

APST**Asia-Pacific Journal of Science and Technology**<https://www.tci-thaijo.org/index.php/APST/index>Published by Research and Innovation Department,
Khon Kaen University, Thailand**Anti-inflammatory and antioxidant effect of tomato extract (*Solanum lycopersicum* L.) in lipopolysaccharide-induced mice macrophage cells**Oeij Anindita Adhika^{1*} and Fen Tih¹¹Faculty of Medicine, Maranatha Christian University, Bandung 40164, West Java, Indonesia

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Received 26 August 2024

Revised 1 September 2025

Accepted 14 October 2025

Abstract

Inflammation is considered a common primary contributor to multiple diseases; therefore, anti-inflammatory agents are important to reduce the associated risks. Tomato (*Solanum lycopersicum* L.) fruit extract systemic lupus erythematosus (SLE) contains numerous bioactive compounds. Therefore, SLE potential as an anti-inflammatory and antioxidant properties were evaluated in this study. SLE was extracted using the maceration method. NO scavenging activity of SLE was analyzed using Griess reagent. Cytotoxicity was performed using the MTS assay. LPS was used to induce RAW264.7 cells in the inflammation model. ELISA was used to measure PGE-2, TNF- α , and IL-1 β protein levels, while colorimetry was utilized to examine total protein levels in LPS-induced RAW264.7 cells with SLE concentrations of 4 and 20 $\mu\text{g/mL}$. From this study, the IC₅₀ value was found to be 33.70 $\mu\text{g/mL}$, indicating that SLE has potential as an antioxidant, while 66.67 $\mu\text{g/mL}$ SLE showed the greatest NO scavenging activity. SLE (4 and 20 $\mu\text{g/mL}$) was a safe concentration based on cytotoxic assay. SLE 20 $\mu\text{g/mL}$ significantly reduced PGE-2, TNF- α , and IL-1 β protein levels at the inflammation cells model. SLE showed its potential as an anti-inflammatory and antioxidant agent.

Keywords: Anti-inflammatory, Antioxidant, Lipopolysaccharide, RAW 264.7, *Solanum lycopersicum***1. Introduction**

The response to infection or tissue damage is known as the inflammatory process, which represents an essential stage in tissue repair [1]. Inflammation occurs in two stages: acute and chronic inflammation. When the body reacts normally to an injury or infection, it causes acute inflammation. However, chronic inflammation happens when the inflammatory response persists longer than necessary because of ongoing exposure to irritants or autoimmune disorders [2], potentially causing local and systemic adverse effects. Numerous investigations on epidemiology, diagnosis, and clinical care have demonstrated associations between chronic illnesses such as cancer, arthritis, arteriosclerosis, neurological conditions, liver disease, and renal problems that caused by a dysregulated inflammatory response [3]. Diseases related to inflammation are estimated to contribute to more than 50% of deaths worldwide, highlighting their major impact on global health [4].

The nitric oxide radical (NO), which is a type of Reactive Oxygen Species (ROS), acts as a factor in worsening inflammation through various pathways [5]. ROS-induced macrophage activation triggers the inflammatory mediators release, with Tumor Necrosis Factor- α (TNF- α) being an early cytokine formed in response to Nuclear factor kappa B (NF- κB) induction via Toll-Like Receptors (TLR) stimulation [6]. The formation of other inflammatory factors, including Interleukin (IL)-1 β , further amplifies the inflammatory response by enhancing the expression of adhesion molecules on endothelial cells, facilitating leukocyte attraction to infection sites [7]. IL-1 β , produced by macrophages through TLR activation, also triggers the inflammasome and induces cyclooxygenase (COX-2) expression, leading to Prostaglandin E2 (PGE-2) production [8]. These cytokines synergistically amplify and prolong inflammation. Therefore, reducing free radicals can be a crucial strategy in managing chronic inflammatory conditions by minimizing excessive inflammation.

Inflammation is usually treated using the common method of steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), used worldwide. Short-term administration correlated to the increasement risk of thrombotic cardiovascular disease, which also raises the risk of bleeding, particularly gastrointestinal bleeding [9]. Furthermore, it increases the risk of systemic toxicity and teratogenic effects, potentially increasing the risk of cardiovascular disease and stroke [10]. Therefore, other alternatives are needed by utilizing plants that have antioxidant, anti-inflammatory, and non-toxic properties.

Tomatoes (*Solanum lycopersicum* L) are widely consumed horticultural crops, with global production exceeding 187 million metric tons in 2021 [11]. In addition to being known as a food source rich in vitamins and minerals, fresh tomatoes contain various bioactive compounds, including quercetin-3-O-rutinoside, naringenin, chlorogenic acid, chalcone, polyphenols, flavonoids, and lycopene [12]. Tomato fruit carotenoids are known to protect against oxidative stress [13]. Beyond their antioxidant properties, tomato extracts have been linked to multiple health advantages such as a lower likelihood of developing chronic conditions, including cardiovascular diseases, cancer, and diabetes, along with the modulation of immune responses [11–13]. Nevertheless, most research has predominantly focused on their antioxidant activity, while their broader biological effects, particularly their role in regulating inflammation, are still not fully understood. This study aimed to investigate the anti-inflammatory and antioxidant effects of tomato fruit extract (SLE) in an in vitro inflammation model.

In this study, the toxicity of SLE was assessed in RAW264.7 mouse macrophage cells. The NO scavenging activity was used to assess the antioxidant activity, and the Lipopolysaccharide (LPS)-induced RAW264.7 cells (LRCs) culture was utilized to assess the anti-inflammatory potential of SLE by measuring TNF- α , IL-1 β , PGE-2 and total protein levels.

2. Materials and methods

2.1 Extract preparation

Tomato fruits collected from Mangunharjo, Bandung, Indonesia were identified by staff from the School of Life and Technology, Bandung Institute of Technology and extracted using the maceration method. After drying and crushing, the tomatoes were extracted with 1850 mL of 70% ethanol. The filtrate was collected at 24-hour intervals until it became colorless and subsequently concentrated using an evaporator at 50 °C, producing SLE with a yield of 38.225 g (equivalent to approximately 2.07% of dried weight) [14–16].

2.2 NO scavenging assay

Sodium nitroprusside 10 mM (106541, Merck) was mixed with the sample in phosphate buffer saline (PBS) (1740576, Gibco) at various concentrations, then incubated for two hours at 25°C. After incubation, Griess reagent was administered, and the chromophore absorbance was determined at 546 nm using a microplate reader [14]. The NO scavenging activity was then calculated using Equation 1.

$$\text{NO scavenging \%} = (Na - Sa) / Na \times 100 \quad (1)$$

Sa = sample absorbance

Na = negative control absorbance (without sample)

2.3 RAW 264.7 cells viability assay

Murine macrophage cells (RAW 264.7) were obtained from Aretha Medika Utama and cultured in complete Dulbecco's Modified Eagle Medium (DMEM) (11995065, Gibco) with 10% FBS until 80%-90% confluent (37°C, 5% CO₂). Five $\times 10^3$ cells were plated in 96-well plates then allowed to adhere before the experiment, and MTS Cell Proliferation Assay Kit (ab197010, Abcam) was utilized to evaluate the viability, as per previous studies [5, 17]. A microplate reader was used to measure absorbance at 490 nm. There were several treatment groups, namely negative control (NC) untreated cells (medium only, without ethanol or extract) and groups treated with SLE (4, 20, 100) $\mu\text{g/mL}$.

2.4 LPS-induced RAW cells and treatments

Several treatment groups were analyzed in this study. Negative control: not induced with LPS and untreated; Positive control: induced with LPS but untreated with SLE, treatment groups: LPS-induced RAW264.7 cells (LRCs) treated with 4 or 20 $\mu\text{g/mL}$ SLE. A total of 4 $\mu\text{g/mL}$ of *Escherichia coli* O55:B5 LPS (L2880, Sigma-

Aldrich) was added (18 h incubation, 37°C, 5% CO₂) to induce inflammatory model cells. The conditioned media were collected, centrifuged, and cell-free supernatants were collected to assess NO, IL-1 β , PGE-2, and TNF- α levels after an additional 24 h incubation [5,17].

2.5 Protein level in LPS-induced RAW 264.7 cells

Bovine serum albumin (BSA) was utilized to create BSA standard solution for the total protein assay. Two mg of BSA (A9576, Sigma Aldrich) was dissolved in 1000 μ l of ddH₂O. In each well, 20 μ l of the standard solution, 200 μ l of Quick Start Dye Reagent (5000205, Biorad), and SLE at various concentrations were added. Absorbance was measured at 595 nm after five minutes of incubation at room temperature [17].

2.6 Quantification of IL-1 β , TNF- α , PGE-2 levels in LRC

Protein levels of IL-1 β (E-EL-M0037, Elabscience), TNF- α (E-EL-M0049, Elabscience), and PGE-2 (E-EL-0034, Elabscience) were calculated using ELISA kits following the instructions from the manufacturer [5,17].

2.7 Statistical analysis

Data were obtained from triplicate wells (technical replicates) for each treatment group. SPSS software (version 20.0) was used for statistical analysis. Data are represented as mean \pm standard deviation (SD). Statistical significance was analyzed using Analysis of Variance (ANOVA) followed by Tukey's HSD post hoc test, with $p < 0.05$ presented as statistically significant [18].

3. Results

3.1 Effect of various SLE concentrations on NO scavenging activity

Figure 1 illustrates how the concentration of SLE affects NO scavenging activity. The highest NO scavenging activity was shown by SLE concentration of 66.67 μ g/mL, with a value of 61.02 ± 1.14 %. Higher concentrations of SLE significantly enhanced antioxidant activity ($p < 0.05$). The median Inhibitory Concentration (IC₅₀) was 35.70 μ g/mL, as determined from the regression curve ($R^2 = 0.99$, Figure 1). This suggests that SLE 35.70 μ g/mL is a useful threshold for a 50% reduction of NO levels.

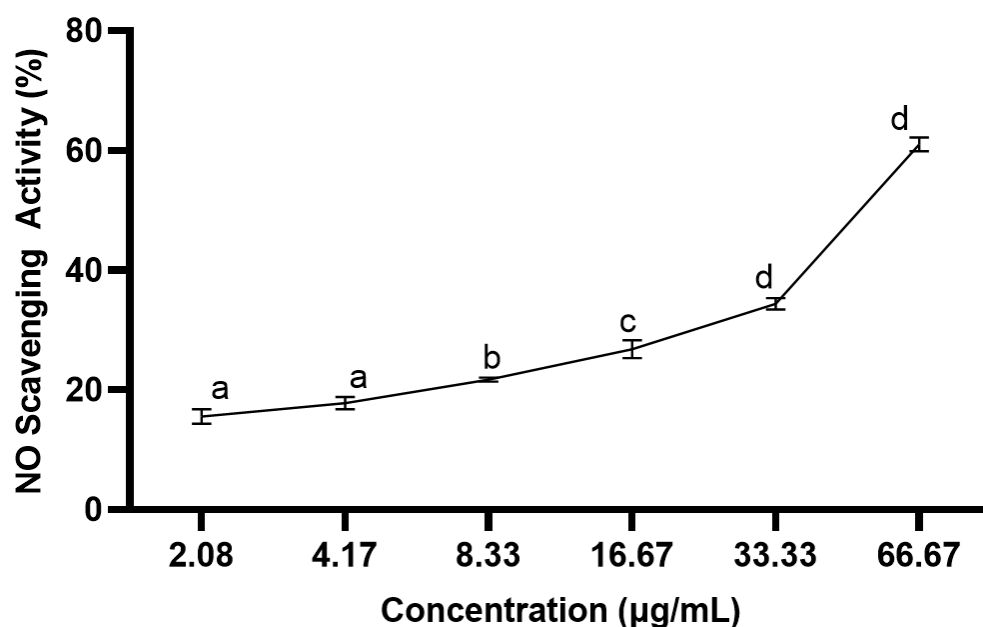


Figure 1 Effect of various SLE concentrations on NO scavenging activity.

*Data are shown as mean \pm SD from triplicate wells. The IC₅₀ value of SLE was 35.70 μ g/mL ($R^2 = 0.99$). Different superscript letters represent statistically significant differences among treatments at $p < 0.05$ (Tukey's HSD post hoc test).

3.2 Effect of various SLE concentrations toward RAW264.7 cytotoxicity

Cell viability and inhibition of RAW264.7 cells are shown in Figure 2 (A-B). The finding showed that cell viability decreased as SLE concentration increased. SLE concentration of 4 $\mu\text{g/mL}$ demonstrated the highest cell viability value compared to other concentrations. SLE concentrations of 4 and 20 $\mu\text{g/mL}$ were considered safe with viability values $>90\%$ and inhibition $<30\%$.

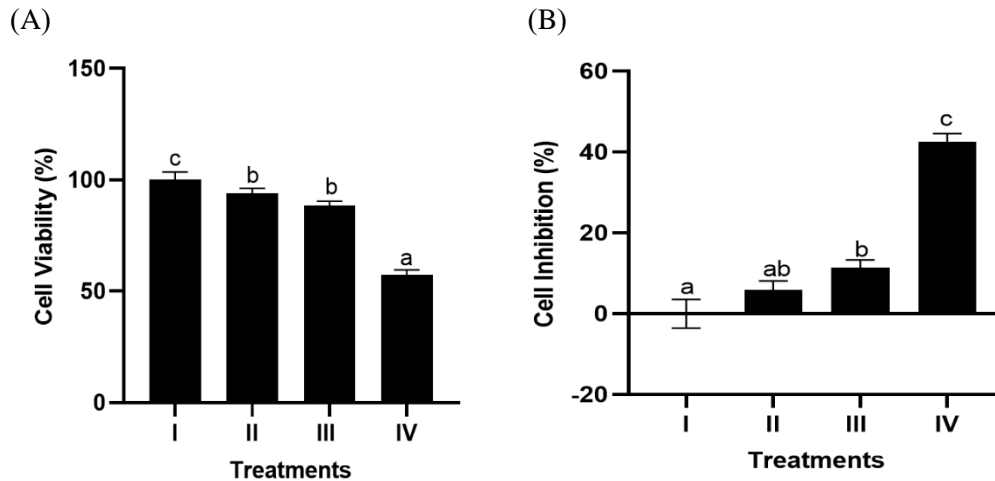


Figure 2 Effect of various SLE concentrations on (A) cells viability, (B) inhibition of RAW264.7 cells.

*Data are shown as mean \pm SD from triplicate wells. Different superscript letters indicate statistically significant differences among treatments at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: SLE: 4 $\mu\text{g/mL}$; III: SLE 20 $\mu\text{g/mL}$; IV: SLE 100 $\mu\text{g/mL}$.

3.3 Effect of SLE on protein levels in LRCs

Figure 3 depicts SLE effect on protein level. LPS induction significantly reduced protein levels. SLE treatment significantly increased protein levels ($p < 0.05$), SLE 20 $\mu\text{g/mL}$ represented the most effective concentration to increased protein level compared to SLE 4 $\mu\text{g/mL}$ and PC significantly ($p < 0.05$).

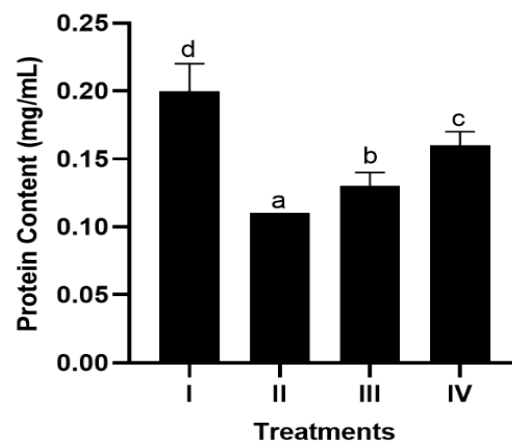


Figure 3 Effect SLE toward protein level on LRCs as inflammation cells model.

*Data are shown as mean \pm SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 $\mu\text{g/mL}$; IV: PC + SLE 20 $\mu\text{g/mL}$.

3.4 Effect of SLE on TNF- α levels in LRCs

LPS induction significantly increased TNF- α levels ($p < 0.05$) in PC compared to NC. The effects 4 $\mu\text{g/mL}$, 20 $\mu\text{g/mL}$ of SLE on TNF- α level can be seen in Figure 4 (A-B). The results indicated that SLE significantly reduced TNF- α levels compared to PC ($p < 0.05$). Both 4 and 20 $\mu\text{g/mL}$ SLE significantly reduced TNF- α levels to values comparable with NC. This data also corresponded to Figure 4C, where SLE 20 $\mu\text{g/mL}$ demonstrated higher TNF- α inhibition activity compared to SLE 4 $\mu\text{g/mL}$.

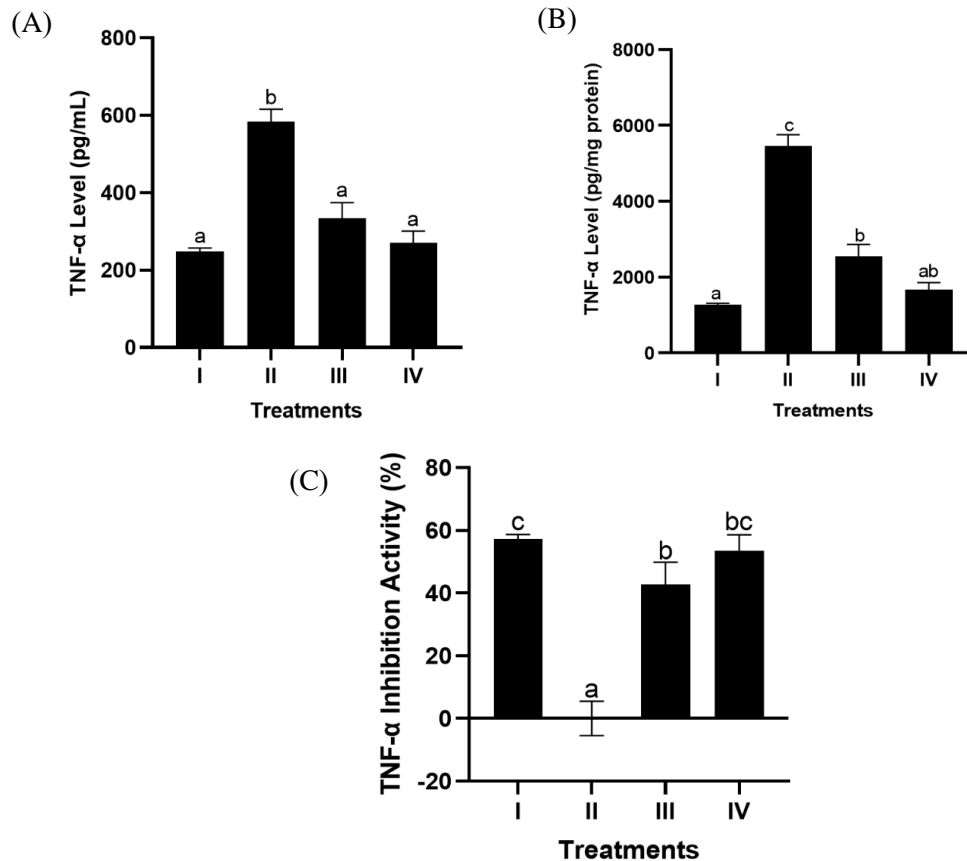


Figure 4 Effect of SLE on TNF- α levels in LRCs as an inflammation cell model. (A) TNF- α levels, (B) TNF- α levels expressed protein and (C) TNF- α inhibition activity (%).

*Data are shown as mean \pm SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 μ g/mL; IV: PC + SLE 20 μ g/mL.

3.5 Effect of SLE on IL-1 β levels in LRCs

The finding showed that LPS increased IL-1 β level significantly ($p < 0.05$) in PC compared to NC. SLE was able to reduce IL-1 β level significantly ($p < 0.05$), SLE 20 μ g/mL was the most effective concentration, significantly reducing IL-1 β levels compared to 4 μ g/mL SLE and PC ($p < 0.05$) (Figure 5A-B). These data are consistent with Figure 5(C), where SLE 20 μ g/mL exhibited higher IL-1 β inhibition activity compared to SLE 4 μ g/mL.

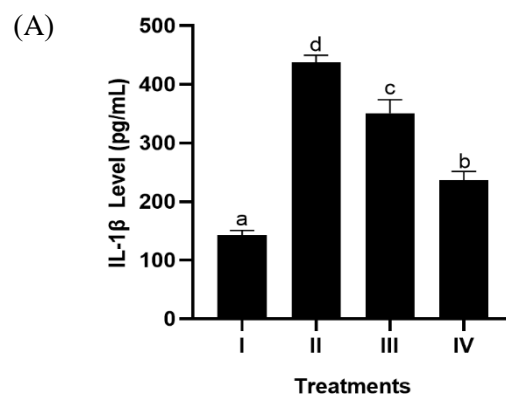


Figure 5 Effect of SLE on IL-1 β levels in LRCs as an inflammation cell model. (A) IL-1 β levels, (B) IL-1 β levels expressed protein and (C) IL-1 β inhibition activity (%).

*Data are shown as mean \pm SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 μ g/mL; IV: PC + SLE 20 μ g/mL.

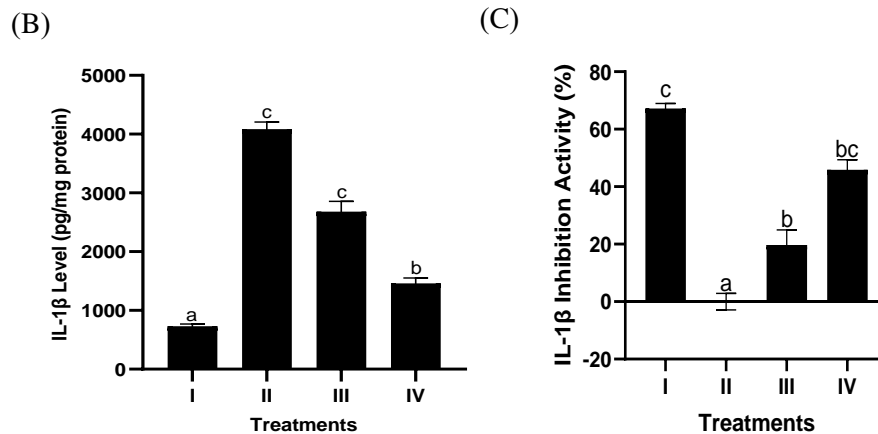


Figure 5 Effect of SLE on IL-1 β levels in LRCs as an inflammation cell model. (A) IL-1 β levels, (B) IL-1 β levels expressed protein and (C) IL-1 β inhibition activity (%).

*Data are shown as mean \pm SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 μ g/mL; IV: PC + SLE 20 μ g/mL.

3.6 Effect of SLE on PGE-2 levels in LRCs

The finding revealed that LPS induction led to increased PGE-2 levels significantly ($p < 0.05$). SLE decreased PGE-2 levels compared to PC, with 20 μ g/mL considered the most effective concentration (Figure 6A-B). These data are consistent with Figure 6C, where SLE 20 μ g/mL was more active in PGE-2 inhibition activity compared to SLE 4 μ g/mL.

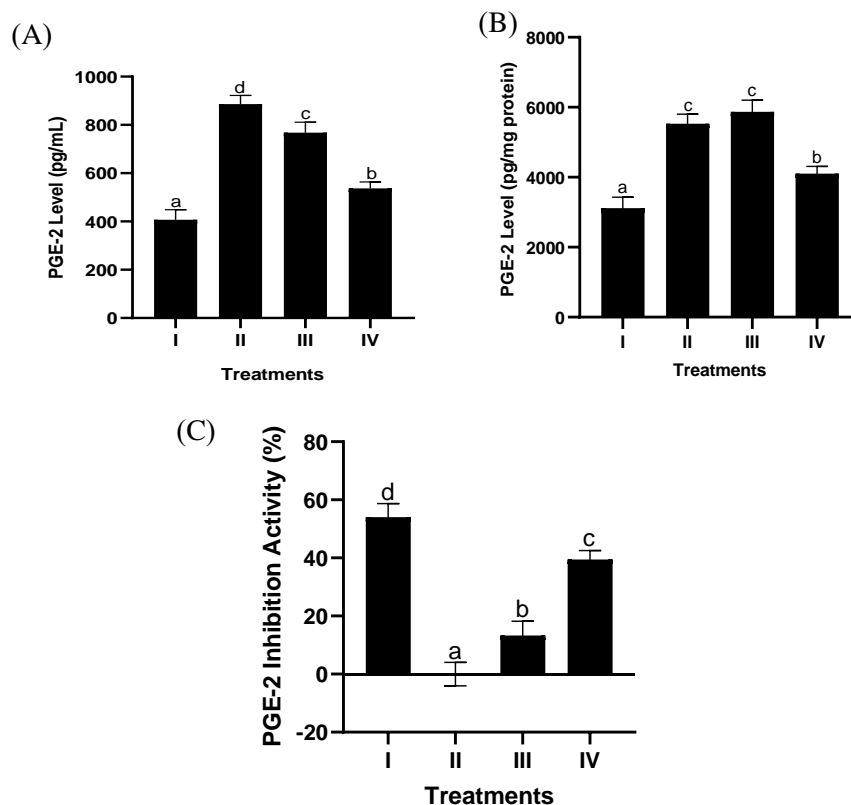


Figure 6 Effect SLE toward PGE-2 level on LRCs as inflammation cells model. (A) PGE-2 levels, (B) PGE-2 levels expressed protein and (C) PGE-2 inhibition activity (%).

*Data are shown as mean \pm SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 μ g/mL; IV: PC + SLE 20 μ g/mL.

4. Discussions

Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, functions as the primary trigger for host inflammatory responses [18], initiates intracellular signaling cascades that propagate through MYD88 and TRIF pathways by interacting with the TLR4-MD2 receptor complex. These pathways converge on the transcriptional machinery of the cell, inducing the production of a suite of inflammatory mediators, including IL-6, IL-1 β , CCL2, IL-8, and TNF- α . The release of these cytokines amplifies the inflammatory signal and mobilizes additional immune components, ensuring a robust and coordinated defense mechanism [19]. LPS also increases ROS production by decreasing AMP-activated protein kinase (AMPK) phosphorylation, resulting in increased oxidative stress and free radicals [20].

In this study, SLE exhibited antioxidant properties, specifically through NO scavenging activity with the highest activity observed at 66.67 $\mu\text{g/mL}$ (Figure 1). The IC₅₀ value of SLE for NO scavenging was 35.70 $\mu\text{g/mL}$, classifying it as a "very strong" antioxidant [21]. Antioxidants are categorized as "very strong" if their IC₅₀ value is below 50 $\mu\text{g/mL}$, "strong" between 50 and 100 $\mu\text{g/mL}$, "moderate" between 101 and 250 $\mu\text{g/mL}$, "weak" between 250 and 500 $\mu\text{g/mL}$, and "inactive" if above 500 $\mu\text{g/mL}$. Compared with tomato extract reported in previous studies with ABTS IC₅₀ value of 86.66 ± 10.58 $\mu\text{g/mL}$, SLE displayed stronger antioxidant capacity [22], DPPH IC₅₀ value of 147.20 ± 16.97 $\mu\text{g/mL}$ [15], H₂O₂ IC₅₀ value of 221.30 ± 1.94 $\mu\text{g/mL}$ [16]. The antioxidant effects of bioactive compounds in tomatoes, including ascorbic acid, β -carotene, vitamin C, lycopene, flavonoids, anthocyanin, and polyphenols, are due to their capacity to bind ions and scavenge free radicals, thus preventing DNA and lipid peroxidation and reducing membrane damage [23].

The administration of extracts to cells can result in either therapeutic or cytotoxic effects, depending on the concentration. Each effect can occur at a certain treatment concentration. Therefore, determining safe and effective concentrations through cytotoxicity assays is a crucial prerequisite for subsequent analyses [24]. According to the findings of the cytotoxicity test on RAW264.7 cells, SLE was considered non-toxic and safe at 4 $\mu\text{g/mL}$ and 20 $\mu\text{g/mL}$ concentrations, both of which showed >90% cell viability and <30% inhibition (Figure 2A-B). The International Organization for Standardization (ISO)-10993-5 explains that >30% cell inhibition indicates toxic effects [25].

Besides evaluating the antioxidant effect, this research also examined the anti-inflammatory properties of SLE. The formation of free radicals from various biological sources causes an imbalance of endogenous antioxidants, resulting in the development of various inflammatory disorders. In response to tissue damage and inflammation, neutrophils are quickly attracted to the inflamed area by the endothelium, as well as by activated macrophages and mast cells in the tissue which release specific mediators [26]. This study examined SLE anti-inflammatory effects by measuring the levels of TNF- α , IL-1 β , PGE-2 in LPS-induced mouse macrophage-like cells (RAW 264.7).

The total protein levels in LRCs are shown in Figure 3, showing that the higher the concentration of SLE (20 $\mu\text{g/mL}$), the higher the protein level. The increase in protein levels suggests that SLE may promote protein synthesis, possibly by activating specific signaling pathways. In addition, SLE may also be able to protect cells from oxidative stress or conditions that usually cause protein degradation. This also simultaneously increases protein levels indicating an increase in cell number, more cells mean more total protein. This may be related to the antioxidant capacity of SLE, as demonstrated by its NO scavenging activity, and to its ability to inhibit inflammatory markers via the MAPK signaling pathway. Research by Ji et al. suggested that kaempferol, through its antioxidant activity, is associated with protein synthesis via the PI3K/AKT and MAPK signaling pathways [27].

Activated macrophages initiate an inflammatory response by producing pro-inflammatory mediators via TLR4, which subsequently triggers the MAPK pathway (JNK, ERK1/2, p38) [5,17]. This pathway phosphorylates transcription factors including NF- κ B [28], which then enter the nucleus and increase the transcription of pro-inflammatory proteins namely TNF- α , IL-1 β , and COX-2 [29].

TNF- α and IL-1 β play key roles in inflammation by activating NF- κ B and increasing the expression of adhesion molecules [30]. SLE was observed to reduce TNF- α and IL-1 β protein levels, with 20 $\mu\text{g/mL}$ being the most effective concentration (Figures 4 and 5). This reduction suggests a decrease in the inflammatory response. These findings are aligned with prior studies which reported that the extract of tomato, through bioactive compounds such as 9-oxo-ODA, lycopene, and daphnetin, can suppress TNF- α [31]. Similarly, Navarrete et al. reported that SLE inhibited IL-1 β expression in LPS-stimulated macrophages [32].

Prostaglandin E Synthase (mPGES-1) and COX-2 activation leads to PGE-2 production, a pro-inflammatory lipid mediator derived from arachidonic acid [33]. This study found that SLE effectively inhibited PGE-2 in LRCs with 20 $\mu\text{g/mL}$ showing the greatest reduction in PGE-2 protein levels (Figure 6). These findings are consistent with previous studies showing that methanolic SLE inhibited LPS-induced PGE-2 [34]. Endothelial cell activation, regulated by the NF- κ B pathway, involves COX-2 expression, which stimulates neutrophil recruitment and the release of PGE-2, ROS, and histamine, thereby contributing to pain and inflammation. Disruptions in these pathways can lead to inflammatory disorders, such as tissue damage and vascular proliferation. Flavonoids

in tomatoes are anti-inflammatory agents that inhibit cytokines, chemokines, and inflammatory enzymes, while phenols can regulate PGE-2 production and COX-2 expression [35].

Based on these results, SLE exhibited antioxidant activity by NO scavenging activity and by lowering PGE-2, TNF- α , and IL-1 β level which suggests its potential as both an antioxidant and anti-inflammatory agent. These findings suggest that SLE may modulate inflammatory processes and oxidative stress, and the consistent effects across multiple markers provide supportive evidence for its potential dual role. To better visualize these findings, the proposed mechanism of action is summarized in Figure 7.

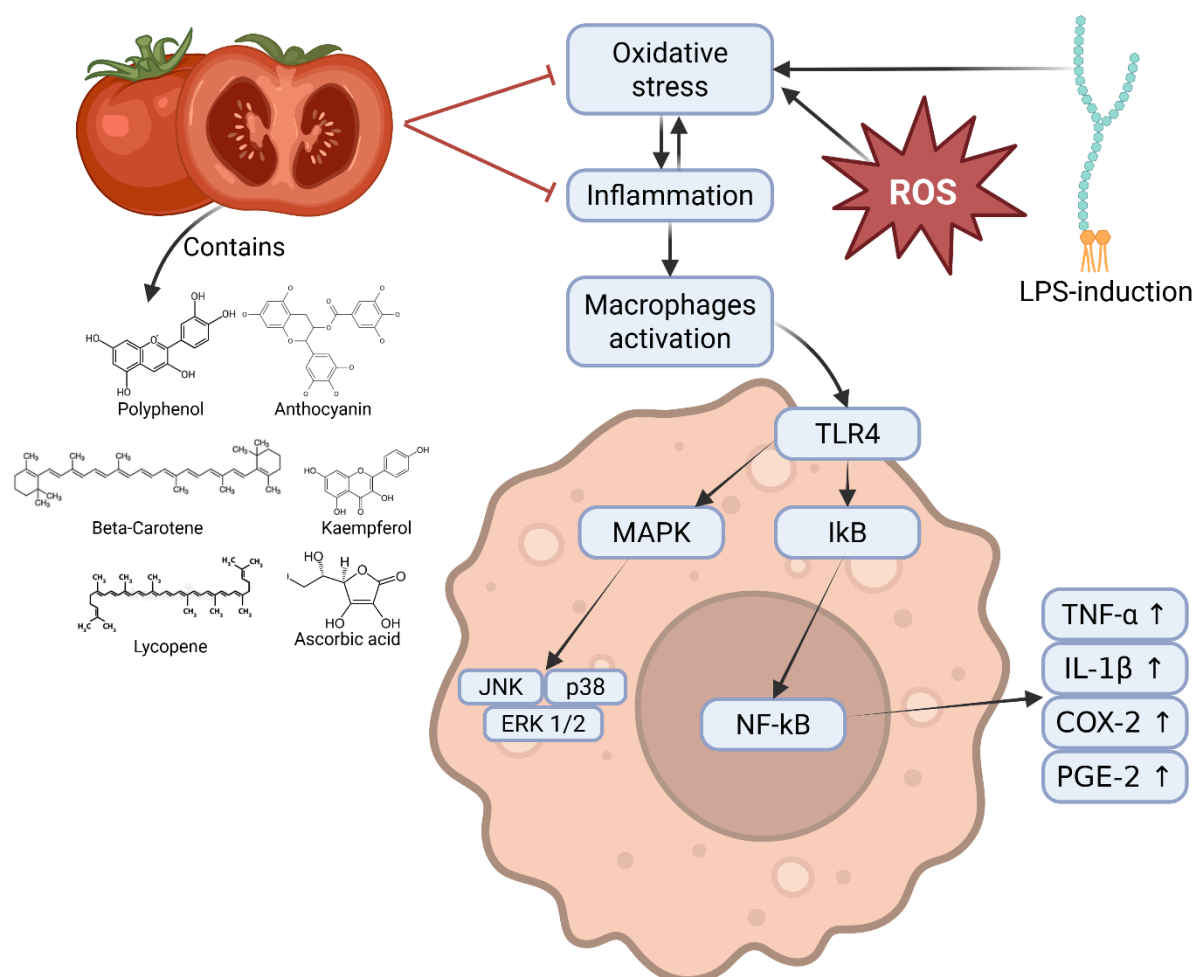


Figure 7 Proposed mechanism of SLE as an anti-inflammatory and antioxidant.

LPS induction triggers oxidative stress and influences the development of inflammation. Inflammation further activates macrophages that produce various pro-inflammatory mediators through the TLR4 pathway, which in turn induces the expression of IL-1 β , TNF- α , and PGE-2. In contrast, SLE may potentially reduce oxidative stress and modulate the TLR4 pathway. These findings suggest that SLE could act as both an anti-inflammatory and antioxidant agent; however, this mechanism remains hypothetical and requires further validation.

Despite these promising results, this study has several limitations. The experiments were restricted to an in vitro model using RAW 264.7 cells, which might not accurately reproduce the complexity of in vivo responses. Moreover, the specific bioactive compounds that contributed to the observed effects were not specified, and advanced techniques such as LC-MS/MS or flow cytometry could provide more comprehensive insights. Another limitation is that the negative control consisted of untreated cells without a vehicle, and the IC₅₀ value was derived from a single regression curve based on mean data. Future studies involving in vivo models and advanced analytical approaches are required to validate and expand upon these findings.

5. Conclusions

Cytotoxicity testing have demonstrated the non-toxic nature of SLE. Additionally, it demonstrates antioxidant qualities; its IC₅₀ value for NO scavenging activity is 35.70 μ g/mL, classifying it as a strong antioxidant. In LRCs, which are used to simulate inflammation, SLE raises total protein levels. Furthermore, SLE can lower these inflammatory cells' levels of IL-1 β , TNF- α , and PGE-2.

6. Conflicts of interest

The authors have no conflict of interest to disclose.

7. Acknowledgments

This research is supported by Maranatha Christian University (Under The Grant of Associate Professor Acceleration Scheme). Therefore, it is such a gratitude for the funding support in this research. In addition, this study was also aided by the AMUBBRC, Bandung, West Java, Indonesia. We also thank to Hanna Sari Widya Kusuma, Adilah Hafizha Nur Sabrina, Faradhina Salfanindya, Fadhilah Haifa Zahiroh, Vini Ayuni, Nindia Salsabila Mia Dewi, Annisa Firdaus Sutendi, and Dwi Nur Tri Harsiwi from Aretha Medika Utama for their valuable contributions.

8. Author Contributions

Oeij Anindita Adhika was responsible for the conceptualization, methodology, and investigation of the study, as well as preparing the original manuscript draft and data visualization. Fen Tih contributed to data curation, formal analysis, and validation, participated in the review and editing of the manuscript, and supervised the overall research project.

8. References

- [1] Caballero-Sánchez N, Alonso-Alonso S, Nagy L. Regenerative inflammation: When immune cells help to re-build tissues. *FEBS J.* 2024; 291(8): 1597-1614.
- [2] Takagi M. Acute and chronic inflammation. 7th edition. In *Macrophages Biology and Tissue Inflammation in Health and Disease*. Academic Press. 2024.
- [3] Rajendran P, Chen YF, Chen YF, Chung LC, Tamilselvi S, Shen CY, Huang CY. The multifaceted link between inflammation and human diseases. *J Cell Physiol.* 2018;233(9):6458-6471.
- [4] Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH. Chronic inflammation in the etiology of disease across the life span. *Nature medicine.* 2019;25(12):1822-1832.
- [5] Widowati W, Kusuma HS, Arumwardana S, Afifah E, Wahyuni CD, Wijayanti CR, Maulana MA, Rizal R. Corilagin potential in inhibiting oxidative and inflammatory stress in LPS-induced murine macrophage cell lines (RAW 264.7). *Iran J Basic Med Sci.* 2021;24(12):1656–1663.
- [6] Kumar SK, Mani KP. Proinflammatory signaling mechanism of endocan in macrophages: Involvement of TLR2 mediated MAPK-NFκB pathways. *Cytokine.* 2024;175:156482.
- [7] Zhao K, Zeng Z, He Y, Zhao R, Niu J, Sun H, Zhou J. Recent advances in targeted therapy for inflammatory vascular diseases. *J Control Release.* 2024;372:730-750.
- [8] Osman EO, Khalil NA, Magdy A, El-Dash Y. New pyrazole-pyridazine hybrids as selective COX-2 inhibitors: design, synthesis, molecular docking, in silico studies and investigation of their anti-inflammatory potential by evaluation of TNF-α, IL-6, PGE-2 and NO in LPS-induced RAW264. 7 macrophages. *RSC Med Chem.* 2024;15(8):2692-2708.
- [9] Paternoster M, Steichen O, Lapeyre-Mestre M, Blanchon T, Rossignol L, Vilcu AM, Souty C. Risk of bleeding associated with nonsteroidal anti-inflammatory drug use in patients exposed to antithrombotic therapy: a case-crossover study. *J Clin Pharmacol.* 2022;62(5):636-645.
- [10] Adel Elnashar A, Kamal HI, Magdy MA, Gamal T, Hamid L, Ragab SF, Khodier SA, Mohamed A, Kamel MM, El-shahawy AA, Yehia DA. Review on diclofenac toxicities in different organs. *Ain Shams J Forensic Med Clin Toxicol.* 2024;42(1):10-24.
- [11] Matei E, Răpă M, Predescu AM, Țurcanu AA, Vidu R, Predescu C, Orbeci C. Valorization of agri-food wastes as sustainable eco-materials for wastewater treatment: Current state and new perspectives. *Materials.* 2021;14(16):4581.
- [12] Kang ES, Jeong SY, Joo MH, Kim MY, Hur YK, Cho BO, Jang SI. Antioxidant and anti-inflammatory effects of a mixture of propolis, red bean and tomato extracts. *Int J Funct Nutr.* 2024; 5(1):1-2.

- [13] Del Giudice R, Petruk G, Raiola A, Barone A, Monti DM, Rigano MM. Carotenoids in fresh and processed tomato (*Solanum lycopersicum*) fruits protect cells from oxidative stress injury. J Sci Food Agric. 2017;97(5):1616-1623.
- [14] Widowati W, Rani AP, Hamzah RA, Arumwardana S, Afifah E, Kusuma HS, Rihibiha DD, Nufus H, Amalia A. Antioxidant and antiaging assays of Hibiscus sabdariffa extract and its compounds. Nat Prod Sci. 2017;23(3):192-200.
- [15] Kristina K, Henderson AH, Djohan D, Lister IN, Girsang E, Fachrial E. Antioxidant and Anticollagenase Activity of Tomato (*Solanum Lycopersicum* L.) and Lycopene. Am Sci Res J Eng Technol Sci. 2019;52(1):57-66.
- [16] Djohab K, Henderson AH, Ehrich Lister IN, Girsang E, Fachrial E. Comparison of Atioxidant and Anti-hyaluronidase Activity of Tomato (*Solanum Lycopersicum* L.) Extract and Lycopene. Am Sci Res J Eng Technol Sci. 2019;52:49-56.
- [17] Widowati W, Jasaputra DK, Gunawan KY, Kusuma HSW, Arumwardana S, Wahyuni CD, Rizal R. Turmeric extract potential inhibit inflammatory marker in LPS stimulated marcophage cells. Int J Appl Pharm. 2021;13(3):7-11.
- [18] Priyandoko D, Widowati W, Lenny L, Novianti S, Revika R, Kusuma HSW, Sholihah IA. Green tea extract reduced lipopolysaccharide-induced inflammation in L2 cells as acute respiratory distress syndrome model through genes and cytokine pro-inflammatory. Avicenna J Med Biotechnol. 2024;16(1): 57-58.
- [19] Page MJ, Kell DB, Pretorius E. The role of lipopolysaccharide-induced cell signalling in chronic inflammation. Chronic Stress. 2022;6:24705470221076390.
- [20] Dong Z, Yuan Y. Accelerated inflammation and oxidative stress induced by LPS in acute lung injury: Inhibition by ST1926. Int J Mol Med. 2018; 41(6):3405-3421.
- [21] Kusumawati AH, Farhamzah F, Alkandahri MY, Sadino A, Agustina LS, Apriana SD. Antioxidant Activity and Sun Protection Factor of Black Glutinous Rice (*Oryza sativa* var. glutinosa). J Nat Prod Res. 2021; 5(11):1958-1961.
- [22] Henderson AH, Lister IN, Fachrial E, Girsang E. Antioxidant and anti-elastase activity of ethanol extract of tomato (*Solanum lycopersicum* L.). Buletin Penelit Tanam Rempah Obat. 2020;31(2):67-74.
- [23] Banihani SA. Tomato (*Solanum lycopersicum* L.) and type 2 diabetes. Int J Food Prop. 2018;21(1):99-105.
- [24] Widowati W, Priyandoko D, Lenny L, Revika R, Novianti S, Kusuma HS, Rizal R. *Camellia sinensis* L. extract suppresses inflammation on acute respiratory distress syndrome cells models via decreasing IL-1B, IL-6 and COX-2 expressions. Trends Sci. 2024;21(1):7010.
- [25] Açarı İK, Turhan DÖ, Kuruçay A, Köytepe S, Ateş B. Synthesis of gum arabic-based biopolymer network and determination of its toxicity properties in *in vitro-in vivo* model systems. Cumhuriyet Sci J. 2024;45(1):54-63.
- [26] Mihlan M, Wissmann S, Gavrilov A, Kaltenbach L, Britz M, Franke K, Lämmermann T. Neutrophil trapping and nexocytosis, mast cell-mediated processes for inflammatory signal relay. Cell. 2024;187 (19):5316-5335.
- [27] Ji XN, Chaozheng Z, Yang J, Tian Y, Kamu L, Yang H. Kaempferol improves exercise performance by regulating glucose uptake, mitochondrial biogenesis, and protein synthesis via PI3K/AKT and MAPK signaling pathways. Foods. 2024;13(7):1068.
- [28] Yu Y, Zhu H, Shen M, Yu Q, Chen Y, Mo S, Xie J. Sulfated *Cyclocarya paliurus* polysaccharides exert immunomodulatory potential on macrophages via Toll-like receptor 4 mediated MAPK/NF-κB signaling pathways. Food Sci. Hum. Wellness. 2024 13(1):115-123.
- [29] Mazzantini C, El Bourji Z, Parisio C, Davolio PL, Cocchi A, Pellegrini-Giampietro DE, Landucci E. Anti-inflammatory properties of cannabidiol and beta-caryophyllene alone or combined in an in vitro inflammation model. Pharmaceuticals. 2024;17(4):467-470.
- [30] Conti PRONCONI, Ronconi G, Caraffa AL, Gallenga CE, Ross R, Frydas I, Kritas SK. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2):327-331.
- [31] Mohri S, Takahashi H, Sakai M, Takahashi S, Waki N, Aizawa K, Suganuma H, Ara T, Matsumura Y, Shibata D, Goto T, Kawada T. Wide-range screening of anti-inflammatory compounds in tomato using LC-MS and elucidating the mechanism of their functions. PLOS ONE. 2018;13(1):e0191305.

- [32] Navarrete S, Alarcón M, Palomo I. Aqueous extract of tomato (*Solanum lycopersicum* L.) and ferulic acid reduce the expression of TNF- α and IL-1 β in LPS-activated macrophages. *Molecules*. 2015;20(8):15319-15329.
- [33] Chen JS, Alfajaro MM, Wei J, Chow RD, Filler RB, Eisenbarth SC, & Wilen CB. Cyclooxygenase-2 is induced by SARS-CoV-2 infection but does not affect viral entry or replication. *BioRxiv*. 2020; 24:312769.
- [34] Naik P, Kumar M. (2019). Receptor interactions of constituents of *Zingiber officinalis* and *Solanum lycopersicum* on COX. *J Pharmacogn Phytochem*. 2019;8(3):4637-4641.
- [35] Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-inflammatory molecules: A review. *Molecules*. 2022;27(9):2901-2905.