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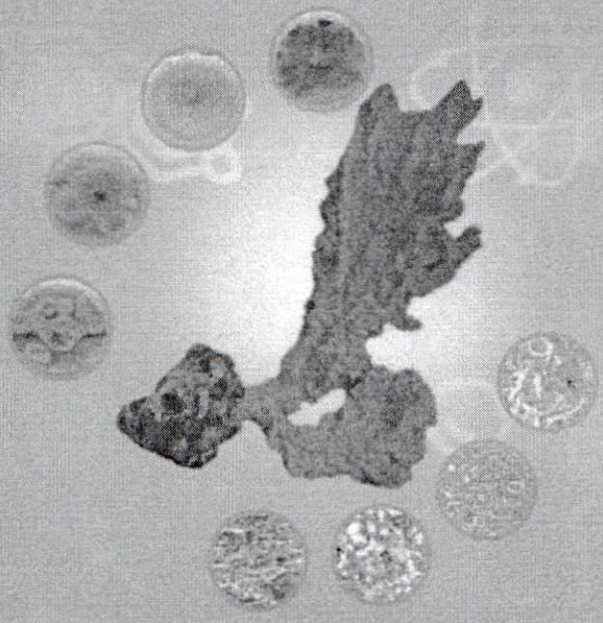

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Effects of Probiotics and Vitamin B Supplementation on IFN-γ and IL-12 Levels During Intensive Phase Treatment of Tuberculosis

Budi Suprapti, Suharjono Suharjono, Rahmawati Raising, Yulistiani Yulistiani, Zamrotul Izzah, Wenny Putri Nilamsari, Prastuti Asta Wulaningrum, Arief Bachtiar

Abstract

Tuberculosis is an acute infectious disease that primarily affects the lungs. Probiotics supplementation can increase the number and activity of NK cell in peripheral blood by modulation of IL-12, thus increasing IFN-γ production by Th1 response. Vitamin B_1 acts on macrophages and affects neutrophil motility. Vitamin B_6 is associated with the release of cytokines and the responsiveness of NK cells, while vitamin B_{12} affects to lymphocytes, Tcell proliferation, $CD4^+$ ratios, and NK cell activity. To analyze the effects of probiotics and vitamin B_1, B_6, B_{12} supplementation on IFN-γ and IL-12 levels during intensive phase of antituberculosis treatment. The study was pre-post test randomised control by time series. The control group was TB patients with standard therapy of antituberculosis and vitamin B6, while the intervention group was TB patients receiving therapy plus once daily probiotics and vitamin B_1, B_6, B_{12}supplementation during the intensive phase. Blood samples were withdrawn at baseline, one month, and two months after therapy to measure plasma IFN-γ and IL-12 levels using the ELISA method. Twenty two patients were divided equally into two groups. There was a tendency to greater increase of IFN-γ in the first month of the intervention group, followed by a significant decline after two-month therapy ($p < 0.05$). In both groups there was a rise in IL-12 levels after one month followed by a decrease in the second month ($p > 0.05$). However, the percentage was higher in the supplementation group. Adding probiotics and vitamins B_1, B_6, B_{12} could improve immune response through IL-12 and IFN-γ modulation during intensive phase therapy.

Keywords

Interleukin-12, Interferon-γ, Probiotics, Tuberculosis, Vitamin B

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Research Article

Effects of Probiotics and Vitamin B Supplementation on IFN-γ and IL-12 Levels During Intensive Phase Treatment of Tuberculosis

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ABSTRACT

Tuberculosis (TB) is an acute infectious disease that primarily affects the lungs. Probiotics supplementation can increase the number and activity of NK cell in peripheral blood by modulation of interleukin-12 (IL-12), thus increasing interfenon-γ (IFN-γ) production by T-helper cells type 1 (Th1) response. Vitamin B_1 acts on macrophages and affects neutrophil motility. Vitamin B_6 is associated with the release of cytokines and the responsiveness of NK cells, while vitamin B_{12} affects to lymphocytes, Tcell proliferation, $CD4^+$ ratios, and NK cell activity. This study aim to analyze the effects of probiotics and vitamin B_1, B_6, B_{12} supplementation on IFN-γ and IL-12 levels during intensive phase of antituberculosis treatment. The study was pre-post test randomised control by time series. The control group was TB patients with standard therapy of antituberculosis and vitamin B6, while the intervention group was TB patients receiving therapy plus once daily probiotics and vitamin B_1, B_6, B_{12} supplementation during the intensive phase. Blood samples were withdrawn at baseline, one month, and two months after therapy to measure plasma IFN-γ and IL-12 levels using the ELISA method. Twenty two patients were divided equally into two groups. There was a tendency to greater increase of IFN-γ in the first month of the intervention group, followed by a significant decline after two-month therapy (p <0.05). In both groups there was a rise in IL-12 levels after one month followed by a decrease in the second month (p>0.05). However, the percentage was higher in the supplementation group. Addition of probiotics and vitamins B_1, B_6, B_{12} could improve immune response through IL-12 and IFN-γ modulation during intensive phase therapy.

Keywords: Interleukin-12, Interferon-γ, Probiotics, Tuberculosis, Vitamin B

INTRODUCTION

Tuberculosis (TB) is an acute infectious disease caused by *Mycobacterium tuberculosis* (Mtb). TB can be transmitted from one individual to another through airbone droplets. Globally, TB is the leading cause of death from a single infectious agent, killing approximately 1.67 million persons in 2016. At least one quarter of persons worldwide, approximately 1.7 billion people, are infected with Mtb. Among these infected persons, approximately 10% or 170 million persons globally, will be expected to develop TB during their lifetimes (WHO, 2018). According to the recent report, there are new high burden countries lists for the period of 2016–2020 (TB, Multidrug-resistant TB (MDR-TB) and TB/ HIV), and Indonesia is among the 20 top countries with the incident of 10.000 per year for TB, and 1,000 per year for TB/HIV (WHO, 2017).

The body's defense system for the intracellular bacterial infections which have important role are macrophages and Th1 cells. Those act as a specific mediator in destroying Mtb. Fagocytic cells that influx bacteria and become apoptosis will be uptaken by lung dendritic cell then transported to lymphe. This is the stimulate adaptive immune phase, T-helper tipe 1 (Th1) stimulates the cytokine secretion (Etna, 2014). Cytokines that have important contribution to TB infection include IFN-γ, TNF-α, IL-12, IL-17, IL-10, and IL-6.

In turn cytokine will stimulate neutrophils and activate macrophages, form granulomas, and form antimicrobial agents such as oxygen and nitrogen reactive to inhibit Mtb (Adrian *et al*, 2015).

Probiotics can modulate the immune system through the activity of epithel cells and immune cell receptors. In respiratory tract infections, there is an increase in the activity of fagocytes from alveolar macrophages after the administration of probiotics, thus increasing the activity of NK cells in the IFN-γ production (Forsythe, *et al.*, 2013; Mortaz, *et al.*, 2013).

Some vitamins can affect to body's immunity, including cell-mediated immunity, humoral immunity, and phagocytic activity of leucocytes. Vitamin B_1 has an action in macrophages and affects neutrophil motility. Vitamin B_6 can release cytokines or chemokines and has responsibility to the responsiveness of NK cells. In addition, vitamin B_{12} increases lymphocytes as well as improves the abnormal CD4/CD8 ratio and NK cell activity (Shetty *et al*, 2010; Spinas *et al*, 2015).

The use of probiotics and vitamin B_1, B_6, B_{12} supplementation in tuberculosis patient has not yet been determined. Therefore, this study was aimed to analyze the effects of those supplementation on IFN-γ and IL-12 levels in tuberculosis patients.

MATERIALS AND METHODS

The study protocol was ethically approved by the Ethics and Law Committee of Airlangga University Hospital on August 2016. The study was pre-post test randomised control by time series applied to the naïve and newly-diagnosed TB patients. The first group consisted of patients with the first-line standard therapy of oral antituberculosis and vitamin B_6 (control), whereas the second group was patients receiving therapy and supplementation of probiotics and vitamin B_1, B_6, B_{12} (intervention). Both standard therapy and supplementation were administered once daily during the intensive phase of treatment. The study was conducted at the Universitas Airlangga Hospital and Primary Healthcare Centers in Surabaya within period of December 2016 and February 2017. The inclusion criteria were patients aged 18-65 years, diagnosed with active TB, started first-line antituberculosis treatment for the intensive phase, had no previous history of probiotics and vitamin B_1, B_6, B_{12} before enrollment, and signed the informed consent. The exclusion criteria were patients with HIV co-infection, pregnancy, lactation, diabetes mellitus, pneumonia, and current administration of corticosteroids or other immunosuppressants.

Multistrain probiotics (*Lactobaccilus acidophilu, L. casei, L. rhamnosus, L. bulgaricus, Bifidobacterium breve, B. longum, Streptococcus thermophilus*), vitamin B_1 100mg, B_6 100mg, B_{12} 5.000mcg were administered once daily in the intervention (second) group. Blood samples were withdrawn at baseline, after one month, and two months of intensive therapy for further plasma IFN-γ and IL-12 assay using the ELISA method. The t-test analysis was performed to evaluate the effects of probiotics and vitamin B supplementation.

RESULTS AND DISCUSSION

The characteristics of patients (Table I) Data were distributed normally, and no significant differences were found between the two groups ($p>0.05$).

The Figure 1A and 2 A showed the plasma IFN-γ levels in both groups. The levels increased from 32.735pg/mL before therapy to 40.325pg/mL ($p=0.445$) after one month followed by a decrease to 39.640pg/mL ($p=0.859$) in the second month. Whereas, plasma IFN-γ levels in the intervention group rose from 73.767pg/mL before therapy to 97.768pg/mL ($p=0.241$) in the first month and next significantly declined to 43.472pg/mL ($p=0.007$) at the end of two-month of intensive therapy.

Similarly, figures 1B and 2B revealed that plasma IL-12 levels in the control group elevated from 2.663pg/mL before therapy to 3.303pg/mL ($p=0.091$) in the first month and diminished to 2.550pg/mL ($p = 0.155$) after two months of therapy. In addition, plasma IL-12 levels of the intervention group increased from 3.173pg/mL before therapy to 4.168pg/mL ($p=0.061$) after one and decreased significantly to 2.567pg/mL ($p=0.003$) in the second month.

Table I. Patients demography

Parameter	Control group N (%)	Intervention group N (%)	*p* value*
Total	11	11	
Gender			
Male	4 (36.4)	4 (36.4)	1.000
Female	7 (63.6)	7 (63.6)	
Age (years)			
18-24	2 (18.2)	2 (18.2)	
25-34	2 (18.2)	2 (18.2)	
35-44	2 (18.2)	5 (45.4)	0.389
45-54	4 (36.3)	1 (9.1)	
55-65	1 (9.1)	1 (9.1)	
AFB smear result			
Positive	7 (63.6)	6 (54.5)	1.000
Negative	4 (36.4)	5 (45.5)	
Duration of symptoms (cough, night sweats)			
≥ 1 month	9 (81.8)	11 (100.0)	0.065
< 1 month	2 (18.2)	0 (0)	
Smoking			
Yes	1 (9.1)	1 (9.1)	1.000
No	10 (90.9)	10 (90.9)	
Co-morbidities			
Asthma	0 (0)	1 (9.1)	
Hyperthyroid	0 (0)	1 (9.1)	0.413
Ulcer	1 (9.1)	2 (18.2)	
None	10 (90.9)	7 (63.6)	
Diagnosed TB			
Pulmonary	7 (63.6)	10 (90.9)	0.311
Extrapulmonary	4 (36.4)	1 (9.1)	

* calculated by chi-square test for categorical variables

This study recruited 22 newly-diagnosed TB patients and were divided equally into each group. The diagnosis was primarily based on the Acid-Fast Bacilli (AFB) smear results or chest x-ray, in addition to clinical features such as cough and night sweats. Although most patients experienced pulmonary TB rather than extrapulmonary type, the process of body immune system response to Mtb for both conditions is similar (Adrian *et al*, 2015). All patients were administered the first-line antituberculosis therapy as standard therapy according to the current WHO guideline (WHO, 2017).

Probiotics are microorganisms alive that given in sufficient quantities to provide benefits. They have shown to increase the amount and activity of cytotoxic NK cells in peripheral blood, with IL-12 immunomodulation increasing the expression of NK cell receptors. Thus, it can be concluded that probiotics are capable of increasing Th1 responses (Kechagia, *et al*, 2013; Nanno, *et al*, 2014). For example, the *L. pentosus* strain significantly increased the activity of NK cells in the spleen through IL-12. Increased levels of IL-12 in dendritic cells cause NK stimulation, thus increasing IFN-production (Forsythe, 2013; Mortaz, *et al*, 2013). Previous studies have shown that combination of multistrain probiotics provide better results because they produce synergistic effects among strains to inhibit more pathogens. Another study also revealed that the use of probiotics is useful in reducing the incidence of respiratory tract infections (Chapman *et al*, 2011; Chapman *et al*, 2012).

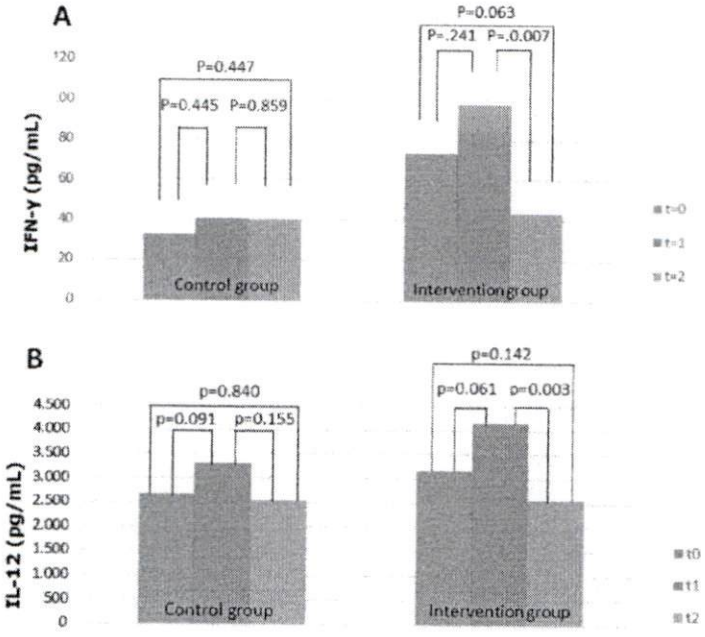

Figure 1. Changes in plasma IFN-γ (A) and IL-12 (B) levels in the control and intervention groups before therapy (t0), after one month (t1), and two months of intensive phase therapy (t2).

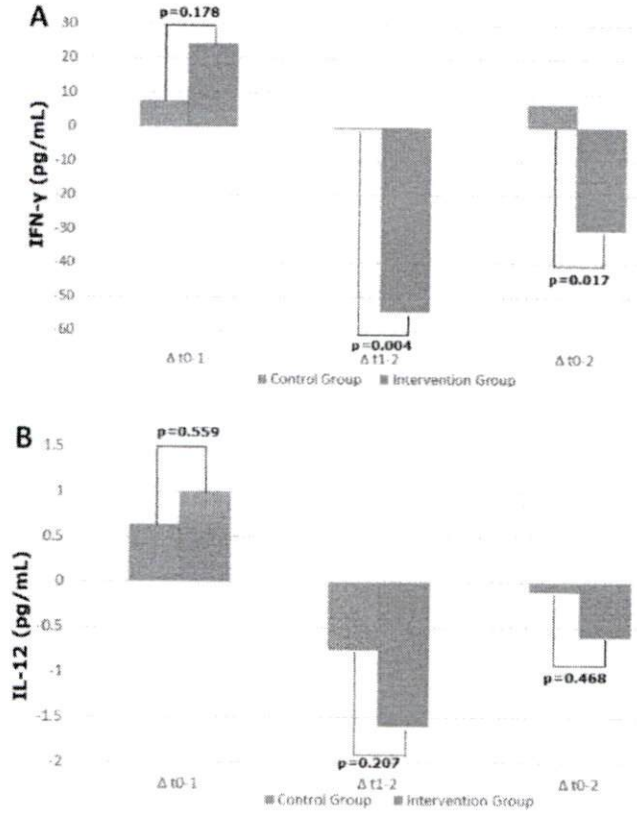

Figure 2. Differences within a month between IFN- γ and IL-12 levels in in the control and intervention groups during the intensive phase therapy

Vitamins also affect the body's immunity, such as vitamin B_1 which works on macrophages and influences the neutrophil motility, vitamin B_6 is associated with the release of cytokines or chemokine's and responsiveness of NK cells, and vitamin B_{12} influences lymphocytes, T cell proliferation, CD4/CD8 and NK cells activity (Shetty *et al*, 2010; Spinas *et al*, 2015).

Furthermore, combination of multistrain probiotics and vitamin B supplementation provides enhanced immunomodulation activities during the intensive phase therapy as shown by the trends of increase in the first month and decrease at the end of intensive therapy between IFN-γ and IL-12 levels in the intervention group compared to the control group. Clifford *et al* (2015) reported that there was an increase in IFN-γ levels in active TB treatment. When the host is infected by Mtb, there will be bacterial influx by phagocytic cells, especially alveolar macrophages and neutrophil, which in turn induce apoptosis. The apototic cells will be captured by pulmonary dendritic cells that act as antigens presenting cell (APC) to be carried into lymph with the help of IL-12 and chemokines. Dendritic cells also produce IL-12 to support differentiation of naive T cells into helper T cells (Th1, Th2, TTh9, Th 17, Th 22 and T regulator cells). In the lung, T cells produce various cytokines such as TNF-α and IFN-γ by Th1 cells (O'Garra *et al*, 2013). In early infection phase and first month of antituberculosis therapy, probiotics and vitamin B supplementation will enhance IFN-γ production, but further the IFN-γ level will gradually decrease along with the decrease of inflammation process at the end of intensive treatment (Abul *et al*, 2016).

Indeed, the levels of IFN-γ were higher in the first month of the intervention group compared to the control. This suggested that the supplementation of probiotics and vitamin B_1, B_6, B_{12} plays a role in the modulation of IFN-γ secretion in response to Mtb infection. Increased IFN-γ levels in the first month may enhance bacteria eradication, as the result the bacteria in the lung or extrapulmonary sites will decrease resulting reduced systemic inflammation. Therefore, at the end of intensive therapy the levels of IFN-γ were diminished as shown by a significant reduction in the intervention group. Nevertheless, Devici *et al* (2005) stated that there was a significant increase in IFN-γ levels in the second month and then decreased in subsequent months.

Interestingly, the similar trends also applied to the IL-12 levels. They increased in the first month and then decreased in the second month of therapy either in control or intervention groups. However, the net differences showed greater in the intervention group rather than in the control. IL-12 supports Th1 cell defferention whose secretes IFN-γ, and then IFN-γ will stimulate NK cell to produce more IFN-γ (Forsythe, 2011). Sai Priya *et al* (2009) revealed a decrease in IL-12 response during treatment. This suggested that supplementation may help increase levels of IL-12 in the first month, regulate the balance of T-cell responses and stimulate NK cells in the spleen through IL-12 and increase production IFN-γ (Spinas *et al*, 2015). IFN-γ will in turn help to eradicate the bacteria. Reduced levels of IL-12 were aligned with the levels of IFN-γ. At the end of intensive therapy, the number of active Mtb has decreased, thus reducing the levels of IFN-γ and IL-12 levels.

Last, this study was conducted in limited number of patients, so the results cannot be directly generalized to greater population. Therefore, multi-center study with more subject is needed.

CONCLUSIONS

Supplementation of once-daily multistrain probiotics and vitamin B_1, B_6 and B_{12} could improve immune system through IFN-γ and IL-12 modulation,–increase plasma levels of IFN-γ and IL-12 in early phase to help speed up Mtb eradication during the intensive phase of tuberculosis treatment.

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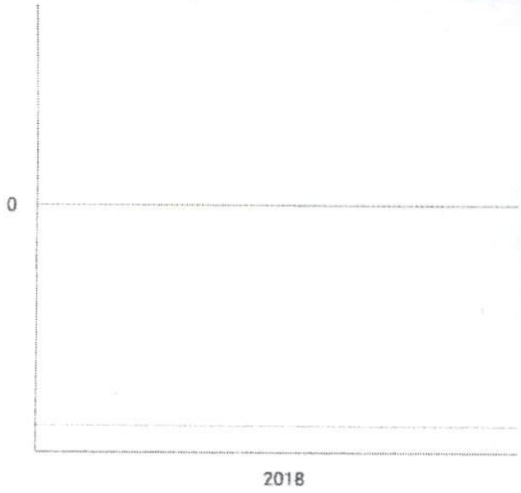

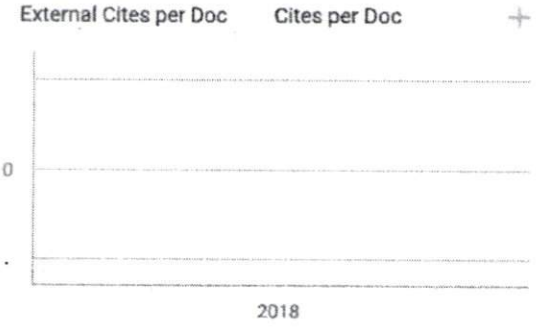

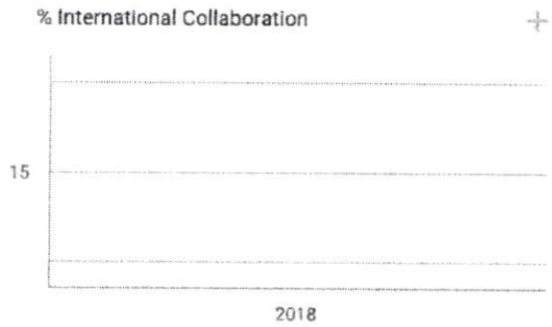

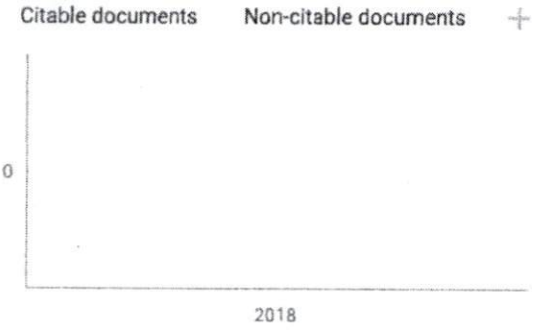

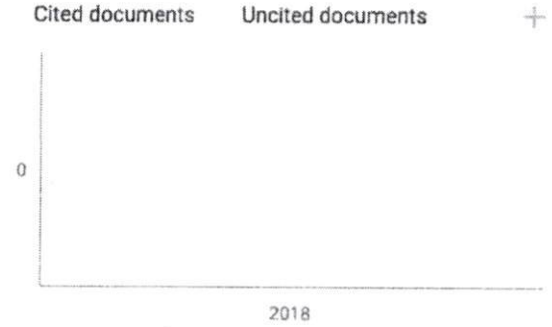

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Indonesian Journal of Pharmacy

Country	Indonesia - SIR Ranking of Indonesia
Subject Area and Category	Health Professions Pharmacy Medicine Pharmacology (medical) Pharmacology, Toxicology and Pharmaceutics Pharmaceutical Science
Publisher	Universitas Gadjah Mada - Faculty of Pharmacy
Publication type	Journals
ISSN	23389486, 23389427
Coverage	2016-2019
Scope	The journal had been established in 1972, and online publication was begun in 2008. Since 2012, the journal has been published in English by Faculty of Pharmacy Universitas Gadjah Mada (UGM) Yogyakarta Indonesia in collaboration with IAI (Ikatan Apoteker Indonesia or Indonesian Pharmacist Association) and only receives manuscripts in English. Indonesian Journal of Pharmacy is Accredited by Directorate General of Higher Education. The journal includes various fields of pharmaceuticals sciences such as: -Pharmacology and Toxicology -Pharmacokinetics -Community and Clinical Pharmacy -Pharmaceutical Chemistry -Pharmaceutical Biology -Pharmaceutics -Pharmaceutical Technology -Biopharmaceutics -Pharmaceutical Microbiology and Biotechnology -Alternative medicines.

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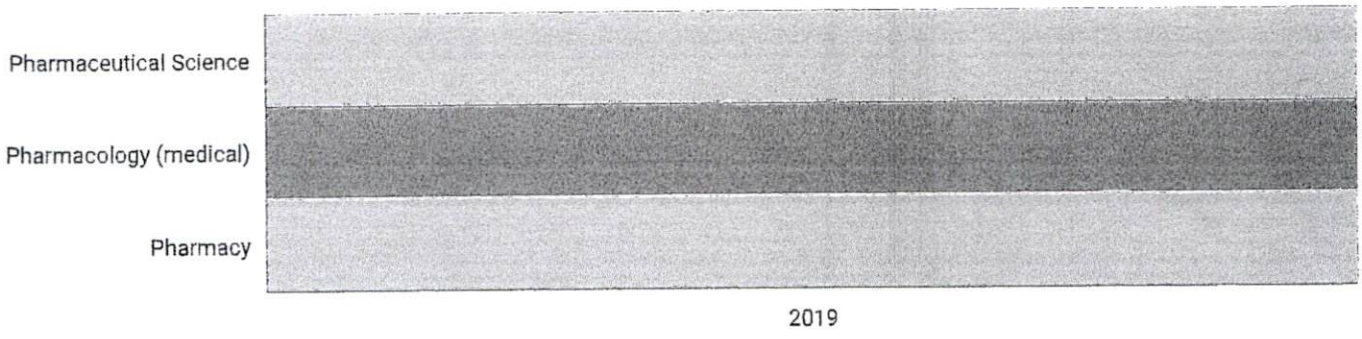

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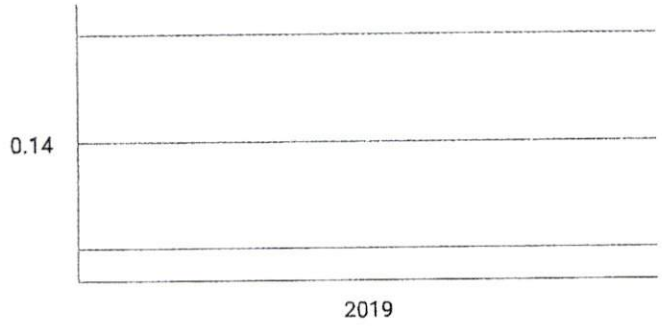

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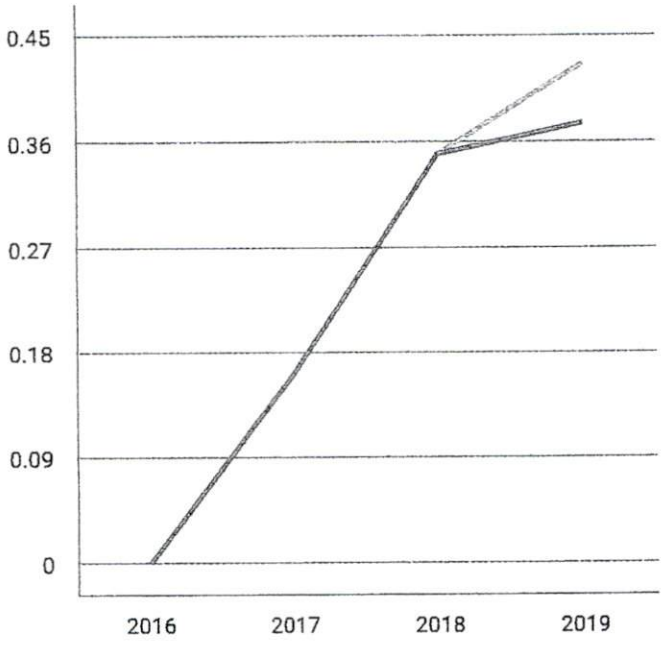

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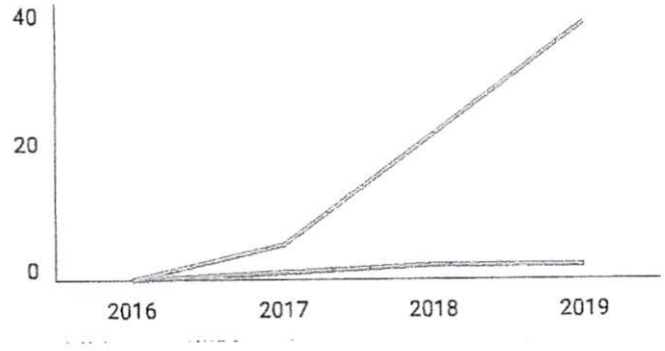

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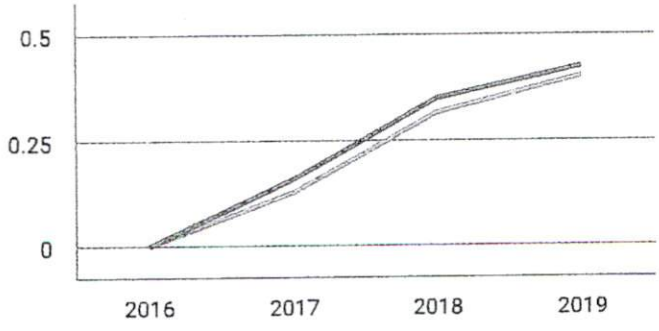

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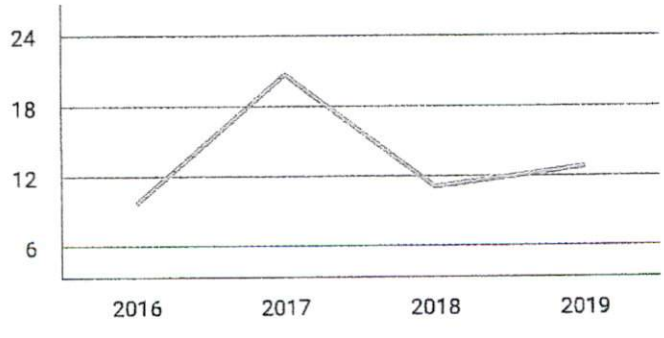

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Niar 2 months ago

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SCImago Team

Melanie Ortiz 2 months ago

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Thank you for contacting us. Our data come from Scopus, they annually send us an update of the data. This update is sent to us around April / May every year. Thus, the indicators for 2019 will be available in June 2020. Best Regards, SCImago Team

faridatulain 9 months ago

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reply

SCImago Team

Melanie Ortiz 9 months ago

Dear user, thanks for your participation! Best Regards, SCImago Team

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(Indonesian J. Pharm)

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Alamat / Address : Fakultas Farmasi Universitas Gadjah Mada Yogyakarta, Jl. Sekip Utara Yogyakarta, 55281
Telp. 62-0274-543120, 6492566, 6492563, Fax. 62-0274-543120 Email : mfi@ugm.ac.id
Homepage site : http://mfi.farmasi.ugm.ac.id

Dear Budi Suprapti, et al

We are pleased to confirm that your manuscript entitled "**Effects of Probiotics and Vitamin B Supplementation on IFN-γ and IL-12 Levels During Intensive Phase Treatment of Tuberculosis**" has been accepted for published on Volume 29 Issue 2 2018, in Indonesian Journal of Pharmacy.

Thank you very much for submitting your manuscript to the Indonesian Journal of Pharmacy.

Yogyakarta, 07 August 2018
Sincerely yours,

Prof. Dr. Sugiyanto, SU., Apt.
Editor In Chief
Indonesian Journal of Pharmacy

Re: Galley Proof

Dari: Budi Suprapti (budiprapti@yahoo.co.id)

Kepada: mfi@ugm.ac.id

Tanggal: Kamis, 9 Agustus 2018 14.21 WIB

Dear Editor of IJP
Thank you for the acceptance of our paper. I added affilitation to me and two other co-authors, write in blue colour.
Thank you,

Regards
Budi Suprapti

> Pada Selasa, 7 Agustus 2018 12.55.13 WIB, Majalah Farmasi Indonesia <mfi@ugm.ac.id> menulis:
>
> Dear Budi Suprapti,
>
> Your manuscript has been accepted for publication in Indonesian Journal of Pharmacy (attached 1). On behalf of Editorial team, we are looking forward to receiving your new paper. Please sign the copyright transfer (attached 2) in order to allow me to process your manuscript. Please check the proof (attached 3) carefully and if you need revision you can write in file (attached 4).
>
> Your revised manuscript and Copyright Form must be returned to us within 4 days (August 10, 2018). Please refer to the attached documents below.
>
> Sincerely,
>
> Editorial Staff

Budi Suprapti LOA.pdf
589.4kB

4. Revised File (Budi S).docx
202kB

Galley Proof

Dari: Majalah Farmasi Indonesia (mfi@ugm.ac.id)

Kepada: budiprapti@yahoo.co.id

Tanggal: Selasa, 7 Agustus 2018 12.55 WIB

Dear Budi Suprapti,

Your manuscript has been accepted for publication in Indonesian Journal of Pharmacy (attached 1). On behalf of Editorial team, we are looking forward to receiving your new paper. Please sign the copyright transfer (attached 2) in order to allow me to process your manuscript. Please check the proof (attached 3) carefully and if you need revision you can write in file (attached 4).

Your revised manuscript and Copyright Form must be returned to us within 4 days (August 10, 2018). Please refer to the attached documents below.

Sincerely,

Editorial Staff

1. LOA.pdf
637.1kB

2. Copyright form - MFI.doc
30kB

3. Galley Proof.pdf
1.5MB

4. File (Budi S).docx
136.4kB

Re: [IJP] Revision Requirement

Dari: Budi Suprapti (budiprapti@yahoo.co.id)

Kepada: mfi@ugm.ac.id

Cc: shj_ms_id@yahoo.com; raising.rahmawati@gmail.com

Tanggal: Jumat, 8 Juni 2018 13.55 WIB

Dear Editorial MFI,
I have attached our revised paper based on correction from MFI reviewer. The paper entitled
"THE EFFECT OF PROBIOTIC AND VITAMIN B SUPPLEMENTATION ON INTERFERON-IFN-γ AND IL-12 LEVELS DURING INTENSIVE PHASE TREATMENT OF THERAPY".
Thanks for the correction.

Regards
Budi Suprapti

> Pada Jumat, 9 Maret 2018 09.48.47 WIB, Majalah Farmasi Indonesia <mfi@ugm.ac.id> menulis:
>
> Dear Rahmawati Raising, dkk
>
> We have reached a decision regarding your submission to INDONESIAN JOURNAL OF PHARMACY, "THE EFFECT OF PROBIOTIC AND VITAMIN B1, B6, B12 SUPPLEMENTATION ON INTERFERON-γ AND INTERLEUKIN-12 LEVELS IN TUBERCULOSIS PATIENT DURING INTENSIVE PHASE OF THERAPY".
>
> Our decision is to:
>
> Editorial MFI
> Faculty of Pharmacy, Universitas Gadjah Mada
> mfi@ugm.ac.id
> ---------- ----------
> Reviewer Comment:
>
> Title:
> The title need to be shortened. Some details can be explained in method section (Title)
>
> Introduction:
> 1. The statistical number of TB in Indonesia should be updated
> 2. The mechanism of probiotic and vitamin should be added
>
> Methodology:
> 1. The study design was not clearly stated
> 2. The sample size was not formulated according to the study design
> 3. There is no ethical review stated in this study
> Note: If the authors can not showed the ethical review, then this manuscript should be rejected
>
> Result and Discussion:
> The authors should explain:
> 1. The "not significant" results could be based on the sample size consideration
> 2. There are two categories of TB (pulmonary and extra pulmo), should be considered as the confounding variable due to the use of probiotic and vitamin
> 3. There are no limitation of study stated in the discussion
> 4. The authors should discuss the reasons of unproven hypothesis.
> 5. What is the result of AFB smear and duration symptoms after two months treatment?
> 6. How to diagnose the TB patient with negative test of AFB smear?
> 7. What kind of symptoms recorded from the TB patients in Table 1?

Conclusion:
The conclusion should be carefully stated. Please based on the study results.

Recommendations:
Accept with major and extensive revision

---------- ----------

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