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Andrographis Paniculata (Burm. F.) Nees Induces Clinical and Sputum Conversion in Pulmonary Tuberculosis Patients

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Abstract

The aim of this study was to determine whether Andrographus paniculata capsule induces clinical and sputum conversion in pulmonary tuberculosis (TB) patients. Randomized, placebo-controlled, double-blind pilot study was conducted to pulmonary tuberculosis patient who admitted to Pulmonology Polyclinic of Persahabatan Central General Hospital, Jakarta. A total of 44 pulmonary TB patients were randomly divided into two groups including one group received standard antituberculosis drugs + Andrographis paniculata (n=21) (AP) and one group received standard antituberculosis drugs + placebo (n=23). APC was given 500 milligram per day for eight weeks. The distribution of sex, body weight and body mass index (BMI) as well as the frequency of cough and feature of chest radiography were not significantly different between groups (P >0.05). The proportion of posi¬tive smears in both groups decreased over time until by the twelve weeks, none remained positive. The rate of decline was more pronounced in the AP group reach statistically at weeks 4 and 6 compared to placebo group (P<0.05). Adjunctive supplementation of Andrographis paniculata (Burm. F.) Nees was to accelerate the beneficial therapeutic effect of TB chemotherapy by improving clinical and sputum response.

Key Words: Antimicrobial, *andrographis paniculata*, sputum conversion, tuberculosis

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Introduction

Today, TB remains a leading human infectious disease and a major public health problem in low-income countries, including Indonesia. Despite the availability of the Bacillus Calmette-Guerin (BCG) vaccine for more than 80 years, the best tuberculosis vaccine is still far to be generated and its protection is unclear [1]. Mycobacterium tuberculosis (MTB) is an intracellular pathogen as the causative agent of TB. This pathogen has infected one third of the world's population and accounts for an estimated 1.8 million worldwide deaths annually. The incidence of TB during 2010 worldwide was 8.8 million cases (128 cases/100,000 inhabitants), 59% of these cases were detected in Asia [2].

TB requires a lengthy treatment period of six months with the cocktail of first-line drugs rifampicin, isoniazid, ethambutol and pyrazinamide [3]. If the treatment fails as a result of several factors, second-line drugs are performed that are generally either less effective or more toxic with serious side effects [4]. Besides, deficiencies of micronutrients can reduce host defenses and immune response to combat MTB [5]. This can potentially affect host response to anti-TB chemotherapy and patient outcome. Regulatory T cells and Th2 type immune response appear to predominate in the early clinical evolution of TB and becomes more pronounced as the disease worsens [6-8]. However, successful chemotherapy causes a return back towards a Th1 state. Thus, improving the immune status by nutrient of herbal of treated pulmonary TB patients may accelerate bacterial clearance and clinical healing through improvement of immune response [9].

The leaves and aerial parts of Andrographis paniculata (Burm. F.) Nees (AP) (Family: Acanthaceae) have been used in traditional systems of medicine for the treatment of several diseases [10]. Previous studies note that ethanol extract of AP leaf showed promising activity against M. tuberculosis [11]. The methanol extract of AP leaves was exhibited strong in vitro antibacterial activity against Gram positive bacteria including clinical isolates of M. tuberculosis [12]. Clinical studies of A. paniculata extract for treatment of acute upper respiratory tract infections, cold symptoms, and adults with sore throat and fever, demonstrated some benefits [13-18]. The putative effects of adjunctive Andrographis paniculata supplementation on clinical and sputum conversion has not been evaluated. The randomized, placebo-controlled, double-blind pilot study was conducted to assess the effectiveness of adjunctive Andrographis paniculata supplementation on the clinical and

sputum conversion of patients being treated for pulmonary TB. We hypothesized that supplementation would accelerate clinical and sputum conversion in pulmonary TB patients.

Materials and Methods

This research was performed during April until October 2013. The APC contained 70% dry extract of AP leaves and was registered for sale in Indonesia. Newly the diagnosed pulmonary TB patients attending to Pulmonology Polyclinic of Persahabatan Hospital, Rawamangun, Jakarta, Indonesia were recruited. Consecutive patients with one times a positive sputum smear, minimal-medium radiologically lesion, 16-23 mg/kg2 body mass index, 2.5 – 4.5 gr/dl albumin levels, without prior history of TB or treatment, and 15-55 years old were eligible for participation. The participants were also not pregnant, breastfeeding, used corticosteroids, or another serious co-morbidity. All patients gave their written and signed informed consent.

Subjects were randomized to the APC or placebo groups. APC group subjects received eight weeks of supplementation with 500 mg/day of APC in capsule. Placebo group subjects received organoleptically identical, matched placebos. All subjects received short-course, directly observed antibiotic therapy: intensive 60-day treatment with isoniazid (300 mg/day), rifampicin (600 mg/day), pyrazinamide (1600 mg/day) and ethambutol (1200 mg/day) followed by a sustained 45-dose therapeutic phase with isoniazid (800 mg/dose) and rifampicin (600 mg/dose). Monitoring of clinical symptoms and chest radiography were done at week 0 and 8. Monitoring of sputum conversion was done at week 0; 2; 4; 6; and 8.

This research has been approved by local ethics committee from Medical Faculty, University of Indonesia, Jakarta, Indonesia.

Data are presented as mean ± standard deviation. Chi square test was conducted to analyze the difference of sex, sign and symptoms, and sputum conversion between groups. $P < 0.05$ was considered statistically significant.

Results

Table 1 shows the subject characteristics, sign and symptoms, and chest radiography in each group. We involved 11 men and 9 women in Andrographis paniculata group, 15 men and 8 women in placebo group. The distribution of sex, body weight, and body mass index were not

significantly different between groups (P > 0.05). In addition, the frequency of cough and feature of chest radiography were not significantly different between groups (P >0.05).

Table 2 displays the proportion of subjects in the two study groups with a positive sputum smear from baseline through study weeks 12. The proportion of positive smears in both groups decreased over time until by the twelve weeks, none remained positive. The rate of decline was more pronounced in the Andrographis paniculata group reach statistically at weeks 4 and 6 compared to placebo group (P < 0.05).

Table 1. Subject characteristics, sign and symptoms, and chest radiography

	Andrographis panniculata group	Placebo group
Subject characteristics		
Sex (male/female)	11/9	15/8
Age (15-35 year/36-55 year)	14/6	15/8
Body weight (<50 kg/>50 kg)	11/9	15/8
Body mass index (kg/m^2)		
Normal	2	0
Underweight	18	23
Obese	0	0
Sign and symptoms (%)		
Cough		
Weekth 0	18	21
Weekth 8	4	6
Chest radiography (%)		
Weekth 0	100	100
Weekth 8	25	35

Note: values are presented as mean ± SD; *p<0.05; in comparison with placebo group

Table 2. Percentage of positive sputum smear in the *Andrographis panniculata* (n=18) and placebo groups (n=18) at baseline (week 0), supplementation period (weeks 0-8)

	Period of supplementation (weeks)						
	0	**2**	**4**	**6**	**8**	**10**	**12**
Andrographis panniculata	100	75	35*	30*	25	0	0
Placebo	100	78	57	39	17	10	0

Note: values are presented as percentage of positive sputum smear; *p<0.05; in comparison with placebo group

Discussion

In this study, we found that eight weeks of Andrographis paniculata supplementation make the rate of positive chest radiography was lower compared to placebo groups, but not statistically different (P > 0.05). The rate conversion of overall sign and symptoms also higher in Andrographis paniculata group compared with placebo group, but not reach statistically different. We hypothesized that Andrographis pannculata may promote lung repair and inhibit mycobacterium growth. The antibacterial and anti-inflammatory effects have been attributed related to the immune system. Previous studies showed that Andrographis paniculata has been recently identified as a potent inhibitor of NF-kB [19-21]. Andrograpanin not block the activation of ERK1/2, JNK MAPKs and NF-κB activation but it only inhibited p38 MAPKs activation [22]. This blockade will inhibit pro-inflammatory cytokines production.

TNF-α in conjunction with IFN-γ plays a key role in the all steps of the inflammatory response produced by MTB. The effects of pro-inflammatory cytokines are counterbalanced by down-regulatory cytokines such as interleukin-10 (IL-10) which is produced by the activated macrophages, monocytes, Th2, and T regs, in response to infection [23]. We found that the rate of positive smear sputum decline was more pronounced in the Andrographis paniculata group reach statistically at weeks 4 until 6 compared to placebo group (P < 0.05). We hypothesized that Andrographis paniculata may have synergistic effect with antituberculosis to inhibit MTB growth may be due to modulate immune system through counterbalanced pro inflammatory cytokines. Several previous studies showed that the terpenoids present in extract of A. paniculata leaves have enough potential to kill drug resistant Gram positive bacteria, including MTB [11, 12]. The anti-inflammatory properties of Andrographis paniculata might be resulted from the inhibition of pro-inflammatory mediators, at least in part via suppression of a signaling pathway such as NF-κB [24].

The results of this initial study suggest that adjunctive supplementation of Andrographis paniculata accelerated the beneficial therapeutic effect of TB chemotherapy by improving sputum conversion response. Larger clinical studies and detail mechanisms are required to verify these initial results.

In conclusion, adjunctive supplementation of Andrographus paniculata accelerated the beneficial therapeutic effect of TB chemotherapy by improving clinical and sputum response.

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