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CENTELLA ASIATICA ETHANOLIC EXTRACTS REDUCES INTERLEUKIN-1β EXPRESSION IN THE GASTRIC MUCOSA OF INDOMETHACIN-INDUCED ULCER RATS

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ABSTRACT
Gastric ulcers are a common gastrointestinal disorder affecting millions worldwide, with complications contributing to high hospitalisation rates. Pro-inflammatory cytokines, particularly IL-1β, play a key role in the inflammatory response and ulcer development. To evaluate the anti-inflammatory effect of Centella asiatica ethanolic extract (CAEE) on indomethacin-induced gastric ulcers in rats, focusing on IL-1β expression. An experimental study was conducted on 18 adult male Wistar rats divided into six groups: negative control (NC), positive controls (PC1 for 24 hours and PC8 for 8 days), and three treatment groups receiving CAEE at 100, 200, and 400 mg/kgBW (T1–T3). Gastric ulcers were induced with indomethacin (30 mg/kgBW), followed by seven days of CAEE administration. Gastric tissue was evaluated histologically using hematoxylin–eosin staining and immunohistochemically for IL-1β expression. Quantitative analysis was performed with ImageJ, and data were statistically tested using one-way ANOVA followed by Tukey's post hoc test. Results:Indomethacin significantly increased IL-1β expression in the gastric mucosa ($p=0.000$). CAEE at 100, 200, and 400 mg/kgBW significantly reduced IL-1β expression compared with the PC8 group ($p<0.05$), with the strongest suppression at 400 mg/kgBW. Conclusions: CAEE demonstrates a dose-dependent anti-inflammatory effect by suppressing IL-1β expression, suggesting its therapeutic potential in gastric ulcer management.

Keywords: anti-inflammatory; centella asiatica; cytokine; gastric ulcer; interleukin-1β; mucosa

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INTRODUCTION

Globally, gastric ulcers contribute significantly to healthcare resource utilization and hospitalization (Z. Zhang et al., 2023), posing clinical and economic challenges. In the United States, they affect about 4.6 million people annually. Although incidence, prevalence, and mortality have declined over recent decades due to reduced Helicobacter pylori (H. pylori) infection and broader use of antisecretory agents, the disease remains a substantial burden. Notably, the incidence of complicated gastric ulcers and hospitalizations has remained stable, partly due to concomitant aspirin and nonsteroidal anti-inflammatory drug (NSAID) use among older people. While H. pylori eradication strategies have lowered recurrence and ulcer-related mortality with cost savings, the overall economic impact remains high (Kowada & Asaka, 2022). The origins of gastric ulcer are multifactorial, but the leading causes are H. pylori infection, NSAID usage, and acetylsalicylic acid consumption (Kumar et al., 2021). A key concern is the increased use of NSAIDs such as indomethacin, which can induce gastric ulcers (Kim et al., 2020). By inhibiting cyclooxygenase in the gastrointestinal tract, indomethacin decreases prostaglandin secretion and its cytoprotective effects, leaving the mucosa susceptible to injury (McEvoy et al., 2021). Indomethacin also induces oxidative stress, triggers apoptotic pathways in gastric epithelial cells, and elevates reactive oxygen species (ROS), causing microvascular injury and further tissue damage (Sayed Abdel-Tawab et al., 2020).

Gastric ulcers arise when protective mechanisms such as the mucus–bicarbonate barrier are overwhelmed by harmful factors like gastric acid (Oncel & Basson, 2022). Pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-8, and IL-2, are released during mucosal inflammation, contributing to tissue damage. Among these, IL-1β plays a central role in NSAID-induced gastric injury, amplifying inflammatory cascades and promoting ulcer formation (M. Zhang et al., 2022). Rat model studies have demonstrated IL-1β upregulation in the gastric mucosa following indomethacin exposure. IL-1β is produced by monocytes, dendritic cells, tissue macrophages, and microglia in response to pattern recognition receptors or tissue-damage signals such as complement components and cytokines (Singh & Singh, 2024). Generally confined to inflammatory cells in the inner mucosa, IL-1β expression spreads to superficial layers during inflammation. Its inhibition reduces ulcer formation and severity, highlighting its role as a key mediator in ulcer pathogenesis (Kumar et al., 2021; Mantovani et al., 2019). Pharmacological therapies such as proton pump inhibitors (PPIs), H2-receptor antagonists (H2RAs), and prostaglandin analogues provide gastroprotection but are associated with side effects (Ommurugan & Rao, 2019; Sverdén et al., 2019). Long-term PPI use has been linked to intestinal dysbiosis, increased risk of gastrointestinal infection, small intestinal bacterial overgrowth (SIBO), kidney disease, cardiovascular complications, and gastric cancer (Al-Aly et al., 2020). Moreover, PPIs are often prescribed inappropriately, particularly for prophylaxis against gastrointestinal haemorrhage in patients on NSAIDs therapy (Targownik et al., 2022), and may lead to reduced efficacy over time, although evidence on resistance is still emerging (Sizgoric & Likic, 2024).

Centella asiatica, a tropical plant native to Indonesia, India, China, and Papua, has a protective effect against gastric mucosal damage (Sun et al., 2020). The anti inflammatory, antioxidant, and wound healing qualities of the active ingredients particularly pentacyclic triterpenes like asiaticoside, madecassoside, asiatic acid, and madecassic acid are well-known (Shafin et al., 2023). Asiatic acid and madecassic acid have anti-inflammatory properties via decreasing the expression of TNF-α, cyclooxygenase-2 (COX-2), IL-1β, IL-6, and inducible nitric oxide synthase (iNos) (Dong et al., 2025; Sun et al., 2020). Additionally, Centella asiatica inhibits neutrophil recruitment and activation in damaged mucous tissue, which is a major cause of ulcer pathogenesis. Due to its effective gastroprotective properties and lower side effects, Centella asiatica is considered a viable alternative to PPIs and H2RAs in ulcer management. Centella asiatica significantly increases gastric mucus secretion and mucosal glycoproteins, which fortify the mucosal barrier against irritants like NSAIDs without reducing acid secretion (Sun et al., 2020). It also promotes recovery of the lesion by stimulating collagen production, fibroblast proliferation, and angiogenesis, thus accelerating the repair of damaged gastric tissue. Previous studies have reported low toxicity and safety of Centella asiatica, which makes it suitable for long-term use without the risks associated with PPIs and H2RAs including increased infection risk, nutrient malabsorption, and changes in gut microbiota (Liu et al., 2022). Moreover, the extract of Centella asiatica downregulate the phosphorylation of IRAK1 and TAK1, upstream kinases that activate NF-κB, thereby decreasing IL-1β production (Cho et al., 2020).

This study aimed to understand the effect of Centella asiatica on the expression of IL-1β in the indomethacin-induced gastric ulcer model rats. The results of this study are expected to provide new insights into the development of natural-based gastroprotective therapy to overcome gastric mucosal inflammation due to NSAIDs.

METHOD

Centella asiatica Ethanolic Extract (CAEE)

Indomethacin (Sigma) and 96% ethanol were obtained from the Pharmacology Laboratory, Faculty of Medicine, Universitas Brawijaya. Centella asiatica was sourced from PT. Materia Medica Batu, East Java, Indonesia. The plant material was cleaned, chopped, and dried at 40–60°C. 100 g of dried material was macerated in 1 L of 96% ethanol, agitated using an orbital shaker for 30 minutes, and left overnight. The extract was filtered through Whatman GF/D paper (90 mm) and concentrated using a rotary evaporator to obtain the ethanolic extract (CAEE).

Experimental Animals and Ethical Approval
Adult male Wistar rats (150–200 g) were purchased from the Pharmacology Laboratory, Faculty of Medicine, Universitas Brawijaya. The animals were maintained under controlled temperature and humidity, with a 12-hour light/dark cycle and free access to food and water. All procedures were approved by the Animal Ethics Committee of Universitas Brawijaya (Ethical Clearance No. 207/EC/KEPK-S2/12/2020).

Experimental Design and Treatment Protocol
Eighteen rats were randomly divided into six groups (n = 3): Negative Control (NC), Positive Control Day 1 (PC1), Positive Control Day 8 (PC8), and treatment groups receiving CAEE at 100 mg/kgBW (T1), 200 mg/kgBW (T2), or 400 mg/kgBW (T3). Except for NC, all rats were fasted for 8 hours before ulcer induction, with water provided ad libitum. Indomethacin (30 mg/kgBW, orally) was administered to PC1, PC8, T1, T2, and T3 groups to induce gastric ulcers. NC and PC1 animals were sacrificed 24 hours post-induction, while PC8 animals were maintained for 8 days. Eight hours after indomethacin administration, T1–T3 groups received CAEE at their respective doses once daily for seven days. All treatment groups were sacrificed 24 hours after the final dose.

Histological Examination and Immunohistochemistry (IHC)
Stomachs were excised, fixed in 10% buffered formalin, and embedded in paraffin. Sections (4 μm) were prepared using a microtome. Hematoxylin and eosin (H&E) staining was performed for histological evaluation. Immunohistochemistry (IHC) was used to assess IL-1β expression. Tissue sections were deparaffinized with xylene, rehydrated through graded alcohols (100%, 90%, 80%), and endogenous peroxidase activity was blocked with Peroxidase Blocking Reagent (ScyTek, ADA100) for 25 minutes at room temperature. Antigen retrieval was performed using decloaking solution for 45 minutes at 90°C. Slides were incubated overnight at 4°C with IL-1β monoclonal antibody (11E5, sc-52012; Santa Cruz Biotechnology, USA), washed with PBS, and treated with Anti-Polyvalent HRP Polymer (ScyTek, ABZ100) for 1 hour at room temperature. Color development was achieved using DAB Chromogen (ScyTek, ACB006), with positive IL-1β expression indicated by brown cytoplasmic precipitate. The reaction was stopped with distilled water, followed by counterstaining with Mayer's hematoxylin (ScyTek, HMM125). After drying, slides were mounted for microscopic evaluation. IL-1β expression was examined under an Olympus BX51 light microscope (Olympus Soft Imaging Solutions GmbH, Münster, Germany). Quantification was performed using Fiji ImageJ software by calculating the mean optical density (MOD) of brown-stained cytoplasmic areas in 10 randomly selected fields at 400× magnification. Data were expressed as mean ± standard deviation. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test with IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

RESULT
The gastric mucosa of the negative control group (NC) exhibited a normal histologic aspect of the gastric wall and an intact mucosal lining (Figure 1).

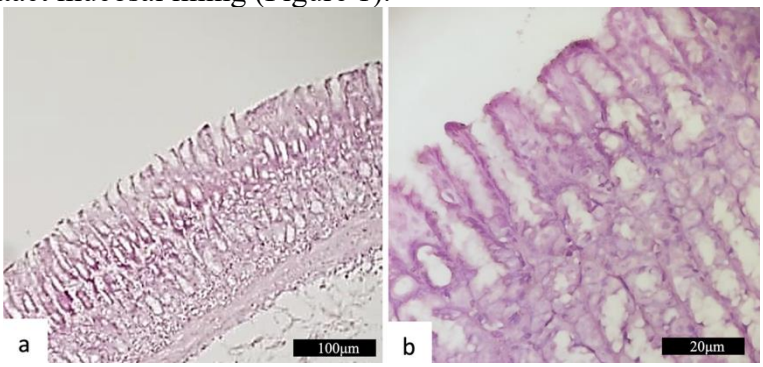

Figure 1. Gastric Tissue of Negative Control Group at 100x (a) and 400x (b) Magnification

a) Normal gastric histology showing an intact mucosa (M), submucosa (SM), and muscularis externa (ME), b) upper part of the gastric mucosa with normal surface epithelial cells

In contrast, ulcer formation is observable in the gastric mucosal epithelial cells at 24 hours post-indomethacin administration (Figure 2). In the positive control group (PC1), ulceration was characterized by damage extending from the gastric mucosal layer to the muscularis mucosa layer. The negative control group exhibited no damage to the mucosal layer. Before administering CA ethanolic extracts, Indomethacin was given to induce ulceration. Subsequently, the treatment groups were categorized into three subgroups, each receiving a distinct dose after the administration of the CA ethanolic extract.

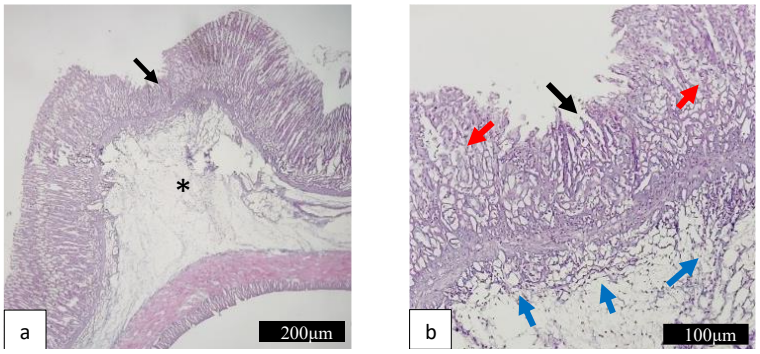

Figure 2. Gastric Tissue of Positive Control Group on Day 1 (PC1) at 40x (a) and 100x (b) Magnification

(a) Mucosal erosion (black arrow) and massive edema in the submucosa (star), (b) Necrosis (black arrow) and damage to the gastric gland structure (red arrow) in the mucosal layer and leukocyte infiltration (blue arrow) in the submucosal layer of gastric tissue

The results of immunohistochemical staining of rat gastric tissue showed increased IL-1β expression in the PC1 and the PC8 compared with the NC, as indicated by more brown-stained cytoplasm and with higher brown color intensity (Figure 3). This is evidenced by the higher mean optical density (MOD) of groups PC1 and PC8, namely 20.10 ± 0.96% and 18.52 ± 1.33%, respectively, when compared with group NC (10.69 ± 0.59%). This indicates that indomethacin at 30 mg/kg BW can increase IL-1β expression in gastric mucosal tissue. The mean MOD value of IL-1β expression in group PC8 was lower than that in group PC1, which likely indicates a self-healing process, so that IL-1β production has begun to decrease. However, the decrease in IL-1β expression in group PC8 did not reach the normal values as in group NC, and therapy is therefore needed.

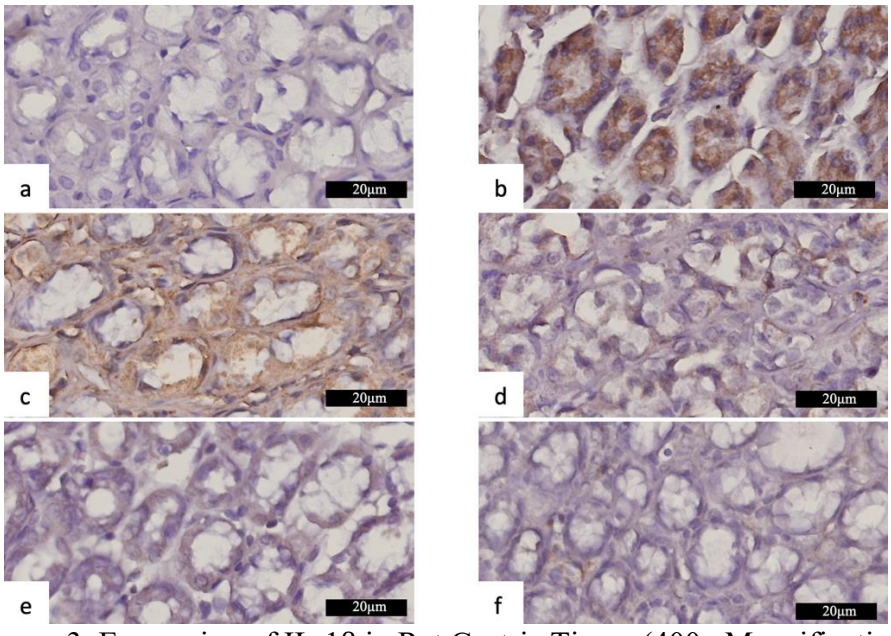

Figure 3. Expression of IL-1β in Rat Gastric Tissue (400x Magnification)

The expression of IL-1β stained brown in the cytoplasm of gastric gland cells. a) negative control group (NC); b) positive control group on day 1 (PC1); c) positive control group on day 8 (PC8); d) treatment group 1 (T1); e) treatment group 2 (T2); f) treatment group 3 (T3).

In all treatment groups, that received indomethacin 30 mg/kgBW and were given CAEE at a certain dose, a lower mean optical density (MOD) was obtained when compared with the P8 group. Group T1, which received CAEE at a dose of 100 mg/kg BW, achieved an average MOD of 13.89 ± 0.75%. Group T2, which received the CAEE at a dose of 200 mg/kg BW, achieved an average MOD of 12.51 ± 1.19%. Group T3, which received an CAEE at a dose of 400 mg/kg BW, obtained the lowest mean MOD (11.89 ± 1.14%) compared with groups T1 and T2. The average MOD of IL-1β expression in all groups can be seen in Table 1.

Table 1.
Mean Optical Density of IL-1β Expression

Experimental Groups	Mean Optical Density ± SD (%)	p-value
Negative control group (NC)	10.69 ± 0.59	
Positive control group on day 1 (PC1)	20.10 ± 0.96	0.000*
Positive control group on day 8 (PC8)	18.52 ± 1.33	0.000*
Treatment 1 group (T1)	13.89 ± 0.75	0.004*
Treatment 2 group (T2)	12.51 ± 1.19	0.173
Treatment 3 group (T3)	11.89 ± 1.14	0.579

The same notation indicates a non-significant difference ($p>0.05$)
*)$p<0.05$ = significant difference compared to the negative control group

DISCUSSION

Indomethacin is a non-selective NSAID with very high ulcerogenic potential. Histological examination in this study revealed edema with leukocyte infiltration in the submucosal layer, sloughing of the stomach pits, glandular damage with architectural deformation of cells, and ulceration and necrosis in the surface mucosal epithelium after indomethacin induction (Sriepindonnta et al., 2021). Previous studies have shown that oral administration of 20 mg/kg BW of indomethacin escalates pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α in gastric tissue (Katary & Salahuddin, 2017). Indomethacin damages the gastric mucosa through several mechanisms, including direct mucosal injury via its acid and ion-trapping properties and inhibition of prostaglandin synthesis through COX inhibition (Hijos-Mallada et al., 2022).

Interleukin-1 alpha (IL-1α), released by damaged gastric epithelial cells, acts as an “alarmin” by binding to macrophage IL-1R1 receptors, activating the inflammasome, and allowing caspase-1 to cleave pro-IL-1β into its mature form (Mantovani et al., 2019; Van Den Eeckhout et al., 2020). IL-1β stimulates adhesion molecules like ICAM-1 on endothelial cells, increasing leukocyte recruitment (Kumar et al., 2021; Mantovani et al., 2019). Its secretion also induces other cytokines, including TNF-α, IL-6, and IL-8 via NF-κB activation (Kadatane et al., 2023; Pyrillou et al., 2020). In turn, bone marrow produces more neutrophils and monocytes, which migrate to the damage site (Kumar et al., 2021; Mantovani et al., 2019).

The PC8 group’s lower MOD of IL-1β expression compared to PC1 could indicate self-healing, though not statistically significant ($p = 0.291$). Gastric ulcer healing is a complex process involving inflammation, granulation, re-epithelialization, matrix production, and remodeling. Pro-inflammatory cytokines rise during the inflammatory phase, with IL-1β promoting inflammation and growth factor release (Mantovani et al., 2019). The integrity of the gastric epithelium is maintained through a continuous cell renewal process by mucosal progenitor cells, which proliferate and differentiate to replace damaged epithelial cells. Generally, this process lasts for 3-7 days, whereas the replacement of glandular cells can take several months. Restitution of the epithelial surface after damage occurs rapidly within minutes, with the migration of cells that are still present in the area of the neck of the gastric glands. The cell replacement process is regulated by growth factors. Gastrin and prostaglandin E2 (PGE2) are known to stimulate cell proliferation by transactivating the epidermal growth factor receptor (EGF-R) in gastric progenitor cells and

triggering the mitogen-activated protein kinase (MAPK) pathway (Yang et al., 2020).

There are early and late healing stages in the ulcer healing process. Rapid epithelial cell migration and contraction near the ulcer's base characterize the early healing phase. The late healing phase is characterized by angiogenesis, granulation tissue remodeling, and re-epithelialization of the ulcer crater. In the late healing phase, fibroblasts and microvessels take the place of inflammatory cells that arise in the early healing phase (Rodrigues et al., 2019; Soliman & Barreda, 2023). In rats, the inflammatory phase of wound healing generally peaks between days 4 to 7 after the formation of the wound . By day 7, levels of IL-1β, IL-6, and TNF-α begin to decline and continue to decrease by day 14 (Raziyeva et al., 2021). However, in this study, the expression of IL-1β in the PC8 group had not yet reached normal values as in the control group, indicating that a therapeutic approach was needed.

While there were no significant changes between the T2 and T3 groups when comparing the treatment groups to the negative control (NC) ($p > 0.05$), there were significant variations in the mean optical density (MOD) of IL-1β expression in all CAEE treatment groups when compared to group PC8 ($p = 0.000$). This demonstrates that the MOD of IL-1β expression in the stomach mucosa may be brought down to normal levels by administering CAEE at dosages of 200 and 400 mg/kgBW. Previous research has shown that *Centella asiatica* extracts have anti-inflammatory qualities via inhibiting the NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways, which stops the generation of pro-inflammatory cytokines like IL-1β (Dong et al., 2025). It is expected that CAEE will accelerate the healing process by shortening the inflammatory phase. These results are supported by studies showing that increasing doses of CAEE further increase growth factors such as bFGF, EGF, and TGF-β, as well as the proliferation factor Ki-67 (Arribas-López et al., 2022).

Previous research also demonstrated that CAEE at doses of 100, 200, and 400 mg/kg BW had cytoprotective effects against gastric mucosal damage (Thirza et al., 2021). The C. asiatica ethanolic extract showed a cytoprotective effect proportional to the increase in dose; the best gastric cell protection was observed at a dose of 400 mg/kgBW. Rats given CAEE before ulcer-induced showed milder edema and less leukocyte infiltration in the gastric submucosal layer. *Centella asiatica* contains pentacyclic triterpenes, including asiaticoside, madecassoside, asiatic acid, and madecassic acid (Shafin et al., 2023). Madecassic acid isolated from *Centella asiatica* has anti-inflammatory effects by lowering the expression of iNOS, COX-2, IL-1β, IL-6, and TNF-α through inhibition of NF-κB activation in lipopolysaccharide-induced murine macrophage cells. Similarly, asiatic acid from *Centella asiatica* can reduce nitric oxide (NO), TNF-α, and IL-1β in serum in a mouse paw edema model induced by λ-Carrageenan (Tan et al., 2021). Furthermore, studies have shown that asiaticoside and madecassoside are absorbed rapidly and distributed in the body after oral administration, reaching a maximum level within 5-15 minutes (K. S. Park, 2021).

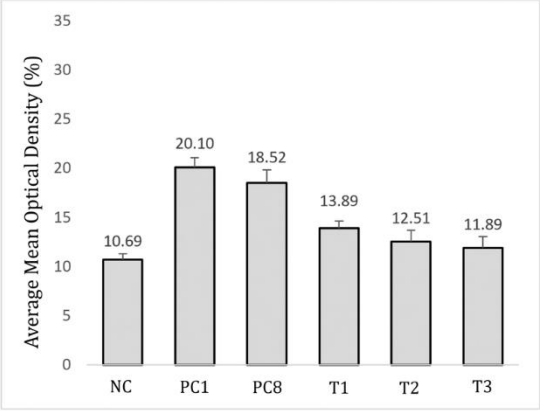

Figure 4. Mean Optical Density of IL-1β Expression Diagram

Different notations indicate significant differences ($p<0.05$) by the one-way ANOVA comparison test and Tukey's post hoc test. NC: negative control group; PC1: positive control group on day 1;

PC8: positive control group on day 8; T1: treatment group 1 dose of CAEE 100 mg/kgBW; T2: treatment group 2 dose of CAEE 200 mg/kgBW; T3: treatment group 3 dose of CAEE 400 mg/kgBW.

Although increasing the dose of CAEE showed a downward trend in the mean optical density (MOD) of IL-1β expression, the differences among treatment groups T1, T2, and T3 were not statistically substancial ($p > 0.05$), as illustrated in Figure 4. The absence of significant variations could be unique to the experimental setup or the specific disease under investigation. Other research have observed similar results. For example, in a model of acetaminophen-induced liver damage, all tested dosages of 50% ethanol extract of *Centella asiatica* substantially decreased IL-1β production, showing a consistent influence across various concentrations (D. W. Park et al., 2021). The lack of notable distinctions is attributable to several factors, encompassing sample size, length of therapy, or methodological limitations in IL-1β quantification. The lack of substantial differences observed with increasing indomethacin dosages in the indomethacin-induced gastric mucosa investigation could be attributed to several confounding variables in the experimental setting or to the saturation of the inhibitory pathways at lower levels.

CONCLUSION

Centella asiatica ethanolic extract (CAEE) exerts a dose-dependent anti-inflammatory effect on indomethacin-induced gastric ulcers in rats. Histological findings confirmed that indomethacin significantly increased IL-1β expression and caused severe mucosal injury, whereas CAEE treatment effectively reduced IL-1β expression and improved gastric mucosal integrity. The most significant suppression of IL-1β was observed at a dosage of 400 mg/kg body weight, suggesting that CAEE may aid in ulcer healing by shortening the inflammatory phase and enhancing gastric mucosal protection. These findings highlight the potential therapeutic role of CAEE as an adjunct in gastric ulcer management. Further studies are needed to elucidate the precise molecular pathways and confirm their clinical relevance.

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