enzymes in an effort to defend themselves against pathogens in the human body [20].

Maruli research results in 2015 and 2018 are in line with what was discovered by Vidhya Rathmavelu in 2016 stated that one of the characteristics of bromelain is an immunomodulator, which is to increase the immunity of PLWHA [21]. The HIV virus that infects ODHA causes the destruction of T lymphocytes, the effect of which is the weakening of the ODHA's immune system against other infections and cancer [22]. The indicators of immunity in PLWHA include CD4 counts and viral load levels. If the normal CD4 cell count increases and the viral load level is little or even undetectable, the PLWHA's immune system is maintained, so it can improve the quality of life for PLWHA and prevent opportunistic infections [20].

The results of research conducted by Puspa Wardhani and Nurbani in 2016 Singkawang region, West Kalimantan, Indonesia, about the effectiveness of giving pineapple juice and papaya juice as complementary herbal therapies to increase and maintain CD4 counts in people with HIV / AIDS [10]. The results of this study are in line with the research conducted by Maruli in 2011, that the content of the bromelain enzyme contained in pineapple has great potential as an alternative herbal treatment to reduce pain in people with HIV / AIDS. In addition, the administration of bromelin enzymes in HIV / AIDS patients has been shown to increase CD4 cell counts in only 2-3 months [6]. The content of bromelain in pineapple which has proteolytic properties is likely to damage the horns of the HIV virus made of proteins. Papaya juice is also given, where in papaya contains the enzyme papain derived from sap papaya. [14] The papain enzyme is a strong hydrolytic that can damage the walls of the HIV virus protein. [23] Besides the papain enzyme, it is reinforced by the enzyme chimopapain which is proteolytic [24] Therefore both the bromelain, papain and chimopapain enzymes that have proteolytic properties can be used as alternative therapies for PLWHA because they might damage the protein layer of the HIV virus.

## CONCLUSION

Human immunodeficiency virus Acquired immunodeficiency syndrome (HIV/AIDS) is a collection of signs and symptoms of disease arising from damage to the human immune system due to retroviruses called the HIV virus. Antiretroviral therapy (ART) has the potential to cause side effects and drug resistance. So that complementary therapy is needed from herbal ingredients, which are useful for improving and or maintaining the immune system. Bromelain enzymes can be used as an alternative cure for PLWHA. This is due to the function of bromelain contained in ananas comosus L. Merr, including immunomodulators and proteolytic properties. Immunomodulator function by raising or maintain stability of CD4 counts while proteolytic functions by damaging the HIV virus protein layer, then blocking the entrance of viral RNA and suppressing proliferation of viral particles so that lower levels of viral load can even cause undetectable PLWHA.

## CONFLICT INTEREST

No conflict of interest

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