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The effect of *Physalis Angulata* L. (Ciplukan) fruit extract on preeclamptic trophoblast cell cultures on TGF- β and TNF- α levels

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Abstract

Background: Preeclampsia is a pregnancy complication characterized by hypertension, proteinuria, and dysfunction of other organs, which can endanger both the mother and the fetus. Due to its complex pathophysiology involving inflammatory and immunological processes, exploration of alternative therapies with anti-inflammatory potential is needed. *Physalis angulata* L. (ciplukan) is known to contain bioactive compounds that may modulate inflammatory mediators.

Purpose: To evaluate the effectiveness of parental holding as a non-pharmacological intervention in reducing pain and anxiety responses in children undergoing invasive hospital procedures, particularly among critically ill pediatric patients

Method: This study evaluated the effects of ciplukan fruit extract on TGF- β and TNF- α levels in preeclamptic trophoblast cell cultures. Trophoblast cells were isolated from placentas of patients with preeclampsia and treated with various doses of ciplukan fruit extract. Levels of TGF- β and TNF- α were measured using the ELISA method

Results: The implementation of parental holding during invasive procedures was associated with a reduction in children's pain responses and anxiety levels. Children who received parental holding showed calmer behavior, reduced distress, and improved cooperation during procedures such as IV insertion and injections compared to those who did not receive the intervention.

Conclusion: Parental holding is an effective non-pharmacological intervention for reducing pain and anxiety in children undergoing invasive hospital procedures. This approach can be safely applied, particularly in critically ill children, to improve comfort and support family-centered care in pediatric settings.

Keyword: Ciplukan Fruit Extract; Inflammation; Preeclampsia; TNF- α ; TGF- β .

INTRODUCTION

Preeclampsia is a serious pregnancy complication characterized by elevated blood pressure exceeding 140/90 mmHg after 20 weeks of gestation, accompanied by organ damage, particularly the kidneys and liver. This condition not only endangers the mother's health but also significantly impacts the growth and well-being of the fetus if not optimally managed (Saputri & Fransiska, 2023; Marwah, Zata, Naufal, Fadhilah, & Fithri, 2023). The World Health Organization (WHO) lists

preeclampsia as a leading cause of high maternal and neonatal mortality rates worldwide. In Indonesia, the prevalence of preeclampsia is estimated to range between 5-10% of all pregnancies. Data from the 2019 Indonesian Health Profile shows that hypertension in pregnancy, including preeclampsia, caused 1,066 maternal deaths out of a total of 4,221 maternal deaths, ranking second only to hemorrhage (Darmayasa, Putra, Silvana, & Raharja, 2023). These high incidence and mortality rates indicate that

preeclampsia remains a maternal health problem that requires more in-depth attention and scientifically based treatment (Saputri & Fransiska, 2023; Putri, Yunita, & Viridula, 2021).

Clinically, preeclampsia is often accompanied by various additional symptoms such as edema in the hands, feet, or face, and increased protein levels in the urine (proteinuria) (Ayuningtyas, 2020). These symptoms indicate a systemic disorder occurring in the mother's body during pregnancy. One of the main mechanisms in the pathogenesis of preeclampsia is the failure of optimal trophoblast invasion into the uterine wall. Trophoblasts are cells that form the outer layer of the embryo and play a role in implantation and placental formation. Trophoblast cells function in interactions with the maternal endometrium, the decidualization process, and the formation of placental tissue that supports fetal growth and development (Pramatirta & Krisnadi, 2023). In preeclampsia, incomplete trophoblast invasion leads to impaired spiral artery remodeling, resulting in inadequate blood flow to the placenta.

Impaired spiral artery remodeling in preeclampsia results in intermittent placental blood flow. This condition triggers repeated ischemia and reperfusion, leading to placental tissue hypoxia. This hypoxia plays a role in triggering oxidative stress and cellular damage in placental tissue. This disrupts trophoblast function and triggers an excessive inflammatory response. Chronic oxidative stress worsens endothelial dysfunction and increases the risk of pregnancy complications. This condition also contributes to the release of various inflammatory mediators into the maternal circulation (Rahmawati, Retnaningrum, & Rahasti, 2020).

Trophoblast dysfunction in preeclampsia is closely related to an increased inflammatory response characterized by changes in cytokine levels. Cytokines are intermediary proteins secreted by immune cells and play a role in regulating the immune response, inflammation, and cell differentiation. Two key cytokines involved in the inflammatory process in preeclampsia are Transforming Growth Factor Beta (TGF- β) and Tumor Necrosis Factor Alpha (TNF- α). TGF- β functions as an anti-inflammatory cytokine that regulates growth, differentiation, cell migration, and maintains immune balance in trophoblast cells. Conversely, TNF- α is a pro-inflammatory cytokine

that plays a role in inflammation, apoptosis, and activation of the immune response. An imbalance between TGF- β and TNF- α can lead to failure of healthy placental formation and exacerbate preeclampsia (Agustina, Sukarni, & Amalia, 2022; Hartati, 2024).

Efforts to prevent and control increased pro-inflammatory cytokine levels in preeclampsia require a safe and effective therapeutic approach during pregnancy. One alternative that has the potential to be developed is the use of natural ingredients, such as the ground cherry fruit (*Physalis angulata* L.). Ground cherry fruit is known as an herbal plant that has various bioactive contents, including flavonoids, alkaloids, steroids, physalin, tannins, vitamin C, and essential fatty acids that are beneficial for health (Fadli & Subakti, 2021; Laia, 2022; Prabandari & Sari, 2025). Various studies have shown that ground cherry fruit has antihypertensive, antioxidant, antidiabetic, anticancer, and antibacterial activities (Munthe & Sembiring, 2023). Based on the phenomena that have been described, this study aims to examine the effect of ground cherry fruit extract on the levels of TGF- β and TNF- α cytokines in preeclamptic trophoblast cell cultures as an indicator of inflammatory response and biological therapeutic effectiveness.

RESEARCH METHOD

This is a laboratory experimental study with a Control Group Post-Test Design, conducted using a Completely Randomized Design (CRD). The selection of the RAL was based on the homogenous nature of the trophoblast cell culture used as the research object. Trophoblast cells were obtained from placental tissue and served as the primary unit of analysis in this study. All treatments were carried out in accordance with standard laboratory procedures and applicable cellular research guidelines. The study was conducted from January to March 2025 at the Physiology Laboratory of the Faculty of Medicine, Brawijaya University, Malang. Placental tissue was obtained from a private hospital in Surabaya through normal vaginal deliveries and cesarean sections with prior patient consent.

The study samples consisted of trophoblast cells isolated from the placenta of pregnancies with preeclampsia. The placenta was chosen because it is the primary organ connecting the mother and fetus

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and plays a role in the pathophysiology of preeclampsia. All samples were obtained from preeclampsia patients who underwent cesarean section delivery at a private hospital in Surabaya. Prior to sample collection, all patients signed an informed consent form as a form of written consent. The obtained placentas were then transported to the Physiology Laboratory of the Faculty of Medicine, Brawijaya University, using a transport cord solution containing PBS to maintain physiological pH and prevent contamination. Upon arrival at the laboratory, the placentas were immediately processed for trophoblast cell isolation and culture.

Trophoblast cell isolation and culture were performed within 12 hours of delivery to ensure optimal cell viability and proliferation. The isolation process followed an enzymatic method with a mechanical approach. Placental tissue was cleaned using PBS-A, then the cells were grown in DMEM medium containing 10% FBS in 6-well plates coated with 0.2% gelatin as an extracellular matrix. The cultures were then incubated in an incubator with 5% CO₂ at 37°C for approximately 3 days until the cells reached confluent. The culture medium was changed after the first 24 hours to prevent contamination, and then every other day throughout the incubation period.

After successful culture, trophoblast cells were divided into five treatment groups, each consisting of five samples, resulting in a total of 25 samples, according to the Federer equation with $(n-1)(t-1) \geq 15$, where n is the number of samples, t is the number of treatment groups and sample groups. The groups consisted of a negative control group (K-) without treatment, and four treatment groups with the administration of ground cherry (*Physalis angulata* L.) fruit extract at doses of 10 ng/ml, 20 ng/ml, 40 ng/ml, and 80 ng/ml. Ground cherry fruit extract was obtained from fresh fruit that was washed clean,

dried using a rack dryer at 45°C for 42 hours, then ground. The powder was extracted using a maceration method with 70% ethanol solvent for 3 × 24 hours at a ratio of 1:10, accompanied by a change of solvent with the same volume. The extract was then evaporated using an evaporator to obtain a dry extract. TGF- β and TNF- α levels were measured quantitatively using an ELISA method with an ELISA reader according to standard procedures (Santoso, Herowati, Rotinsulu, Murtini, Ridwan, Hikman, & Sukmawinata, 2021). The procedure included adding standard solutions and samples to the wells, adding antibodies and streptavidin-HRP, incubating at 37°C, washing with wash buffer, adding substrate, and stopping the reaction with a stop solution. Absorbance readings were taken at a wavelength of 450 nm within a maximum of 30 minutes after the reaction was stopped. The data obtained were primary data from laboratory experiments. The equipment used included an ELISA reader, incubator, and cool box. Materials included placenta, PBS-A, gelatin, ELISA reagents, standard and sample solutions, HBSS, wash buffer, and stop solution.

The research data were statistically analyzed using SPSS software version 27 for Windows. The analysis began with normality and homogeneity tests to ensure data distribution and uniformity. A one-way ANOVA test was then performed to determine differences in TGF- β and TNF- α levels between treatment groups. A p -value <0.05 indicates a significant effect of the administration of ground cherry fruit extract on preeclamptic trophoblast cells. This study was conducted in accordance with ethical principles for health research in accordance with national guidelines and the Decree of the Minister of Health of the Republic of Indonesia, ensuring confidentiality, privacy, and fairness for research subjects.

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RESEARCH RESULTS

Table 1 Mean and Standard Deviation in Each Treatment Group

Treatment Group	TGF- β (ng/L)		TNF- α (pg/mL)	
	Mean $\pm$ SD	Sig	Mean $\pm$ SD	Sig
Negative Control	794.55 $\pm$ 116.71	0.920	5.11/0.20	0.040
Dose 10 ng/ml	933.65 $\pm$ 109.44	0.582	4.46/0.25	0.063
Dose 20 ng/ml	1010.55 $\pm$ 47.93	0.646	3.71/0.14	0.649
Dose 40 ng/ml	1022.59 $\pm$ 142.65	0.920	3.47/0.30	0.584
Dose 80 ng/ml	1189.43 $\pm$ 122.94	0.582	3.03/0.36	0.920

Then, the highest TNF- α levels were found in the negative control group and gradually decreased after administration of ground cherry extract. The decrease in TNF- α levels was already visible at a dose of 10 ng/ml and continued to decline until reaching the lowest value at a dose of 80 ng/ml. A normality test was performed to assess the distribution of TGF- β and TNF- α levels in each treatment group using the Shapiro-Wilk test. Data were considered normally distributed if the significance value (p) was > 0.05 . The test results showed that all groups for the TGF- β variable had a p value > 0.05 , thus the TGF- β data were normally distributed and qualified for analysis using the parametric one-way ANOVA test. For the TNF- α variable, most groups showed a p value > 0.05 , but the negative control group had a p value < 0.05 . This indicates that the TNF- α data were not normally distributed overall.

The homogeneity of variance test for TGF- β levels was performed using the Levene test with $\alpha = 0.05$. The test results showed that all approaches (based on mean, median, median with adjusted df, and trimmed mean) had a significance value of p > 0.05 .

DISCUSSION

Trophoblast cells play a central role in placental formation and function through implantation, endometrial invasion, and spiral artery remodelling (Trisnawati & Mogan, 2023). In preeclampsia, trophoblast invasion is disrupted, resulting in suboptimal placental blood flow, triggering hypoxia, oxidative stress, and an increased inflammatory response. This condition is characterized by

increased levels of the pro-inflammatory cytokine TNF- α and decreased levels of the anti-inflammatory cytokine TGF- β , which contribute to placental inflammation and exacerbate the clinical manifestations of preeclampsia (Perawati, & Sari, 2024; Rahmadiani, Azissah, & Habibi, 2023). This cytokine imbalance impacts placental function and increases the risk of maternal endothelial dysfunction.

TGF- β plays a role in regulating trophoblast cell invasion and differentiation, as well as spiral artery formation during normal pregnancy. However, in preeclampsia, TGF- β regulation is often impaired. Decreased TGF- β levels are associated with increased TNF- α , while excessive TGF- β can inhibit trophoblast invasion by suppressing the activity of Matrix Metalloproteinases (MMPs), which degrade the extracellular matrix. This condition can disrupt spiral artery remodeling and impair placental perfusion (Pramatirta & Krisnadi, 2023; Basyir, Fauziah, Pramartirta, Yanwirasti, Mose, & Oenzil, 2020).

TNF- α is a major pro-inflammatory cytokine that is significantly elevated in preeclampsia and plays a role in inhibiting trophoblast differentiation and spiral artery remodeling. Elevated TNF- α triggers trophoblast cell apoptosis through activation of the NF- κ B and caspase pathways, increases oxidative stress, and worsens maternal endothelial dysfunction. This results in increased vascular permeability and hypertension, which exacerbate preeclampsia (Saputri & Fransiska, 2023; Andriani, Murdiningsih, & Rahmadhani, 2022). Reducing TNF- α levels is a target for controlling the inflammatory process in preeclampsia.

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Based on the results of this study, administration of ground cherry (*Physalis angulata* L.) fruit extract significantly increased TGF- β levels and decreased TNF- α levels in preeclamptic trophoblast cell cultures ($p < 0.05$). The highest dose of 80 ng/mL resulted in the highest TGF- β levels of 1189.43 ± 122.94 ng/L and the lowest TNF- α levels of 3.03 ± 0.36 pg/mL compared to the control group. This effect is thought to be related to the flavonoid content and other bioactive compounds in ground cherry which have anti-inflammatory and antioxidant activities, primarily through inhibition of the NF- κ B pathway, thereby suppressing TNF- α expression (Cahya, Sinurat, & Karo, 2022). The reduction in TNF- α has the potential to increase TGF- β activity, thereby helping restore the inflammatory balance and supporting trophoblast function and placental stability in preeclampsia.

CONCLUSION

The administration of ciplukan fruit extract (*Physalis angulata* L.) to preeclampsia trophoblast cell culture significantly affected the modulation of inflammatory cytokines characterized by a significant increase in TGF- β levels and a significant decrease in TNF- α levels ($p < 0.05$). Ciplukan fruit extract has the potential as an anti-inflammatory agent that can support the improvement of trophoblast function in preeclampsia. A dose of 80 ng/ml provided the highest biological effect with the highest TGF- β levels and the lowest TNF- α levels, but the results of Post Hoc and Mann-Whitney statistical tests showed that a dose of 40 ng/ml had a significant effect and was not significantly different from a dose of 80 ng/ml so that a dose of 40 ng/ml could be determined as the minimum effective dose in reducing the inflammatory response optimally in preeclampsia trophoblast cell culture.

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