



Potential Effects of Gandaria (*Bouea macrophylla* Griff.) Fruit Ethanol Extract on IL-6 Gene Expression in the Brain of Carbon Tetrachloride (CCl₄)-Induced White Rats (*Rattus norvegicus* L.)

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Abstract: This study aimed to evaluate the effect of gandaria fruit ethanol extract on IL-6 expression in the brain tissue of CCl₄-induced rats. A completely randomized experimental design was employed using 20 male white rats (*Rattus norvegicus* L.), which were assigned to five groups: normal control (KN), positive control (K+), treatment group 1 (P1) receiving 100 mg/kgBW of gandaria fruit ethanol extract, treatment group 2 (P2) receiving 150 mg/kgBW, and treatment group 3 (P3) receiving 200 mg/kgBW. IL-6 gene expression in brain tissue was analyzed using reverse transcription polymerase chain reaction (RT-PCR), followed by band intensity and relative density analyses. The relative density analysis revealed that the greatest reduction in IL-6 gene expression occurred in the P1 treatment group administered 100 mg/kgBW of gandaria fruit ethanol extract, with a fold change value of 2.5. These findings suggest that gandaria fruit ethanol extract may attenuate the inflammatory response induced by CCl₄ exposure through the suppression of IL-6 expression, with the 100 mg/kgBW dose exhibiting the most pronounced reduction based on relative density analysis.

Keywords: Oxidative stress; CCl₄; gandaria fruit ethanol extract

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INTRODUCTION

The brain is the largest and most complex organ of the nervous system and plays a central role in maintaining physiological homeostasis. Various essential processes, including movement, hormone regulation, cognition, and emotional responses, are regulated by the brain (Handayani, 2021). Although the brain represents only approximately 2% of total body weight, it consumes nearly 20% of the body's oxygen and energy supply. Despite variations in individual metabolic demands, the brain maintains a consistently high metabolic rate (Raichle & Gusnard, 2002). This high metabolic activity makes the brain highly dependent on oxidative processes and particularly vulnerable to oxidative stress. Due to its high oxygen consumption and abundance of neuronal cells, the brain is susceptible to oxidative damage when antioxidant defense mechanisms are insufficient.

Oxidative stress occurs when the production of *reactive oxygen species* (ROS) and *reactive nitrogen species* (RNS) exceeds the capacity of endogenous antioxidant systems. This imbalance may lead to oxidative and nitrosative damage through interactions between ROS/RNS and cellular macromolecules, including proteins, lipids, and nucleic acids. Oxidative stress has been associated with various pathological conditions, including diabetes, Alzheimer's disease, and other neurodegenerative disorders (Butterfield & Halliwell, 2019). In addition to direct

cellular damage, excessive oxidative stress can activate inflammatory signaling pathways and promote neuroinflammation. Exposure to toxic compounds, such as carbon tetrachloride (CCl_4), is one of the factors capable of inducing oxidative stress and inflammatory responses in biological tissues, including the brain (Wahyuni & Idami, 2025).

Carbon tetrachloride (CCl_4) is a toxic chemical compound widely used in industrial applications, including as a solvent, degreasing agent, and refrigerant precursor. Despite its industrial importance, CCl_4 is highly toxic because its metabolism generates reactive free radicals that can damage cellular structures in various organs, including the liver, kidneys, testes, and other tissues (Angela & Sumbayak, 2017). Following exposure, CCl_4 is metabolized by cytochrome P450 (CYP450) enzymes, producing trichloromethyl radicals ($\text{CCl}_3\cdot$) and trichloromethyl peroxy radicals ($\text{CCl}_3\text{O}_2\cdot$). These reactive metabolites initiate lipid peroxidation and increase ROS production through interactions with cellular components, resulting in oxidative damage (Cohen et al., 2023).

Although CCl_4 is primarily recognized for its hepatotoxic effects, the oxidative stress generated by its reactive metabolites may also influence extrahepatic tissues, including the central nervous system (CNS). In brain tissue, excessive ROS accumulation can disrupt cellular homeostasis and stimulate inflammatory signaling pathways, thereby contributing to neuroinflammation. Therefore, understanding the effects of CCl_4 -induced oxidative stress on brain inflammatory responses is important, particularly regarding molecular markers associated with inflammation (Ayunda et al., 2026).

Interleukin-6 (IL-6) is a multifunctional pro-inflammatory cytokine that plays an important role in regulating immune and inflammatory responses. Increased IL-6 expression is commonly associated with the activation of inflammatory pathways and is therefore widely used as an indicator of inflammatory responses (Putra & Pratama, 2025). Within the CNS, IL-6 is produced by various cell types, including neurons, astrocytes, microglia, and endothelial cells. This cytokine exhibits both protective and detrimental effects depending on the physiological context. Under normal conditions, IL-6 contributes to neuronal survival and tissue regeneration; however, excessive or prolonged IL-6 activation may promote neuroinflammation and contribute to neurodegenerative processes (Erta et al., 2012). Therefore, IL-6 expression represents an important molecular marker for evaluating inflammatory responses caused by oxidative stress and toxic exposure (Dewi & Dewi, 2025).

Oxidative stress induced by CCl_4 is closely associated with cellular injury through free radical-mediated mechanisms. The formation of reactive metabolites promotes lipid peroxidation, membrane disruption, mitochondrial dysfunction, and cellular damage (Triyudha et al., 2025). Although these mechanisms have been extensively studied in hepatic injury, oxidative stress caused by ROS can also affect the CNS by altering cellular signaling and cytokine regulation. Oxidative damage mediated by ROS may disrupt lipids, proteins, and DNA, while oxidative stress in the CNS may influence the production of inflammatory cytokines, including IL-6 (Kumar et al., 2015; Gusnirwan & Sangging, 2024). Thus, reducing oxidative stress and regulating inflammatory signaling represent potential strategies for mitigating tissue damage caused by toxic exposure.

Natural products containing antioxidant and anti-inflammatory compounds have received increasing attention as potential therapeutic agents for controlling oxidative stress and inflammation. Gandaria (*Bouea macrophylla* Griff.), a member of the Anacardiaceae family, is a tropical fruit widely distributed in Southeast Asia, including

Indonesia. Gandaria fruit contains various bioactive compounds, including phenolics, flavonoids, tannins, terpenoids, and vitamin C, which contribute to its biological activities (Rusli et al., 2023). Previous research demonstrated that 70% ethanol extract of gandaria fruit exhibited strong antioxidant activity, with an IC_{50} value of 47.064 $\mu\text{g/mL}$ based on the DPPH free radical scavenging assay. The extract also demonstrated tyrosinase inhibitory activity with a maximum inhibition rate of 47.529%, indicating its potential biological activity (Jayantie et al., 2022).

The antioxidant and anti-inflammatory properties of gandaria fruit may be associated with its phenolic and flavonoid constituents. These compounds have been reported to regulate inflammatory signaling pathways, including nuclear factor-kappa B (NF- κ B) and signal transducer and activator of transcription 3 (STAT3), which are important regulators of pro-inflammatory cytokine expression. Modulation of these pathways may contribute to the suppression of inflammatory mediators, including IL-6 (Papilaya et al., 2024). Therefore, gandaria fruit may have potential as a natural source of bioactive compounds capable of modulating oxidative stress-related inflammatory responses.

Although previous studies have demonstrated the antioxidant potential and phytochemical properties of gandaria fruit, information regarding its anti-inflammatory effects, particularly in oxidative stress-induced brain tissue, remains limited. Specifically, the ability of gandaria fruit ethanol extract to regulate IL-6 gene expression in CCl_4 -induced brain injury models has not been extensively investigated. Therefore, this study aimed to evaluate the effect of gandaria fruit (*Bouea macrophylla* Griff.) ethanol extract on IL-6 gene expression in the brain tissue of CCl_4 -induced white rats (*Rattus norvegicus* L.). This study is expected to provide additional scientific information regarding the potential role of gandaria fruit as a natural source for modulating inflammatory responses associated with oxidative stress.

METHOD

Research Design

This study employed a **completely randomized experimental design (CRD)**. Fifteen male white rats (*Rattus norvegicus* L.) were used as experimental animals. The rats were randomly assigned into five experimental groups, with three animals in each group ($n = 3$). The experimental treatments are presented in Table 1.

Table 1. Research design

Group	Treatment	Description
Normal control	Standard feed and drinking water, and weekly olive oil infusions.	There is no CCl_4 induction
Positive control	Induction of CCl_4 (1 mL/kgBW, i.p) every 3 days for 30 days.	Without giving gandaria extract
Treatment 1	a. CCl_4 induction (1 mL/kgBW, i.p) b. Gandaria extract (100 mg/kgBW p.o) every day until the 30th day.	The extract is given starting from the 2nd week after induction.
Treatment 2	a. CCl_4 induction (1 mL/kgBW, i.p) b. Gandaria extract (150 mg/kgBW p.o) every day until the 30th day.	
Treatment 3	a. CCl_4 induction (1 mL/kgBW, i.p) b. Gandaria extract (200 mg/kgBW p.o) every day until the 30th day.	

Materials

The materials used in this study were: 15 male white rats (*Rattus norvegicus* L), rat feed, husks as rat cage bedding, ethanol extract of gandaria fruit (*Bouea macrophylla*), carbon tetrachloride, CMC, olive oil, distilled water, *Phosphate Saline Buffer* (PBS), 0.9% NaCl, IL-6 forward and reverse primers, *housekeeping gene* (GAPDH), RNA isolation kit (*Tissue Total RNA Purification Mini Kit*), *reverse transcriptase II kit* (SMOBIO), *RNA loading dye*, PCR Kit (*PowerPol 2X PCR Mix with Dye*) and agarose gel.

Rat Brain Organ Harvesting

Fifteen male white rats (*Rattus norvegicus* L.) were randomly divided into five treatment groups, with three rats assigned to each group ($n = 3$). The sample size of three animals per group was selected for this preliminary experimental study to provide an initial evaluation of the effect of gandaria fruit ethanol extract on IL-6 expression in rat brain tissue.

Prior to tissue collection, the rats were anesthetized by chloroform inhalation and euthanized by cervical dislocation according to the Institutional Animal Care and Use Committee (IACUC) guidelines (Parawansah et al., 2020). The brain tissues were collected using sterile surgical instruments, washed with phosphate-buffered saline (PBS) to remove residual blood and tissue debris, and stored in 1.5 mL tubes containing 70% ethanol storage solution at 4°C until further analysis (Su et al., 2004).

RNA Extraction from Mouse Brain

Total RNA extraction was performed using 30 mg of brain tissue samples and the *Tissue Total RNA Purification Mini Kit* (Favorgen) according to the manufacturer's protocol. The concentration and purity of extracted RNA were determined using a UV-Vis spectrophotometer by measuring the absorbance ratios at A260/A280 and A260/A230.

A total of 1 µg RNA from each sample was used for complementary DNA (cDNA) synthesis. The RNA volume was adjusted according to the measured RNA concentration before reverse transcription using the reverse transcriptase II kit (SMOBIO). The reverse transcription reaction mixture consisted of Rtase/RI enzyme mix, 5× RT buffer containing DTT/dNTPs, oligo(dT), and DEPC-treated H₂O. The reaction mixture was incubated sequentially at 70°C, 25°C, 50°C, and 85°C.

IL-6 Gene Amplification by PCR

IL-6 gene amplification was performed using the polymerase chain reaction (PCR) method with *PowerPol 2X PCR Mix with Dye*. The PCR reaction mixture consisted of cDNA template (2–10 µL), forward and reverse primers (0.1–0.5 µM), dNTPs (0.2 mM), 10× Taq buffer (5 µL), Taq DNA polymerase (0.25 µL), and nuclease-free water to achieve the required final reaction volume.

The PCR amplification conditions consisted of initial denaturation at 98°C, denaturation at 98°C, annealing at 52.1°C, extension at 72°C, and final extension under predetermined conditions. The primer sequences used for IL-6 amplification and the GAPDH housekeeping gene are presented in Table 2.

Table 2. Table sekuens gen IL-6 dan GAPDH

Primer	Desain Primer	Referensi
GAPDH	Forward 5'-ACAGTCCATGCCATCACTGCC-3' Reverse 5'-GCCTGCTTCACCACCTTCTTG-3'	(Hu et al., 2020)
Interleukin-6	Forward 5'-GCCCTTCAGGAACAGCTATGA-3' Reverse 5'-TGTCAACAACATCAGTCCCAAGA-3'	

The PCR amplification products were analyzed by agarose gel electrophoresis. PCR products were loaded into agarose gel wells using a micropipette and electrophoresed in electrophoresis buffer at 100 V for 30 minutes. The DNA bands were visualized using a UV transilluminator and documented for further analysis.

Data Analysis

The intensity of PCR bands was analyzed using ImageJ software by calculating the relative intensity of IL-6 expression normalized against the GAPDH housekeeping gene. The data distribution was initially evaluated using the Shapiro–Wilk normality test. Normally distributed data were subsequently analyzed using one-way analysis of variance (ANOVA) to determine differences among experimental groups. When significant differences were observed, Tukey’s honestly significant difference (HSD) post hoc test was performed for pairwise comparisons. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Results of Purity and Concentration of White Mouse Brain RNA

The purity and concentration of RNA extracted from rat brain tissue were evaluated using a UV–Vis spectrophotometer. The absorbance ratios at A260/A230 and A260/A280, as well as RNA concentrations, were used to assess RNA quality prior to reverse transcription and PCR analysis. The results are presented in Table 3.

Table 3. Results of purity of mouse brain RNA

Sample	A260/A230	A260/A280	Concentration	Information
KN	1.846	2.050	32.229 µg/mL	Pure
K+	1.846	1.857	64.888 µg/mL	Pure
P1T1	1.957	2.115	46.374 µg/mL	Pure
P1T1	1.958	2.011	123.286 µg/mL	Pure
P1T3	2.103	2.198	64.458 µg/mL	Pure
P2T1	1.080	1.901	25.792 µg/mL	Pure
P2T2	1.119	1.368	89.501 µg/mL	Impure
P2T3	1.655	1.986	41.738 µg/mL	Pure
P3T1	1.063	1.473	24.388 µg/mL	Impure
P3T2	1.369	1.811	40.574 µg/mL	Pure
P3T3	1.517	2.064	30.316 µg/mL	Pure

Variations in RNA purity among samples represent a limitation of the RNA extraction process. Samples with A260/A280 ratios outside the recommended range may contain residual proteins or other contaminants that can interfere with reverse transcription and subsequent PCR amplification. Therefore, differences in RNA quality may contribute to variations in PCR band intensity (Sanjaya & Ratnawati, 2025). However, all RNA samples were processed under identical reverse transcription and PCR conditions, and IL-6 expression was normalized against the GAPDH housekeeping gene to minimize the influence of differences in RNA input and sample quality.

RNA concentration is an important factor affecting the efficiency of cDNA synthesis because sufficient RNA input is required for optimal reverse transcription reactions. Differences in RNA concentration among samples may be influenced by variations in tissue quality and RNA isolation efficiency. Therefore, RNA normalization was performed to ensure that comparable RNA amounts were used for downstream molecular analysis.

PCR Reaction Mixture Preparation

The PCR reaction mixture used in this study was prepared according to the composition and volume requirements presented in Table 4.

Table 4. PCR reaction mixture composition

Composition	Volume (25 µl)	Number of samples	Human Error	Total reaction
PowerPol 2X PCR Mix with Dye	12,5 µl	11	1	150 µl
Forward Primer	0,5 µl			6 µl
Reverse Primer	0,5 µl			6 µl
DNA Template	2 µl			24 µl
Nuclease Free Water	9,5 µl		1	276 µl

Each PCR reaction was prepared with a final volume of 25 µL, consisting of 12.5 µL of PowerPol 2X PCR Mix with Dye, 0.5 µL of forward primer, 0.5 µL of reverse primer, 2 µL of DNA template, and nuclease-free water to achieve the final volume.

To improve pipetting accuracy and minimize technical variation, the PCR master mix was prepared in advance without adding DNA templates. This approach was particularly useful because the primer volumes were relatively small (0.5 µL), which increases the risk of pipetting errors. One additional reaction volume was included to compensate for potential volume loss during preparation. After preparation, 23 µL of master mix was distributed into each PCR tube, followed by the addition of 2 µL of DNA template, resulting in a final reaction volume of 25 µL per sample.

IL-6 and GAPDH Gene Expression Analysis

IL-6 gene expression was analyzed using conventional polymerase chain reaction (PCR) followed by agarose gel electrophoresis to evaluate the presence and relative intensity of amplified DNA fragments. The IL-6 amplification product was detected at approximately 280 base pairs (bp), consistent with previous findings demonstrating a 280 bp IL-6 amplification fragment (Sudo et al., 2008). Although the fragment appeared close to the 300 bp marker position, this observation was likely influenced by the limited resolution of agarose gel electrophoresis.

To improve the accuracy of gene expression analysis, IL-6 expression was normalized against GAPDH (*Glyceraldehyde-3-phosphate dehydrogenase*) as an internal housekeeping control. GAPDH is commonly used as a reference gene because its expression is relatively stable across different tissues. Normalization allows differences in target gene expression to be distinguished from variations caused by technical factors.

PCR analysis showed that IL-6 produced an amplified fragment of approximately 280 bp, whereas GAPDH produced a fragment of approximately 300 bp (Figure 1). The similar fragment sizes resulted from the primer design characteristics used in previous studies rather than similarities in nucleotide sequences. The GAPDH primer had an annealing temperature of approximately 51°C, while the IL-6 primer had an annealing temperature of approximately 52.1°C, indicating comparable amplification conditions.

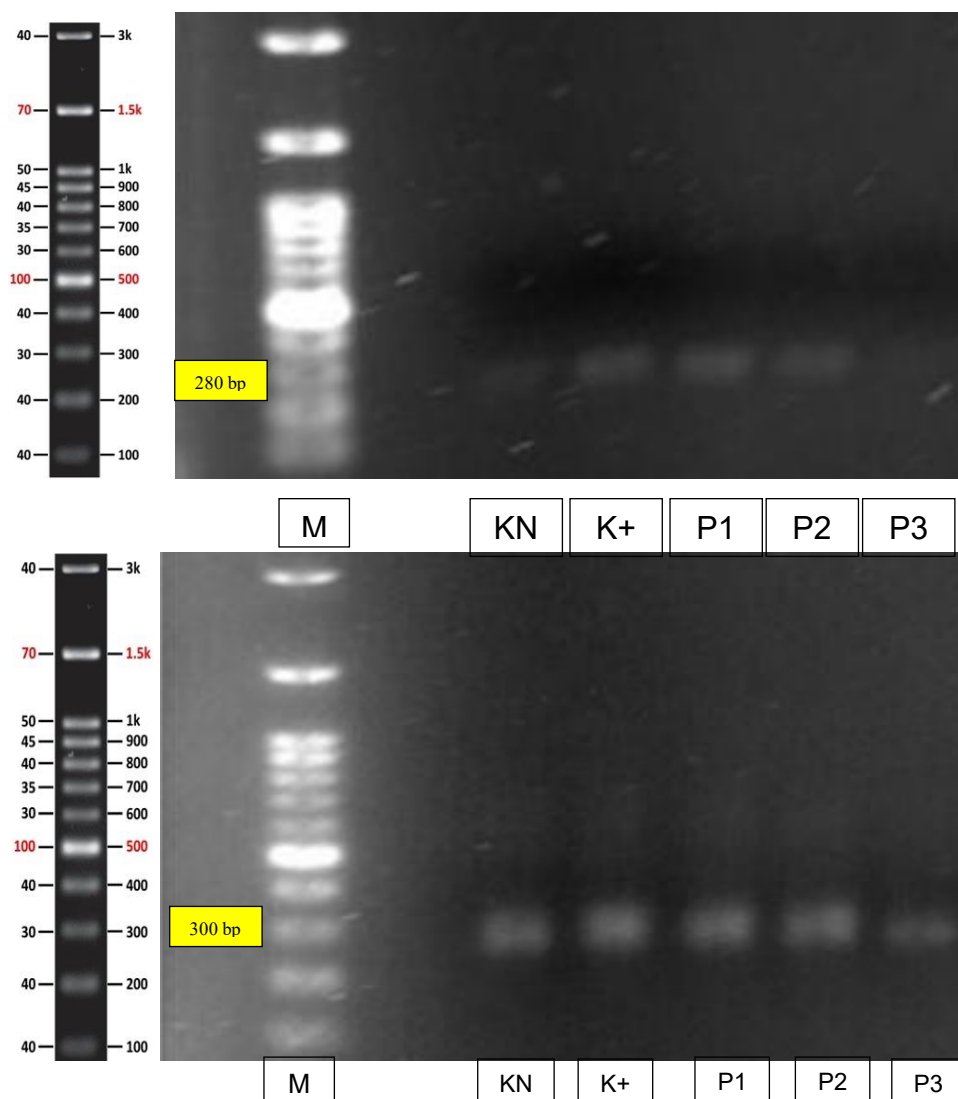


Figure 1. Visualization of IL-6 gene expression (A) and GAPDH gene expression (B) using Gel Documentation System (Marker (M); Normal control (KN); CCl₄-induced group (K+); CCl₄ + gandaria extract 100 mg/kgBW (P1); CCl₄ + gandaria extract 150 mg/kgBW (P2); CCl₄ + gandaria extract 200 mg/kgBW (P3))

Electrophoresis results demonstrated differences in IL-6 band intensity among experimental groups. The normal control group (KN) exhibited relatively weak IL-6 bands, whereas the CCl₄-induced group (K+) showed the strongest band intensity, indicating increased IL-6 expression following oxidative stress induction.

The P1 and P2 treatment groups receiving gandaria extract at doses of 100 and 150 mg/kgBW, respectively, showed relatively strong IL-6 bands, which appeared comparable to the positive control group. This suggests that IL-6 expression remained elevated at these doses. In contrast, the P3 group receiving 200 mg/kgBW gandaria extract showed reduced band intensity, approaching the pattern observed in the normal control group.

The lower IL-6 band intensity observed in the P3 group may indicate a greater suppression of IL-6 expression at the highest tested dose. However, differences in DNA concentration among samples may also have contributed to variations in band intensity. For example, spectrophotometric analysis showed a relatively low DNA

concentration in some samples, which may influence the visual intensity of electrophoretic bands.

Relative Density Analysis of IL-6 Expression Normalized to GAPDH

Relative density analysis represents the intensity of IL-6 bands normalized against the GAPDH housekeeping gene. The results of IL-6 expression analysis are presented in Figure 2.

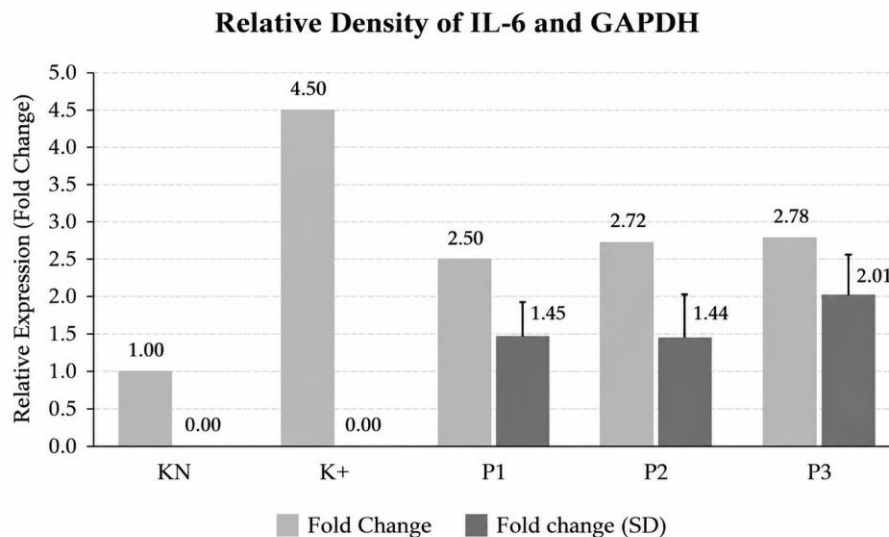


Figure 2. Relative expression of IL-6 gene normalized against GAPDH (Fold change represents relative expression changes compared with the control group; Fold change SD represents variation among replicates)

Fold change analysis was performed using the normal control group (KN) as the reference value, which was assigned a value of 1. A fold change value closer to 1 indicates expression levels comparable to the control condition. The standard deviation (SD) was used to evaluate variation among experimental replicates, where lower SD values indicate greater consistency.

The relative density analysis showed differences in IL-6 expression among experimental groups. In the normal control group (KN), IL-6 expression was used as the baseline reference with a fold change value of 1. CCl₄ induction in the positive control group (K+) increased IL-6 expression by approximately 4.5-fold compared with the normal control group, indicating that CCl₄ successfully induced an inflammatory response associated with oxidative stress.

Administration of gandaria fruit ethanol extract reduced IL-6 expression compared with the CCl₄-induced group. The P1 treatment group (100 mg/kgBW) showed a fold change value of 2.5 with a standard deviation of 1.45, indicating that this dose reduced CCl₄-associated IL-6 elevation. The P2 and P3 groups showed fold change values of 2.7 and 2.78, with SD values of 1.44 and 2.01, respectively.

These findings indicate that all tested gandaria extract doses (100–200 mg/kgBW) reduced IL-6 expression compared with the CCl₄-induced group. However, the gradual increase in IL-6 expression observed at higher doses (P2 and P3) suggests a possible biphasic response pattern.

A biphasic dose response, known as hormesis, describes a phenomenon in which a compound produces different biological effects depending on the dose. At lower concentrations, a compound may induce protective effects, whereas higher concentrations may reduce or reverse these effects (Mattson, 2008). In this study,

the observed pattern may indicate that the lower dose of gandaria extract provided a stronger suppressive effect on IL-6 expression, while increasing doses resulted in a less pronounced reduction. However, further studies using a broader dose range are required to confirm the presence of a hormetic response.

Overall, the results suggest that gandaria fruit ethanol extract has potential to modulate IL-6 gene expression under CCl₄-induced oxidative stress conditions. This effect may be associated with the presence of bioactive compounds, including flavonoids, phenolic compounds, and tannins, which possess antioxidant and anti-inflammatory activities. These compounds may regulate inflammatory signaling pathways and reduce pro-inflammatory cytokine expression, including IL-6. Therefore, the findings support the potential role of gandaria fruit as a natural source of bioactive compounds capable of attenuating oxidative stress-associated inflammatory responses.

CONCLUSION

This study demonstrated that CCl₄ induction was associated with an increase in relative IL-6 gene expression, as indicated by a 4.5-fold increase in IL-6 band intensity compared with the normal control group. Administration of gandaria fruit extract (*Bouea macrophylla* Griff.) at doses of 100, 150, and 200 mg/kgBW reduced the relative IL-6 expression levels compared with the CCl₄-induced group, with fold change values of 2.5, 2.72, and 2.78, respectively. Among the tested doses, the 100 mg/kgBW treatment exhibited the lowest relative IL-6 expression level. These findings suggest that gandaria fruit extract may attenuate the CCl₄-induced inflammatory response by reducing IL-6 gene expression, with the 100 mg/kgBW dose showing the greatest reduction under the conditions of this study.

RECOMMENDATION

Further research is needed using variations in doses of gandaria fruit extract (*Bouea macrophylla* Griff) that are lower than 100 mg/kgBW to obtain an effective dose range and to determine the optimal dose in suppressing the inflammatory response.

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