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Short Communication

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Dieffenbachia seguine extract nanoemulsion as an intranasal inflammation-inducing agent in rats

Siti Sadiah[1,2]*, Ke Yong Leong[3], Ni Luh Putu Ika Mayasari[4], Leliana Nugrahaning Widi[2], Hamzah Alfarisi[5]

[1] Division of Pharmacology and Toxicology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, West Java, Indonesia
[2] Tropical Biopharmaca Research Center, IPB University, Bogor, West Java, Indonesia
[3] Study Program of Veterinary Medicine, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, West Java, Indonesia
[4] Division of Medical Microbiology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, West Java, Indonesia
[5] Division of Anatomy, Histology, and Embriology, School of Veterinary Medicine and Biomedical Sciences, IPB University, Bogor, West Java, Indonesia

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Abstract

Background *Dieffenbachia seguine* (Jacq.) Schott, commonly known as the dumb cane, is a tropical ornamental plant known for its toxic and proinflammatory properties. Its potential as a natural inducer of inflammation warrants further investigation, particularly via the intranasal route.

Objective This study aimed to evaluate the proinflammatory effect of *D. seguine* leaf extract nanoemulsion by measuring the levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in bronchoalveolar lavage fluid (BALF) following intranasal administration in rats.

Methods Wistar rats (n= 24) were divided into six groups: water for injection (WFI, negative control); emulsion base; lipopolysaccharide (LPS, positive control); and *D. seguine* extract nanoemulsions at concentrations of 1%, 2%, and 4%. Each rat received an intranasal instillation, and IL-6 and TNF-α concentrations in the BALF were quantified using ELISA.

Results Only the 4% *D. seguine* nanoemulsion group showed a significant increase in IL-6 and TNF-α levels compared to the control. Lower concentrations (1% and 2%) did not induce significant cytokine elevation. All treatment groups showed significantly lower cytokine levels than the LPS group.

Conclusion *D. seguine* extract nanoemulsion at 4% concentration demonstrates potential as a natural inflammation-inducing agent via the intranasal route, although its effect remains lower than that of LPS.

Keywords *Dieffenbachia seguine*, dumb cane, IL-6, intranasal inflammation, nanoemulsion, TNF-α

***Corresponding author** Email: sitisa@apps.ipb.ac.id

Introduction

Dieffenbachia seguine (Jacq.) Schott, or dumb cane, is an ornamental plant native to tropical regions and known for its toxic properties. Ingestion may cause temporary speech loss, whereas contact with the sap can lead to edema and irritation (Alwan, 2022; Nguyen *et al.*, 2019). Despite its toxicity, recent research suggests that *D. seguine* extract may serve as a natural inflammatory inducer in laboratory models (Japri *et al.*, 2023).

Inflammation can be experimentally induced via various routes, including intraplantar and intranasal administration. The intraplantar route is commonly used to induce localized inflammation and assess paw edema (Cong *et al.*, 2015), whereas the intranasal route is advantageous for targeting the respiratory tract and bypassing the gastrointestinal metabolism (Lofts *et al.*, 2022; Prasetyo *et al.*, 2023).

This study aimed to assess the proinflammatory potential of *D. seguine* extract by measuring TNF-α and IL-6 levels in the bronchoalveolar lavage fluid (BALF) of Wistar rats following intranasal induction. These cytokines were quantified using an enzyme-linked immunosorbent assay (ELISA) to evaluate the inflammatory responses induced by the route. This study provides preliminary insights into the immunomodulatory effects of *D. seguine* and supports its application in the development of inflammation models.

Methods

Nanoemulsions of 1%, 2%, and 4% *Dieffenbachia seguine* extract were prepared as described by Sadiah *et al.* (2024). The *in vivo* induction protocol was developed by the same research group, and all procedures involving animals were reviewed and approved by the Animal Ethics Committee of the School of Veterinary Medicine and Biomedical Sciences, IPB University (No. 009/KEH/SKE/I/2023).

A total of 24 male Wistar rats were randomly assigned to six groups (n = 4 per group). The animals were acclimatized for 14 days under standard laboratory conditions with *ad libitum* access to food and water. The treatment groups included: (1) water for injection (WFI, negative control), (2) nanoemulsion base, (3) positive control (lipopolysaccharide at 3 mg/kg BW), and (4–6) *D. seguine* extract nanoemulsions at 1%, 2%, and 4% concentrations, respectively.

Each rat received an intranasal instillation of 125 µL (6 mg/mL) of the assigned solution using a micropipette. After 24 h, the animals were anesthetized with a combination of 60 mg/kg body weight (BW) ketamine, 10 mg/kg BW xylazine, and 2 mg/kg BW acepromazine via intraperitoneal injection. Exsanguination via cardiac puncture was performed to minimize blood contamination during the necropsy. The thoracic cavity was exposed, and BALF was collected by inserting a blunt needle into the trachea and instilling 1 mL of sterile saline, followed by gentle aspiration. The recovered BALF was stored at −20°C until further analysis.

The cytokine levels of IL-6 and TNF-α in the BALF samples were quantified using ELISA kits (FineTest®, Wuhan Fine Biotech Co., Ltd., China) according to the manufacturer's instructions. Briefly, 100 µL of standards or samples was added to each well of the ELISA plate and incubated at 37°C for 90 min. After two washes, 100 µL of biotin-labeled antibody was added, followed by incubation at 37°C for 60 min. The plate was washed thrice with wash buffer, and 100 µL of horseradish peroxidase (HRP)-streptavidin conjugate (SABC) was added to each well and incubated for 30 min. After additional washes, 90 µL of TMB substrate was added and incubated at 37°C for 10–20 minutes. The reaction was stopped by adding 50 µL stop solution, and the absorbance was read at 450 nm.

Data were analyzed by one-way analysis of variance (ANOVA) ($\alpha \leq 0.05$) using SPSS version 27. Duncan's multiple range test was used for post hoc analyses. The data were visualized using GraphPad Prism version 7.

Results

Figure 1 shows the concentrations of IL-6 and TNF-α in BALF of Wistar rats following intranasal administration of various treatments. For IL-6, the base formulation group showed a slight but statistically insignificant increase in IL-6 levels compared to the WFI group. Similarly, the IL-6 levels in the 1% and 2% nanoemulsion groups were not significantly different from those in the WFI group. However, the 4% concentration resulted in a significantly higher IL-6 level than the WFI ($P<0.05$), although this level was not significantly different from that of the base formulation group.

Similarly, TNF-α levels were not significantly elevated in the 1% and 2% treatment groups compared with those in the WFI group. Only the 4% nanoemulsion group showed a statistically significant increase in TNF-α levels ($P<0.05$) relative to the WFI group. The base formulation group did not differ significantly from the WFI group.

The IL-6 and TNF-α levels in all *D. seguine* groups remained substantially lower than those observed in the LPS-induced group. These findings show that the application of *D. seguine* nanoemulsion at 4% resulted in a modest inflammatory response, as measured by IL-6 and TNF-α levels. However, a crucial aspect of this finding is that the observed effect on IL-6 was not significantly different from that of the base control, suggesting that the nanoemulsion vehicle, rather than the active component, is the primary inducer of this response.

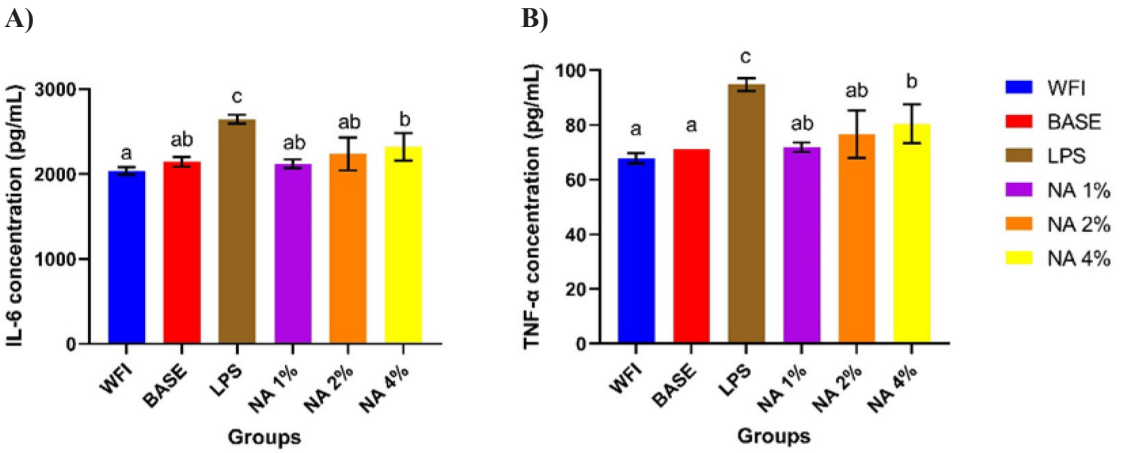

Figure 1 Levels of IL-6 and TNF-α in bronchoalveolar lavage fluid (BALF) of Wistar rats following intranasal administration. (A) IL-6 levels; (B) TNF-α levels. All treatment groups (NA 1%, NA 2%, and NA 4%) showed increased cytokine levels compared to WFI (negative control). IL-6 levels were not significantly different among the treatment groups, whereas TNF-α levels were significantly higher in the NA 4% group. WFI: Water for Injection (negative control); BASE: Nanoemulsion base only; LPS: Lipopolysaccharide (positive control); NA 1%: *D. seguine* nanoemulsion 1%; NA 2%: *D. seguine* nanoemulsion 2%; NA 4%: *D. seguine* nanoemulsion 4%. Statistical analysis was performed using one-way ANOVA with a completely randomized design (CRD) at a 95% confidence level ($\alpha \leq 0.05$).

Discussion

Among the treatment groups administered via the intranasal route, only the 4% *D. seguine* extract nanoemulsion significantly increased IL-6 and TNF-α levels compared to the negative control (WFI). In contrast, the 1% and 2% concentrations did not elicit a significant inflammatory response. This suggests a concentration-dependent effect, in which a higher dose is required to overcome mucociliary clearance and enzymatic degradation in the nasal passages (Widegren *et al.*, 2007). The base formulation also induced a slight, non-significant elevation in IL-6 levels, potentially due to local irritation from the emulsion components (Karasulu *et al.*, 2008).

A previous study (Sadiah *et al.*, 2024) showed that intraplantar administration of *D. seguine* extract induced elevated IL-6 and TNF-α levels even at lower concentrations. While paw edema volume was correlated with treatment concentration, serum cytokine levels were not as responsive. This may be due to the localized nature of paw inflammation, and a more accurate assessment may be achieved through cytokine analysis of homogenized paw tissue (Mansouri *et al.*, 2015).

IL-6 and TNF-α are well-characterized proinflammatory cytokines. IL-6 is involved in both acute and chronic inflammatory responses and plays a key role in hematopoiesis and immune regulation (Tanaka *et al.*, 2014; Hogea *et al.*, 2023). TNF-α produced by activated macrophages induces apoptosis and mediates early inflammatory responses (Idriss & Naismith, 2000). This study measured both cytokines using sandwich ELISA, a specific and sensitive method based on antigen–antibody interactions (Sakamoto *et al.*, 2018; DeForge & Remick, 1991).

LPS was used as a positive control to simulate bacterial infection-related inflammation in the respiratory tract. As a component of Gram-negative bacterial membranes, LPS induces robust systemic inflammation and is commonly used in experimental rhinosinusitis models (Rylander, 2002; Kim *et al.*, 2011).

The inflammatory potential of *D. seguine* is attributed to its bioactive compounds, including raphides, oxalic acid, and proteolytic enzymes (Ummuhan, 2020). Calcium oxalate crystals (raphides) can physically damage mucosal tissues and trigger immune cell recruitment and cytokine release (Haneef & Veetilakathu, 2020). The resulting cascade (histamine release, bradykinin-mediated permeability, and prostaglandin-induced nociception) could explain the clinical signs such as tachypnea and irritation observed post-administration (Iyer *et al.*, 2015; Ajuru *et al.*, 2018).

Overall, these findings demonstrate that *D. seguine* nanoemulsion, particularly at higher concentrations, can act as a moderate natural inducer of inflammation via the intranasal route, although less potent than LPS. Further studies are warranted to explore their mechanistic pathways and applicability in respiratory inflammation models.

Conclusion

Intranasal administration of 4% *Dieffenbachia seguine* extract nanoemulsion significantly elevated IL-6 and TNF-α levels in bronchoalveolar lavage fluid, indicating a measurable proinflammatory response. These findings suggest that the *D. seguine* nanoemulsion, particularly at higher concentrations, has potential as a natural agent to induce localized respiratory inflammation in experimental models.

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Author contribution: SS: conceptualization, funding acquisition, methodology, supervision, and writing – review & editing; LKY: formal analysis, investigation, and writing – original draft; NM: supervision, validation, data curation; LNW: investigation, HA: visualization, software, and writing – review & editing.

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