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ANTI-INFLAMMATORY EFFECTS OF *Graptophyllum pictum* (L.) GRIFF EXTRACT IN PRECLINICAL RATS HIND-PAW EDEMA MODELS : A LITERATURE REVIEW

Alifya Rayyani Shofiy[1], Feda Anisah Makkiyah[2]
Faculty of Medicine, Universitas Pembangunan Nasional "Veteran" Jakarta[1,2]
Coresponding author: fedaanisah@upnvj.ac.id

ABSTRACT

Graptophyllum pictum (L.) Griff or *daun ungu* is a common medical plant in Indonesia that possesses many promising medical properties, including anti-inflammation. This review aims to discuss the anti-inflammatory effects of *Graptophyllum pictum* (L.) Griff extract in preclinical hind-paw edema animal models. Through literature search and analyze based on keywords, PICO, inclusion, and exclusion criteria, a total of four studies were included in this review. As a result, ethanol extract of *Graptophyllum pictum* (L.) Griff shows anti-inflammatory effects significantly reducing the volume of edema and having high anti-inflammatory power by inhibition of the arachidonic inflammatory pathway. Therefore, these preclinical test studies confirmed the anti-inflammatory effects of *Graptophyllum pictum* (L.) Griff. However, further studies and human trials are required to confirm the efficacy and develop a standardized formula for *Graptophyllum pictum* (L.) Griff.

KEYWORDS

Graptophyllum pictum (L.) Griff, *Daun Ungu*, Paw Edema, Anti-Inflammation

INTRODUCTION

In response to harmful stimuli, immune systems activate inflammation to eradicate the stimulus and initiate the healing process. Although inflammation serves a vital function as a defense mechanism, uncontrolled inflammation may progress to chronic inflammation and contribute to various inflammatory diseases, such as ischemic heart disease, stroke, cancer, etc. (Chen *et al.*, 2017). More than 50% of deaths are attributable to chronic inflammatory diseases, making them recognized as one of the most significant contributors to death in the world, thus future research to intervent inflammation serves as a promising avenue (Furman *et al.*, 2019). As research progressed, various animal models and methods were developed to measure inflammation, including the edema volume of hind paws in preclinical animal studies. In this animal model, hind paws edema is induced by subplantar injection of edemogens, including carrageenan solution (Shejawal, Menon and Shailajan, 2014).

The development of anti-inflammatory drugs leads to various options of therapy. Despite being commonly used, available anti-inflammatory drugs, namely immunosuppressants, steroids, and non-steroid anti-inflammatory drugs, come with adverse effects, therefore alternative medications are sought to achieve drugs with the highest efficacy while having the least adverse effects (Ghasemian, Owlia and Owlia, 2016). Approach to natural products that possess therapeutic bioactive compounds such as plants serve as excellent potential for the development of novel drugs, including anti-inflammatory medicine. Several well-used plants such as curcumin, chili peppers, and green tea, have been tested in clinical trials for their anti-inflammatory properties, (Fürst and Zündorf, 2014).

More than 85–90% of the population in the world depends on traditional medicine, the utilization of herbal products was paved by traditional medicine systems prior to the exploration of pharmaceutical products (Nasim, Sandeep and Mohanty, 2022). With a tropical climate and abundant biodiversity, Indonesia is home to numerous herbal plants and herbal remedies have been a part of Indonesian culture (Ikrar Musyaffa *et al.*, 2024). Yet in Indonesia, by 2021, while having more than 24.000 known herbal medicines, less than 250 of it has been certified as standardized herbal medicine (*Portal Satu Data BPOM*, 2021).

Graptophyllum pictum (L.) Griff of the Acanthaceae family is one of the medical plants that has been applied to traditional medicine practice as an analgesic, antipyretic, and treatment of hemorrhoid and menstrual problems (PRIYANTO *et al.*, 2024). Locally known as *daun ungu*, *G. pictum is* reported to possess anti-inflammatory, antibacterial, antioxidant, immunomodulator, analgesic, wound-healing activity, anti-diabetic, anti-hemorrhoid, and estrogenic properties (Makkiyah *et al.*, 2021). Although having lists of outstanding properties, the anti-inflammatory properties of *Graptophyllum pictum* (L.) Griff has yet to be discussed thoroughly, especially in pre-clinical tests on animal models. Therefore, this study aims to review the anti-inflammatory effects of *Graptophyllum pictum* (L.) Griff extract in preclinical hind-paw edema animal models.

MATERIALS AND METHODS

Through several online databases, we searched and selected studies containing the keywords "(Graptophyllum pictum) OR (Daun Ungu)" AND "(Paw Edema)." From a total of 12 studies, we reviewed the eligibility of collected studies based on the inclusion and exclusion, and PICO (Table 1) criteria that had been determined. We included (1) primary study; (2) available in English or Bahasa Indonesia; while we excluded: (1) study without full-text available. After analyzing available studies, we included four studies that fit our study design.

Table 1. Population, Intervention, Control, Outcome model criteria for study selection

Population	Rats with hind-paw edema model
Intervention	Extract of *Graptophyllum pictum*
Control	Placebo negative control; anti-inflammatory drugs positive control
Outcome	Anti-inflammatory effect on hind-paw edema

RESULTS

Following the analysis of included studies, we extracted data from four experimental studies with characteristics as seen in Table 2. All of the studies used a Carrageenin-Induced Hind-Paw Edema Model compared to anti-inflammatory drugs such as steroids and non-steroid anti-inflammatory drugs. Studies by Ozaki et. al. in 1989, Ratnasari et. al. in 2020, and Ocvinta et. al. in 2024 administered *Graptophyllum pictum* (L.) Griff extract solution orally, while Rikomah et. al. in 2019 used *Graptophyllum pictum* (L.) Griff extract suspended in cream. As shown in Table 3, all studies used ethanol extract of *Graptophyllum pictum* (L.) Griff and significantly inhibited edema compared to the negative control group, thus displaying similar effects to the positive control group.

Table 2. Study characteristics of included studies

Author, Year	**Hind-Paw Edema-Model**	***G. pictum* extract Administration Route**	**Positive control**
(Ozaki et. al., 1989)	Carrageenin-Induced	Peroral	Indomethacin
(Rikomah, Elmitra and Mauri, 2019)	Carrageenin-Induced	Topical (Cream)	Hydrocortisone cream
(Ratnasari, Susanti and Dhiani, 2020)	Carrageenin-Induced	Peroral	Diclofenac sodium
(Ocvinta *et al.*, 2024)	Carrageenin-Induced	Peroral	Diclofenac sodium

Table 3. Anti-inflammatory effects of *Graptophyllum pictum* (L.) Griff extract on hind-paw edema volume

Author, Year	Extract	Dose	Outcome
(Ozaki *et al.*, 1989)	Ethanol	3g/kg	Inhibition of edema induced by carrageenin during 6 hours significantly inhibits edema compared to control
(Rikomah, Elmitra and Mauri, 2019)	Ethanol	10%, 15%, 20%	Significantly inhibits inflammation, with the highest effect on 20% cream with 62.72% inhibitory and 49.76% anti-inflammation power
(Ratnasari, Susanti and Dhiani, 2020)	Ethanol	100, 600, 3000 mg/kg	600 and 3000 mg doses of Ethanol extracted significantly inhibit paw edema up to 90% in minute 360.
(Ocvinta *et al.*, 2024)	Ethanol	50, 100 mg/kg	Significant reduction in edema in 6 hour after administration with the highest volume decrease in 100 mg/kg dosage group.

DISCUSSION

As a medical plant that is widely used, *Graptophyllum pictum* (L.) Griff carries several organic compounds that exhibit beneficial pharmacological activities, especially anti-inflammation (Makkiyah *et al.*, 2021). Through phytochemical and pharmacological investigation studies by Tahseen et.al., ethanol extract of *Graptophyllum pictum* (L.) Griff contains compounds that possess anti-inflammatory activities. Active organic compounds such as alkaloids, flavonoids, tannins, and glycosides and inorganic content of calcium, iron, chloride, and phosphate are detected. Through Gas chromatography-mass spectrometry (GC-MS), Phytol and Stigmasterol phytoconstituents are identified. (Tahseen, Bhatnagar and Bhatnagar, 2023).

Exact pathway of anti-inflammation properties of *Graptophyllum pictum* (L.) Griff extract is yet to be studied. However, alkaloids, flavonoids, and tannins contents reduce inflammation and oxidative stress by targeting NF-κB (nuclear factor kappa B), MAPK (mitogen-activated protein kinase), ERK (extracellular signal-regulated kinase), and Phosphoinositide 3 kinase (PI3K)/Akt pathways, thus reducing several pro-inflammatory cytokines (TNF [Tumor Necrosis Factor]-α, IL [Interleukin]-6, IL-8, IL-1β, IL-17, and IFN [Interferon]-γ) and enzymes (iNOS, COX2, glucuronidase, and lysozyme) (Abegaz and Kinfe, 2019; Bai *et al.*, 2021; Jing *et al.*, 2022), while glycoside inhibits cyclooxygenase (COX) and lypoxygenase (LOX) pathways then blocking prostaglandin E2 (PGE_2) production as an inflammation-mediating agent (Khan *et al.*, 2020). Phytol also shares an anti-inflammation pathway through the inhibition of NF-κB and COX enzymes (Islam *et al.*, 2020), while Stigmasterol inhibits inflammation by exhibiting agonistic activity to the glucocorticoid receptor, thus suppressing immune response prior to the inflammation process (Morgan *et al.*, 2021).

In carrageenan-induced rat paw edema, acute swelling is stimulated by injection of carrageenan and saline solution. Injection of Carrageenan as a non-antigenic phlogistic agent triggers activation of the complement system and inflammatory mediators by the interaction of sulfated sugar. This leads to the activation of arachidonic acid pathway through enzyme activation of phospholipase A2 and COX. Through recruitment of leukocytes and production of pro-inflammatory mediators, carrageenan causes distention of postcapillary venules and exudation of inflammatory fluid (Negi *et al.*, 2023). According to this carrageenan paw edema model, *Graptophyllum pictum* (L.) Griff extract displays anti-inflammatory properties through inhibition of arachidonic acid pathway, mainly by reducing COX enzyme concentration (Azhar *et al.*, 2020; Ratnasari, Susanti and Dhiani, 2020).

Several studies have tested *Graptophyllum pictum* (L.) Griff extract's anti-inflammation ability in treating specific inflammatory-related diseases. Research on hemorrhoid-like rats shows that a dose of 100mg/Kg *Graptophyllum pictum* (L.) Griff extract significantly reduces the serum concentration of COX-2 and increases superoxide dismutase (SOD) enzyme concentration (Azhar *et al.*, 2020). A similar study also showed a significant decrease in IL-6 and leukocyte concentration with a phlebotropic effect on the hemorrhoids of rats (Hutagalung, 2019; Prasetyo *et al.*, 2023). Another research on peridontitis displays a significant reduction in fibroblast cell accumulation through 2.5%, 5%, and 10% concentrations of *Graptophyllum pictum* (L.) Griff extracts through irrigation, achieving a better average score compared to the positive control group (Rachim, Kurniawati and Astuti, 2021). A significant decrease in macrophage number in tooth extraction injuries and speed up wound healing progress (Sunaryo, 2024).

CONCLUSIONS

While being a normal defense mechanism, uncontrolled inflammation may progress to a chronic inflammation that contributes to many concerning diseases that serve as a global mortality burden. However, many commonly used anti-inflammatory drugs have side effects thus initiating the development of safer alternatives, including medical plants. As a well-used medical plant, *Graptophyllum pictum* (L.) Griff possesses many promising medical properties, including anti-inflammation. Ethanol extract of *Graptophyllum pictum* (L.) Griff shows anti-inflammatory effects in preclinical hind-paw edema animal models by significantly reducing the volume of edema and having high anti-inflammatory power. In this model, active compounds and phytoconstituents of *Graptophyllum pictum* (L.) Griff inhibits the arachidonic inflammatory pathway by inactivation of COX and phospholipase A2 enzyme. Therefore, these preclinical test studies confirmed the anti-inflammatory effects of *Graptophyllum pictum* (L.) Griff, making it a promising anti-inflammatory drug. However, further studies and human trials are required to confirm the efficacy and develop a standardized formula for *Graptophyllum pictum* (L.) Griff.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

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