TRENDS IN SCIENCES 2026; 23(2): 11240
https://doi.org/10.48048/tis.2026.11240
RESEARCH ARTICLE

Soybean Tempeh Extract on Improving Oxidative Stress, Angiogenic, Cardiovascular Dysfunction, And Fetal Outcome in A Rat Model of Preeclampsia

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Received: 11 July 2025, Revised: 7 September 2025, Accepted: 17 September 2025, Published: 20 November 2025

Abstract

Preeclampsia is a pregnancy complication that affects multiple organs. Antioxidant approaches have been widely studied to address it, but their bioavailability is limited. This study aims to analyze effects of Soybean Tempeh Extract (STE) on improving oxidative stress, cardiovascular function, angiogenic and fetal weight in preeclamptic rats. A total of 30 Sprague Dawley pregnant rats were divided into five groups: Normal, negative control, positive control (MgSO4), Treatment 1 (STE), and Treatment 2 (STE + MgSO4). Induction of preeclampsia was carried out with L-NAME, and STE was given at a dose of 400 mg/kgBW/day. MDA, NT-proBNP, sFlt-1, Angiotensin II and urine protein levels were measured using ELISA or other biochemical methods. Examination of the labyrinthine/junction zone ratio and ventricular thickness using histology. Measurement of blood pressure and protein is measured periodically. Data were analyzed by one-way ANOVA and repeated-measure ANOVA. STE significantly reduced MDA, NT-proBNP, sFlt-1, Angiotensin II, blood pressure, proteinuria, and fetal weight ($p < 0.001$) and improved the labyrinthine/junction ratio in histopathology placental tissue ($p < 0.001$) compared to the negative control group. Heart ventricular thickness in histopathology also showed similarities to the normal group although not significant. STE improves clinical and molecular parameters in preeclamptic rats, especially in reducing oxidative, angiogenic, cardiovascular stress, and fetal weight. Soybean tempeh extract has the potential as a local food-based adjuvant therapy in efforts to improve preeclampsia.

Keywords: Angiogenic, Cardio vascular, Oxidative stress, Preeclampsia, Soybean tempeh

Introduction

Preeclampsia is a pregnancy disorder characterized by high blood pressure, high oxidative stress, and endothelial dysfunction [1]. Cases of death due to preeclampsia are 9% - 26% of maternal deaths in developing countries and 16% in developed countries [2]. The pathophysiology itself is still being studied. The problem of preeclampsia does not end after birth; hypertension persists three months after birth [3]. In the long term, a history of preeclamptic pregnancy also has an impact on cardiovascular problems in the mother [4]. Finding safe, efficient, and easily accessible interventions is still the number one health concern worldwide because of the condition's complexity and severity.

Several pharmacological interventions for preeclampsia aim to reduce complications and seizures [5,6]. Preventive interventions such as aspirin and calcium supplementation may be options in high-risk groups, but are not always successful in late-onset [7]. While pharmacological interventions may reduce some risks, they do not address the underlying causes of preeclampsia, highlighting the need for further research into its pathogenesis and the development of more targeted therapies for oxidative stress [6].

The development of antioxidant isolates using natural ingredients is now starting to be explored as an additional method or a safe alternative [8]. A systematic review shows that using antioxidants has good potential, but still experiences limitations in low bioavailability in inhibiting clinical implementation [9]. One effort to increase food bioavailability is by using fermentation. Fermentation significantly increases bioavailability of important micronutrients such as Fe, Ca, Mg, and Zn in food [10].

Phytate content and other anti-nutrients, including antioxidants, can increase absorption and reduce oxidative stress [10]. Soybean fermentation is a traditional practice in many Asian countries. In Indonesia, the most common fermented product is tempeh. Tempeh is made from fermented soybeans and Rhizopus Sp. Fungi. Soybeans have protein, unsaturated fat, and isoflavone content. Peptide content and soybean antioxidants have anti-inflammatory activity [11]. Soybean fermentation increases nutritional value, essential amino acids, and bioactive compounds. This process also reduces anti-nutritional factors, making soybeans easier to digest and beneficial for health [12,13].

Fermentation of soybeans into tempeh can increase the highest bioactive peptides and isoflavone compounds (especially genistein and daidzein) compared to other soy products [14]. The content of isoflavones and phenolics plays a role in maintaining endothelial function and regulating hormonal activity, while bioactive peptides have antioxidant and antihypertensive activities. Tempeh has potential agents in antidiabetes, lowering cholesterol and hypertension, improving cognitive function, antitumor activity, anti-aging effects, and intestinal health [15]. A review shows the potential of tempeh in developing functional rights involving activating the antioxidant signaling pathway mediated by Nuclear factor erythroid 2-related factor 2 (Nrf2), which protects cells from oxidative stress by increasing the expression of antioxidant enzymes such as catalase (Cat) and Superoxide Dismutase (SOD) [16]. However, interventions involving antioxidant compounds or new drugs developed in vulnerable patients cannot be directly tested on humans. The *in vitro* and *in vivo* stages are then continued with clinical trials. *In vitro* studies on tempeh extract on cell death have been carried out, but have never been carried out on preeclampsia models and experimental animals [17].

One of the mouse animal models shows the response angiogenic, namely Nω-nitro-L-arginine methyl ester (L-NAME), inhibiting the angiogenic process in pregnancy [19,20]. STE can be assumed to have the potential to treat preeclampsia by reducing inflammatory reactions and increasing angiogenic factors. This can be an alternative companion therapy or may be an alternative substitute to overcome the problem of preeclampsia. This study aims to determine the Effect of STE on improving oxidative stress, angiogenic, cardiovascular dysfunction, and fetal outcome in a rat model of preeclampsia.

Materials and methods

Chemicals

The author used serum reagent Enzyme-linked immunosorbent assay (ELISA) by BT Laboratory (China) for blood serum Malondialdehyde (MDA), soluble fms-like tyrosine kinase-1 (sFLT-1), N-terminal pro-B-type natriuretic peptide (NT-proBNP) and Angiotensin II. Protein Bradford protein Assay (BCA) by Elabscience (China), L-NAME by Tokyo Chemical Industry (Japan), Magnesium Sulfat (MgSO4) by Medikbio (Indonesia), the Hematoxilin and Eosin (HE) by Histoline Laboratories (Italy), dehydration and clearing by JT Baker (USA).

Product material and screening phytochemicals

Researchers used local tempeh from a local soybean tempeh producer fermented with *the fungus Rhizopus Sp* for 48 - 60 h [21] in Bandar Lampung. Tempe is then determined, dried using an oven, and ground into 50 mesh. Tempe powder extract with 70% alcohol content for 3×24 h. The filtrate results are filtered and the water content is removed using a rotary

evaporator, then stored in an oven at 40 °C until absolute to be STE. Processing done by the Functional Service Unit of Tawangmangu Traditional Health Services, Dr. Sarjito General Hospital, Central Java.

A phytochemical STE test was conducted at the Integrated Research and Testing Laboratory of Gadjah Mada University for total flavonoid and phenolic testing. Total flavonoid and phenolic testing uses flavonoid testing. Standard weight: Quercetin standard 10.0 mg. Add 0.3 mL of 5% sodium nitrite. After 5 min, add 0.6 mL of 10% aluminum chloride, wait 5 min, and add 2 mL of 1 M sodium hydroxide. Add distilled water up to 10 mL with a measuring cup. Move to the cuvette, fixed absorption at a wavelength of 510 nm. Weigh ± 50 mg of sample, add 2 mL of 4N HCl, and hydrolyze in an autoclave at 110 °C for 2 h. Filter the sample, and add ether to the filtrate. Extraction with ether, take the ether phase. Repeat as much as 3x—dry phase ether. Add 0.3 mL of 5% sodium nitrite to the dry sample. After 5 min, add 0.6 mL of 10% aluminum chloride, wait 5 min, and add 2 mL of 1 M sodium hydroxide. Add distilled water up to 5 mL with a measuring cup. Dilute according to need. Move to the cuvette, fixed absorption at 510 nm.

Testing Phenolic Standard weight standard sour error 10.0 mg add 0.5 mL of reagent folin-ciocalteu and 7.5 mL of aquabides. The mixture is left for 10 min at room temperature, then 1.5 mL of 20% sodium carbonate is added. The mixture is then heated in a water bath at 40 °C for 20 min and quickly cooled in ice water. Dilute with aquabidest to a volume of 10 mL. Transfer into a cuvette, and keep the absorbance at a wavelength of 760 nm. Weigh ± 50 mg of sample, add 1 mL of ethanol, 50% sonication for 10 min. Add 0.5 mL of Folin-Ciocalteu reagent and 5 mL of aquabides. The mixture is left for 10 min at room temperature, then 1.5 mL of 20% sodium carbonate is added. Add aquabidest to a volume of 10 mL. Dilute as needed. Transfer into a cuvette, keep the absorbance at a wavelength of 760 nm. Mineral and biopeptide testing was conducted at PT Saraswati Indo Genetech (SIG), Bogor, Indonesia with certificate number: SIG.LHP.I.2025.311053021 and SIG.LHP.II.2025.281611071. Antioxidant tests were carried out at the Integrated. Research and Testing Laboratory of Gadjah Mada University using the DPPH Ic50 method with Certificate 822/UN1/LPPT/TR/2025.

Animal preparation

This research was conducted in an integrated laboratory. Biomedical Faculty of Medicine, Universitas Islam Sultan Agung (UNISSULA), Semarang, Indonesia. This study used Sprague-Dawley rats. Dawley was obtained from the Integrated Biomedical Laboratory of the Faculty of Medicine, UNISSULA. 30 female rat weighing 200 - 250 g, aged 8 -10 weeks. The rat were kept in standard laboratory cages for seven days with room conditions of 26° ± 3C and a dark and light pattern every 12 h.

***In vivo* study**

Rats acclimatized for seven days are then mated when they reach the estrus cycle with a male rat by monomating. The diagnosis of pregnancy is obtained approximately 17 h after mating, by checking for the presence of a copulatory plug that closes the vagina to the cervix, as well as the presence of sperm in the vaginal smear. If proven pregnant, the female rat will be declared on day 0 Gestational Day (GD) 0. The mice were then randomly divided into 5 groups. These groups were divided into: Normal (N) with No Treatment, Negative Control (C–) induction with L-NAME group only, Positive control (C+) treatment with L-NAME + MgSO4, Treatment 1 (T1) treatment with STE, Treatment 2 (T2) L-NAME + MgSO4 + STE. The dose of L-NAME was given at 75 mg/ kgBW /day subcutaneously. On 9-19 GD [23]. Administration of MgSO4 270 mg/KgBW/day on 17 and 19 GD [5]. The optimum dose of STE, based on preliminary studies of 100, 200 and 400 mg/kgBW/day, and the optimum dose of 400 mg/kg/BW was found to be the best at lowering blood pressure in the preeclampsia rat model (**Figure 1**).

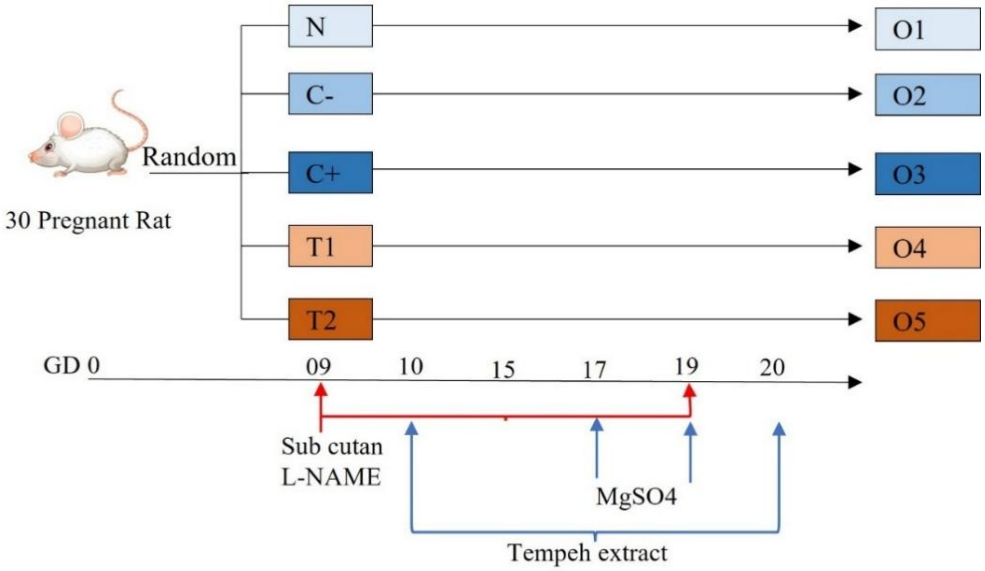

Figure 1 Design study.

Assessment marker in preeclampsia

Routine monitoring of rats, such as urine protein and blood pressure examinations on GD-8, 16 and 20, was carried out. Rats were placed individually in metabolic cages for 12 h to collect urine samples, which were centrifuged and analyzed using the BCA kit. Blood pressure measurements were made using the tail-cuff (non-invasive CODA) method to avoid pain and stress. On the 20th day of GD, the rats' blood was taken and then given intraperitoneal anesthesia using a mixture of ketamine and xylazine at a dose of 75 - 100 mg/kg: 5 - 10 mg/kg (ratio 10:1). After the animal was completely unconscious, the euthanasia procedure was continued with cervical dislocation. The placenta and heart organs were taken for histopathological analysis. The fetuses were taken, and the weight of each fetus was calculated and then averaged.

MDA marker analysis of oxidative stress, NT-ProBNP cardiac marker, sFlt-1 marker angiogenic, and Angiotensin blood pressure marker using blood serum and ELISA testing. The ELISA procedure uses the sandwich method. The procedure begins with adding 50 µl of standard into the well. 40 µl of sample was added to the well, then 10 µl of biotinylated antibody was added. Into the sample well, 50 µl Streptavidin-HRP was added to the wells (except blank control), mixed, covered the plate with sealer, and incubated for 60 min at 37 °C. Remove the sealer. Then wash the plate 5 times with wash buffer (300 µl per wheel), then let stand for 30 - 60 s. Dry the plate on absorbent paper. Add 50 µl of substrate per well and incubate for 10 min at 37 °C in the dark, then add 50 µl of stop solution until the well turns from blue to yellow (10 min). Measurement of absorbance values at a Wavelength of 450 nm using a microplate reader [25].

Histology

Histopathological measurements on the heart and placenta organs using the HE staining method. Cardiac ventricular thickness indicates cardiovascular disorders. The ratio zone labyrinthine/junction shows the balance between the exchange of substances and hormonal structures in the placenta and the preeclampsia model. The heart and placental tissues were cut and then fixed in 10% formalin solution, and dehydration was continued with 70% ethanol until absolute ethanol. Oxylene was used for clearing, infiltration, and embedding in paraffin. The tissue was cut with a 3 - 5 µm thickness using a microtome, then attached to a glass slide. The samples were dried, deparaffinized, dehydrated, and stained with H&E using the protocol from Histoline [26]. Analysis using a light microscope (Leica, Germany). Measurement of ventricular thickness using the transverse zone from the endocardium to the epicardium [27]. In the labyrinthine zone and junction zone, use the central cut and then

count the ratio from the long labyrinthine to the junction [23].

Analysis statistics

After the data is obtained, it is divided into groups. The data is analyzed using SPSS version 24 software. The mean and standard deviation values are calculated. The normality test uses Shapiro-Wilk in each group, and the homogeneity test uses Levene's test. Analyze every group using a way analysis of variance test, followed by a post hoc Tukey test or a Games-Howell test. Repeated-measure analysis of variance was used to test blood pressure and protein in urine. Research. This is significant with alpha 0.05 and CI 95%.

Ethical approval

This study was conducted principle of the National Institute of Health Guidelines on the Use of Laboratory Animals and fulfill the Declaration of Helsinki which has been approved by the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University, Semarang, Central Java, Indonesia with the number: No. 80/II/2025/ Bioethics Commission. During the study, the authors adhered to the research protocol with Replacement, Reduction, and Refinement principles.

Results and discussion

Phytochemicals, total phenols and flavonoids, minerals, and bioactive peptides

The results of phytochemical tests using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) Inhibitory Concentration 50% (IC50) method showed antioxidant activity of 4,875 mg/mL. The total flavonoid content was 2.5 mg/g. The total phenolic content, the equivalent of gallic acid, was recorded at 71.90 mg/g. This shows that the antioxidant potential of STE is high in anti-inflammatory properties (**Table 1**).

Content and bioactive peptides in the STE. There is mineral content of potassium (111.89 mg/100 g), magnesium (6.37 mg/100 g), manganese (0.17 mg/100 g), sodium (19.91 mg/100 g), and calcium (6.46 mg/100 g). There is much content of bioactive amino acids, such as L-alanine (653.85 mg/kg), L-leucine (632.18 mg/kg), L-proline (570.09 mg/kg), L-glutamate (929.63 mg/kg), L-Arginine, and L-Lysine. Results. This shows that tempeh powder has its own mineral and peptide content, which is bioactive, showing that the extract of tempeh has its benefits for Nutrition and Health (**Table 1**).

Table 1 Content of the extract tempeh.

No	Properties	Level	Unit
	Antioxidant activity		
1	DPPH IC50	4,875	mg / mL
	Mineral		
1	Potassium (K)	111.89	mg /100 g
2	Magnesium (Mg)	6.37	mg /100 g
3	Manganese (Mn)	0.17	mg /kg
4	Sodium (Na)	19.91	mg /100 g
5	Calcium (Ca)	6.46	mg /100 g
	Peptides		
1	L-Alanine	653.85	mg /100 g
2	L- Arginine	920.60	mg /100 g
3	Glutamic Acid	929.63	mg /100 g
4	L- Histidine	-	mg /100 g
5	L- Sistine	-	mg /100 g
6	L- Leucine	632.18	mg /100 g

No	Properties	Level	Unit
7	L-Lysine	534.97	mg /100 g
8	L-Tryptophan	<402.34	mg /100 g
9	L- Valine	917.14	mg /100 g
10	L- Proline	570.09	mg /100 g

Extract tempeh to repair oxidative stress, Angiogenic and Cardiac dysfunction

Examination of MDA levels showed high oxidative stress in the preeclamptic rat model. MDA levels C– had the highest MDA levels in groups T1 and T2, and the STE and combination supplementation had MDA levels almost the same as N. There were significant differences in all groups ($p < 0.001$) (**Table 2**). MDA levels in the C– group were significantly higher than the N, C+, T1, and T2 groups ($p < 0.05$). No significant difference existed between the N, C+, T1, and T2 groups. The results showed that STE and MgSO4 supplementation could significantly reduce MDA levels in the preeclamptic rat model (**Figures 2(A)**).

The administration of L-NAME includes the critical development phase of the placenta and organogenesis to fetal growth, thus showing a pattern of preeclampsia at early onset [23]. L-NAME works as an endothelial Nitric Oxide Synthase (eNOS) inhibitor, inhibiting Nitric Oxide (NO) production so that vasoconstriction and blood flow to the placenta occur and cause hypertension symptoms similar to preeclampsia, endothelial dysfunction and increased risk of multi-organ complications [28]. This finding is the first to show that the combination of STE 400 mg/kgBW/Day on GD 10 - 19 with MgSO4 270 mg/kgBW/Day on GD 17 and 19 can improve the pathological pathway of preeclampsia through decreasing MDA. Tempeh extract has been shown to increase the expression of major antioxidant enzymes such as CAT, superoxide dismutase-2 (SOD2), and superoxide dismutase-3 (SOD3) in HepG2 cells, which are very important for reducing oxidative stress by neutralizing Reactive Oxygen Species (ROS) [29]. Tempeh has been suggested to activate the Nrf2-mediated antioxidant response, which reduces inflammation and oxidative stress. This pathway increases the expression of antioxidant proteins that protect against cellular damage [30]. The combination with MgSO4 in this study showed the best results and was almost close to the MDA levels in the normal group. MgSO4 increases vasodilatory activity by increasing nitric oxide and prostacyclin levels, which help reduce vascular resistance and improve endothelial function in preeclamptic pregnancy. Combining MgSO4 with antioxidants can provide a dual approach to managing preeclampsia by addressing the preeclamptic condition's seizure and oxidative components. The role of MgSO4 in reducing oxidative stress through its effects on nitric oxide and prostacyclin levels and its interaction with free radicals complements antioxidant strategies to enhance the body's natural defenses against oxidative damage [31].

Serum sFlt-1 levels were measured as a marker of angiogenic problems in preeclampsia. The results found that the C– group had the highest sFlt-1 levels, while the treatment group 2 had the lowest (p value < 0.001) (**Table 2**). sFlt-1 levels in the K-group were significantly higher in all groups. In addition, there was no significant difference between the N, C (+), T1, and T2 groups. The combination of STE and MgSO4 significantly reduced sFlt-1 levels to close to the normal group (p value 0.001) (**Figures 2(B)**). The results showed that soybean STE and MgSO4 supplementation can help angiogenesis disorders in preeclamptic rats by reducing sFlt-1 levels.

Table 2 Differences in MDA, sFlt-1, Angiotensin II, and Nt-ProBNP levels in the model mouse preeclampsia given STE.

Group	n	Mean±SD	*p value*
MDA (nmol/mL)			
N	6	1.26 ± 0.05	<0.001**
C (-)	6	4.17 ± 1.21	
C (+)	6	1.94 ± 0.89	
T1	6	1.42 ± 0.24	
T2	6	1.39 ± 0.16	
sFlt-1 (ng/L)			
N	6	4.26 ± 0.93	<0.001**
C (-)	6	9.65 ± 1.60	
C (+)	6	6.27 ± 1.83	
T1	6	5.65 ± 2.24	
T2	6	3.84 ± 0.98	
Angiotensin II (pmol/L)			
N	6	163.26 ± 46.70	0.012*
C (-)	6	239.86 ± 21.22	
C (+)	6	203.95 ± 54.64	
T1	6	174.09 ± 35.12	
T2	6	167.06 ± 30.12	
NT- ProBNP (ng/L)			
N	6	193.54 ± 33.43	
C (-)	6	293.95 ± 95.33	
C (+)	6	276.05 ± 39.68	
T1	6	282.43 ± 23.99	
T2	6	220.79 ± 50.30	
Ventricular thickness (nm)			
N	6	1,732.93 ± 174.07	0.414
C (-)	6	1,987.18 ± 318.94	
C (+)	6	1,572.76 ± 480.56	
T1	6	1,691.98 ± 537.27	
T2	6	1,762.00 ± 132.48	
Labyrinthine /Juction Zone Ratio (mm/mm)			
N	6	13.68 ± 1.36	<0.001
C (-)	6	3.71 ± 1.29	
C (+)	6	5.54 ± 0.82	
T1	6	5.06 ± 1.75	
T2	6	8.98 ± 1.15	

Test description: * significant at alpha = 0.05, **significant at 0.001.

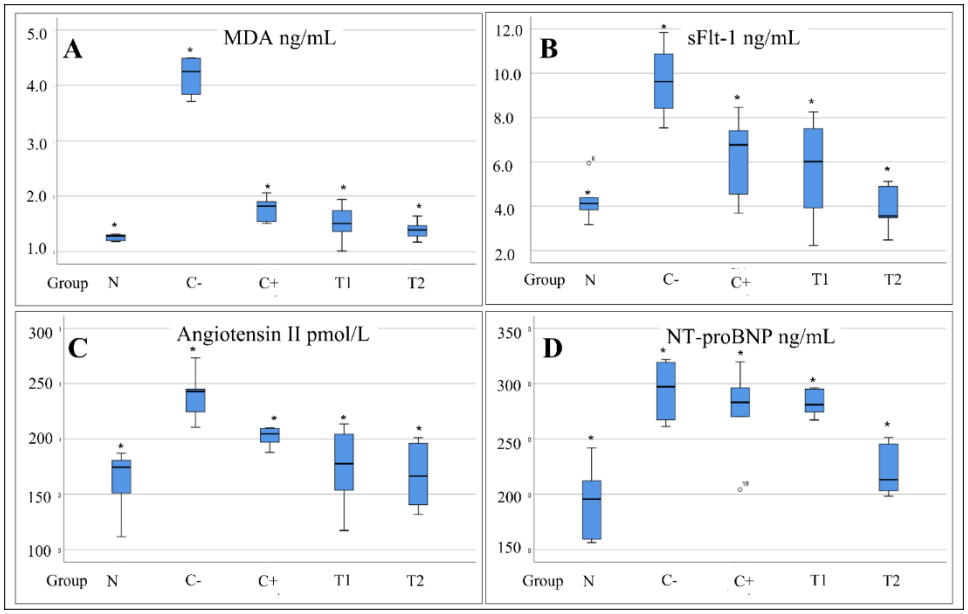

Figure 2 Effect of Supplementation extract tempeh on serum MDA, sFLT-1, Angiotensin II, and NT-proBNP in preeclampsia model. The results showed that the combination of extract Tempeh 400 mg/ KgBB and MgSO4 significantly differed from the negative control and approached to Normal (*p value < 0.05).

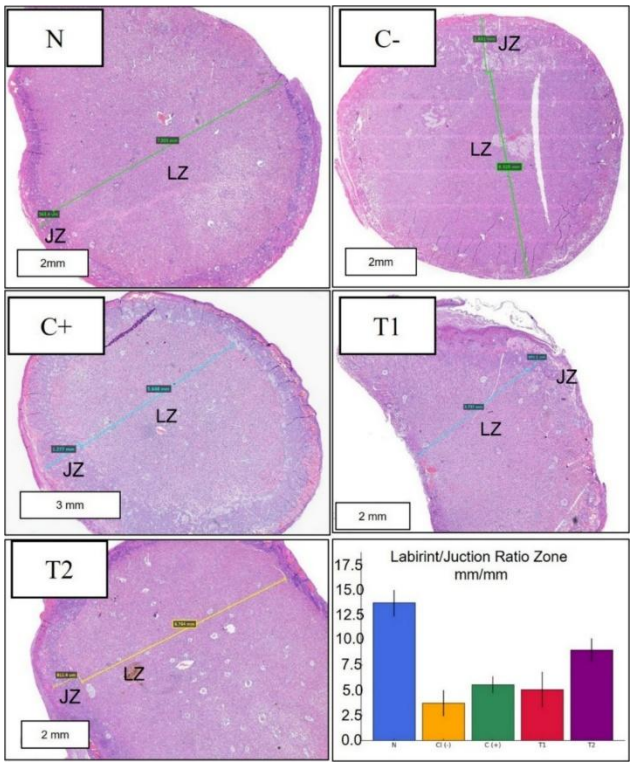

Figure 3 Effects of Supplementation STE On Placental Repair. N, C–, C+, T1 and T2 Histology Placenta Evaluated At GD-20. The Placenta Was Excised and Then Colored Using Hematoxylin and Eosin to See The labyrinthine/junction zone Ratio in The Five Groups. ratio long average of labyrinthine zone and junction zone analyzed statistics showed p < 0.05 in all groups. LZ: Labyrinthine Zone, JZ: Junction Zone.

The labyrinthine/junction ratio is an important indicator of angiogenic activity and the potential for preeclampsia development. The ratio of the labyrinthine zone to the junction of the N group had the highest ratio, and the K-group experienced a sharp decrease. The ratio of the C+ group was almost the same as T1. STE and

MgSO4 supplementation significantly increased this ratio in treatment group T2 (p value < 0.001). The results of the Post hoc test of the labyrinthine zone/junction ratio showed that the T2 group showed a significant increase compared to N, K-, T1, and T2 ($p < 0.05$), although still below normal values. Overall, these results indicate that administration of STE and MgSO4 can improve the structure of the labyrinthine zone and placental junction as well as the ratio of both in the preeclampsia model, although it has not completely matched the normal group (**Figure 3**).

The decrease in sFlt-1 in the group receiving STE and the combination dose showed a decrease in sFlt-1 levels to near normal levels, indicating an improvement in the maternal angiogenic and endothelial environment. The entry of sFlt-1 into the maternal circulation binds to Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF). The sFlt-1 protein is similar to VEGFR1 but does not have a membrane-spanning domain [32]. This causes a decrease in the ratio of angiogenic factors such as VEGF and PlGF. [33]. The protective effect of the intervention is likely derived from the content of isoflavones, phenolics, and bioactive peptides in tempeh which are able to inhibit oxidative stress and inflammation, so that the production of sFlt-1 by the placenta can be suppressed. These results are consistent with recent literature that suggests that sFlt-1 reduction and improved angiogenic balance are critical for improving placental function and pregnancy outcomes in preeclampsia [18]. Soybean extract, rich in isoflavones, has been shown to significantly reduce sFLT-1 levels *in vitro*, suggesting a potential therapeutic role in managing preeclampsia. Isoflavones in soy products such as tempeh may exert antioxidant effects, reducing oxidative stress and sFLT-1 production [18,34]. Although MgSO4 does not directly affect sFLT-1 levels, it helps manage preeclampsia symptoms, such as hypertension and seizures, providing symptomatic relief [31]. The combination of STE and MgSO4 potentially offers a comprehensive approach to preeclampsia by addressing the underlying pathophysiology (via sFLT-1 reduction) and clinical symptoms (via MgSO4). This dual strategy may improve maternal and fetal outcomes by reducing the severity of preeclampsia symptoms and potentially prolonging pregnancy [35,36].

The increase in the labyrinthine/junction zone ratio in the placenta confirms these results. The combination group showed better results, although it could not match normal. The ratio of the labyrinthine/junction zone, especially the ratio of angiogenic factors to antiangiogenic factors, is closely related to the pathogenesis of preeclampsia through its impact on angiogenesis. This study showed that the ratio of the labyrinth junction zone in the normal group was 13.68 ± 1.36, while in the control group it was 3.71. The study is in line, explaining that the reported range of the labyrinthine/junction ratio (10 - 15) is consistent with the morphological changes observed in the rat placenta during the last pregnancy [39]. Stress and other physiological conditions can alter placental development, potentially affecting the balance between the labyrinthine and junction zones. Previous studies have shown that L-NAME induction decreases the labyrinthine junction ratio below four [23]. The potential increase in the reduction of antiangiogenic factors, such as sFLT-1, by soy extract may also contribute to improved placental function and nutrient transport, especially in conditions such as preeclampsia [18]. Isoflavones or their mechanisms related to antioxidant and anti-inflammatory activities in inhibiting ROS formation or increasing the expression of angiogenic factors such as VEGF. This mainly focuses on the antiangiogenic role of various flavonoids, including their effects on signaling pathways and the expression of factors such as VEGF, but the mechanism of isoflavones in improving the angiogenic pathway [40]. It is significant in preventing adverse outcomes such as severe preeclampsia or fetal growth retardation.

The vascular response to Angiotensin II in preeclampsia increased, so blood pressure rises more than in a normal pregnancy (**Table 2**). The results of the Angiotensin II measurements showed a significant difference between groups ($p = 0.012$), where group K had the highest levels of Angiotensin II. In contrast, the normal group and T2 showed almost the same level. Supplementation with the STEin groups T1 and T2 can lower Angiotensin II levels, meaning approaching values in the normal group (**Figures 2(C)**) Hypertension can cause damage to the heart with NT-proBNP indicators and thickening of the ventricles, which can lead to preeclampsia. NT- ProBNP levels in rat models of preeclampsia show a significant difference between

groups ($p < 0.001$), with group C having the highest NT-ProBNP levels. On the other hand, group N has the lowest NT-ProBNP levels, followed by group T2, which received a combination, showing NT-ProBNP levels. Post hoc test showed NT-proBNP levels in group N were significantly lower than those in group C–, C+, and T1 ($p < 0.05$) (**Table** 2). NT-proBNP levels in the T2 group were significantly lower than those in group C– and T1, but not significantly lower than those in group C+ and group N (**Figures 2(D)**). The results showed that NT-proBNP levels can be decreased significantly more in the near-normal group in the mouse model of preeclampsia when tempeh soya bean extract is added with MgSO4 (T2).

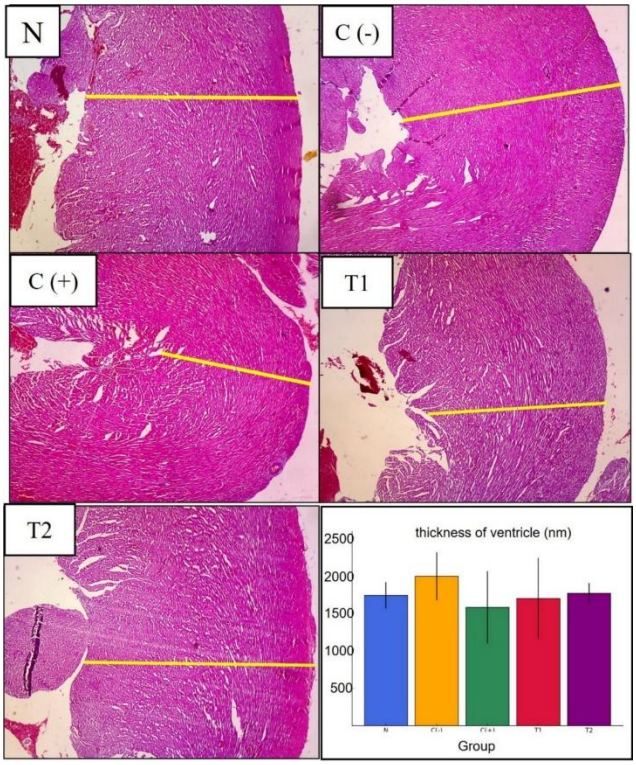

Figure 4 Effect of tempeh extract supplementation on heart repair. The heart's N, C–, C+, T1, and T2 histology were evaluated at GD20. The transverse section of the heart was stained with Hematoxylin and Eosin in the heart's 5 groups of ventricular sections. The calculation used 4 - 6 fields of view, which were averaged, and the calculation results were analyzed statistically. There was no significant difference in the average thickness of the ventricle; the N and T2 groups had almost the same average thickness.

Comparison of the thickness of the heart ventricles in 5 groups of preeclampsia model rats with various treatments. The average thickness of the ventricles in the normal pregnant group without intervention was 1,732.93 ± 174.07 µm. The C– group showed the highest ventricular thickness, indicating a tendency for ventricular hypertrophy. In contrast, the C+ had a lower average ventricular thickness. In the T1 and T2 groups, respectively, the values were relatively close to the normal group. The results of the statistical test showed that there was no significant difference between groups ($p = 0.414$). This shows that preeclampsia induction does not cause significant morphological changes in the thickness of the ventricles; however, the presence of this thickening change is a consideration in the problem of preeclampsia (**Table 2** and **Figure 4**).

In this study, the change in ventricular thickness in the combination group (T2) was almost the same as that of the normal group (N), although there was no significant difference. L-NAME induction increased hypertension in rats, but this damage did not cause significant changes [41]. NT-proBNP levels are associated with structural changes in the heart, such as increased left ventricular mass and left atrial dimensions, which are markers of cardiac remodeling [42]. NT-proBNP is produced and released by the

heart's ventricles in response to mechanical load and wall pressure, making it a reliable indicator of cardiac function and stress [43]. Increased NT-proBNP levels are associated with increased left ventricular end-systolic volume, decreased ejection fraction, and impaired contractility, indicating impaired ventricular function in cases of preeclampsia [44,45].

Administering soybean tempeh extract to preeclamptic rats has significantly reduced urine protein levels, especially in the combination treatment group, compared to the negative control and positive control groups. In animal studies, tempeh has been shown to improve protein malnutrition. Mice fed with freeze-dried tempeh powder showed normalized serum protein levels and increased gut flora, indicating improved protein metabolism [46]. The content of bioactive peptides in green beans can inhibit enzymes such as Angiotensin Converting Enzyme (ACE), which plays a role in blood pressure regulation. This activity can indirectly affect urea metabolism by affecting kidney function and nitrogen excretion [47].

Extract tempeh repair pressure blood and Protein Urine

Measurement of blood pressure, including systolic and diastolic pressure, in 5 groups of preeclampsia model rats was observed in three examinations, namely GD-8, GD-16 and GD-19. In GD-8, all relatively stable groups under pressure systolic and diastolic blood pressure (p value = 0.766; 0 = 0.246). Group C– showed a increase significant in both systolic and diastolic blood pressure ($p < 0.001$), indicating severe preeclampsia. The C+ group also experienced a significant increase in blood pressure on GD-16 and a slight decrease on GD-19 ($p < 0.001$). Group T1 experienced an increase in blood pressure, systolic and diastolic, at the end of the observation, but its value was still lower compared to group C. In group T2, both systolic and diastolic blood pressure were relatively stable during the entire research period ($p = 0.268$), and its value is closest to the normal group. One-way ANOVA test at each time measurement shows no meaningful difference between groups on GD-8. However, there is a significant difference in GD-16 and GD-19 for blood pressure systolic and diastolic (p value < 0.001) (**Table 3** and **Figure 4**). These results show that supplementation with STE and MgSo4 effectively stabilizes blood pressure and prevents hypertension and weight gain in the preeclampsia rat model, so the approach restores the normal blood pressure pattern in the group.

The administration of combination doses also improves the cardiovascular system. Angiotensin II levels are lower, blood pressure is more controlled, so it protects against heart damage, such as decreased NTpro-BNP levels, and prevents anatomical damage to the heart. Angiotensin II increases the pro-inflammatory and pro-fibrotic effects in the kidneys, worsening kidney damage and causing further impairment of kidney function [48]. Angiotensin II contributes to oxidative stress by promoting ROS production, which inactivates NO, a critical vasodilator, thereby disrupting endothelial function [49]. The intervention effect is most likely derived from the ability of isoflavones and bioactive peptides in tempeh which can suppress the activity of the Angiotensin-Converting Enzyme (ACE) enzyme, so that Angiotensin II production is reduced [50]. Thus, tempeh extract plays a role in improving blood pressure regulation and reducing oxidative stress and inflammation in pregnancy with preeclampsia. These findings align with recent studies that confirm that nutritional interventions that lower Angiotensin II can potentially improve cardiovascular outcomes in preeclampsia [51]. In line with previous studies, black soybean and adzuki bean extracts, which contain isoflavones, have been found to lower blood pressure by modulating the renin-angiotensin system. These extracts significantly reduced angiotensin-converting enzyme and Angiotensin II levels in SHR, suggesting a direct impact on this critical blood pressure regulatory pathway. Soy isoflavone supplementation resulted in a significant reduction in systolic blood pressure compared to the control group. This effect was attributed to increased antioxidant defenses and modulation of the renin-angiotensin system [52]. The potential for isoflavones and bioactive peptides in tempeh to inhibit ACE activity is important in the broader context of dietary interventions in managing hypertension. The effectiveness of these compounds may vary based on factors such as bioavailability, stability during digestion, and interactions with other food components [53].

Table 3 Differences in blood pressure (systole and diastole) and urine protein in the fifth group in the rat model of preeclampsia given supplementation of soya bean tempeh extract.

Variables	GD-8	GD-16	GD-19	*p* value *
Systolic				
N	115.58 ± 6.90	114.78 ± 6.25	112.78 ± 6.90	0.766
C (–)	117.42 ± 7.42	142.68 ± 6.38	172.00 ± 11.75	<0.001
C (+)	113.47 ± 7.03	150.51 ± 10.04	131.38 ± 11.04	<0.001
T1	118.80 ± 4.93	126.94 ± 7.37	133.60 ± 7.99	0.016
T2	118.94 ± 4.53	122.2 ± 6.56	122.43 ± 11.19	0.574
p value **	0.518	<0.001	<0.001	
Diastolic				
N	78.86 ± 5.90	82.28 ± 4.21	83.25 ± 4.36	0.249
C (–)	81.33 ± 3.61	95.77 ± 10.66	131.56 ± 17.42	< 0.001
C (+)	79.39 ± 4.89	112.66 ± 14.71	101.22 ± 12.51	0.003
T1	81.64 ± 4.21	88.72 ± 6.18	98.28 ± 10.02	0.010
T2	81.96 ± 8.04	89.11 ± 6.17	87.10 ± 13.00	0.268
p value **	0.816	<0.001	<0.001	
Urine protein				
N	10.65 ± 0.19	10.92 ± 0.50	11.29 ± 0.16	0.085
C (–)	10.06 ± 1.13	18.06 ± 1.15	19.14 ± 0.94	<0.001
C (+)	10.21 ± 0.57	17.11 ± 0.52	14.30 ± 0.94	<0.001
T1	11.21 ± 0.32	12.41 ± 0.64	12.18 ± 0.50	0.005
T2	10.20 ± 1.33	13.72 ± 1.19	12.54 ± 0.23	0.01
p value **	0.148	<0.001	<0.001	

Test description: * repeated measures ANOVA, ** One Way ANOVA Test.

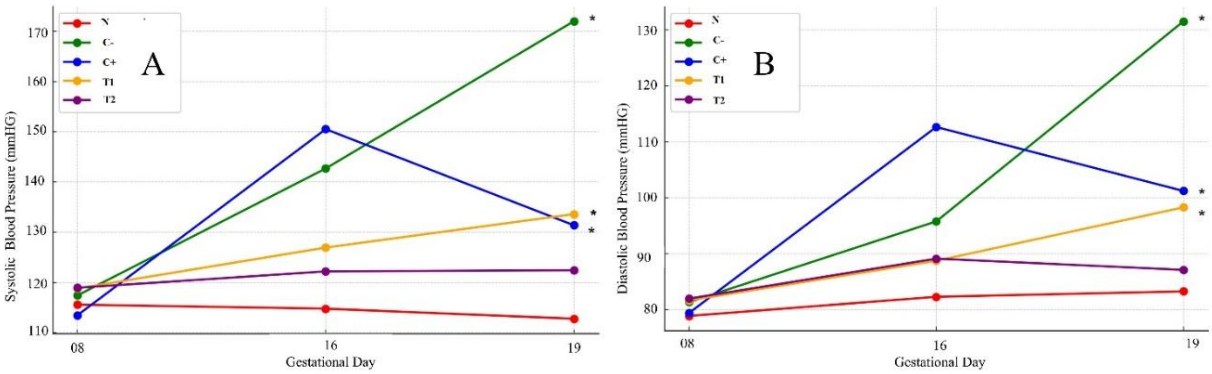

Figure 3 Effects of Supplementation extract tempeh under pressure blood (systolic and diastolic in the preeclampsia model. These results show an effect combination, which shows a pattern change in blood pressure that is almost stable. The same is true for the normal group (*p* value > 0.0%), while groups C (–) and C (+) showed a significant increase (**p* value < 0.05).

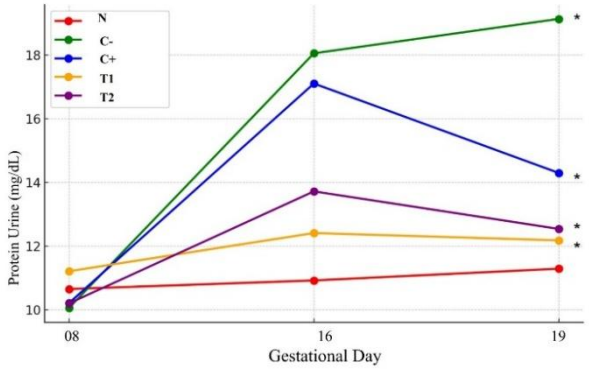

Figure 4 Trend of differences in urine protein in each group. These results show that there is an effect combination that shows a pattern of changes in urine protein that are closest to normal, whereas groups C (–) and C (+) showed a significant increase (**p* value < 0.05).

The effect of STE on protein repair can be seen from Group N having stable urine protein levels from GD-8 to GD-19 (*p* value > 0.05). In contrast, the negative C– experienced a significant increase in urine protein from GD-8 to GD-16 (*p* value < 0.001). The C+ also showed a similar increase pattern, but not as high as C– (<0.001). Groups T1 and T2 showed lower urine protein levels but still had a significant increase (*p* value < 0.05). The inter-group test showed no significant difference in GD-8 (*p* value 0.148), but there was a significant difference in GD-16 and GD 19 (*p* value < 0.001). This confirms that STE effectively reduces or prevents increased proteinuria in the preeclampsia rat model (**Table 4**).

STE has shown significant antioxidant activity, which can protect against oxidative stress. This is important for maintaining cellular health and can affect metabolic processes related to urea and protein metabolism [54]. Bioactive compounds in tempeh, such as isoflavones, contribute to its anti-inflammatory properties. This can further support metabolic health and potentially affect urea metabolism by reducing inflammation-related metabolic disorders [29].

STE to improve fetal weight outcomes

Fetal weight measurement in this study directly indicates the effect of intervention on the ability to improve or protect fetal growth amid preeclampsia stress. The results showed a significant difference between the N and C– groups. The N group had the highest fetal weight, while the C+ and T1 groups had almost the same fetal weight, 4.41 ± 0.74 g and 4.40 ± 0.34 g; and the T2 group had a higher fetal weight (*p* value < 0.001. The Post hoc test results showed that the fetal weight in the N group was significantly greater than the C–, C+, and T1 (*p* value < 0.05), but not significant in the T2 group (**Table 5**). The results showed that the combination of STE and MgSO4 in the T2 group was able to significantly increase fetal weight compared to the untreated preeclampsia group, with results approaching the normal group.

Tempeh extract, rich in soy isoflavones, has significantly reduced sFLT-1 levels in human umbilical vein endothelial cell cultures exposed to preeclamptic plasma, indicating its potential in reducing endothelial dysfunction in preeclampsia. The antioxidant properties of soy isoflavones can reduce oxidative stress, a key factor in the pathophysiology of preeclampsia, thus potentially enhancing the therapeutic effects of MgSO4 [18]. Combining STE and MgSO4 may offer a comprehensive approach to managing preeclampsia by targeting the angiogenic imbalance and oxidative stress. While MgSO4 addresses the vascular and endothelial aspects, STE may enhance antioxidant defenses and subsequently reduce antiangiogenic factors, potentially leading to improved clinical outcomes.

Finally, the outcome of fetal weight increased in the combination and was almost close to normal. Preeclampsia involves dysregulation of angiogenic factors, such as an imbalance between sFlt1 and placental growth factor (PGF), contributing to placental insufficiency and affecting fetal growth [55]. The renin-angiotensin and immune system changes are also involved in preeclampsia, affecting placental development and fetal weight [56]. This study showed that the STE group experienced increased fetal weight

and improved oxidative stress, angiogenic, and cardiovascular system parameters. Administration of MgSO4 effectively treats and prevents eclampsia by increasing blood flow in the uterine, cerebral, umbilical, and fetal arteries, which can improve fetal circulation and growth [57]. It acts as a neuroprotective agent for premature babies and helps delay preterm labor, which can contribute to increased fetal weight by providing more time for fetal development [58]. Combining MgSO4 and STE can provide a dual approach: MgSO4 increases blood flow and nutrient delivery to the fetus, while STE reduces oxidative stress, contributing to increased fetal weight.

Table 4 Differences in fetal weight in the preeclampsia rat model given soybean tempeh extract.

Group	n	Mean±SD	*p value*
Fetal Weigh (g)			
N	6	5.68 ± 0.29	<0.001**
C (–)	6	3.86 ± 0.61	
C (+)	6	4.41 ± 0.74	
T1	6	4.40 ± 0.34	
T2	6	4.91 ± 0.69	

Test description: * significant at alpha = 0.05, **significant at 0.001.

Conclusions

This study's results indicate that administering STE and MgSO4 in preeclamptic rats can reduce oxidative stress, improving angiogenesis. The placental structure is balanced, and STE also plays a role in ACE inhibitors to reduce Angiotensin II so that blood pressure decreases, cardiovascular function increases, and fetal weight approaches normal. These results are valuable because STE can be an adjuvant therapy as an anti-inflammatory and antihypertensive agent in cases of preeclampsia. Further research is needed in several stages to achieve clinical practice in its application.

Acknowledgements

The author would like to thank the Center for Higher Education Funding and Assessment Ministry of Higher Education, Science and Technology of the Republic of Indonesia (No: 02336/J5.2.3./BPI.06/9/2022) for providing Beasiswa Pendidikan Indonesia (BPI) in the Doctoral Study Program of Medical Sciences, Faculty of Medicine, Universitas Sebelas Maret, Indonesia.

Declaration of Generative AI in Scientific Writing

The author uses AI to draw blood pressure data to improve the image quality with the original data owned by the author. The author declares that he does not use AI tools in writing, editing and no images are manipulated using AI.

CRediT Author Statement

Apri Sulistianingsih: Conceptualization, Investigation, writing-Original Draft, formal analysis, Data curation. **Soetrisno:** Supervision, Conceptualization, data analysis, Writing-Review & editing. **Adi Prayitno:** Supervision, Resources, Writing-Review & editing. **Risya Cilmiaty:** Supervision, Conceptualization, Cata curation, editing. **Brian Wasita:** Resources, Investigation, Vizualization, formal analysis. **Vitri Widyaningsih:** Methodology, Formal analysis, Writing-Review & editing. **Paramasari Dirgahayu:** Supervision, data Curation, Writing-Review & editing.

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