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CENTELLA ASIATICA LEAF EXTRACT INCREASES FGF2 AND IMPROVES PAW HISTOPATHOLOGY IN ACUTE-INFLAMMATION RATS

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ABSTRACT
Excessive acute inflammation causes oedema and tissue injury, while conventional anti-inflammatory drugs are limited by adverse effects. Centella asiatica contains bioactive compounds with anti-inflammatory and pro-healing properties; VEGF and FGF2 mediate angiogenesis and tissue repair. To evaluate the effect of C. asiatica leaf ethanol extract on serum VEGF and FGF2 levels and paw histopathology in rats with acute inflammation. Thirty male Wistar rats were randomised into five groups: normal, negative control (carrageenan), positive control (sodium diclofenac), and extract 2 and 4 g/kgBW orally. Acute inflammation was induced by subplantar carrageenan; paw volume, serum VEGF and FGF2 (ELISA), and haematoxylin-eosin histopathology were assessed. Data were analysed by ANOVA and post hoc LSD. FGF2 differed significantly among groups ($p<0.001$); carrageenan lowered FGF2 whereas the extract increased it (2 g/kgBW 410.76; 4 g/kgBW 335.42 pg/mL). VEGF was unchanged ($p=0.713$). The 4 g/kgBW dose reduced oedema and neutrophil infiltration comparably to the positive control. C. asiatica leaf ethanol extracts increased FGF2 and improved acute-inflammation histopathology, particularly at 4 g/kgBW.

Keywords: acute inflammation; centella asiatica; histopathology, FGF2; VEGF

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INTRODUCTION

Inflammation is a protective tissue response to physical trauma or microbial exposure that, when excessive or uncontrolled, aggravates tissue injury. It involves the release of inflammatory mediators that cause vasodilation, increased vascular permeability, and migration of inflammatory cells to the injury site, producing the classical signs of redness, heat, swelling, pain, and loss of function (Hannoodee & Nasuruddin, 2022; Pahwa et al., 2022). Unlike acute inflammation, a persistent inflammatory process contributes to chronic tissue damage (Pahwa et al., 2022), and inflammatory activity is commonly assessed through established biological markers (Hannoodee & Nasuruddin, 2022).

Conventional anti-inflammatory therapy, particularly non-steroidal anti-inflammatory drugs and glucocorticoids, is widely used but associated with gastrointestinal, cardiovascular, and renal adverse effects during long-term use (Ong et al., 2007; Rhen & Cidlowski, 2005). These limitations have encouraged the use of natural products that are relatively safer and readily available, in line with the traditional medicine strategy promoted by the World Health Organization (World Health Organization, 2002).

Pegagan (Centella asiatica (L.) Urban) is a herb widely distributed in tropical regions and traditionally used for wound healing and inflammation (Biswas et al., 2021). It contains

triterpenoids (asiaticoside, madecassoside, asiatic acid), flavonoids, saponins, tannins, and phenolics that act as antioxidant, anti-inflammatory, and tissue-repair agents (Sun et al., 2020; Biswas et al., 2021; He et al., 2023). Its anti-inflammatory activity has been demonstrated through the reduction of TNF-α levels in experimental models (Nurdin et al., 2021; Nafiisah et al., 2021).

Tissue repair following inflammation involves several growth factors. Vascular Endothelial Growth Factor (VEGF) regulates the proliferation, differentiation, and migration of endothelial cells during angiogenesis, whereas Fibroblast Growth Factor 2 (FGF2) is mitogenic and angiogenic, stimulating the proliferation of fibroblasts and endothelial cells at the site of injury (Irma et al., 2025). Hence, VEGF and FGF2 levels may serve as indicators of the tissue-repair response under inflammatory conditions.

The carrageenan-induced rat paw oedema model is a standard method for evaluating anti-inflammatory activity because oedema can be measured directly, accurately, and reproducibly (Sangi & Fatimah, 2020). Although the anti-inflammatory activity of C. asiatica has been reported, data on its effect on VEGF and FGF2 levels together with paw histopathology in an acute-inflammation model remain limited. This study aimed to analyse the effect of C. asiatica leaf ethanol extract on serum VEGF and FGF2 levels and paw histopathology in Wistar rats with an acute-inflammation model.

METHOD

Study design and ethical approval

This was a true-experimental laboratory study using a post-test only control group design, conducted at the Phytopharmacy, Integrated, and Anatomical Pathology laboratories, Faculty of Medicine, Universitas Methodist Indonesia. All procedures followed internationally accepted principles for the care and use of laboratory animals (Percie du Sert et al., 2020) and were approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Methodist Indonesia.

Plant material and extraction

Fresh C. asiatica leaves were collected from an agricultural area in Medan, North Sumatra, and authenticated as Centella asiatica (L.) Urban var. asiatica (Apiaceae). The dried, powdered simplicia (mesh 40) was extracted by percolation using 70% ethanol. The percolate was concentrated with a rotary evaporator at ±40°C to obtain a thick extract, then dried to constant weight and the yield calculated (Biswas et al., 2021).

Phytochemical screening and total phenolic and flavonoid content

Phytochemical screening for alkaloids (Mayer, Bouchardat, Dragendorff reagents), flavonoids, tannins, saponins, glycosides, and steroids/triterpenoids was performed following standard methods (Biswas et al., 2021). Total phenolic content was determined by the Folin-Ciocalteu method with gallic acid as standard (expressed as mg gallic acid equivalent, GAE, per gram extract) and total flavonoid content by the $AlCl_3$ method with quercetin as standard (expressed as mg quercetin equivalent, QE, per gram extract); absorbance was read with a UV-Vis spectrophotometer (Biswas et al., 2021).

Experimental animals and grouping

Thirty healthy male Wistar rats (Rattus norvegicus), aged 2.5–3 months and weighing 150–220 g, were acclimatised for two weeks with food and water ad libitum. The sample size per group was determined by the Federer formula, and rats were randomly allocated into five groups (n=6): (1) normal (no treatment); (2) negative control (carrageenan only); (3) positive control (carrageenan + sodium diclofenac 10 mg/kgBW orally, as the reference standard; (4) treatment I (carrageenan + extract 2 g/kgBW orally); and (5) treatment II (carrageenan + extract 4 g/kgBW orally). The extract and reference drug were administered one hour before induction (Katzung, 2018).

Acute inflammation induction and paw oedema measurement
Before induction, the right hind-paw volume was measured with a plethysmometer as the baseline. Acute inflammation was induced by subplantar injection of 0.1 mL of 1% λ-carrageenan in 0.9% NaCl into the hind paw, identically for all carrageenan groups. Paw volume was re-measured every hour for four hours, and the percentage inhibition of oedema was calculated relative to the normal group (Sukmawati et al., 2015).

Serum VEGF and FGF2 assay
After the final oedema measurement (five hours after carrageenan injection), the rats were sacrificed and blood was collected by cardiac puncture. Serum was separated and VEGF and FGF2 levels were measured by quantitative sandwich enzyme-linked immunosorbent assay (ELISA) using commercial rat VEGF and rat FGF2 (basic FGF) ELISA kits, following the manufacturer's protocol; levels were expressed in pg/mL.

Histopathological examination
The hind paw was collected five hours after carrageenan injection, fixed in 10% formalin, processed, embedded in paraffin, and stained with haematoxylin-eosin. Preparations were examined under an Olympus CKX41 microscope equipped with a digital camera and semi-quantitatively scored (score 0–3) for tissue edema and neutrophil infiltration at 100× and 200× magnification, following the scoring criteria described previously (Sukmawati et al., 2015).

Statistical analysis
Data are presented as mean ± standard deviation. After the assumptions of normality and homogeneity were met, differences among groups were analysed by one-way ANOVA followed by the post hoc Least Significant Difference (LSD) test; histopathological data were analysed descriptively. A p-value < 0.05 was considered significant.

RESULT

Phytochemical screening
Authentication confirmed the sample as *Centella asiatica* (L.) Urban var. *asiatica* (Apiaceae). Phytochemical screening of the leaf ethanol extract was positive for flavonoids, alkaloids, saponins, tannins, phenolics, glycosides, and steroids/triterpenoids. Quantitative determination yielded a total phenolic content of 36.11 ± 0.265 mgGAE/g and a total flavonoid content of 10.94 ± 0.283 mgQE/g extract. These compounds are known to possess antioxidant and anti-inflammatory activity, acting through inhibition of cyclooxygenase and lipoxygenase enzymes, suppression of NF-κB activation, and reduction of pro-inflammatory cytokine production (Sun et al., 2020; Biswas et al., 2021; He et al., 2023).

Table 1.
Mean serum VEGF levels among groups

Group	VEGF (pg/mL), Red ± SD	p
Normal	43.22 ± 1.97	0,713
Negative control	44.67 ± 6.82	
Positive control	43.56 ± 9.49	
Treatment I (2 g/kgBW)	44.74 ± 5.26	
Treatment II (4 g/kgBW)	47.69 ± 4.00	

One-way ANOVA; Significant at p < 0.05. SD = standard deviation.

VEGF Serum
Serum VEGF levels did not differ significantly among the five groups (p=0.713; Table 1). This suggests that C. asiatica leaf ethanol extract did not alter VEGF within this acute-inflammation model. The absence of change may reflect the kinetics of VEGF and the limitations of the model:

VEGF is predominantly involved in the angiogenesis phase that unfolds over days, whereas the carrageenan acute model spans only hours, so the observation window may be insufficient to capture VEGF changes. Moreover, serum measurement may not represent local growth-factor concentrations at the inflamed tissue (Irma et al., 2025).

Table 2.
Mean serum FGF2 levels among groups

Group	FGF2 (pg/mL), Red ± SD	p
Normal	320.30 ± 50.96	<0.001
Negative control	222.37 ± 43.82	
Positive control	272.59 ± 98.87	
Treatment I (2 g/kgBW)	410.76 ± 50.67	
Treatment II (4 g/kgBW)	335.42 ± 63.99	

**One-way ANOVA; Significant at p < 0.05.*

Table 3.
Post hoc LSD comparison of FGF2 levels among groups

Group	Comparator	p
Normal	Negative control	0,012*
	Positive control	0,219
	Treatment I	0,015*
	Treatment II	0,679
Negative control	Positive control	0,196
	Treatment I	<0.001*
	Treatment II	0,004*
Positive control	Treatment I	0,001*
	Treatment II	0,109
Treatment I	Treatment II	0,040*

**Significant at p < 0.05 (LSD test).*

FGF2 Serum

FGF2 levels differed significantly among groups (p<0.001; Table 2). Carrageenan induction lowered FGF2 in the negative control relative to the normal group, whereas extract administration restored and even increased FGF2, with the highest value in treatment I (2 g/kgBW). Post hoc analysis (Table 3) showed significant differences between the negative control and both treatment groups, between the positive control and treatment I, and between treatment I and treatment II, indicating a dose-related effect of the extract on FGF2. FGF2 is a mitogenic and angiogenic growth factor essential for fibroblast and endothelial cell proliferation during tissue repair (Irma et al., 2025). The increase in FGF2 is consistent with reports that asiaticoside, madecassoside, and asiatic acid in C. asiatica stimulate growth-factor production and accelerate tissue repair (Witkowska et al., 2024; He et al., 2023). The non-linear dose response (2 g/kgBW higher than 4 g/kgBW) suggests a possible biphasic effect commonly seen with natural compounds, indicating the need to study a wider dose range to establish the optimal dose (Witkowska et al., 2024).

Table 4.
Mean paw oedema volume (mL) among groups by observation time

Time	Normal	NC	PC	T I (2 g)	T II (4 g)	p
Baseline	0.98±0.06	0.93±0.07	0.86±0.06	0.83±0.05	0.83±0.08	0,001*
Hour 1	0.94±0.06	1.03±0.03	1.10±0.07	1.04±0.04	1.01±0.03	0,001*
Hour 2	0.94±0.05	0.98±0.05	1.02±0.08	0.99±0.02	0.96±0.13	0,503
Hour 3	0.88±0.12	0.97±0.08	0.99±0.12	0.97±0.08	0.92±0.09	0,312
Hour 4	0.95±0.05	1.03±0.12	1.04±0.08	1.05±0.05	1.01±0.03	0,180

*One-way ANOVA; *significant at p < 0.05. NC = negative control; PC = positive control; T = treatment.*

Paw oedema

Paw oedema volume (Table 4) differed significantly among groups only at baseline and at hour 1 (p=0.001), but not from hour 2 to hour 4. In the early phase of carrageenan inflammation, histamine

and serotonin are the dominant mediators and are relatively more susceptible to inhibition by the bioactive compounds of the extract; in the later phase, more pathways and mediators are involved, making the inhibitory effect less evident (Sukmawati et al., 2015). The significant baseline difference indicates variation in initial paw volume among groups; therefore, analyses based on the change in volume or the percentage inhibition are recommended for future studies to avoid confounding by baseline imbalance.

Histopathology

Histopathological examination of paw tissue (Figure 1) showed normal tissue without oedema or neutrophil infiltration in the normal group. The negative control exhibited severe dermal oedema with dense neutrophil infiltration. The positive control (sodium diclofenac) showed persistent oedema but reduced neutrophil infiltration. Treatment I (2 g/kgBW) still showed severe oedema with clustered neutrophils, though less dense than the negative control, whereas treatment II (4 g/kgBW) showed markedly reduced oedema with scattered neutrophils, comparable to the positive control. This tissue-level improvement is likely mediated by inhibition of inflammatory-mediator production and suppression of neutrophil migration and accumulation by the bioactive compounds of C. asiatica (Witkowska et al., 2024; Mardiyah, 2022). The clearer histopathological improvement at the higher dose, contrasted with the less sensitive oedema-volume parameter, underscores the value of tissue assessment as a complement to macroscopic measurement.

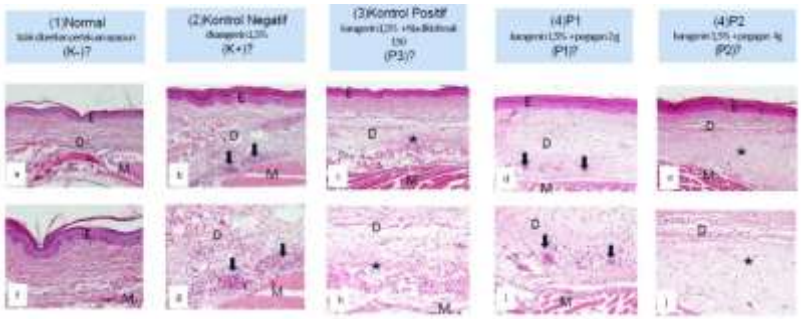

Figure 1. Paw tissue histopathology (haematoxylin-eosin). Arrows indicate neutrophil infiltration; Asterisks indicate reduced neutrophil infiltration.

Table 5.
Semi-quantitative histopathological findings among groups

Group	Tissue edema	Neutrophil infiltration
Normal	None	None
Negative control	Severe	Severe
Positive control	Moderate–severe	Reduced
Treatment I (2 g/kgBW)	Severe	Moderate (clustered)
Treatment II (4 g/kgBW)	Mild	Scattered (≈ positive control)

Descriptive severity based on haematoxylin-eosin scoring (0–3) as defined in Section 2.7.

This study has several limitations. VEGF and FGF2 were measured in serum at a single acute time point and thus do not capture local or temporal dynamics; the baseline difference in paw volume may confound oedema interpretation; and molecular mechanisms were not confirmed by immunohistochemistry. Further studies should incorporate tissue immunohistochemistry, local-level measurement, and a broader range of doses and time points (Nurdin et al., 2021; Nafiisah et al., 2021).

DISCUSSION

This study showed that the administration of ethanol extract of C. asiatica leaves (Centella asiatica) had different biological effects on acute inflammatory parameters. The main findings of this study were a significant increase in serum FGF2 levels, improvement in the histopathological picture of

rat leg tissue, and no significant changes in VEGF levels. These results indicate that the anti-inflammatory effects of C. asiatica are not only related to the suppression of inflammatory processes, but also related to the stimulation of tissue repair mechanisms through an increase in fibroblast growth factors.

The absence of differences in VEGF levels between groups was likely due to the characteristics of the acute inflammatory model used. In carrageenan-induced models of rat leg edema, the inflammatory process lasts only a few hours, whereas VEGF expression is generally elevated in the proliferation and angiogenesis phases that occur a few days after injury (Irma et al., 2025). Thus, the sampling time of five hours after induction may not be sufficient to detect systemic changes in VEGF levels. In addition, serum VEGF measurements do not necessarily reflect local VEGF concentrations in inflamed tissues because VEGF production occurs more paracrine at the site of injury (Irma et al., 2025). These results are in line with the research of Irma et al. (2025) which stated that changes in VEGF are more reflective of the process of medium-to-advanced angiogenesis than of the acute inflammatory response.

In contrast, this study found a significant increase in FGF2 levels after the administration of the C. asiatica extract. Fibroblast Growth Factor-2 is one of the main mediators in fibroblast proliferation, endothelial cell migration, extracellular matrix formation, and tissue regeneration (Irma et al., 2025). Decreased FGF2 levels in the negative control group suggest that acute inflammation due to carrageenan may inhibit the tissue repair process. On the other hand, the administration of C. asiatica extract was able to increase FGF2 levels to exceed the normal group, especially at a dose of 2 g/kgBB. These findings reinforce the suspicion that triterpenoid content such as asiaticoside, madecassoside, and asiatic acid is able to activate tissue healing pathways through stimulation of growth factor expression and collagen synthesis (Witkowska et al., 2024; He et al., 2023).

The increase in FGF2 in this study may also be influenced by the fairly high content of flavonoids and phenolic compounds in the C. asiatica extract. The compound is known to have antioxidant activity that is able to suppress the formation of Reactive Oxygen Species (ROS) during the inflammatory process so that tissue damage becomes lighter (Sun et al., 2020; He et al., 2023). This decrease in oxidative stress allows fibroblasts to maintain proliferation activity and increase FGF2 production so that the tissue healing process takes place faster. This mechanism is also supported by the research of Witkowska et al. (2024) who reported that C. asiatica formulations accelerate wound healing through increased fibroblast proliferation and collagen deposition.

Interestingly, the highest FGF2 levels were actually found at a dose of 2 g/kgBB compared to a dose of 4 g/kgBB. This pattern shows a non-linear dose-response relationship. This hormesis phenomenon is often found in natural compounds, where moderate doses produce more optimal biological effects than higher doses (Witkowska et al., 2024). At high doses, several phytochemical components can interact with each other, reducing biological activity or triggering negative feedback mechanisms for growth factor expression. Therefore, follow-up research with a wider dose range is needed to determine the most effective therapeutic dose.

The improvement in tissue histopathology observed in this study supports the results of FGF2 biomarker examination. The group that received C. asiatica extract at a dose of 4 g/kgBB showed a decrease in tissue edema and neutrophil infiltration that was almost equivalent to the diclofenac sodium group. Neutrophils are the first inflammatory cells to migrate to the site of injury and play a role in producing various pro-inflammatory mediators such as TNF-α, IL-1β, and proteolytic enzymes that can aggravate tissue damage if the amount is excessive (Xiao et al., 2025). The decrease in neutrophil infiltration shows that C. asiatica extract is able to inhibit the recruitment process of inflammatory cells so that the inflammatory response becomes more controlled. These findings are consistent with the research of Nurdin et al. (2021) and Nafiisah et al. (2021) who

reported that Centella asiatica extract was able to reduce TNF-α levels in various inflammatory models.

Although the histopathological improvement is quite obvious, the volume of edema shows only a significant difference in the early phase of inflammation. This can be explained by the fact that carrageenan inflammation takes place in two phases. The first phase is dominated by the release of histamine and serotonin, while the second phase is affected by prostaglandins, bradykinin, leukotrienes, as well as various pro-inflammatory cytokines (Sukmawati et al., 2015). Flavonoid and triterpenoid compounds in C. asiatica are thought to be more effective at inhibiting inflammatory mediators in the early phases so that the effect on edema volume becomes less pronounced after a few hours. In addition, the difference in baseline volume between groups also has the potential to affect the results of edema measurement, so in the next study it is recommended to use a change in relative volume or percentage of edema inhibition as the main parameter.

Overall, the results of this study strengthen the evidence that C. asiatica leaf extract has the potential as a natural anti-inflammatory agent that works through two main mechanisms, namely suppressing the infiltration of inflammatory cells and accelerating the tissue repair process through an increase in FGF2. The combination of these two mechanisms provides advantages over conventional anti-inflammatory drugs that generally focus only on suppressing the inflammatory response without directly stimulating tissue regeneration (Ong et al., 2007). However, this study still has several limitations, including biomarker measurements only performed at one point in time, VEGF and FGF2 tests only performed on serum without tissue analysis, and molecular mechanism confirmation using immunohistochemistry or gene expression analysis. Therefore, follow-up research with observation time variations, wider dose ranges, and molecular analysis is needed to clarify the mechanism of action Centella asiatica in the process of inflammation and tissue healing.

CONCLUSION

C. asiatica leaf ethanol extract significantly increased serum FGF2 levels and improved the histopathological picture of acute inflammation, marked by reduced tissue oedema and neutrophil infiltration, particularly at 4 g/kgBW, whereas serum VEGF levels were unchanged and the effect on oedema volume appeared only in the early phase of inflammation; these findings support the potential of C. asiatica as a natural anti-inflammatory candidate that warrants further mechanistic confirmation.

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