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by Ilhamjaya Patellongi

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The Effect of Miana (*Coleus Scutellarioides* [L]) on Vascular Endothelial Growth Factor Expression in Balb/C Mice Infected with *Mycobacterium Tuberculosis*

Rosa Marlina¹, Mochammad Hatta², Eva Sridiana³, Irawaty Djaharuddin⁴, Ilhamjaya Patellongi⁵ and Farida Murtiani¹

¹Sulianti Saroso Infectious Diseases Hospital, Jakarta, Indonesia.

²Molecular Biology and Immunology Laboratory, Faculty of Medicine Hasanuddin University, Makassar, Indonesia.

³Pasar Rebo General Hospital, Jakarta, Indonesia.

⁴Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Hasanuddin University, Makassar, Indonesia.

⁵Department of Physiology, Faculty of Medicine Hasanuddin University, Makassar, Indonesia.

¹⁶Corresponding author E-mail: hattaram@yahoo.com

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11 Tuberculosis (TB) is still a major global health problem. The increasing prevalence of antibiotic resistance has posed a major threat towards the mission of TB eradication. Traditional medication has been a staple alternative and adjuvant to conventional treatment for Indonesians. Miana leaves (*Coleus scutellarioides*) is one such traditional medicine that has a potential role as immunoregulator, antiinflammation, and antimicrobial agent. Several studies have shown that Miana leaves extract can regulate TLR 4, the number of CD4 T cells, IFN- γ levels, and TNF- α . Vascular Endothelial Growth Factor (VEGF) mediates angiogenesis and vasodilatation to provide oxygenation and access for immune cells in hypoxic and inflamed site due to infection focus. This study aims to study the effect of Miana leaves on VEGF expression. Balb/c mice were infected with *Mycobacterium tuberculosis* and were treated using Miana leaves extract, rifampicin, and rifampicin plus Miana. VEGF protein levels before infection, after infection, and after treatment were measured using ELISA. The results showed that there was a significant difference in VEGF level means between treatment groups. VEGF levels in rifampicin, Miana, and rifampicin plus Miana groups were significantly lower than placebo. VEGF level was significantly lower in rifampicin group compared to Miana group. VEGF level was significantly lower in rifampicin plus Miana group compared to Miana group. There was no significant difference of VEGF level between rifampicin and rifampicin plus Miana group. The results indicate that Miana leaves does have an effect on VEGF level in mice infection with *Mycobacterium tuberculosis*.

Keywords: *Coleus scutellarioides*; *Mycobacterium tuberculosis*; Miana; VEGF

Tuberculosis (TB) is one of the major health problem in the world. It ranks tenth as the cause of death in the world. World Health

Organization (WHO) reported 10 million cases of TB cases and 1.3 million deaths globally in 2016. It is estimated that two thirds of TB burden lies in

34)nt countries which are India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) dan South Africa (3%). WHO 2018 report estimated there were more than 1 million new TB cases in indonesia.^{1,2,3}

The problem in battling TB is the increasing antibiotic resistant TB cases in indonesia. Indonesia is rank 11th out of 27 countries with the highest cases of multi drug resistant (MDR) TB in the world.^{4,5,6} This showed that there is a need for additional means to treat TB in addition to the administration of antibiotic. While antibiotic work to eradicate pathogen bacteria, it is important to increase host immune response to *M. tuberculosis* bacterial virulence to create a synergy between antibiotics and immunoregulators.^{7,8}

When *M. tuberculosis* invade the host cell, inflammation occurs as the host immune response. This inflammatory response creates local hypoxia due to increased metabolic activity and thus creating increased temperature in the inflamed tissue. The rise in local tissue temperature affect the amount and pressure of local oxygen and creates cellular hypoxia and inflammation.²⁶ Low oxygen level and inflammatory cytokines IL-1 α and IL-6⁵ induces the expression of VEGF mRNA.^{11,12} Vascular endothelial growth factor (VEGF) plays a role in angiogenesis and angiogenesis increases blood flow to ischemic cells and tissues and corrects hypoxia.^{13,14}

The use of traditional herbal medicine widely in infectious diseases^{15,16,17,18,19,20,21,22,23} and non infectious diseases such as has been a staple alternative to western medicine for indonesian people.^{24,25,26,27,28} Recently, traditional herbal medicine may become an alternative or adjuvant to standard therapy. Miana (*Coleus scutellarioides [L] Benth*) is known as one of the traditional herbal medicine that is often used. It contains flavonoid, tannin, triterpenoid, steroid and atsiri oil that has antibacterial, antioxidant and antiinflammatory effects.^{29,30,31,32}

Miana leaves have endophyte bacteria that have the ability to synthesize antibacterial agent that contains phtalic acid derivate. In one in vitro study, Miana extract can suppress the growth of *Candida albicans* and *Salmonella typhi*.^{33,34,35} A study found that Miana extract can improve host immunity by modifying the degree and quality of immune response from T cell, B cell, IL-10 and

IL-37. Miana extract can affect proliferation of T cells in mice that was given 510mg/kgBW of Miana extract. Administration of Miana extract also increases the number of CD4 T cells, IFN- γ levels, IL37 and TNF- α and also reduces the bacterial colonies in Wistar mice's lungs.^{31,32,36,37}

Other that immunostimulant and immunoregulatory effects, Miana also has²⁵ antiinflammatory and antioxidant properties. In *Salmonella typhi* infected Balb/c mice²⁴ model, Miana leaves extract can suppress the expression of toll like receptor-4 (TLR-4) m-RNA which is similar to the effect produced by antibiotics.³²

However, not much is known about the effect of Miana leaves extract on VEGF, one of the pivotal factor on combing cell hypoxia due to *M. tuberculosis* infection. This study aims to³² evaluate the effect of Miana on VEGF expression in Balb/c mice infected with *M. tuberculosis*.

MATERIAL AND METHODS

Experimental design

This study is an experimental study using 16 BALB/c mice conducted in July 2020 in Molecular Biology and Immunology Laboratory, Microbiology Division, Faculty of Medicine, Hasanuddin University (UNHA³⁰ Makassar, Indonesia. The mice were grouped into four groups of four mice. Group 1 is a negative control group that was treated with placebo. Group 2 is a positive control group that was treated with antituberculosis drug. Group 3 is an intervention group that was treated with Miana extract. Group 4 is also an intervention group that was treated with Miana extract and antituberculosis drug.

Balb/c Mice

Sixteen 12 weeks old pathogen free BALB/c mice weighing 30-40 grams were used in this experiment. The mice were granted by UNHAS Molecular Biology and Immunology Laboratory, Faculty of Medicine, Makassar, Indonesia.

Miana Extract

Miana leaves were obtained from Toraja, South Sulawesi, Indonesia. The Miana extract was made using 10 grams of plucked Miana Leaves that were washed and dried in 50°C oven. The dried leaves were grinded using a grinder and sieved using size 100 mesh to achieve fine powder from. A total of 30 grams of Miana powder was diluted with

ethanol with 1:10 ratio and mixed using a shaker for 24 hours in room temperature. The mixture was filtered using Whatman filter paper number 50. The filtrate was evaporated using a rotary evaporator in 50°C temperature until concentrated and then dried using a freeze dryer. The concentrated extract was made into a pellet.

The pellets were stored in a refrigerator until use. The dosage of Miana extract used in this experiment was 510 mg/kgBW. The pellets will be diluted with aquades and given to the mice using a nasogastric tube.^{32,33}

M. tuberculosis Induction

M. tuberculosis induction was done by injecting 10³ CFU/ml of *M. tuberculosis* into the peritoneal cavity using a 0.6 ml syringe.^{16,17,18}

Miana treatment in mice

All 16 Balb/c mice were put into groups of 4 (group 1-4) randomly. On day 0, 0.2 ml of venous blood was drawn (before induction and before treatment blood sample) from all mice in all groups and *M. tuberculosis* induction was done on all mice. On day 1, the second blood draw (after induction before treatment blood sample) was done on all groups. Group 1 was given 10 mg/kgBW/day of aquades as placebo, group 2 was given 1.95 mg/day of rifampicin, group 3 was given 750 mg/kgBW of Miana extract, group 4 was given 1.95 mg/day of rifampicin and 750 mg/kgBW of Miana extract. From day 1 to day 7, the treatment specific to each group was continued. On day 8, the third blood draw (after treatment blood sample) was done.

Venous blood sample was centrifugated to obtain the blood serum. The serum was stored in -20°C until analysis. VEGF protein level was measured using Mouse VEGF Elisa Kit Catalog No. LS-F978. Protein concentration was measured in pg/ml. VEGF protein level before induction, before treatment, and after treatment of all groups were done. All sample analysis was done in duplicate to ensure validity of ELISA analysis results.

Statistical Analysis

Normality test was done using Shapiro-Wilk test and Levene's test was done for homogeneity test. Protein levels of each groups were presented in means and standard deviation. One way ANOVA test was used to determine whether there are any statistically significant

differences between the means of VEGF protein levels of the treatment groups as a whole. Post hoc test was done to determine which group is statistically significantly different from other groups. P value below 0.05 is determined as statistically significant. All statistical analyses were done using SPSS 20.0 software for Windows.

RESULTS

VEGF protein levels before induction, after induction, and after treatment

Table 1 showed the means of VEGF protein level before *M. Tuberculosis* infection, after infection, and after treatment of all four treatment groups. The mean ± SD of VEGF in group 1 (placebo) was 3,631.360 ± 2,261.273 pg/ml before infection, 17,575.417 ± 2,041.037 pg/ml after infection, and 21,595.533 ± 2,442.347 pg/ml after treatment. In group 2 (rifampicin), the mean ± SD of VEGF was 2,393.661 ± 1,747.450 pg/ml before infection, 18,083.191 ± 1,876.923 pg/ml after infection, and 4,655.215 ± 1,731.676 pg/ml after treatment. In group 3 (Miana), the mean ± SD of VEGF was 3,901.364 ± 2,234.894 pg/ml before infection, 17,125.172 ± 1,738.783 pg/ml after infection, and 7,419.336 ± 1,765.879 pg/ml after treatment. Lastly, the mean ± SD of VEGF in group 4 (Miana and Rifampicin) was 2,128.043 ± 865.085 pg/ml before infection, 17,195.564 ± 1,856.413 pg/ml after infection, and 3,837.384 ± 957.187 pg/ml after treatment.

From the description of the obtained data, it can be seen that there is a steep increase of VEGF protein levels after *M. tuberculosis* infection. The level of VEGF protein kept increasing after placebo treatment in group 1 while the VEGF levels in other groups decreased after treatment. One-Way ANOVA test was done to see whether there is a significant difference of means after treatment in general. The test result showed a significant difference of VEGF protein level means between groups after treatment in general (Table 2; F = 105.710, p value = 0.000). To further analyse the difference of VEGF protein level means between groups, a post hoc analysis was done.

Post hoc analysis (Table 3) showed that VEGF protein level was significantly lower after administration of rifampicin (4,655.215 ± 1,731.676 pg/ml, p value = 0.000), Miana

(7,419.336 ± 1,765.879 pg/ml, p value = 0.000), and rifampicin plus Miana (3,837.384 ± 957.187 pg/ml, p value = 0.000) compared to placebo (21,595.533 ± 2,442.347 pg/ml). VEGF protein level was significantly lower in mice treated with rifampicin (4,655.215 ± 1,731.676 pg/ml, p value = 0.028) compared to the mice treated with Miana (7,419.336 ± 1,765.879 pg/ml) and no significant difference between rifampicin group and rifampicin plus Miana group (p value = 0.484). There was also a significantly lower VEGF protein level in mice treated with rifampicin plus Miana (3,837.384 ± 957.187 pg/ml, p value = 0.006) compared to mice treated with Miana (7,419.336 ± 1,765.879 pg/ml).

DISCUSSION

Tuberculosis is infectious diseases which their pathomechanisms has been involve the several immune system both cellular and humoral system.¹⁹ Serum VEGF levels is known to be elevated in patients with active pulmonary tuberculosis and lowered after successful treatment.⁴⁰ In this study, VEGF levels were also elevated after the mice was infected with *M. tuberculosis* and decreased after treatment whereas VEGF level in placebo treated mice kept increasing. This indicates the role of VEGF in *M. tuberculosis* infection.

Table 1. VEGF Protein Levels of All Groups

Group	Before infection	After Mtb Infection	After Treatment
Group2 (Rifampicin)	2393.661 ± 1747.450	18083.191 ± 1876.923	4655.215 ± 1731.676
Group3 (Miana)	3901.364 ± 2234.894	17125.172 ± 1738.783	7419.336 ± 1765.879
Group4(Rif+ Miana)	2128.043 ± 865.085	17195.564 ± 1856.413	3837.384 ± 957.187
Group 1 (Placebo)	3631.360 ± 2261.273	17575.417 ± 2041.037	21595.533 ± 2442.347

*Mtb = *M. tuberculosis*

Table 2. One Way ANOVA Differences of Means Between Groups

Group	After Treatment	F	P value
Group 2 (Rifampicin)	4655.215	105.710	0.000
Group 3 (Miana)	7419.336		
Group 4 (Rif+ Miana)	3837.384		
Group 1 (Placebo)	21595.533		

Table 3. Post Hoc Analysis of Mean Differences

Group	Subgroup	Mean differences	P value
Rifampicin	Miana	-2764.12160*	.028
	Rif+ Miana	817.83080	.484
	Placebo	-16940.31780*	.000
Miana	Rif	2764.12160*	.028
	Rif+ Miana	3581.95240*	.006
	Placebo	-14176.19620*	.000
Rifampicin + Miana	Rif	-817.83080	.484
	Miana	-3581.95240*	.006
	Placebo	-17758.14860*	.000
Placebo	Rif	16940.31780*	.000
	Miana	14176.19620*	.000
	Rif+ Miana	17758.14860*	.000

¹⁰ This study found that there was a significant difference in VEGF level means between groups in general. Further investigation showed that VEGF levels were significantly lower in *M. tuberculosis*-infected mice treated with rifampicin, Miana, and rifampicin plus Miana compared to placebo. VEGF level was also lower in rifampicin group compared to Miana group. There was also a significantly lower VEGF level in rifampicin plus Miana group compared to Miana group. However, there was no significant difference of VEGF level between rifampicin group and rifampicin plus Miana group. This result indicate that Miana extract administration does have an effect on VEGF protein levels. Our result showed that rifampicin with Miana extract as adjuvant can be an acceptable Tuberculosis treatment.

However, the exact mechanism of how Miana extract affect VEGF in Tuberculosis infection remains unclear. To elucidate the possible mechanism of the effect of Miana extract on VEGF production, understanding of tuberculosis infection immune response pathway and the mechanism of Miana extract as antimicrobial, anti-inflammatory, and antioxidant are crucial.

During infection such as tuberculosis infection, inflamed site due to infection is relatively hypoxic. Hypoxic environment increases the cellular level of HIF-1 α . The increase in HIF-1 α will increase the level of VEGF. There are multiple other pathways of VEGF production induction in during infection.⁴⁰ Inflammation caused by infection stimulates the production of cyclooxygenase (COX) 1 and COX 2 which will induce the production of prostaglandin E2 (PGE2). PGE2 and HIF-1 α upregulates the production of cellular VEGF. Upregulation of cellular VEGF enhances angiogenesis, vasodilatation, mediate extravasation of monocytes under hypoxic condition, and works together with histamine to increase vascular permeability which causes plasma exudation.⁴¹

Miana is one of the traditional herbal medicine commonly used to treat infectious diseases and immune booster by the Toraja people in South Sulawesi, Indonesia. It is also commonly used as a complement to antituberculosis treatment. To be used, Miana leaves needs to be extracted. Miana leaves extract contains compounds such as alkaloids, tannins, flavonoids, saponins and

terpenoids. Flavonoids have antimicrobial, antiinflammatory and antioxidant properties. One study stated that flavonoid content in miana extract is on average 8.59 mg/gram extract. Flavonoid antibacterial mechanism consists of inhibition of nucleic acid synthesis and causing damage to bacterial cell wall, microsomes, and lysosomes. Flavonoids also has very strong antioxidant activity. Flavonoid in Miana increases T lymphocytes, CD4 T cells, IFN- γ , IL-37, TNF- α , TLR4 and NRAMP1. Tannin, saponin, and terpenoid also have antimicrobial activity.^{31,32,33,36}

From the explanation above, it is clear that *M. tuberculosis* infection causes inflammation and hypoxia and activates a cascade of immune response in which at one of the ends of the line increases VEGF protein levels to combat the bacteria as well as hypoxia. Miana extract, which contains flavonoids and others, directly acts on the bacteria as a type of antibacterial as well as immunoregulator to increase host immune response to combat the bacteria and anti-inflammatory action. The elimination or reduction of the cause of the inflammation diminishes the signal for the induction of upregulation of VEGF. This may explain the possible mechanism of the effect of Miana on VEGF levels. Further study is needed to elucidate the immunoregulatory pharmacodynamics of Miana leaves extract.

CONCLUSION

¹ There were significant differences in VEGF protein levels between treatment groups. VEGF protein levels in Balb/c mice treated with rifampicin, Miana, and rifampicin plus Miana were significantly lower than placebo. VEGF protein levels were significantly lower in rifampicin treatment group compared to Miana group; significant lower VEGF protein level in rifampicin plus Miana treatment group compared to Miana group; and no significant difference between rifampicin group and rifampicin plus Miana group.

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Ethical Clearance

Ethics committee of the Medical Faculty of Hasanuddin University, Makassar, Indonesia. No. : 177/UN4.6.4.5.3t/PP36/2A21 date 17 March 2021

Conflict of Interest

There are no potential conflict of interest to be disclosed.

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