# СОЕВОЕ МОЛОКО И ИМБИРЬ (*SULEHE*) УВЕЛИЧИВАЮТ ЭКСПРЕССИЮ PPAR-γ В ЭКСПЕРИМЕНТАЛЬНОЙ МОДЕЛИ ИНСУЛИНОРЕЗИСТЕНТНОСТИ У КРЫС

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**ВВЕДЕНИЕ**. Сахарный диабет 2-го типа (СД2) – метаболическое заболевание, характеризующееся гипергликемией вследствие дефекта секреции инсулина и формированием резистентности тканей организма к инсулину. Заболевание вызывает нарушение работы различных органов, включая глаза, почки и сердце. Одним из альтернативных продуктов, подходящих для употребления пациентами с СД2, является смесь соевого молока и имбиря (*Susu kedelai dan jahe (Sulehe)*, индонезийский). *Sulehe* содержит изофлавоны, полиненасыщенные жирные кислоты (ПНЖК) и гингеролы, которые влияют на инсулинорезистентность.

**Целью** данного исследования было изучение влияния *Sulehe* на экспрессию рецепторов, активируемых пероксисомными пролифераторами типа γ (англ. peroxisome proliferator-activated receptors-γ, (PPAR-γ)), при экспериментальной инсулинорезистентности у крыс

**МЕТОДЫ**. Данное лабораторное экспериментальное исследование in vivo было проведено на 24 крысах, которые были разделены на 6 групп: (1) группа отрицательного контроля, (2) группа положительного контроля, (3) группа крыс линии BioBreeding (BB), получавших соевое молоко по 5 г/кг, (4) группа BB крыс, получавших имбирь по 500 мг/кг, (5) группа BB крыс, получавших *Sulehe* (соевое молоко 2500 мг/кг + имбирь 250 мг/кг), (6) группа BB крыс, получавших *Sulehe* (соевое молоко 5000 мг/кг + имбирь 500 мг/кг). Все животные были предварительно рандомизированы. Мы применяли модель итогового исследования с использованием контрольной группы (без предварительного исследования).

**РЕЗУЛЬТАТЫ**. Средний уровень активности PPAR-γ в контрольной группе составил 578±82,02. Добавление в пищу *Sulehe* (соевое молоко 5000 мг/кг + имбирь 500 мг/кг) повышало экспрессию PPAR-γ до 1158±53,74. Сравнение показателей проводили с помощью дисперсионного анализа (ANOVA); различия между группами считали достоверными при p <0,05. Нами было обнаружена достоверная разница в уровнях экспрессии PPAR-γ между животными, получавшими соевое молоко + имбирь 500 мг, и контрольными животными, составившая –345,5.

**ЗАКЛЮЧЕНИЕ**. Таким образом, *Sulehe* является потенциальным средством, способным оказывать влияние на экспрессию PPAR-γ.

КЛЮЧЕВЫЕ СЛОВА: имбирь; инсулинорезистентность; PPAR-γ; соевое молоко

# SOY MILK AND GINGER (*SULEHE*) INCREASE PPAR-γ EXPRESSION IN A RAT MODEL OF INSULIN RESISTANCE

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**BACKGROUND**: Diabetes mellitus type 2 is metabolic disease characterized by hyperglycemia due to a defect in insulin secretion resulting in insulin resistance. This disease leads to dysfunction of various organs including eyes, kidneys, and heart. One of the alternative diets which can be consumed is a mixture of soy milk and ginger (Indonesian: Susu kedelai dan jahe (*Sulehe*)). *Sulehe* contains isoflavones, PUFAs, and gingerols that are affected by insulin resistance.

**AIM**: This study was aimed to discover the effect of *Sulehe* on peroxisome expression proliferator-activated receptor gamma (PPAR-γ) in a rat model of insulin resistance.

**METHODS**: Twenty-four rats were divided into six study groups: (1) negative control, (2) positive control, (3) soy milk 5 g/kg BB diet, (4) ginger 500 mg/kg BB diet, (5) *Sulehe* (soy milk 2500 mg/kg BB + ginger 250 mg/kg BB) diet, (6) *Sulehe* (soy milk 5000 mg/kg BB + ginger 500 mg/kg BB) diet. This research belonged to experimental in vivo laboratory study with all replications of each treatment across all subjects is completely randomized, and data retrieval with a post-test only control group design.

**RESULTS**: The mean PPAR-γ activity in normal (control) rats was 578 ± 82.02. *Sulehe* (soy milk 5000 g + ginger 500 mg) diet can increase rat PPAR-γ activity up to 1158 ± 53.74. The significant different result achieved when p-value on ANOVA analysis is less than 0.05 (p<0.05). According to the ANOVA analysis, there was a significant difference in PPAR-γ in the combination of soy milk + ginger 500 mg, with a difference of –345.5, compared with control.


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**CONCLUSION**: In summary, *Sulehe* may be a potential agent to influence PPAR-γ expression.

KEYWORDS: ginger; insulin resistance; PPAR-γ; soy milk

Diabetes mellitus (DM) is one of the significant human health threats of the 21st century [1]. Indonesia ranks seventh out of the ten countries with the highest prevalence of DM in the world, [2]. Among cases of DM, almost 90–95% is diabetes mellitus type 2 (DMT-2). DMT-2 is a metabolic disease characterized by chronic hyperglycemia. DM is closely related to the condition of insulin resistance. Medical efforts to improve insulin resistance in DMT-2 can be made pharmacologically and non-pharmacologically [3]. Pharmacologic improvement is achieved by administering drugs to improve insulin sensitivity, while a non-pharmacological improvement, in the form of lifestyle changes, physical exercise, and nutritional therapy, can improve the body's metabolic system. Nutritional therapy in DMT-2 can be achieved using a mixture of soy milk and ginger (*Sulehe*) as an alternative diet which contains isoflavones, PUFAs, and gingerol, and can lower blood glucose levels. Research conducted by [4] showed the giving of soybean milk and ginger 430 ml/day with 25gram protein content and addition of 3 gram of powdered ginger for 14 days in prediabetic women could significantly decrease fasting blood glucose levels with an optimal decrease of 12 mg/dl.

In DMT-2, peroxisome proliferator-activated receptor (PPAR) -1 specific ligand is an antidiabetic component that can decrease hyperglycemia primarily in fatty tissue [5]. The activation of PPAR-γ will increase the free fatty acids entry into adipose tissue. It can decrease the concentration of fatty acids in the plasma, causing the Tumor necrosis factor gamma (TNF-γ) response to decrease, resulting in increased transmission of insulin signals through increased activity of tyrosine kinase on insulin receptors. Reduced availability of free fatty acids can reduce insulin resistance. Several studies have shown that isoflavones, polyunsaturated fatty acids (PUFAs), and gingerol compounds can increase PPAR-γ expression [6,7,8]. PPAR has three isoforms: α, β/δ, and γ. PPAR-γ is the main regulator of adipogenesis which plays an important role in the storage of fat and glucose and cholesterol metabolism. PPAR-γ is most widely expressed in adipose tissue [9].

The isoflavones genistein and daidzein can bind directly and activate PPAR-α and PPAR-γ, thus causing increased beta-oxidation and insulin sensitivity; consequently, the concentration of fat in the blood and liver will decrease [10]. Kim et al. [11] also concluded that genistein and daidzein could increase PPAR-γ expression. Besides that, isoflavones turn out to work not only through bonds with Endoplasmic Reticulum (ERs) but also bind to PPAR-γ [9-13]. PUFAs consisting of omega-3 fatty acids can increase adiponectin levels due to suppression of inflammatory mediators, by decreasing Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation and PPAR-γ activation, thus decreasing liver glucose production, and increasing glucose uptake and free fatty acid oxidation in muscle [14-16]. Also, omega 3 (n-3) is a ligand for PPAR-γ that regulates expression of genes involved in glucose homeostasis. Activation of PPAR-γ causes an increase in expression of the gene encoding glucose transporter type 4 (GLUT4), resulting in up-regulation of GLUT4. GLUT4 is required to transport glucose into muscle cells. PPAR activation (PPAR-Ak) of insulin resistance results in an increase of insulin sensitivity in the liver, causing suppression of glucose production in the liver, and insulin sensitivity in skeletal muscle that causes increased glucose uptake [9].

Gingerol provides pharmacological and physiological activity such as antioxidant, anti-inflammatory, analgesic, anticarcinogenic, and cardiotonic effects [17]. Gingerol compounds can lower blood glucose levels by decreasing apoptosis of β-pancreatic cells, by increasing production and insulin sensitivity or by decreasing intestinal glucose absorption in hyperglycemia [18]. Based on these circumstances, this study will test in vivo the interaction of active compounds contained in *Sulehe*, and protein activity in insulin resistance conditions.

## AIM

This research aims to discover the effect of active compounds in *Sulehe* in the form of isoflavones, PUFAs, and gingerol against PPAR-γ expression in a rat model of insulin resistance.

## METHODS

### Research design

This test of the potential of *Sulehe* diet for improving insulin resistance to PPAR-γ expression is a true experimental laboratory in vivo study with a post-test only group design approach. This study used 24 healthy male Sprague Dawley rats aged 12 weeks and weighing 150–200 g. Rats were divided into six experimental groups: (1) negative control (C–), (2) positive control (C+), (3) soy milk 5000 mg/kg BB diet, (4) ginger 500 mg/kg BB diet, (5) *Sulehe* (soy milk 2500 mg/kg BB + ginger 250 mg) diet, 6) *Sulehe* (soy milk 5000 mg/kg BB + ginger 500 mg) diet.

### PPAR-γ activity examination

Insulin resistance was induced in rats using a high-fat and fructose diet (DTLF) method; their blood glucose levels were measured using a glucometer (Onetouch Ultra 2 (Lifescan Inc, USA) to confirm insulin resistance. Measurement of insulin resistance using HOMA-IR method (homeostatic model assessment - insulin resistance) which obtained by multiplying fasting glucose (mg/dL) with fasting insulin level (ng/mL)/405. Rats were insulin resistance if the value of HOMA-IR is 2. HOMA β was obtained by the formula (360 x Insulin levels): (Fasting glucose (mg/dl) - 63) x %.

A small drop of blood, obtained by pricking the skin with a lancet, was placed on a disposable test strip glucometer to calculate the blood glucose level. Level of glucose was displayed in units of mg/dl or mmol/l.

### Western blot

Soy milk, ginger, and *Sulehe* were given once a day using a feeding tube, for 30 consecutive days. PPAR-γ activity was examined using a western blot method with rat skeletal muscle tissue samples. Each tissue samples was suspended with a buffer containing 20mM Tris-HCl, 1mM EDTA, and 0.1 mM PMSF. The cell suspension was centrifuged at 12,000 rpm for

**Table 1.** Descriptive statistics analysis

| Group | PPAR-γ | |
|---|---|---|
| | Mean | SD |
| Negative control (normal) | 578 | 82,02 |
| Positive control | 81.5 | 119.50 |
| Soy milk (only) 5 g | 711 | 123.04 |
| Ginger (only) 500 mg | 499.5 | 118.09 |
| Soy milk + ginger (*Sulehe*) 250 mg | 864 | 172.53 |
| Soy milk + ginger (*Sulehe*) 500 mg | 1158 | 53.74 |

5 minutes, at 4°C then centrifuged again at 15,000 rpm for 1 hour at 4°C. The sample was reconstituted with 15% SDS-PAGE gel. The electrophoresis gel was washed with distilled water and soaked in a blotting buffer. The nitrocellulose (NC) membrane was soaked with Phosphate Buffer Saline (PBS) for 10 minutes at room temperature and immersed in blotting buffer before blotting process. The further transfer was carried out for 12 hours at 25 volts at 4°C. The membrane was then blocked in PBS-T Skim milk 5% for 1 hour while shaking and washed 3x5 minutes in PBS-T. The membrane was incubated with primary antibodies in PBS-T Skim 5% (1: 200) overnight at 4°C and washed 3x5 minutes with TBS. The membrane was then incubated with secondary antibody Alkaline Phosphatase (AP) conjugated (1: 2500 in TBS) for 1 hour at room temperature and washed with PBS-T for 4x5 minutes. Further protein or antigen bands detection was conducted with the addition of Western Blue substrate (in dark room) to the membrane overnight. The reaction was stopped by washing the membrane with distilled water.

### Ethical review

This study has been approved by Animal Care and Use Committee University of Brawijaya No. 687/KEP/UB signed on Jan 20, 2017.

### Statistical analysis

The data were analyzed for normality and homogeneity. The data used to conclude are group data with Shapiro–Wilk normality test values > 0.05 and with homogeneity of variance test values > 0.05. Data were analyzed by one-way ANOVA, followed by a least significant difference (BNT) test to determine the significant differences between treatments ($p < 0.05$).

## RESULTS

The results of this study are presented below: (1) descriptive statistical analysis, (2) homogeneity test results, (3) normality test results, and (4) one-way ANOVA test results.

### Descriptive statistics analysis

The results of analysis of PPAR-γ descriptive statistics are presented in Table 1.

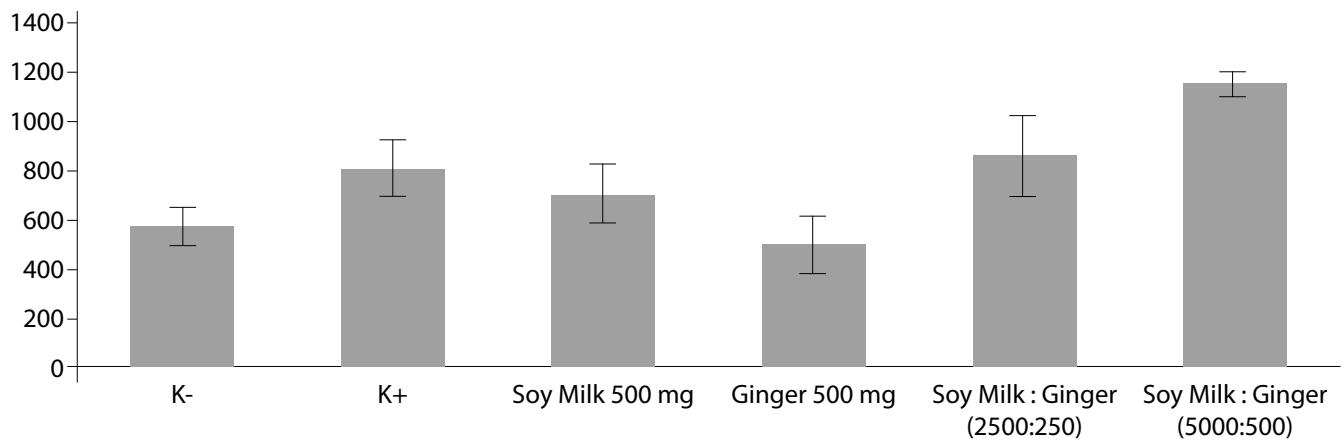


**Fig. 1.** Histogram of GLUT4, PPAR-gamma, and serine expression for each experimental treatment.

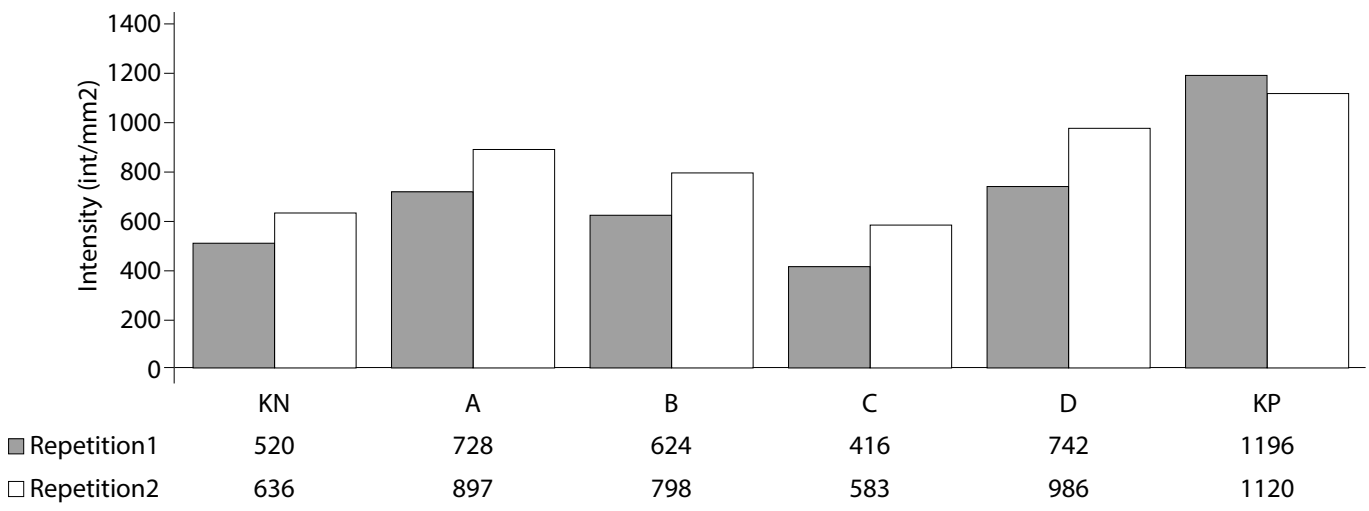


**Fig. 3.** Western blotting results for PPAR-γ, GLUT4, and serine for each treatment group.

**Table 2.** Normality test

| Variable | Sig | Status |
|---|---|---|
| PPAR-γ | 0.960 | Normal |

**Table 3.** Homogeneity test

| Variable | Sig | Status |
|---|---|---|
| PPAR-γ | 0.000 | Not homogenous |

**Table 4.** ANOVA test results

| | Sum of squares | Df | Mean square | F | Sig |
|---|---|---|---|---|---|
| Between groups | 460465.000 | 4 | 115116.250 | 7.572 | .024 |
| Within groups | 76019.000 | 5 | 15203.800 | | |
| Total | 536484.000 | 9 | | | |

**Table 5.** Summary of ANOVA test results

| Variable | Sig | Status |
|---|---|---|
| PPAR-γ | 0.024 | Significantly different |

The PPAR-γ level in normal rats was 578 ± 82.02. The *Sulehe* diet given to group 6 (soybean milk 5000 mg/kg BB + ginger 500 mg/kg BB) yielded the highest mean level of PPAR-γ, 1158 ± 53.74. The lowest average, 449.5 ± 118.09, was found in the group given only 500 mg ginger (Figure 1).

**Table 6.** Descriptive statistics analysis

| (I) group | (J) group | Mean difference (I – J) | Std. error | Sig. | 95% confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower bound | Upper bound |
| Positive control | P1 | 101.50000 | 123.30369 | .448 | −215.4622 | 418.4622 |
| | P2 | 313.00000 | 123.30369 | .052 | -3.9622 | 629.9622 |
| | P3 | −51.50000 | 123.30369 | .694 | −368.4622 | 265.4622 |
| | P4 | −345.50000* | 123.30369 | .038 | −662.4622 | −28.5378 |
| P1 | Positive control | −101.50000 | 123.30369 | .448 | −418.4622 | 215.4622 |
| | P2 | 211.50000 | 123.30369 | .147 | −105.4622 | 528.4622 |
| | P3 | −153.00000 | 123.30369 | .270 | −469.9622 | 163.9622 |
| | P4 | −447.00000* | 123.30369 | .015 | −763.9622 | −130.0378 |
| P2 | Positive control | −313.00000 | 123.30369 | .052 | −629.9622 | 3.9622 |
| | P1 | −211.50000 | 123.30369 | .147 | −528.4622 | 105.4622 |
| | P3 | −364.50000* | 123.30369 | .032 | −681.4622 | −47.5378 |
| | P4 | −658.50000* | 123.30369 | .003 | −975.4622 | −341.5378 |
| P3 | Positive control | 51.50000 | 123.30369 | .694 | −265.4622 | 368.4622 |
| | P1 | 153.00000 | 123.30369 | .270 | −163.9622 | 469.9622 |
| | P2 | 364.50000* | 123.30369 | .032 | 47.5378 | 681.4622 |
| | P4 | −294.00000 | 123.30369 | .063 | −610.9622 | 22.9622 |
| P4 | Positive control | 345.50000* | 123.30369 | .038 | 28.5378 | 662.4622 |
| | P1 | 447.00000* | 123.30369 | .015 | 130.0378 | 763.9622 |
| | P2 | 658.50000* | 123.30369 | .003 | 341.5378 | 975.4622 |
| | P3 | 294.00000 | 123.30369 | .063 | −22.9622 | 610.9622 |

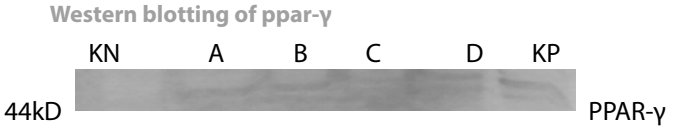


**Fig. 2.** Western blot of GLUT4, PPAR-γ, and Ser-636 for each treatment group

**Least significant difference (LSD) statistics results**

a. Normality test results

A Shapiro–Wilk test was used because of n < 50. The results obtained are shown in Table 2.

The results of the normality test on the PPAR-γ variable show a sig value > 0.05, concluding that the data have a normal distribution.

b. Homogeneity test results

This test used Levene's test, and results are shown in Table 3.

The homogeneity results indicate that the PPAR-γ variable is not homogeneous (p-value < 0.000).

c. One-way ANOVA test results

Normality of terms was fulfilled, and the variety of data already known. The test was continued to determine whether there were differences in overall results based on the treatment provided (Table 4 and 5).

Based on the ANOVA test results, there were differences in all four treatments (sig ANOVA < 0.05). The significant differences for each treatment can be seen in the following LSD post hoc results (Table 6).

## DISCUSSION

From Table 7, it can be seen that there was a significantly different PPAR-γ result only for the combination of soy milk +

**Table 7.** Summary of post hoc LSD results

| | PPAR-γ | |
|---|---|---|
| | **Difference** | **IK 95%** |
| C+ vs soy milk (only) 5 g | 101.5 | 0.448 |
| C+ vs ginger (only) 500 mg | 313 | 0.052 |
| C+ vs *Sulehe* (soy milk 2500 mg + ginger 250 mg) | −51.5 | 0.694 |
| C+ vs *Sulehe* (soy milk 5000 mg + ginger 500 mg) | −345.5 | 0.038 |

ginger 500 mg, with a difference value is −345.5. The results of this study show that PPAR-γ expression increased in insulin resistance-modeled rats, but *Sulehe* (soy milk 5000 mg + ginger 500 mg) showed a higher rate of PPAR-γ than the insulin resistance model. From these results, it is clear that the treatment provided in this study up-regulates PPAR-γ activity. PPAR-γ is important in the proliferation and differentiation of adipocytes, through the activity of free fatty acid influx into adipocytes, and decreases cytokine expression [19]. This statement explains that the combination *Sulehe* therapy blocks serine-636 phosphorylation and improves insulin sensitivity, as evidenced by increased PPAR-γ post-treatment activity in the combination therapy group. This explains that *Sulehe* consumption during treatment inhibits the access of inflammatory cytokines through the PPAR-γ activation pathway.

As described by Kintscher and Law, the loss of PPAR-γ activity in skeletal muscle results in insulin resistance conditions through impaired insulin levels in adipose and liver tissue [20]. This was validated by the results of this study, in that the PPAR-γ activity in the non-treated DM control group was higher than that in the normal group (578). This could be explained by the brief induction of the high-fat diet during the manufacture of insulin resistance models so that acute induction will increase PPAR-γ activity as a form of homeostatic compensation [12], but there is no explanation regarding the procedure of making an insulin resistance model. PPAR-γ agonist application gives a more direct effect on skeletal muscle. This explains why the *Sulehe* diet affected PPAR-γ in skeletal muscle (rat insulin resistance model) compared to other experimental groups. In fact, the expression of PPAR-γ in skeletal muscle is only about 5–10% of its expression level in adipose tissue, and PPAR deficiency in muscle causes secondary insulin resistance in adipose and liver tissue. This study suggests further study on the importance of looking at the comparison of PPAR-γ in adipose tissue and a liver peripheral resistance model after administration of *Sulehe* [20].

## CONCLUSION

Based on the results of this study, it can be concluded that *Sulehe* or combination of soy milk and ginger at certain concentration could increase PPAR-γ expression significantly. Hence, *Sulehe* could be an alternative diet for people with type 2 diabetes melitus to reduce the insulin resistence.

## ADDITIONAL INFORMATION

**Source of funding.** This research had no financial funding.

**Conflict of interests.** Authors declare no explicit and potential conflicts of interests associated with the publication of this article.

**Author's involvement**. Wiwik Handayani developed the study design and edited manuscript, Sri Andarini collected the data and performed statistical analysis, Diana Lyrawati drafted and edited the manuscript, and Achmad Rudijanto performed laboratory testing and edited the manuscript.

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