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THE EFFECT OF PROPOLIS SUPPLEMENTATION TO CD4/CD8 RATIO IN HIV-INFECTED PATIENTS RECEIVING ANTIRETROVIRAL REGIMEN THERAPY

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Abstract

Background: The HIV infection affects the immune system by decreasing CD4/CD8 ratios. Previous studies reported that the use of nutrient supplements in HIV patients was quite high. Propolis is one of nutrient supplements that are reported to be beneficial in the immune system but evidences of its clinical benefits are limited. The aimed of this study was to reveal the advantageous outcome of propolis supplementation in patients on antiretroviral regimen therapy.

Methods: The research was conducted in a double blind randomized controlled trial, pre and post-test control group including the treatment group (antiretroviral regimen + propolis) and the control group (antiretroviral regimen + placebo). CD4/CD8 ratio was checked at baseline and 6 months after the trial, as well as their safety profile, any side effect was documented and treated properly.

Results: Forty-three subjects managed to reach the end of the study, consisting of 19 subjects in the treatment group and 21 subjects in the control group. Duviral-Neviral is the most widely used ARV regimen (51.2%). After 6 months of treatment, there was an increase in the mean CD4/CD8 ratio in the propolis group, but it was not statistically significant (p = 0.22). Interestingly, the delta CD4/CD8 ratio between propolis and placebo was significantly different (0.06 vs -0.01; p = 0.02).

Conclusion: There were non-life-threatening side effects that occur in the propolis group subjects which improve after supplementation was stopped. To conclude, the effect of propolis supplementation on increasing CD4/CD8 ratio in HIV patients who had received antiretroviral regimen therapy did not reach statistical significance.

Keywords: *HIV, CD4/CD8 ratio, antiretroviral regimen, propolis*

Introduction

Treatment of HIV/AIDS in Indonesia refers to WHO standard therapy is conducted by using an antiretroviral regimen (ARV) which aims to suppress HIV viral load and prevent its progression to AIDS [*MoH, 2015*]. The implementation of ARV therapy is influenced by various factors that cause ARV therapy not to work properly. One of them is barrier therapy such as knowledge and the presence of ARV side effects, which affect patient compliance and the tendency of patients to combine ARV therapy with alternative therapies or supplements [*Peltzer K et al., 2010, Reda AA, Biadgilign S, 2012, Yuniar Y et al., 2013*]. Supplement use is increasingly widespread in line with reports of its benefits for immunity, increased antioxidant status and assisting in antiretroviral activity [*Hasan SS et al., 2010, Su D, Li L, 2011, Cichello S et al., 2014*]. One supplement that is widely used today is propolis, which is a resin material collected by bees from buds and plant exu-

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dates [*Oses S et al., 2016*]; but it is still unclear whether its use as a supplement to HIV standard drugs has a good effect on patients clinically and immunologically.

HIV infection is a global pandemic that is a threat to individuals throughout the world. At the end of 2013, an estimated 35 million people lived with HIV infection [*Hyle EP, Sax PE, 2013; Fauci AS, Lane HC, 2015*]. In Indonesia, since 1999 there has been an increase in the number of HIV patients with an average prevalence of 0.4% making Indonesia a concentrated HIV epidemic category. In 2012, there were 591,823 HIV positive people in Indonesia and only 8.3% were recorded as receiving ARV therapy ([*MoH, 2015*].

A study of HIV patients who had received ARV therapy reported that the use of supplementary and alternative therapies ranged from 60% to 90% [*Jernewall E et al., 2005*]. This may be triggered by the patient's lack of understanding of the pathological processes underlying his illness and the importance of antiretroviral drugs as an effort to overcome the pathological processes that occur. If the condition is not resolved soon, it is very likely that the patient will stop ARVs as the backbone of HIV therapy and trust other medicines that are actually only as supplements. This can further increase the morbidity and mortality of HIV/AIDS patients with all the medical and socioeconomic consequences [*Suarez-Garcia I et al., 2014*].

There is a tendency for patients to take ARV drugs with supplements such as propolis. This is probably due to the relatively cheap price, more accessible and the existence of reports and testimonials that propolis can reduce ARV side effects or as a supporter of the immune system [*Power R et al., 2002, Cichello S et al., 2014*].

The use of supplements such as propolis needs to be evaluated and monitored, so that there is no misunderstanding and excessive trust in supplement use in patients with HIV/AIDS. Several studies have shown that patients who use such supplements are more likely to not adhere to antiretroviral drugs or skip control schedules to doctors [*Jernewall E et al., 2005, Peltzer K et al., 2010, Tamuno I, 2011*]. The clinical benefits of propolis need to be examined in a clinical trial with good and correct design. One of the immunological parameters that can be evaluated in HIV patients is the CD4/CD8 ratio. Based on the data and information presented above, the researchers wanted to find out the effect of supplementation of nutrient propolis on CD4/CD8 ratios in HIV patients who received ARV at Dr. Soetomo, Surabaya. It is expected that this research will be a preliminary study that can be developed into better advanced research and can be a scientific reference for the use of propolis along with ARV drugs.

MATERIAL AND METHODS

This research is experimental analytic with a double-blind randomized controlled trial design. The study was took place in the Outpatient Unit of HIV/AIDS Polyclinic, Department of Internal Medicine, Dr. Soetomo Hospital - Surabaya, conducted in June 2016 - February 2017. There were 50 subjects included in this study, which were appointed randomly to be included in treatment or control group. All the subjects were stage 1 and 2 HIV patients. Sampling was done consecutively from HIV patients who came to the HIV/AIDS polyclinic who fulfills the inclusion criteria until a number of "n" (sample size) are met.

Research material

The research material was a blood serum sample of the study subjects for CD4 and CD8 examination. CD4 and CD8 were performed by flow cytometry. The CD4/CD8 ratio was calculated by comparing the absolute levels of CD4 with the absolute levels of CD8 derived from the blood serum of the study subjects.

Research products

The research product used in this study is propolis. Propolis is a product of PT High Desert Indonesia (HDI) which with the trademark Propoelix® which contains 100 mg of propolis extract in 1 preparation. Propolis preparations are packaged in brown capsules, the same size and shape as placebo.

Propoelix® has been registered in the category of traditional medicinal products and is permitted in circulation in Indonesia since August 2015 with registration number TR102318611 by the Directorate of Assessment of Traditional Medicines, Food Supplements and Cosmetics, Drug and Food Supervisory Agency Rebuplik Indonesia (BPOM, 2016).

Dispensing

The process of dispensing propolis and placebo (accepting and validating prescriptions, providing,

giving appropriate containers and etiquette, distributing drugs and providing information to research subjects) is prepared by the Pharmacy staff.

Data Analysis

Data collection is done through a data collection sheet and were analyzed using the IBM SPSS Statistics 23. The data were displayed as mean ± SD in each group or as a median (minimum-maximum). A p value of less than 0.05 was considered statistically significant.

The Kolmogorov Smirnov test is used to check data distribution. Analysis of CD4/CD8 ratio before and after treatment used a 'student paired-t-test' test. To compare the CD4/CD8 ratio between the propolis and placebo groups, the Independent sample-t-test test was used.

RESULTS

This study was conducted on 50 subjects in HIV patients as shown in table 1. The end point of this study was the participation of research subjects for 6 months of treatment. The subjects of this study were adults with an average age of 36.8 years in the propolis group and 37.1 years in the placebo group.

Characteristic of subjects ARV is shown in table 2. In this study, the duration of ARV was divided into 2 categories, namely <5 years and >5 years with consideration to simplifying data analysis and in accordance with research which states that the probability of increasing CD4/CD8 ratio will be higher in the subject who has received 5 years ARV. Of a total of 43 research subjects, 58.1% of subjects used ARVs under 5 years and 41.9% had used ARVs for more than 5 years. When viewed in each study group, it was found that 68.4% of the subjects of the propolis group were patients who received ARVs less than 5 years and 31.6% who received ARVs for more than 5 years. Subjects in the placebo group, the percentage between subjects receiving less ARV and more than 5 years, was balanced at 50% each.

Characteristic of CD4 and CD8 concentration in subjects is shown in table 3. In this study, the mean nadir CD4 level was 128.42 *cells/μL* in the propolis group and 129.58 *cells/μL* in the placebo group.

Ratio of CD4/CD8 of Subjects

Value of CD4 dan CD8 for pre and post treatment in Propolis Group and Placebo Group is shown in table 3. The results of paired-t-test analysis of mean CD4 levels in the propolis group showed that there was no significant difference (p=0.11) after propolis supplementation for 6 months. Likewise in the placebo group, a p value of 0.97 showed that there was no difference in CD4 levels before and after treatment.

DISCUSSION

The result shown in table 1 similar to study conducted by Simanjuntak E (2010) in Medan where the age group 25-44 years was the highest age group of HIV, which was 78.3% with a ratio of men and women 3: 1 [*Simanjuntak E, 2010*]. The 2016 HIV/AIDS situation report from the Ministry of Health states that the highest percentage of HIV infections is in the age group of 24-49 years (70%) with an average age of 37.7 years (Ministry of Health, 2016). This is also in accordance with demographic data on the average age of HIV patients in Asia at 37.07 years [*Petoumenos K et al., 2017*].

Treatment of HIV infection with ARV regiment will reduce viral replication and increase the number of CD4 cells. The initiation of antiretroviral drugs will be followed by a biphasic response,

TABLE 1.

Subject demography

Characteristic	Total n = 50	Propolis n = 25	Placebo n = 25
Men	23 (46%)	11 (44%)	12 (48%)
Women	27 (54%)	14 (56%)	13 (52%)
Age year	37 (18-51)	36.8 (23-51)	37.1 (18-51)
body mass index	21.9 (15.3-32.9)	22.0 (16.6-32.9)	21,9 (15.3-32.5)

NOTES: *Data were presented as Mean (min-max) or total (percent).*

TABLE 2

Subject characteristic

Characteristic	Propolis n = 19	Placebo n = 24	p
HIV <5 thn	13 (68.4%)	12 (50%)	0.35
HIV > 5thn	6 (31.6%)	12 (50%)	
Duviral & Neviral	9 (47.4%)	13 (54.2%)	0.48
Duviral & Efaviren	2 (10.5%)	5 (20.8%)	
Fixed dose drugs*	5 (26.3%)	5 (20.8%)	
Removable drugs**	3 (15.8)	1 (4.2%)	

NOTES: **- fixed dose combination containing Tenofovir/Lamivudin/Efaviren; ** - removable drugs consisting of Tenofovir, Lamivudin and Nevirapin.*

TABLE 3.

Analysis of CD4 and CD8 levels pre- and posttetreatment of subject

	Propolis (n=19)		Placebo (n=24)		p value
	Mean±SD	**Median (Range)**	**Mean±SD**	**Median (Range)**	
Nadir CD4	128.42 ± 111.08	154 (4 – 380)	129.58 ± 115.75	99 (2 – 393)	0.97
CD4					
Pretreatment	391.58 ± 262.96	392 (7 – 909)	407.04 ± 186.80	421 (68 – 925)	0.82
Posttreatment	434.68 ± 290.42	459 (6 – 1189)	406.42 ± 191.99	427 (58 – 763)	0.70
CD8					
Pretreatment	882.37 ± 357.06	822 (337 – 1604)	907.08 ± 313.87	901 (488 – 1594)	0.81
Posttreatment	912.00 ± 358.83	848 (193 – 1548)	896.29 ± 286.76	893 (476 – 1747)	0.87
CD4/CD8					
Pretreatment	0.45 ± 0.29	0.43 (0.02 - 1.03)	0.47 ± 0.21	0.47 (0.12 - 0.95)	0.22
Posttreatment	0.49 ± 0.30	0.55 (0.02 - 1.02	0.46 ± 0.22	0.46 (0.12 - 0.88)	0.16

NOTE: *Data were presented as Mean ± SD or Median (min-max) or total (percent). SD - standard deviation*

which is a high increase in CD4 cells at the beginning of the use of antiretrovirals due to reduced CD4 cell apoptosis and redistribution of memory CD4 cells from lymphoid tissue, followed by slow CD4 cell increase [*Gaardbo J et al., 2012*]. A cohort study states that CD4 cell recovery requires at least 5 years of antiretroviral therapy if the CD4 cell count is <500 cells/μL [*Mocroft A et al., 2007*].

ARV regimens used by 43 subjects consisted of 4 types, namely 1) Duviral and Neviral containing Zidovudin/Lamivudin and Nevirapin; 2) Duviral and Efaviren which contain Zidovudin/Lamivudin and Efaviren; 3) fixed dose combination (FDC) containing Tenofovir/Lamivudin/Efaviren; and 4) Removable drugs consisting of Tenofovir, Lamivudin and Nevirapin. Duviral and Neviral are the more dominant regimens used in this study, where 47% of the subjects in the propolis group and 54% of the subjects in the placebo group used them. The selection of this ARV regimen was in accordance with the guidelines for managing HIV infection and ARV therapy in Indonesia in 2011 in which Duviral and Neviral were the first-line therapy in naive HIV patients [*MoH, 2012*]. Fixed dose combination is the next regimen that is widely used by the subjects of this study, 26.3% for the propolis group and 20.8% for the placebo group. This might be due to a policy change from the Ministry of Health in 2015, where fixed dose combination became the first choice of HIV first-line therapy [*MoH, 2015*].

A more rarely used regimen is a regimen consisting of 3 drugs, namely Tenofovir, Lamivudin and Nevirapin, 15.8% in the propolis group and 4.2% in the placebo group. This regimen is the least used regimen, this is probably due to the higher number of pills and drinking doses compared to other regimens [*Pomerantz RJ, Horn DL, 2003*]. The difference in the ARV regimen above, besides being based on HIV therapy guidelines set by the Indonesian government, can also be caused by other considerations, such as comorbidity, the availability of antiretrovirals at the time of ARV initiation, price, side effects, number of pills and drug dosage. Whereas those included in the patient's consideration are the patient's clinical conditions such as pregnancy, tuberculosis, hepatitis, allergy history and patient preferences to improve medication adherence [*AidSinfo A, 2016*].

In this study, the mean nadir CD4 level was not significantly different between the propolis group and the placebo group (p = 0.974). The Petoumenos K. et al. (2017) study, which involved 2,620 HIV subjects in Asia, obtained a mean nadir CD4 level of 176.87 *cells/μL*. In line with this study, Leung V. (2013) reported a mean nadir CD4 in 4,206 HIV subjects in Canada, namely 190 *cells/μL*. The mean nadir CD4 in this study was lower than the comparative study, this could be due to the possibility that the subjects included in this study were late in seeking treatment so that CD4 levels dropped to lower than subjects from other studies Ainun N et al., (2017) and/or has experienced an infection or co-infection [*Ray K et al., 2006*] but is asymptomatic (such as TB, hepatitis B, hepatitis C, toxoplasma, cytomegalovirus) that were not excluded

in this study [*Pomerantz RJ, Horn DL, 2003, Leung V et al., 2013, Ainun N et al., 2017*].

In acute HIV infection, activation and expansion of the CD8 cell compartment occurs. CD8 cell expansion continues throughout the course of the disease, even CD8 counts do not return to normal levels in most patients, although pharmacological therapy has succeeded in suppressing viral replication. This is presumably due to the occurrence of inflammatory residues that contribute to CD8 cell expansion [*Mudd JC, Lederman MM, 2014*]. Chronic inflammation in HIV is associated with microbial translocation through the intestinal epithelium that is sustained during the acute phase of HIV infection and is not fully reversible even after antiretroviral therapy characterized by markers of microbial products continues to increase in the systemic circulation of HIV patients receiving ARV therapy [*Mudd JC, Lederman MM, 2014*].

CD4 and CD8 profiles before treatment in this study in the two groups were as follows: mean CD4 levels of 391.58 *cells/μL* in the propolis group and 407.04 *cells/μL* in the placebo group. The highest CD4 level in the propolis group was 909 *cells/μL*, while the placebo group was 925 *cells/μL*. Parametric difference test of independent sample-t-test was used to determine the difference in mean CD4 levels between propolis groups and placebo groups. The results of the analysis showed that there was no significant difference between the mean propolis and placebo group CD4 levels before treatment (p = 0.823). Similarly, the analysis between the mean CD8 levels of the propolis group (882.37 *cells/μL*), and the placebo group (907.08 *cells/μL*) did not show significant differences (p = 0.81). This shows that the research subjects of the two groups had relatively homogeneous baseline CD4 and CD8 levels.

In normal adult individuals, CD4 levels are higher than CD8 levels and the proportion of these two lymphocyte subsets is relatively stable and controlled [*Jiménez E et al., 2001*]. Normal values of CD4 410-1590 *cells/μL* whereas CD8 190-1140 *cells/μL*. If these two values are compared, it will produce a normal value of CD4/CD8 ratio above 1 [*Wilson DD, 2007*].

This study compared the CD4/CD8 ratio of two groups, namely propolis and placebo. To get a higher CD4/CD8 ratio after 6 months of treatment, one of the factors that determines is an increase in CD4 levels and a decrease in CD8 levels.

After propolis supplementation for 6 months, it was seen that there was no significant difference between the mean CD4 level of the propolis group and the placebo group (p = 0.704). This shows that supplementation of nutrient propolis for 6 months did not give a different effect between the propolis and placebo groups, where there was no significant increase in CD4 levels in the propolis group. There was a slight decrease in the mean CD8 level in the placebo group after the treatment became 896.29 *cells/μL*, but this decrease was not significant (p = 0.765) based on paired-t-test.

CD4/CD8 ratio is obtained by comparing CD4 levels with CD8 levels. This ratio in normal individuals ranges from 1.0-1.6. In chronic HIV patients, the absolute number of CD4 cells is often lower and the absolute number of CD8 cells is higher than normal individuals Margolick J.B. et al., (2006) resulting in an inversion of CD4/CD8 ratios with numbers below 1 [*Margolick JB et al., 2006; Mudd JC, Lederman MM, 2014*].

In this study, the minimum and maximum CD4/CD8 ratio of each group was 0.02 in the propolis group and 1.03 in the placebo group. The minimum CD4/CD8 ratio is a very low value compared to the CD4/CD8 ratio in the normal population even when compared with HIV patients, as reported by Saracino V.S. and co-authors, (2014) in HIV subjects in Italy, obtained the minimum-maximum CD4/CD8 ratio is 0.08-0.21. Another study by Petoumenos K. et al. (2017) in Asia also reported similar values, where the minimum minimum CD4/CD8 ratio of HIV subjects was 0.09-0.30. This illustrates the minimum-maximal value of the CD4/CD8 ratio in the subjects of this study is much lower than the HIV population in general [*Saracino VS et al., 2014, Petoumenos K et al., 2017*].

The mean CD4/CD8 ratio before treatment was 0.45 (SD ± 0.29) in the propolis group and 0.47 (SD ± 0.21) in the placebo group. The average ratio is not much different from the research by Ray K. et al. (2006) in India which reported a mean CD4/CD8 ratio in 137 asymptomatic HIV subjects was 0.50 (SD ± 0.27) and Buggert and co-authors (2014) in Sweden who reported a median CD4/CD8 ratio in HIV-positive subjects receiving ARV for 2-4 months at 0.44 (IQR 0.70-0.27).

Leung V. and co-authors (2013) explained that the causes of low CD4/CD8 ratios in HIV subjects who received ARVs included nadir CD4 levels below 200 *cells/μL* and CD8 levels above 750 *cells/μL* at the time of ARV initiation. This is also confirmed by Petoumenos K. and co-authors, (2017) who explained one reason for the low CD4/CD8 ratio in the HIV population in Asia is a low Nadir CD4 level before starting ARVs. A cohort study of 112 HIV subjects by Saracino V.S. and co-authors (2014) found 63% of HIV subjects who had CD4/CD8 ratios <0.9 were subjects with a mean nadir CD4 level of 136 *cells/μL* (min 50-136) *cells/μL*. In this study, the average CD4 nadir level in all study subjects was 129.07 *cells/μL*, which might be one of the contributors to the low CD4/CD8 ratio [*Leung V et al., 2013, Petoumenos K et al., 2017*].

Other researchers reported higher mean ratio values than this study, such as Serrano Villar et al. (2013) in Spain who reported a median CD4/CD8 ratio in HIV subjects who had ± 3 years ARV of 1.0 (IQR 0.7-1.6). In contrast, studies that reported lower mean ratios, such as De Salvador-Guillouet F and co-authors (2015) in France who reported a median baseline CD4/CD8 ratio in 567 HIV-positive HIV-positive subjects of 0.36 (IQR 0.19-0.56) and Petoumenos K. and co-authors (2017) reported a mean CD4/CD8 ratio in HIV subjects in Asia of 0.22 (IQR 0.09-0.30). The difference in the high and low of this ratio may be due to differences in nadir CD4 levels, genetic variation and regional diversity.

Parametric difference test of independent sample t-test was used to determine the mean difference of CD4/CD8 ratio between propolis groups and placebo groups. The results of the analysis of the mean CD4/CD8 ratio before treatment showed that there was no significant difference between the CD4/CD8 ratio in the propolis group and placebo group (p = 0.746). This shows that the average baseline CD4/CD8 ratio between the two groups is evenly distributed.

The treatment in this study was supplementation of nutrient propolis and placebo in HIV patients who had used ARVs. Propolis contains more than 300 constituents which are proven in vitro to inhibit HIV replication enzymes, including CAPE, moronic acid, and quarcetin. CAPE is reported to inhibit enzyme integrase activity by inhibiting strand transfer [*Fesen MR et al., 1993; Fesen MR et al., 1994; Burke TRJ et al., 1995; Gekker G et al., 2005; Erdemli HK et al., 2015; Silva-Carvalho R et al., 2015*]. CAPE is also reported to inhibit NFkB by preventing the translocation of p65 subunits from NFkB to the nucleus [*Natarajan K et al., 1996, Armutcu F et al., 2015*]. Moronic acid, according to an in vitro study inhibits HIV replication in T cell cultures of H9 lymphocytes with weak inhibitory power [*Yu D et al., 2006*]. Quarcetin has been reported to inhibit HIV protease enzymes in an in vitro study and is also reported to be able to suppress NFKB activity [*Afroz R et al., 2016*]. Supplementation of nutrient propolis against HIV standard drugs is expected to have an effect on suppressing the viral replication process which indirectly supports recovery of CD4/CD8 ratio.

After 6 months of treatment, it was expected that the average propolis CD4/CD8 ratio increased higher than the average placebo CD4/CD8 ratio. This can occur if you get an increase in CD4 levels or a decrease in CD8 levels or both. The results of the analysis of CD4 levels in both groups showed that there was an increase in CD4 levels which was not statistically significant in the propolis group and placebo group, and there was no significant reduction in CD8 levels in either group (all p> 0.05). This can be influenced by various factors such as Hepatitis B infection, Hepatitis C, cytomegalovirus and TB which were not examined in this study [*Sajadi MM et al., 2012; Saracino VS et al., 2014*].

Analysis of CD4/CD8 ratio data showed a tendency to increase the average CD4/CD8 ratio in the propolis group, which was from 0.45 ± 0.29 to 0.49 ± 0.30 while the placebo group was relatively stable at 0.47 ± 0, 21 and 0.46 ± 0.22. However, the increase in the mean CD4/CD8 ratio in this propolis group did not reach the normal CD4/CD8 ratio. This may be due to low nadir CD4 levels and relatively short duration in the subjects of this study. Low nadir CD4 will also produce a low CD4/CD8 ratio. Petoumenos K et al. (2017) states that a low CD4/CD8 ratio at the time of ARV initiation in HIV subjects in Asia is one of the causes of the difficulty in achieving normalization of the CD4/CD8 ratio, even after 5 years of ARV use [*Petoumenos K. et al., 2017*]. For example, Leung V. (2013) reported that normalization of the CD4/CD8 ratio only occurred in 6% of 4206 HIV patients who had a nadir CD4 level <200 *cells/μL* at ARV initiation, compared

with 21% who had a nadir CD4 level> 350 *cells/μL* during ARV initiation so that it can be concluded that the increase in CD4/CD8 ratio in HIV subjects with nadir CD4 levels below 200 *cells/μL* runs more slowly than HIV subjects who have higher nadir CD4 levels [*Leung V et al., 2013*]. Thornhill J. and co-authors (2014) also added that normalization of the CD4/CD8 ratio in HIV subjects was rare, although there was a trend in the increase in the ratio of patients receiving ARVs, but rarely achieved normal ratio values.

Analysis of CD4/CD8 ratio for pre and post treatment is shown in Table 3. Paired-t-test analysis of the propolis group showed that the increase in the mean CD4/CD8 ratio in the propolis group before and after treatment was not statistically significant (p = 0.22). As far as the knowledge and literature have been carried out by researchers, until now there has been no comparative study of CD4/CD8 ratios in HIV patients that can be compared with this study. This is because this study has different research subjects and/or has a different type of treatment than other studies, besides that very few studies have reported on the use of traditional medicine, especially propolis in HIV patients [*Orisatoki R, Oguntibeju O, 2010*].

Descriptively, the research data shows that of 43 subjects who reached the end point, there was only 1 study subject who had a CD4/CD8 ratio above 1, which was 1.03 which was the subject of the propolis group.

In this study, the mean difference in CD4/CD8 ratio in the propolis group was higher than in the placebo group (0.06 vs -0.01). There was a statistically significant difference (p = 0.025). This may be influenced by the effect of supplementation of nutrient propolis which in vitro can inhibit HIV replication enzymes which might influence suppressing the viral replication process which indirectly supports recovery of CD4/CD8 ratio [*Gekker G et al., 2005*].

In addition to the above, there are several other factors that influence the normalization of the CD4/CD8 ratio in HIV patients including effective antiretroviral therapy, duration of antiretroviral therapy, time of ARV initiation, viral load levels when starting ARVs, immune activation rates and co-infection. infection and immunocensence [*Mogensen TH, 2010; Leung V et al; 2013; Serrano-Villar et al., 2014; Tinago, 2014; Lu W et al., 2015; Caby F, 2016*].

Adverse Events

In this study there were 3 adverse events in the form of symptoms of nausea, vomiting, palpitations, coughing, and urticaria, all of which were not life treatening. All the above subjects are in good condition until the end of the study period. The researcher stopped the treatment, provided symptomatic therapy, eliminated the subjects and reported the adverse event to the Research and Development Section of Dr. Soetomo Hospital.

Propolis is a complex natural product with a diversity of chemical structures and biological activities. It is reported to be harmless but vigilance needs to be considered, asthe product has a large variety of origin and activity. The absence of quality control may be detrimental to human health [*Miguel MG, Antunes M, 2011*].

The main allergens that have been reported are 3-methyl-2-butenyl caffeate and phenylethyl caffeate, a compound found in poplar propolis [*Lieberman HD et al., 2002*]. Clinical manifestations of allergies in the form of contact dermatitis or oral mucositis, especially occur in beekeepers. Nevertheless there has been an increase in the incidence of allergies allegedly due to the increasing popularity of natural products such as propolis [*Miguel MG, Antunes M, 2011*].

Conclusion

Based on the results of this study it can be concluded that the supplementation of propolis resulted in a slight increase in the mean CD4/CD8 ratio in patients although it was not statistically significant. Meanwhile, the delta of CD4/CD8 ratio between propolis and placebo was significantly different. In addition, the supplementation caused several adverse events such as urticaria, nausea, vomiting and and palpitations in few patients.

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