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## Reduce Spleen-IFN- $\gamma$ Correlated with CXCL9 Levels During Cerebral Malaria Phase in *Annona muricata*-Treated Swiss Mouse Study

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**Background:** Cerebral malaria (CM) cause malaria mortality. Anti-plasmodial and immunomodulatory properties of *A. muricata*-leaf extract (AME) may provide benefices for CM-patients. IFN- $\gamma$ , a pivotal cytokine in the CM-immunopathology, is modulated by CXCL9, IL-10 and IL-12. The study objective was to determine factors correlated with spleen-IFN- $\gamma$  production in health and CM phase with/without ethanolic AME treatment. **Method:** A post test only controls group design study using 36 Swiss mice randomly divided into 6 groups was performed. The *Plasmodium berghei* ANKA (PbA)-inoculated and healthy mice were grouped in C(+) and C(-). The healthy mice treated with AME 100 and 150 mg/Kg BW/day were grouped in X<sub>1</sub> and X<sub>2</sub>. The PbA-inoculated and received either AME dose was grouped in X<sub>3</sub> and X<sub>4</sub>. Phytohemagglutinin (PHA) induced spleenocyte IFN- $\gamma$  production, while lipopolysaccharide (LPS) induced IL-10, IL-12 and CXCL9. Elisa was used to measure the observed cytokine production. One-way ANOVA and post hoc test were applied in normally distributed data; otherwise, Kruskal-Wallis and Mann-Whitney test were used. **Results:** IFN- $\gamma$  was significantly lower in C(+), X<sub>3</sub> and X<sub>4</sub> than C(-) group, and this was also observed in CXCL9. IL-10 was significantly higher in X<sub>3</sub> and X<sub>4</sub> than C(+) group ( $p = 0.003$  and  $p = 0.004$ ). IL-12 was not different among all six groups ( $p = 0.071$ ). Spearman correlation test showed a correlation between IFN- $\gamma$  and CXCL9 produced during CM-phase regardless AME treatment ( $r = 0.581$ ;  $p = 0.009$ ), while IFN- $\gamma$  was correlated with IL-10 levels in healthy groups with/without AME treatment ( $r = 0.544$ ;  $p = 0.029$ ). **Conclusion:** The reduce spleen-IFN- $\gamma$  production might regulate differently in health and CM phase.

**Keywords:** *Annona muricata*, Cerebral Malaria, IFN- $\gamma$ , CXCL9.

### 1. INTRODUCTION

Cerebral Malaria or CM was a severe malaria and contributes in malaria fatal case that 60% people were at risk.<sup>1</sup> CM pathogenesis had been studied extensively.<sup>2</sup> It was proposed that an adjuvant therapy contributed in alleviating vascular endothelial dysfunction might benefice CM patients.<sup>3</sup> Endothelial dysfunction of CM or experimental CM (ECM) is influenced by many factors including inflammation and oxidative stress.<sup>4-6</sup> The anti-inflammatory agent is capable of alleviating endothelial dysfunction in CM.<sup>7</sup> Nitric oxide (NO) having an anti-inflammatory effect may improve endothelial dysfunction and associate with increase survival of ECM.<sup>8,9</sup> Natural products are used as a traditional medication for malaria patients in the endemic area.<sup>10,11</sup> Many natural products, including ethanolic-*Annona muricata*-leaf extract (AME), had been studied for its anti-malaria, anti-inflammatory and immunomodulatory effects.<sup>12-19</sup> AME treated mice showed

reduced tumor necrosis factor-alpha (TNF- $\alpha$ ) and increased NO produced by LPS-stimulated-spleen cells of Swiss mice during CM phase.<sup>20</sup> AME had no association with IFN- $\gamma$  produced by stimulated spleen of Swiss mice during CM phase.<sup>21</sup> TNF- $\alpha$  and IFN- $\gamma$  are protective since they contribute in controlling *Plasmodium* infection. High levels of those cytokines, however, are pathologic during CM phase.<sup>22-24</sup> There are cytokines and chemokines influence IFN- $\gamma$  levels including IL-12, IL-10 and CXC motif ligand 9 (CXCL9). Mice developed CM earlier had a higher number of splenic IL-12 secreting DCs and IFN- $\gamma$ -secreting T cells, which were Th1 and Treg cells, than those mice develop CM later or normal control group.<sup>25</sup> IL-10 secreting DCs and splenic-CXCL9 production, however, were not measured in this previous study.<sup>26</sup> IL-10 secreting DCs and DC subpopulation did not support the development of IFN- $\gamma$ -secreting T cell which ruled the immunopathology of severe malaria.<sup>26-28</sup> CXCL9 attract IFN- $\gamma$ -secreting T cell which expresses CXCR3, a CXCL9 receptor, to the brains of ECM-susceptible mice.<sup>29</sup> The higher number of

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**1** cells found in the brain links to the higher CXCR3 expression of T cell develop in the spleen of CM susceptible mice than resistant mice.<sup>30</sup> The recent study done in Swiss mice was aimed to reveal whether splenic IL-12, IL-10, and CXCL9 correlated with IFN- $\gamma$  production in healthy and CM phase with/without ethanolic AME treatment. The aim of this study was to reveal factors associated with spleen-IFN- $\gamma$  production in health and CM phase with/without ethanolic AME treatment.

**2. METHOD**

The raw material preparation and processing of ethanolic AM leaf extract (AME) were both done by experts from SidoMuncul Company, Indonesia. The extract analyses were also done in SidoMuncul Company that certified that the extract was in the acceptable standard. The post test only control group design was performed in this study. The animal model used was Swiss mouse, an animal model for ECM. The mouse strain and health were both confirmed by Agriculture Department of Indonesian Republic. This study was carried out in Medical Faculty of Diponegoro University (MFDU) along with ethical committee Karyadi Hospital Semarang released the ethical approval. The healthy mice without treatment were used as negative control group (C(-)), while the PbA inoculated mice without treatment was grouped as a positive control (C(+)). X<sub>1</sub> and X<sub>3</sub> groups were healthy mice and PbA-inoculated Swiss mice which both received AME 100 mg/kg BW/day. X<sub>2</sub> and X<sub>4</sub> groups were similar groups which both received AME 150 mg/kg BW/day. The treatment was done for a total period of 14 days. The treated group of PbA-inoculated Swiss mice received AME for 7 days before and 7 days after PbA-inoculation. The PbA-inoculation dose used was 10<sup>7</sup> pRBC. PbA was provided by Parasitology Department of UGM. The parasitemia levels were observed at three-time points which were day 3, 5 and 7. The mice were sacrificed on day 7 represented CM phase. The spleen cell culture method was modified from the method used before. The cells used were 10<sup>7</sup> cells/wells in 24 well culture plates. The spleens of the mice were cultured and stimulated either by using 10  $\mu$ g/ml lipopolysaccharide (LPS) or 10  $\mu$ l phytohemagglutinin (PHA) in each well. Elisa kit and microplate reader were used for measuring IFN- $\gamma$ , CXCL9, IL-12p70, and IL-10. IFN- $\gamma$  was measured in PHA-stimulated spleen cell culture supernatant. Another cytokine-chemokine was measured in LPS-stimulated spleen cell culture supernatant. One-way ANOVA and post hoc test were done in normally distributed data; otherwise Kruskal-Wallis and Mann-Whitney test were used. Ethical clearance of this study was provided by health research ethic committee of medical faculty Diponegoro University-Dr. Kariadi hospital (No. 426/EC/FK-RSDL/2015).

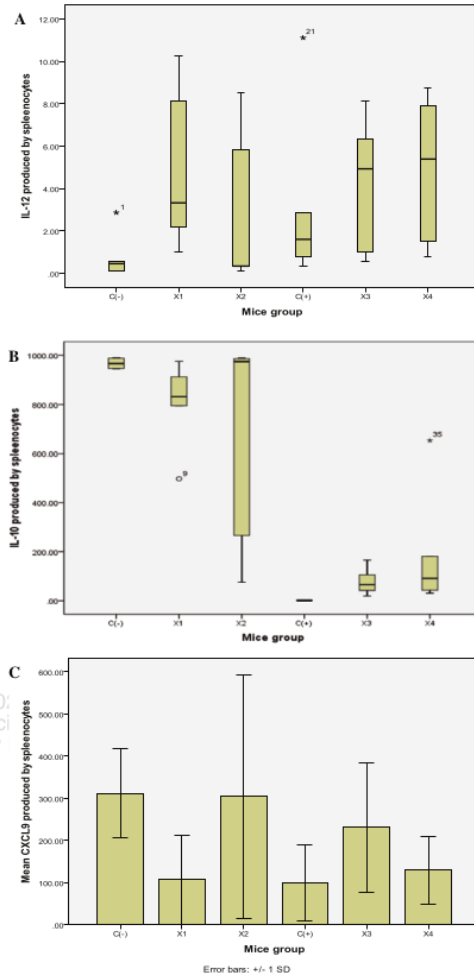
**3. RESULTS**

**3.1. IL-12 Produced by Stimulated Splenocytes**

IL-12 p70 produced by spleen-macrophage was not normally distributed in negative and positive control groups ( $p = 0.003$ ;  $p = 0.006$ ) (Fig. 1(A)). Data transformation was not successful, thus Kruskal-Wallis Test was performed. It showed that IL-12 p70 level produced by LPS-stimulated splenocytes was not different among six-studied groups ( $p = 0.071$ ).

**3.2. IL-10 Produced by Stimulated Splenocytes**

Kruskal-Wallis test on IL-10 produced by splenocyte stimulated with LPS showed significant differences among six group studied



**Fig. 1.** Box plot of Swiss mice in the ethanolic-AME study. (A) and (B) was box plot of splenic-IL-12 and IL-10 production, respectively. (C) was a graph of splenic-CXCL9 production. C(-), X<sub>1</sub> and X<sub>2</sub> groups were healthy Swiss mice. C(-) group received no AME treatment, while X<sub>1</sub> and X<sub>2</sub> groups were treated with AME 100 and 150 mg/kg BW/day, respectively. C(+), X<sub>3</sub> and X<sub>4</sub> groups were PbA-inoculated Swiss mice. C(+) group received no AME treatment without AME treatment. X<sub>3</sub> and X<sub>4</sub> groups treated with AME 100 and 150 mg/kg BW/day, respectively.

( $p = 0.0001$ ) (Fig. 1(B); Table I). Negative control group showed significantly higher IL-10 levels than all groups inoculated with PbA (positive control,  $p = 0.004$ ; X<sub>3</sub>,  $p = 0.003$ ; X<sub>4</sub>,  $p = 0.004$ ). Interestingly, C(+) group showed significantly lower IL-10 levels than X<sub>3</sub> and X<sub>4</sub> groups ( $p = 0.003$  and  $p = 0.004$ , respectively).

**3.3. CXCL9 Produced by Stimulated Splenocytes**

CXCL9 level of negative control group was significantly higher than positive control (C(+)) and X<sub>4</sub> groups ( $p = 0.019$  and

**Table I.** Mann-whitney *U* tests for IL-10 level.

Mice groups	p-value					
	C(-)	X <sub>1</sub>	X <sub>2</sub>	C(+)	X <sub>3</sub>	X <sub>4</sub>
C(-)		0.045*	0.715	0.004*	0.003*	0.004*
X <sub>1</sub>			0.754	0.006*	0.004*	0.011*
X <sub>2</sub>				0.006*	0.012*	0.045*
C(+)					0.003*	0.004*
X <sub>3</sub>						0.568
X <sub>4</sub>						

$p = 0.042$ , respectively) (Fig. 1(C); Table II). No difference was observed between those produced by C(+) and X<sub>3</sub> groups ( $p = 0.123$ ). Alike this finding, no difference was found between C(+) and X<sub>4</sub> groups ( $p = 0.727$ ). CXCL9 produced by C(-) group which was significantly higher than those in X<sub>1</sub> group ( $p = 0.024$ ), but similar to those in X<sub>2</sub> group.

Figures were box plot of Swiss mice in the ethanolic-AME study. Figures 1(A) and (B) was box plot of splenic-IL-12 and IL-10 production, respectively. Figure 1(C) was a graph of splenic-CXCL9 production. C(-), X<sub>1</sub> and X<sub>2</sub> groups were healthy Swiss mice. C(-) group received no AME treatment, while X<sub>1</sub> and X<sub>2</sub> groups were treated with AME 100 and 150 mg/kg BW/day, respectively. C(+), X<sub>3</sub> and X<sub>4</sub> groups were PbA-inoculated Swiss mice. C(+) group received no AME treatment, without AME treatment. X<sub>3</sub> and X<sub>4</sub> groups treated with AME 100 and 150 mg/kg BW/day, respectively.

**3.4. Levels of IFN- $\gamma$  and Correlation Analysis with IL-12, IL-10, and CXCL9 Released by Splenocytes**

The difference of IFN- $\gamma$  produced by splenocytes among six studied groups analyzed by Kruskal-Wallis test ( $p = 0.001$ ). Further analyses were done using Mann-Whitney *U* test (Table IV). Those produced by C(+) group was significantly lower than C(-) group ( $p = 0.004$ ). Those produced by X<sub>3</sub> and X<sub>4</sub> groups were also significantly lower than C(-) group ( $p = 0.003$  and  $p = 0.01$ ) (Tables III and IV). The IFN- $\gamma$  level were comparable among PbA-inoculated groups as it showed no difference between C(+) and X<sub>3</sub> groups ( $p = 0.668$ ). A similar finding was obtained by comparing those which produced by C(+) and X<sub>4</sub> groups ( $p = 0.873$ ). IFN- $\gamma$  levels released by C(-) was significantly higher than X<sub>1</sub> groups ( $p = 0.045$ ). The parallel finding was also found by comparing C(-) and X<sub>2</sub> groups ( $p = 0.028$ ). Correlation between splenic-IFN- $\gamma$  and IL-12, IL-10, CXCL9 production was also analyzed (Table V). IFN- $\gamma$  produced by all healthy groups including those of C(-), X<sub>1</sub> and X<sub>2</sub> groups, was correlated with IL-10 produced in the spleen ( $r = 0.544^*$ ;  $p = 0.029$ ). The PbA-inoculated groups including the C(+), X<sub>3</sub> and

**Table II.** Post hoc test for CXCL9 levels.

Mice groups	p value					
	C(-)	X <sub>1</sub>	X <sub>2</sub>	C(+)	X <sub>3</sub>	X <sub>4</sub>
C(-)		0.024*	0.931	0.019*	0.335	0.042*
X <sub>1</sub>			0.037*	0.926	0.146	0.797
X <sub>2</sub>				0.030*	0.407	0.062
C(+)					0.123	0.727
X <sub>3</sub>						0.231
X <sub>4</sub>						

**Table III.** IFN- $\gamma$  produce by stimulated splenocytes.

Mice group	IFN- $\gamma$ (pg/mL) median (min-max)
C(-)	554.36 (468.85–599.49)
X <sub>1</sub>	461.25 (14.22–499.73)
X <sub>2</sub>	113.27 (1.63–527.52)
C(+)	7.81 (1.15–17.78)
X <sub>3</sub>	6.37 (4.72–22.77)
X <sub>4</sub>	5.91 (2.82–518.49)

**Table IV.** Mann-whitney *U* test for IFN- $\gamma$  produce by stimulated splenocytes.

Mice groups	p-value					
	C(-)	X <sub>1</sub>	X <sub>2</sub>	C(+)	X <sub>3</sub>	X <sub>4</sub>
C(-)		0.045*	0.028*	0.004*	0.003*	0.010*
X <sub>1</sub>			0.465	0.011*	0.007*	0.068
X <sub>2</sub>				0.068	0.121	0.273
C(+)					0.668	0.873
X <sub>3</sub>						0.829
X <sub>4</sub>						

**Table V.** Correlation between IFN- $\gamma$  and others.

Cytokine	IFN- $\gamma$
Healthy group	
IL-12	$r = -0.373$ ; $p = 0.155$
IL-10	$r = 0.544^*$ ; $p = 0.029$
CXCL9	$r = 0.256$ ; $p = 0.339$
PbA-inoculated group	
IL-12	$r = -0.073$ ; $p = 0.766$
IL-10	$r = 0.107$ ; $p = 0.664$
CXCL9	$r = 0.581^{**}$ ; $p = 0.009$

Notes: Spearman test; \*significant with  $p < 0.05$ .

X<sub>4</sub> groups, was correlated with CXCL9 production (Table V;  $r = 0.581^{**}$ ;  $p = 0.009$ ).

**4. DISCUSSION**

There was no difference level of IL-12 p70 produced by splenocytes among six studied groups of mice ( $p = 0.071$ ). AME affects splenic IL-12 p70 production during CM phase has not been proved in Swiss mice. This also happened in healthy mice. Additionally, the possible influence of splenic-IL-12 p70 level in CM phase of Swiss mice, were not proved. There was no previous study showing IL-12 p70 level produced by splenocytes of Swiss mice during CM phase. IL-12 had been evaluated in different animal model and organs of ECM. IL-12 studied in PbA inoculated mice were recently done in C57BL/6, an ECM-susceptible mice, and it observed splenic-DC secreting IL-12 by using flow cytometry analysis. Earlier CM phase in phenylhydrazine treated mice was associated with higher number of splenic-DC secreting IL-12.<sup>25</sup> Pathologic effect of IL-12 was showed in IL-12-treated PbA inoculated mice deficient in interferon regulatory factor.<sup>31</sup> This pathologic effect was also showed in CpG treated-PbA inoculated Balb/c, ECM resistant mice.<sup>32</sup> The dependent protective effect of IL-12 p40 was evidence in Flt3 treated-PbA inoculated C57BL6 mice.<sup>33</sup> Other study showed the protective effect of IL-12 p70 was studied in PbA-inoculated C57BL6 mice treated *Toxoplasma gondii* antigen. This protective effect was confirmed

by exogenous IL-12 p70 treated PbA inoculated C57BL6 mice.<sup>34</sup> The immunopathologic and protective effects of IL-12, therefore remain controversial. The protective effect of IL-12 p70 was indicated by reducing parasitemia and protection from the death and CM development.<sup>34</sup> The earlier increase of IFN- $\gamma$  induced by IL-12 p70, contribute in the protective effect. Whether this occurs in PbA-inoculated Swiss mice treated AME warrant to be studied by observing those cytokines in the earlier time. This AME study showed no correlation between splenic-IL-12 p70 and IFN- $\gamma$  in all PbA-inoculated groups ( $r = -0.073$ ;  $p = 0.766$ ) (Table V).

By comparing positive and negative control groups, it indicated that low IL-10 produced by splenocytes associated with CM phase of Swiss mice. Although, AME was not able to normalize splenic-IL-10 production during CM phase. AME was associated with higher splenic-IL-10 production during CM phase (Fig. 1(B); Table I). Comparable IL-10 levels of  $X_3$  and  $X_4$  groups ( $p = 0.568$ ), was suggested that AME dose of 100 mg/kg BW/day was sufficient for up-regulating splenic-IL-10 production of Swiss mice during CM phase. The protective effect of higher IL-10 level in AME treated group need to be elucidated by evaluating the survival of IL-10-deficient mice treated AME and inoculated with PbA. By using IL-10-deficient mice, it was noticed that ECM protection was the independent of IL-10.<sup>34</sup> In the other hand, several studies support the protective effect of IL-10.<sup>35,36</sup> IL-10 was a predominant cytokine produced by PbA-inoculated mice treated with combination of Artemisone and other anti-malaria medication which successfully control PbA-infection.<sup>37</sup> Whether AME is suitable for adjuvant therapy of standard anti-malaria therapy, merits to be further studied.

By comparing C(-) and C(+) group, it was demonstrated that low level of CXCL9 produced by splenocytes associated with CM phase of Swiss mice. Although AME might not affect the splenic-CXCL9 levels during CM phase as indicated by the comparable CXCL9 level of C(+),  $X_3$  and  $X_4$  (Fig. 1(C); Table II). Splenic-CXCL9 levels of  $X_3$  group was comparable to those produced by C(-) group. These suggested that AME in somehow might modulate splenic-CXCL9 production during CM phase. AME might also modulate splenic-CXCL9 production in healthy Swiss mice as indicated by significantly lower CXCL9 level of  $X_1$  than C(-) group. CXCL9 is a chemokine which capable of attracting Th1 cells and lead the differentiation to Th1 cells.<sup>38</sup> CXCL9 and CXCR3, a receptor of CXCL9, are both linked to the development of CM in susceptible mice.<sup>29,30</sup> Inhibition of CXCL10, a chemokine that has similar function and similar receptor as CXCL9, may result in either protection or progression of different diseases.<sup>39,40</sup> These two later studies open possibility that low level of splenic-CXCL9 is pathologic while the normal of it is protective. This, however, necessitates being further studied.

The lower IFN- $\gamma$  produced by splenocytes was associated with CM phase of Swiss mice. This was indicated by a significantly lower of IFN- $\gamma$  levels in positive control than negative control groups (Table IV). A similar finding was also observed by comparing IFN- $\gamma$  levels of  $X_1$  and  $X_3$  groups. These findings were accompanied by the association of the lower splenic-IL-10 levels and CM phase. No correlation, however, was found between IFN- $\gamma$  and IL-10 production of all PbA-inoculated groups ( $r = 0.107$ ;  $p = 0.664$ ) (Table V). Instead, low level of splenic-IFN- $\gamma$  was correlated with low splenic-CXCL9 ( $r = 0.581^{**}$ ;  $p = 0.009$ ) (Table V) during CM phase. This correlation was weak. Factor(s)

having stronger relation with splenic-IFN- $\gamma$  production should be further elucidated.

## 5. CONCLUSION

AME might not influence both of splenic-IL-12 p70 and IFN- $\gamma$  production of CM-phase Swiss mice. AME, however, might increase splenic-IL-10 and normalize CXCL9 production of those mice. CXCL9 might regulate IFN- $\gamma$ -produced by the spleen of CM-phase Swiss mice regardless AME treatment. It is recommended to use CXCL9 deficient mice in order to strengthen this study before recommend the use of AME in the community.

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