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Efficacy of Propolis Supplementation to Accelerate Healing Process and Body Weight Recovery of Pulmonary Tuberculosis Patients

Mahani[1,2], Ahmad Sulaeman[1*], Faisal Anwar[1], Muhammad Rizal Martua Damanik[1], Hardinsyah[1], Angelika Ploeger[3]

[1]Department of Community Nutrition, Faculty of Human Ecology, Bogor Agricultural University, Bogor 16680, Indonesia
[2]Department of Food Technology, Faculty of Agricultural Industrial Technology, Padjadjaran University, Jatinangor 45363, Indonesia
[3]Department of Organic Food Quality and Food Culture, Faculty of Organic Agricultural Sciences, University of Kassel, D-37213, Germany

ABSTRACT

This study aimed to evaluate the pace of curing process and body weight recovery of pulmonary tuberculosis (Tb) patients receiving propolis supplementation. This study was a randomized controlled trial conducted on 50 pulmonary Tb patients that were assigned into three groups as follows: receiving standard-dose antituberculosis drugs (ATDs) + 20 drops of placebo propolis (P0); receiving standard-dose ATDs + 20 drops of propolis with concentration of 6% (P1); and receiving standard-dose ATDs + 20 drops of propolis with concentration of 30% (P2). The results showed that the mean time ratio needed for sputum smear conversion to negative present of acid resitant bacteria in P0, P1 and P2 groups were weeks 10, 8 and 5, respectively. In the second week, mean body weight of P0 and P1 groups decreased by 2.4% and 0.2%, respectively. In contrast, the mean body weight in P2 group increased by 1.5% ($p<0.05$; Mann-Whitney test). In the same week, mean body mass index (BMI) of P0 and P1 groups decreased by 1.6 and 0.1, respectively. Conversely, the mean BMI of P2 group increased by 0.3. The changes were significantly different ($p<0.05$). The results conclusively indicated that supplementation of 20 drops of propolis with a concentration of 30% as an adjuvant to standard ATDs for the treatment of pulmonary Tb patients was beneficial to accelerate treatment effect and body weight recovery.

Keywords: body weight, cure, liquid propolis, pulmonary Tb

INTRODUCTION

Tuberculosis (Tb) is a global infectious disease problem and becoming the second leading cause of death after HIV/AIDS infection. Indonesia is ranked 2nd out of 30 high burden countries in the world (WHO 2016). Tb treatment and cure requires regular consumption of anti-tuberculosis drugs (ATDs) every day without interruption for a substantially long term period. One of the problems faced in the use of ATDs to date is its hepatotoxic properties (Chowdhury *et al.* 2006; WHO 2013). The hepatotoxic effects of ATDs can cause decrease in appetite, nausea, dizziness, insomnia, fever and weight loss (Kemenkes 2009; Sudarsanam & Tharyan 2014; Sari *et al*. 2014). These hepatotoxic effects further cause decline in nutritional status of the patients, whereas good nutritional status strongly supports cure (Semba & Bloem 2001). Thus, the provision of hepatoprotective materials is expected to reduce hepatotoxic effects that eventually may restore body weight (BW) faster.

Other studies conducted by Bhadauria *et al*. (2007), Hashmi *et al*. (2013) and Cevik *et al*. (2012) showed that propolis has a hepatoprotective properties, characterized by its ability to decrease SGPT and SGOT approaching the normal values and protection from liver damage in mice models. Pranandaru *et al*. (2011) found that propolis had the ability to fight Tb infection characterized by the sputum conversion --where acid-resistant bacteria (ARB) in the acid stained sputum smear is found negative--in Tb patients. Wahyunitisari *et al*. (2006) stated that altough propolis's ability to fight Tb infection was limited, it has several advantages when supplemented for Tb treatment such as it does not stimulate *Mycobacterium tuberculosis* to develop resistance and is more compatible with normal intestinal flora of Tb patients. Therefore, propolis has a potential to help overcome Tb problem in Indonesia. A num-

[*]**Corresponding Author:** asulaema06@gmail.com

ber of studies have also revealed that propolis synergizes with ampicillin, gentamycin and streptomycin to eradicate *M. tuberculosis* (Scazzocchio *et al*. 2006); synergizes with streptomycin, rifampicin, isoniazid and ethambutol (Scheller *et al*. 1999); as well as synergizes with streptomycin and cloxacyllin (Krol *et al.* 1993). The synergy of propolis with antibiotics commonly use for Tb treatment, lead to potential acceleration of the healing process. However, a study from Halim *et al*. (2012) suggested that Indonesian propolis had a potential good efficacy, thus needs further study.

Based on the above reasoning, propolis with its dual ability (as hepatoprotector and also fighting *M. tuberculosis* infection) has a potential properties to accelerate the cure process and BW recovery of pulmonary Tb patients. Thus, this study aimed to evaluate the ability of propolis to accelerate the cure process and BW recovery of pulmonary Tb patients.

METHODS

Design, location, and time

The design used was randomized controlled trial, consisting of one positive control group and two treatment groups. The study was conducted in 24 public health centers (Puskesmas) in Bogor City, which lasted from December 1, 2015 to November 29, 2016. ATDs' packages were obtained from Puskesmas. Liquid propolis used was derived from the extraction of *Geniotrigona incisa* bee propolis from South Sulawesi that had passed a series of screening process.

Number of subjects and sampling

A total of 50 Tb patients were determined according to sample size table for controlled clinical trial with α of 0.05 and 80% power, resulting in 13 subjects per group (Chow *et al*. 2008). The subjects were recruited from all *Puskesmas* in Bogor City with a) inclusion criteria: Tb patients, adults aged 15-60 years, were willing to participate in the study by signing informed consent; and b) exclusion criteria: recurrent Tb patients, smoking, had hepatitis or other diseases that interfered the study, alcohol drinkers, pregnant, breastfeeding, using contraception, taking other drugs/herbal medicine/supplements. The subjects' age criterion was based on National Guidelines for Tuberculosis Control (Kemenkes 2014); i.e. adult patients (15 years or older). However, it was stated in the guidelines that adult patients aged over 60 years old were not able to tolerate drug dose of >500 mg/day, thereby the subjects in this study were adult patients aged 15-60 years. Considering that the age range was too wide and it had the potential to produce different responses to the intervention, the adult patients in this study were divided into two groups based on the age groupings by Ministry of Health (*Kemenkes*) (2009), namely adolescents (15-25 years) and adults (26-60 years).

The research consisted of one positive control group and two treatment groups (Table 1). Each subject received 6-month intervention according to National Guidelines for Tuberculosis Control (Kemenkes 2014). Permuted block randomization was used to obtain subjects with equal sex and age groups (Chow & Liu 2004). Intervention and analysis were double-blinded (not known by the subjects, researchers, assistant or analyst).

Each group (P0, P1 and P2) had an equal number of subjects, either based on sex (male and female) or age groups (adolescents aged 15-25 years and adults aged 26-60 years), by using permuted block randomization. The blocks in each group were made based on sex (male and female) and age groups (adolescents and adults). Thus, each group consisted of four blocks; i.e. 1) male-adolescents, 2) male-adults, 3) female-adolescents and 4) female-adults. Each time a subject was obtained, the placement in the group was done by taking a roll of paper containing P0, P1 and P2 codes. The subjects were placed according the group code drawn. Placement of the subjects was repeated if there was a sequential placement more than once in the group and the block.

Table 1. Description of control and treatment provision on the subjects

Group	Intensive phase every day for 8 weeks RHZE (150/75/400/275)+ Propolis	Continuation phase 3 times a week for 16 weeks RH (150/150) + Propolis
P0	(4 4FDC tablets + 20 drops of placebo propolis)	(4 2FDC tablets + 20 drops of placebo propolis)
P1	(4 4FDC tablets + 20 drops of 6% propolis)	(4 2FDC tablets + 20 drops of 6% propolis)
P2	(4 4FDC tablets + 20 drops of 30% propolis)	(4 2FDC tablets + 20 drops of 30% propolis)

Description: FDC = Fixed-Dose Combination. The dose of ATDs used was the dosage for adult patients according to the National Guidelines for Tuberculosis Control (Kemenkes 2014).

Recruitment and screening of prospective subjects were performed by Tb program officers in all *Puskesmas* in Bogor City. The screening was conducted by listing, checking the sputum and interviewing the visitors in Tb eradication program section in *Puskesmas*. If the visitors met the inclusion and exclusion criteria, they were determined as prospective subjects. Prospective subjects were then offered to be research subjects. If they agreed, the Tb program officers in *Puskesmas* reported it to the researchers. Subsequently, the signing of informed consent was done by the researchers and the subjects, and continued with baseline data collection immediately before the intervention was conducted.

Distribution of ATDs to the subjects was conducted by *Puskesmas's* Tb program officers. Meanwhile, propolis distribution was done by the research assistant who also acted as a drug consumption supervisor (DCS). During the intensive treatment period (the first two months), the DCS visited the subjects every day to ensure that they actually consumed the ATDs and propolis. During the continuation treatment period (the 3rd-6th months), the DCS visited three times a week.

This study had obtained ethical approval from Health Research Ethics Committee, Faculty of Medicine of University of Indonesia number: 1036/UN2.F1/ETIK/2015.

Data types and data collection methods

The observation parameters covered: 1) *M. tuberculosis* acid-resistant bacteria (ARB) that included positive 3, positive 2, positive 1 and negative in ARB; 2) anthropometric measurements: body height (measured once at the beginning), BW and body mass index (BMI). The data were collected in week 0 (before intervention as baseline data), every week during intensive treatment phase in the first two months, and every month during continuation treatment phase (from the 3rd month to the 6th month).

The materials used for sputum's ARB analysis (Ziehl-Neelsen stain method) were sputum of the subjects, 70% alcohol, carbol fuchsin, 3% alcohol, water, 0.3% methylene blue solution, 0.1% methylene blue solution and oil immersion. Meanwhile, the tools used were microscope slide, spirit lamp, sterile inoculating loop, staining rack and microscope. The tools used for anthropometric measurements were questionnaires, weight scales and height measurement tools.

Data on sputum's ARB status were obained at *Puskesmas* where subjects were asked to bring their collected morning sputum, the sputum at the time the patients were in *Puskesmas* was also collected for analysis. Bacteriological collection and analysis of ARB were conducted by *Puskesmas* officers. Body height data were obtained by measuring height of the Tb subjects at the beginning of the study using SH-2A height measurement tool, and it was performed by the *Puskesmas* officers. BW data were obtained by weighing the subjects using Camry EB9005 step-on scale in their respective homes, which was performed by the research assistant. BMI data were obtained by dividing the BW (kg) with the square of height (m^2).

Data processing and analysis

Sputum's ARB status data was processed and presented descriptively. Kruskal-Wallis test was used to analyze mean values of BW and BMI, while Mann-Whitney advanced test with significance level of 0.05 and 0.1 was used to analyze the significance of the difference in mean BW and BMI between treatments.

RESULTS AND DISCUSSION

Subjects' characteristics

The important characteristics of subjects that affected the response were sex and age. Therefore, this study used permuted block randomization to ensure that each group received equal distribution of sex and age resulted in distribution of sex (male-female) between the groups; i.e. 50.00%:50.00% in P0 group, 50.00%:50.00% in P1 group and 53.33%:46.67% in P2 group. Meanwhile, in terms of age, the mean age obtained were 30 years in P0 group, 30.1 years in P1 group and 29.3 years in P2 group. Thus, sex and age characteristics between groups were relatively equal, thereby the response that emerged was the result of the provison of intervention. Detailed subjects' characteristics are presented in Table 2.

Acid resistant bacteria (ARB) conversion

The bacteriological evidence treatment success of "cured" of Tb subjects was characterized by the occurrence of sputum smear conversion, from sputum smear positive in ARB into negative in ARB. The results of baseline sputum's ARB status analysis (before the intervention) are presented in Figure 1. Based on the figure, sputum's ARB status composition of P0 and P1 groups were relatively equal. Meanwhile, P2 group was tend to be more severe, dominated by nine Tb subjects (60%) with positive 3 in sputum's ARB status.

Table 2. Subjects' characteristics of the randomization results

Variable	Group		
	P0 N (%)	P1 N (%)	P2 N (%)
Initial number (N0)	17	17	16
Drop out	3 (17.64)	3 (17.64)	1 (6.25)
The final number (NA)	14 (82.36)	14 (82.36)	15 (93.75)
Sex (NA)			
Male	7 (50.00)	7 (50.00)	8 (53.33)
Female	7 (50.00)	7 (50.00)	7 (46.67)
Age range (NA);(years)	15-47	17-55	17-54
Mean age (NA);(years)	30	30.1	29.3
Education (NA)			
Did not have an education	2 (14.29)	0 (0.00)	0 (0.00)
Dropped out of elementary school	1 (7.14)	3 (21.43)	1 (6.67)
Graduated from elementary school	2 (14.28)	3 (21.43)	4 (26.67)
Graduated from junior high school	4 (28.57)	3 (21.43)	7 (46.67)
Graduated from senior high school	5 (35.71)	5 (35.71)	3 (20.00)
Occupation (NA)			
Civil servant	0 (0.00)	0 (0.00)	1 (6.67)
Private employee	3 (21.43)	2 (14.28)	1 (6.67)
Entrepreneur	1 (7.14)	1 (7.14)	0 (0.00)
Others*	10 (71.43)	11(78.57)	13 (86.67)
Income (IDR); (NA)			
Do not have income	2 (14.29)	0 (0.00)	0 (0.00)
Less than IDR 1,500,000/month	9 (64.29)	10 (71.42)	13 (86.67)
IDR 1,500,000- <5,000,000/month	3 (21.43)	4 (28.57)	2 (13.33)

Description: *Others=other categories such as casual agricultural laborer, construction worker, etc. P0: ATDs + placebo propolis group, P1: ATDs + 6% propolis group, and P2: ATDs + 30% propolis group. All dropped-out (DO) subjects were found in the first two weeks of intervention because the subjects were known not to take the drugs in one day, except one subject in P0 group who resigned and one subject in P1 group who was later defined as not Tb patient by the doctor.

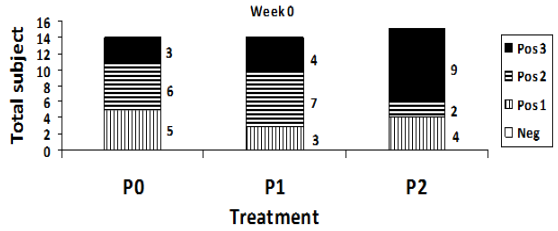

Figure 1. Bar chart of analysis results of the subjects' ARB in P0, P1 and P2 groups before intervention

The rate of sputum's ARB conversion process in each group was different. In P0 group, the conversion of sputum's ARB started to occur in the 6th week on one subject (7.1%). The next conversion in sputum's ARB occurred at weeks 7, 8, 12 and 24 with conversion accumulation of 28.6%, 64.3%, 92.9% and 100%, respectively. Conversion in sputum's ARB in P1 began to occur in the 6th week on one subject (7.1%). The subsequent conversion in sputum's ARB occurred at weeks 7, 8 and 12 with conversion accumulation of 35.7%, 78.6% and 100%, respectively. In P2 group, sputum's ARB conversion began to occur in the 3rd week on four subjects (26.7%). The next conversion happened at weeks 4, 5, 7 and 12 with conversion accumulation of 66.7%, 86.7%, 93.3% and 100%, respectively.

There were differences in conversion rate of sputum's ARB in the three groups; i.e. the sputum smear conversion in P2 group occurred earlier than the other groups. In the 3rd and 7th weeks, conversion of sputum's ARB in P2 group had reached 93.3%. In the same week (the 7th week), the sputum's ARB conversion in P0 and P1 groups only reached 28.6% and 35.7% conversion, respectively. Furthermore, when the data was compared to the composition of baseline sputum's ARB status, the P2 group was in fact more severe than other groups.

Based on mean conversion time the healing of P2 group was the fastest, which was five weeks faster than P0 group and three weeks faster than P1 group. Therefore, the order of healing process was P2>P2>P0. The differences in healing rates between groups are presented in Figure 2.

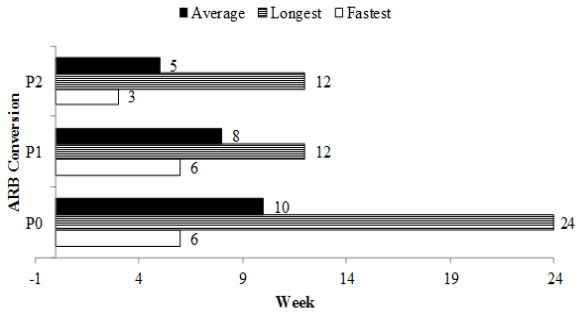

Figure 2. Bar chart of ARB conversion rates in-P0, P1 and P2 groups

A faster recovery will give significant benefits to the subjects; i.e. nutrient intakes will be fully utilized to restore nutritional status, health and productivity maintenance, and can be used for growth for the subjects who are still in the growth period. Nutrient intakes of the subjects that had not cured were partially mobilized to fight infection. It was seen in the P2 group that directly experienced BW and BMI improvements since the first week. P1 group took three and four weeks to restore BW and BMI. P0 group took five weeks to restore BW and had not been able to restore the BMI until the end of the intervention.

Based on the above sputum smear bacteriological conversion data, propolis has shown good ability to fight *M. tuberculosis* infection. This result is in agreement with the study results of Syamsudin *et al*. (2008) and Pranandaru *et al*. (2011). The result also strengthens the study results of Scazzocchio *et al.* (2006), Scheller *et al.* (1999), and Krol *et al*. (1993) who have suggested that propolis synergizes with ATDs in fighting *M. tuberculosis* infection. The ability of propolis to fight *M. tuberculosis* is influenced by the active components in it, which is known to have anti-mycobacterial ability. Cantrell *et al*. (2001) have mentioned that compounds of diterpene, triterpene and sesquiterpene classes have anti-mycobacterial activity, even some of their derivatives show anti-tuberculin activity almost similar to ATDs. The compounds are found in propolis. Toreti *et al*. (2013) have reviewed the compounds contained in the propolis that act as antibacterial and antibiotic; i.e. flavanones, flavones, phenolic acids and esters, prenylated p-coumaric, labdane diterpenes, prenylated flavanones, and prenylated benzophenones. The study results of Katerere *et al*. (2012) have revealed that pinocembrin has anti-mycobacterial activity, and the activity of this compound is increased when coupled with other phytochemicals.

Body weight (BW)

Body weight is a standard measure of nutritional status and is sensitive to sudden changes such as infection and food consumption (Gershwin *et al*. 2004). The patterns of BW changes in P0 and P1 groups had similarities, whereas the pattern of BW change in P2 group was different. The percentages of mean BW changes are presented in Figure 3.

There was a decrease in BW of the subjects in P0 group until the 4th week. Their weight began to recover (equal or higher than baseline BW) in the 5th week, with an increase of 0.8%. Decreased BW was thought to be caused by hepatotoxic effects of ATDs (i.e. nausea, dizziness and decreased appetite), thus the food intake was lower than normal. The data on differences in food intakes between P0 group (ATDs + placebo propolis) and P2 group (ATDs + 30% propolis) in this study have been reported by Pranajaya (2017) as presented in Table 3. These data showed that nutritional adequacy level of P2 group was higher than P0 group.

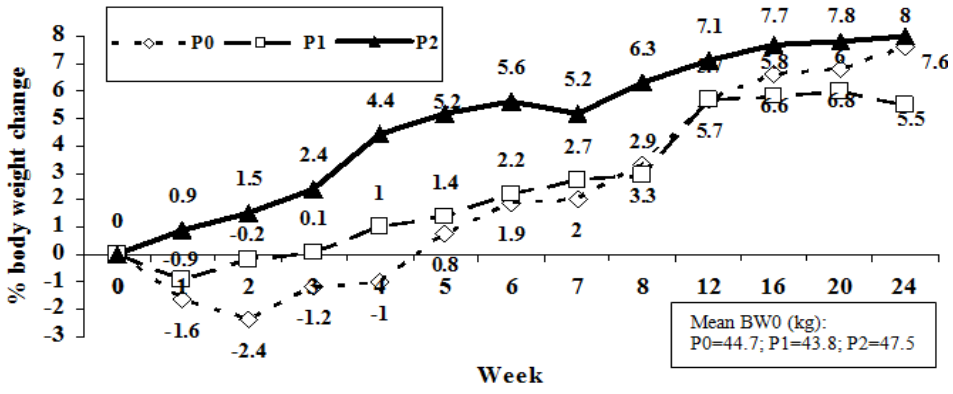

Figure 3. Percentage of mean body weight changes of the subjects in P0, P1 and P2 groups during intervention

The subjects in the P1 group lost weight during the first two weeks. Their weight began to recover in the 3rd week with an increase of 0.1%. If compared with the changes in BW of P0 group, the BW of P1 group recovered two weeks earlier. It was allegedly due to the effect of hepatoprotective activity of propolis so that the hepatotoxic effects of ATDs decreased which leaded to appetite recovery, thereby the BW recovered faster.

In contrast to the other groups, the P2 group did not experience weight loss and immediately gained weight from the start of intervention. The BW continued to increase until the end of intervention. The increase in BW was proposed as the cause of propolis supplementation with a dose of 30% that effectively reduced the hepatotoxic effects of ATDs. The BW changes shown by all groups proved that 30% propolis supplementation was able to reduce the hepatotoxic effects of standard-dose ATDs. The differences in BW changes were particularly prominent, observed from the 2nd week to the 6th week of intervention. Statistically, BW changes in the 2nd week were significantly different ($p<0.05$) (Table 4).

Based on the observation on weight changes, there was a strong indication that intensive

Table 3. Mean nutritional adequacy level of the subjects (pulmonary Tb patients) receiving propolis supplementation and placebo before and after the intervention

		Before intervention	After intervention	Mean change
Placebo group	Energy	56.6 ± 17.7[a]	62.3 ± 13.7[a]	5.7 ± 13.6[1]
	Protein	34.4 ± 15.6[a]	40.9 ± 16.1[a]	6.5 ± 14.9[1]
	Fat	48.8 ± 23.6[a]	57.9 ± 22.7[a]	9.1 ± 27.8[1]
	Carbohydrates	66.0 ± 24.4[a]	66.5 ± 14.3[a]	0.6 ± 21.8[1]
Treatment groups	Energy	52.3 ± 21.8[a]	65.1 ± 16.1[b]	12.8 ± 20.7[1]
	Protein	31.1 ± 15.6[a]	48.8 ± 12.0[b]	17.8 ± 13.2[1]
	Fat	48.7 ± 27.7[a]	61.6 ± 28.1[a]	12.9 ± 29.4[1]
	Carbohydrates	59.1 ± 25.3[a]	68.1 ± 17.9[b]	9.0 ± 27.2[1]

Description: [1]Different figures in the same column indicate significant differences between groups ($p<0.05$); [a]different letters in the same row show significant differences between time ($p<0.05$).

Table 4. Kruskal-Wallis test and Mann-Whitney advanced test on the difference in mean BW of the subjects at weeks 1, 2, 6, 8 and 24

No	Response	Model test (Kruskal-Wallis)	Mann-Whitney advanced test		
		p	Treatment	p	Description
1	BWW1-BW0 difference	0.028*	P0-P1	0.454	Not significantly different
			P0-P2	0.158	Not significantly different
			P1-P2	0.029	Significantly different at 5% level
2	BWW2-BW0 difference	0.006*	P0-P1	0.635	Not significantly different
			P0-P2	0.002	Significantly different at 5% level
			P1-P2	0.023	Significantly different at 5% level
3	BWW6-BW0 difference	0.000*	P0-P1	0.062	Significantly different at 10% level
			P0-P2	0.000	Significantly different at 5% level
			P1-P2	0.000	Significantly different at 5% level
4	BWW8-BW0 difference	0.000*	P0-P1	0.104	Not significantly different
			P0-P2	0.000	Significantly different at 5% level
			P1-P2	0.000	Significantly different at 5% level
5	BWW24-BW0	0.229	P0-P1	0.804	Not significantly different
			P0-P2	0.186	Not significantly different
			P1-P2	0.134	Not significantly different

*Significantly different at 5% level.

use of ATDs caused a decrease in BW through the hepatotoxic mechanism. Hepatotoxic effects includes decreased in appetite, nausea and dizziness (Sari *et al*. 2014), thus the food intake decreased drastically that led to weight loss. The weight recovery was noticeable after entering continuation treatment period (the 9th week until the 24th week), either in the group not receiving propolis supplementation (P0) or the groups receiving propolis supplementation (P1 and P2). It indicated that the subjects could recover from the toxic effects of ATDs. Statistically, the mean BW in all groups at the end of intervention were not significantly different.

Propolis supplementation in this study provided additional benefit of liver protection from the toxic effects of ATDs, especially in the first two weeks of intensive treatment phase. Liver protection by the propolis was ultimately useful to accelerate the BW recovery of the subjects. The results of this study strengthened the study results of Bhadauria *et al*. (2007), Hasmi *et al*. (2013) and Cevik *et al*. (2012) who stated that propolis was hepatoprotective. It was also seen that the higher the dosage of propolis supplementation, the faster and higher the BW recovery is. In this study, the BW recovery of the patients in P2, P1 and P0 groups occurred at weeks 1, 3, and 5, respectively.

Body mass index (BMI)

BMI is one of the adult nutritional status indicators. Based on the changes in mean difference of BMI, P0 group experienced a decrease in BMI since the beginning of intervention and had not recovered until the end of intervention (24 weeks). The final BMI remained negative (-0.2). The decrease in BMI was very drastic during the 1st and 2nd weeks (W1 and W2) and it continued until the 8th week (W8). In continuation treatment period (from the 9th week to the end of intervention), BMI had increased slowly. These data indicated that intensive provision of ATDs could suppress the nutritional status of the subjects as a result of its hepatotoxic effects. The changes in mean BMI are presented in Figure 4.

In the continuation treatment phase (ATDs administered only 3 times a week), the strength of pressure on nutritional status was also reduced. In the P1 group, the decrease in BMI occurred during the first three weeks and started to be positive in the 4th week (0.1). In the 24th week, BMI increased by 0.9. When compared to P0 group, the decrease in nutritional status in P1 group was smaller, and it occurred in shorter duration. It means that supplementation of 20 drops of 6% propolis in ATDs provide benefits for nutritional status recovery of the subjects.

Unlike the other groups, the P2 group immediately experienced an increase in BMI from the beginning of intervention and it continued to increase until the end of intervention. In the first week, the BMI increased by 0.2. BMI continued to increase until the 8th week (W8) and the increase reached 1.2. Therefore, the BMI increased by 1.2 during the intensive treatment period. The final BMI (W24) reached 1.5. Thus, it could be said that the BMI increased only by 0.3 during the four months of continuation treatment period. These data showed that P2 group had a rapid increase in nutritional status in the intensive period. It showed a strong indication that daily supplementation using 20 drops of 30% propolis in ATDs could accelerate the nutritional status recovery of the subjects.

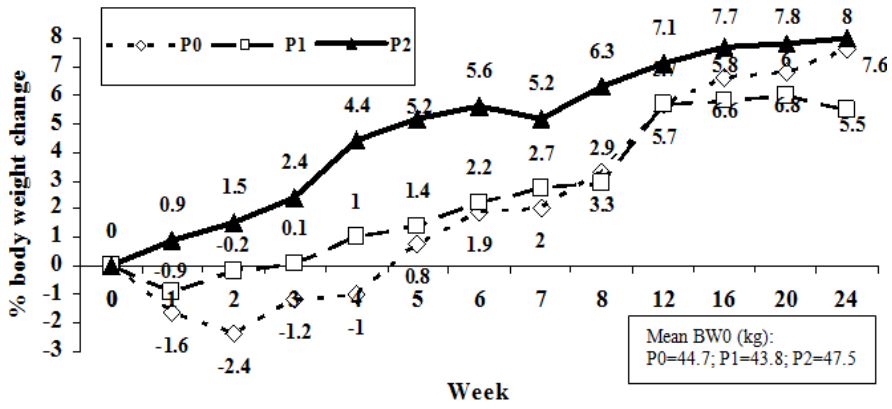

Figure 4. Changes in mean body mass index differences of the subjects in P0, P1 and P2 groups during intervention

Table 5. Kruskal-Wallis test and Mann-Whitney advanced test on the difference in mean BMI of the subjects at weeks 1, 2, 6, 8 and at the 6th month

No	Response	Model test (Kruskal-Wallis)	Mann-Whitney advanced test		
		p	Treatment	p	Description
1	BMIW1-BMI0 difference	0.030*	P0-P1	0.769	Not significantly different
			P0-P2	0.051	Significantly different at 10% level
			P1-P2	0.063	Significantly different at 10% level
2	BMIW2-BMI0 difference	0.001*	P0-P1	0.125	Not significantly different
			P0-P2	0.000	Significantly different at 5% level
			P1-P2	0.037	Significantly different at 5% level
3	BMIW6-BMI0 difference	0.014*	P0-P1	0.482	Not significantly different
			P0-P2	0.006	Significantly different at 5% level
			P1-P2	0.029	Significantly different at 5% level
4	BMIW8-BMI0 difference	0.054**	P0-P1	0.329	Not significantly different
			P0-P2	0.023	Significantly different at 5% level
			P1-P2	0.123	Not significantly different
5	BMIW24-BMI0 difference	0.135	P0-P1	0.541	Not significantly different
			P0-P2	0.063	Significantly different at 10% level
			P1-P2	0.158	Not significantly different

Description: *) Significantly different at 5% level, **) Significantly different at 10% level.

The statistical evidence of benefit from propolis supplementation to restore BMI was also reinforced by Kruskal-Wallis test and Mann-Whitney advanced test, which showed that the changes in BMI in P2 and P0 groups were significantly different from the first week until the 24th week ($p<0.05$ and $p<0.1$) (Table 5).

Observation on the pattern of BMI changes showed that the BMI recovery of P1 and P2 groups occurred at week 4 and week 1, respectively. Meanwhile, BMI of the P0 group had not recovered until the 24th week. It was also seen that intensive use of ATDs might cause a decrease in nutritional status (as shown from the decreased in BMI of P0 and P1 groups within the intensive treatment period). Conversely, the supplementation of 20 drops of 30% propolis alongside the ATDs could reduce the effect of decreased nutritional status due to ATDs consumption. Moreover, it also could improve nutritional status of the subjects.

In line with the results of this study, Shetty (2010) stated that there was an interaction between undernutrition and infection. The BMI data above showed that *M. tuberculosis* infection might decrease the nutritional status of the subjects through certain mechanism. The results of this study were also in agreement with the research results of Moses *et al*. (2009); Tungdim and Kapoor (2008); Lombardo (2012); Patra *et al.* (2010), Sultan *et al.* (2012), and Chung-Delgado *et al.* (2014), who found that Tb patients significantly had lower nutritional status compared to the healthy population.

CONCLUSION

Based on the sputum smear ARB conversion, the propolis supplementation groups (P1 and P2) recovered faster than the placebo propolis supplementation group (P0). Higher concentration of propolis lead to faster sputum's conversion. Similarly with the changes in mean BW, in which higher concentration of propolis supplement result in faster BW recovery. Furthermore, BW of P2 group had increased immediately from the beginning. Thus, supplementation of 20 drops of propolis with a concentration of 30% along with ATDs during the treatment are effective to accelerate the cure and BW recovery processes of pulmonary Tb patients. Considering that propolis is clinically proven to be able to accelerate cure and BW recovery of pulmonary Tb patients, it has a potential to be used as a supplement for national Tb control.

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