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Anti-inflammatory and antioxidant effect of tomato extract (*Solanum lycopersicum* L.) in lipopolysaccharide-induced mice macrophage cells

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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-1β protein levels, while colorimetry was utilized to examine total protein levels in LPS-induced RAW264.7 cells with SLE concentrations of 4 and 20 µg/mL. From this study, the IC_{50} value was found to be 33.70 µg/mL, indicating that SLE has potential as an antioxidant, while 66.67 µg/mL SLE showed the greatest NO scavenging activity. SLE (4 and 20 µg/mL) was a safe concentration based on cytotoxic assay. SLE 20 µg/mL significantly reduced PGE-2, TNF-α, and IL-1β 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-kB) induction via Toll-Like Receptors (TLR) stimulation [6]. The formation of other inflammatory factors, including Interleukin (IL)-1β, further amplifies the inflammatory response by enhancing the expression of adhesion molecules on endothelial cells, facilitating leukocyte attraction to infection sites [7]. IL-1β, 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-1β, 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 (37ºC, 5% CO_2). Five × 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) µg/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 µg/mL SLE. A total of 4 µg/mL of *Escherichia coli* O55:B5 LPS (L2880, Sigma-

Aldrich) was added (18 h incubation, 37ºC, 5% CO_2) to induce inflammatory model cells. The conditioned media were collected, centrifuged, and cell-free supernatants were collected to assess NO, IL-1β, 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 µl of ddH2O. In each well, 20 µl of the standard solution, 200 µl 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-1β, TNF-α, PGE-2 levels in LRC

Protein levels of IL-1β (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 ± 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 µg/mL, with a value of 61.02 ± 1.14 %. Higher concentrations of SLE significantly enhanced antioxidant activity ($p < 0.05$). The median Inhibitory Concentration (IC_{50}) was 35.70 µg/mL, as determined from the regression curve (($R^2 = 0.99$, Figure 1). This suggests that SLE 35.70 µg/mL is a useful threshold for a 50% reduction of NO levels.

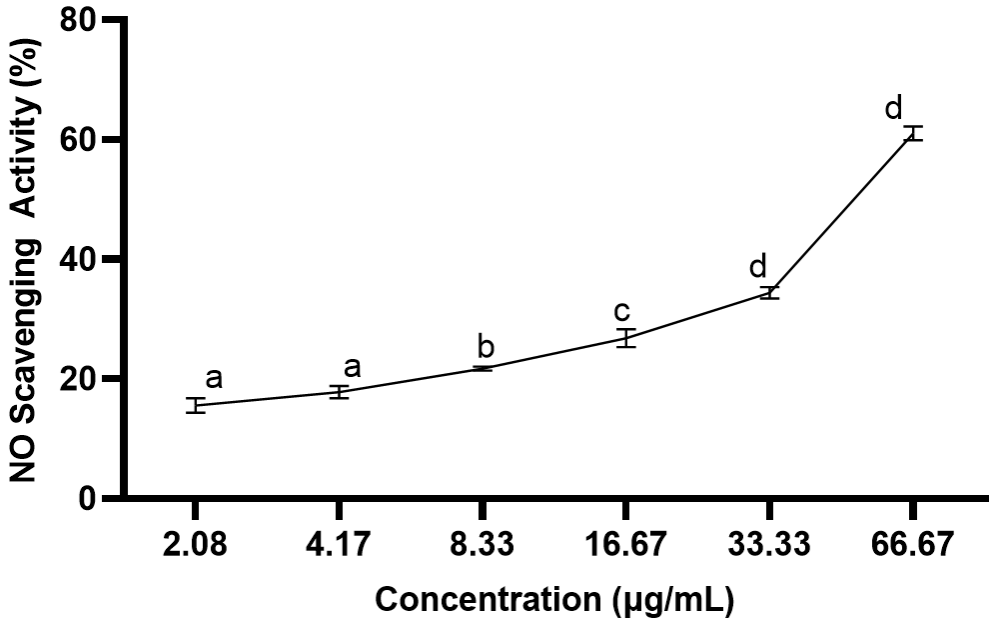

Figure 1 Effect of various SLE concentrations on NO scavenging activity.
*Data are shown as mean ± SD from triplicate wells. The IC_{50} value of SLE was 35.70 µg/mL ($R^2 = 0.99$). Different superscript letters represent statistically significant differences among treatments at $p < 0.05$ (Tukey's HSD 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 µg/mL demonstrated the highest cell viability value compared to other concentrations. SLE concentrations of 4 and 20 µg/mL were considered safe with viability values >90% and inhibition <30%.

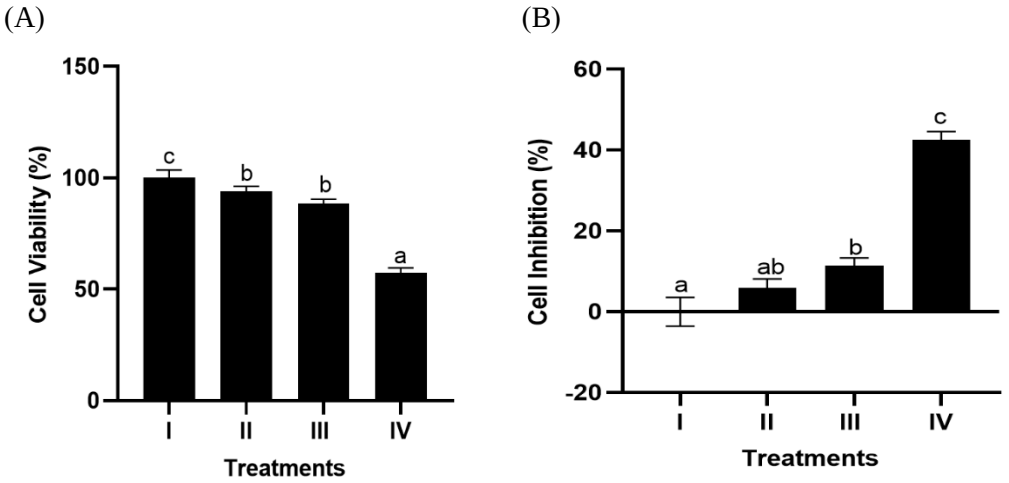

Figure 2 Effect of various SLE concentrations on (A) cells viability, (B) inhibition of RAW264.7 cells.
*Data are shown as mean ± SD from triplicate wells. Different superscript letters indicate statistically significant differences among treatments at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: SLE: 4 µg/mL; III: SLE 20 µg/mL; IV: SLE 100 µg/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 µg/mL represented the most effective concentration to increased protein level compared to SLE 4 µg/mL and PC significantly (p<0.05).

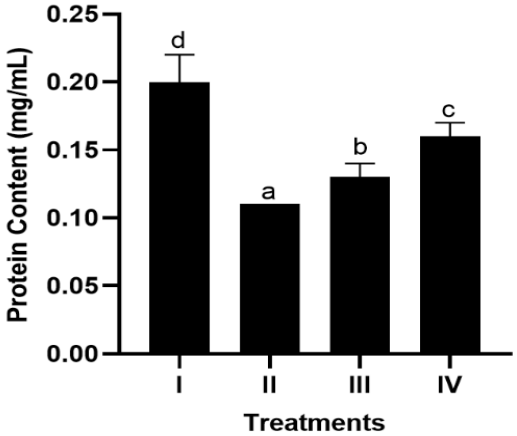

Figure 3 Effect SLE toward protein level on LRCs as inflammation cells model.
*Data are shown as mean ± SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 µg/mL; IV: PC + SLE 20 µg/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 µg/mL, 20 µg/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 µg/mL SLE significantly reduced TNF-α levels to values comparable with NC. This data also corresponded to Figure 4C, where SLE 20 µg/mL demonstrated higher TNF-α inhibition activity compared to SLE 4 µg/mL.

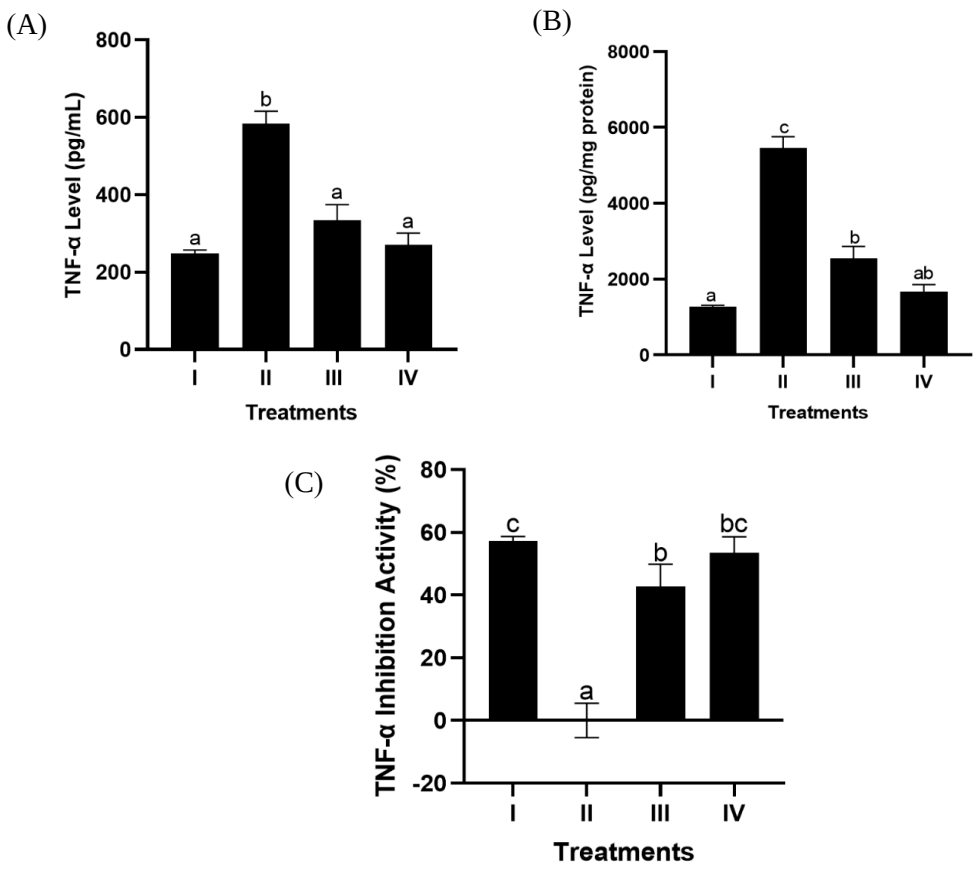

Figure 4 Effect of SLE on TNF-α levels in LRCs as an inflammation cell model. (A) TNF-α levels, (B) TNF-α levels expressed protein and (C) TNF-α inhibition activity (%).
*Data are shown as mean ± SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 µg/mL; IV: PC + SLE 20 µg/mL.

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

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

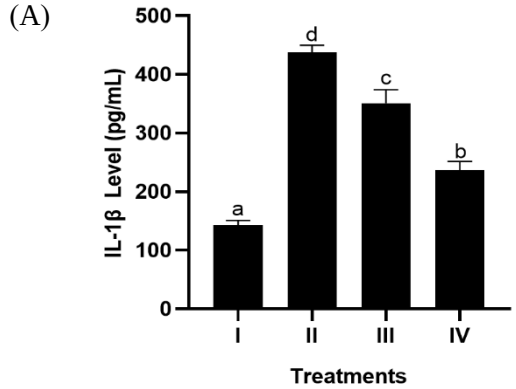

Figure 5 Effect of SLE on IL-1β levels in LRCs as an inflammation cell model. (A) IL-1β levels, (B) IL-1β levels expressed protein and (C) IL-1β inhibition activity (%).
*Data are shown as mean ± SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 µg/mL; IV: PC + SLE 20 µg/mL.

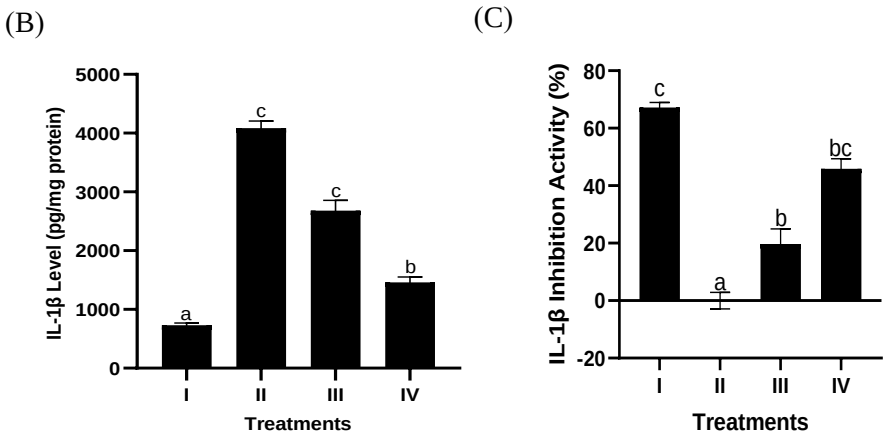

Figure 5 Effect of SLE on IL-1β levels in LRCs as an inflammation cell model. (A) IL-1β levels, (B) IL-1β levels expressed protein and (C) IL-1β inhibition activity (%).
*Data are shown as mean ± SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 µg/mL; IV: PC + SLE 20 µg/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 µg/mL considered the most effective concentration (Figure 6A-B). These data are consistent with Figure 6C, where SLE 20 µg/mL was more active in PGE-2 inhibition activity compared to SLE 4 µg/mL.

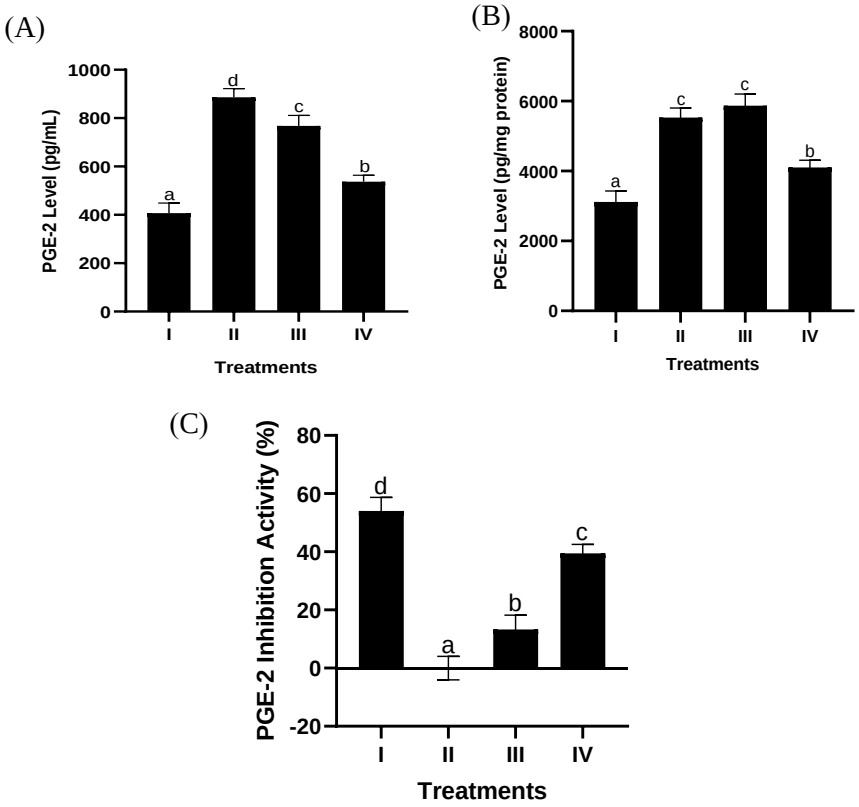

Figure 6 Effect SLE toward PGE-2 level on LRCs as inflammation cells model. (A) PGE-2 levels, (B) PGE-2 levels expressed protein and (C) PGE-2 inhibition activity (%).
*Data are shown as mean ± SD from triplicate wells. Values with different superscript letters indicate significant differences at $p < 0.05$ (Tukey's HSD post hoc test). I: Negative Control (NC) untreated cells (medium only); II: Positive Control (PC): LRCs; III: PC + SLE: 4 µg/mL; IV: PC + SLE 20 µg/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-1β, 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 µg/mL (Figure 1). The IC50 value of SLE for NO scavenging was 35.70 µg/mL, classifying it as a "very strong" antioxidant [21]. Antioxidants are categorized as "very strong" if their IC_{50} value is below 50 µg/mL, "strong" between 50 and 100 µg/mL, "moderate" between 101 and 250 µg/mL, "weak" between 250 and 500 µg/mL, and "inactive" if above 500 µg/mL. Compared with tomato extract reported in previous studies with ABTS IC_{50} value of 86.66 ± 10.58 µg/mL, SLE displayed stronger antioxidant capacity [22], DPPH IC_{50} value of 147.20 ± 16.97 µg/mL [15], H_2O_2 IC_{50} value of 221.30 ± 1.94 µg/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 µg/mL and 20 µg/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-1β, 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 µg/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-κB [28], which then enter the nucleus and increase the transcription of pro-inflammatory proteins namely TNF-α, IL-1β, and COX-2 [29].

TNF-α and IL-1β play key roles in inflammation by activating NF-κB and increasing the expression of adhesion molecules [30]. SLE was observed to reduce TNF-α and IL-1β protein levels, with 20 µg/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-1β 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 µg/mL showing the greatest reduction in PGE-2 protein levels (Figure 6). These finding are consistent with previous studies showing that methanolic SLE inhibited LPS-induced PGE-2 [34]. Endothelial cell activation, regulated by the NF-κB 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-1β 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.

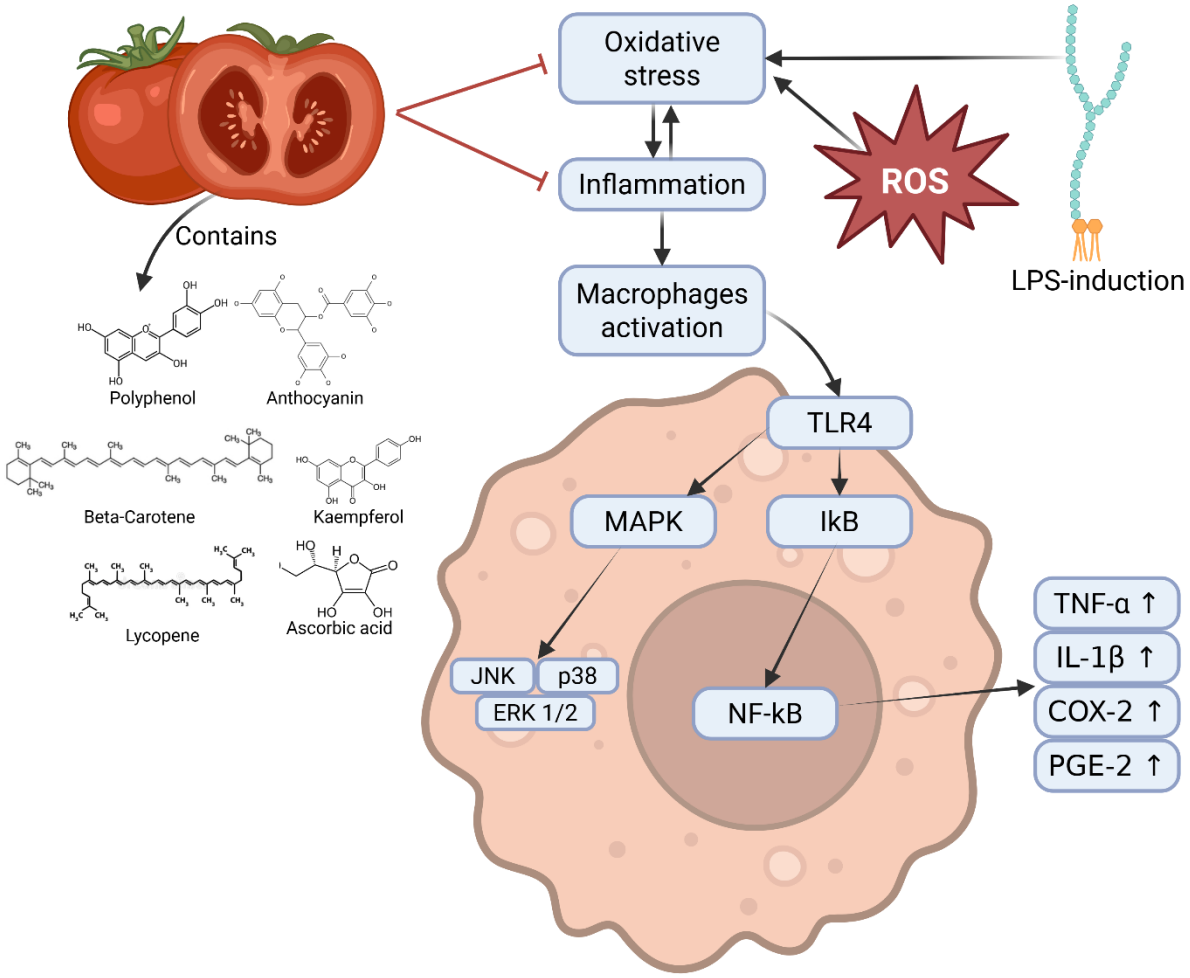

Figure 7 Proposed mechanism of SLE as an anti-inflammatory and antioxidant.
LPS induction triggers oxidative stress and influences the development of inflammation. Inflammation further activates macrophages that produce various pro-inflammatory mediators through the TLR4 pathway, which in turn induces the expression of IL-1β, 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 IC_{50} 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 µg/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-1β, TNF-α, and PGE-2.

6. Conflicts of interest

The authors have no conflict of interest to disclose.

7. Acknowledgments

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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.

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