The Flavonoids Content of Graptophyllum pictum (L.) Griff as an Antiplatelet Aggregation and Anti-inflammatory Agent: A Systematic Literature Review

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Abstract. Graptophyllum pictum (L.) Griff., a shrubby stove plant, has been traditionally used to treat various diseases. This study aims to determine the antiinflammatory and antiplatelet aggregation activities of the ethanolic extract of Graptophyllum pictum. A systematic literature review was conducted from January 2014 until December 2024. Articles were identified according to the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines, with data collected from ScienceDirect, SpringerLink, and PubMed. Medical Subject Headings (MeSH) were utilized with various terminology: "Graptophyllum pictum (L.) Griff", "antiplatelet aggregation", and "antiinflammatory". The inclusion criteria were: (1) resources categorized as original research reports, case reports, case studies, letters to the editor, brief communications, commentaries, editorials, and news; (2) publications with accessible full text; and (3) articles providing information on the Graptophyllum pictum (L.) Griff. The exclusion criteria were papers categorized as systematic reviews, meta-analyses, or bibliometric analyses. The findings suggest that Graptophyllum pictum contains bioactive compounds such as flavonoids, alkaloids, and saponins, which contribute to its anti-inflammatory and antiplatelet properties.

1 INTRODUCTION

Graptophyllum pictum (synonym: Justicia picta) is widely recognized as a traditional medicinal plant across several countries, including Indonesia. For over thirty years, its red leaf ethanolic extract has demonstrated notable anti-inflammatory properties [1], making it a traditional remedy for conditions such as hemorrhoids. Numerous studies have documented the therapeutic benefits of G. pictum [2]. However, there remains a lack of in-depth investigation regarding the specific influence of its anti-inflammatory effects on platelet aggregation.

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The initiation of inflammatory responses is precipitated by the secretion of critical mediators, such as histamine, serotonin, prostaglandins, and thromboxane A2, predominantly via the cyclooxygenase pathway [3]. These compounds originate from arachidonic acid, which serves as the main precursor. Once bound to platelet membrane receptors, arachidonic acid stimulates the release of intracellular granules, enhancing platelet aggregation. Through enzymatic action, arachidonic acid is transformed by thromboxane synthase into prostaglandin H2 (PGH2), which is then converted to thromboxane A2, a potent aggregator of platelets [3]. As a result, suppression of inflammation is expected to concurrently inhibit platelet aggregation.

Belonging to the Acanthaceae family, the purple leaves of *G. pictum* originate from Papua New Guinea and have traditionally been used in Indonesian medicine to treat various ailments. These leaves are rich in phenolic and polyphenolic constituents, particularly flavonoids, tannins, and saponins, which function as powerful natural antioxidants [4]. Additional secondary metabolites include alkaloids, glycosides, alcohols, steroids, and calcium oxalate [5]. The flavonoid constituents present in ethanolic extracts derived from purple foliage have exhibited significant anti-inflammatory properties through the inhibition of prostaglandin biosynthesis, in conjunction with other bioactive compounds such as tannins and saponins. Moreover, flavonoids possess the capacity to neutralize free radicals and attenuate the activity of inflammatory enzymes, including cyclooxygenase-2 and inducible nitric oxide synthase [5]. They furthermore function as antiplatelet pharmacological agents by obstructing thrombus formation in vascular pathologies such as coronary artery disease and cerebrovascular accidents. The underlying mechanism encompasses the selective blockade of adenosine diphosphate (ADP) interaction with the P2Y12 platelet receptor, which subsequently inhibits the activation of the GP IIb/IIIa complex, consequently diminishing platelet aggregation. [6]. This study explores the potential of flavonoids in *Graptophyllum pictum* as both anti-inflammatory and antiplatelet agents—an area not yet extensively explored.

Consequently, this systematic review endeavors to address the following research inquiry: What are the anti-inflammatory and antiplatelet properties associated with the flavonoid constituents of Graptophyllum pictum (L.) Griff, as evidenced by in vivo and in vitro investigations published from 2014 to 2024?

2 MATERIALS AND METHODS

This review meticulously examines previous investigations centered on the anti-inflammatory and antiplatelet aggregation effects of Graptophyllum pictum (L.) Griff. The methodological framework incorporates essential elements, such as the study's aim, targeted academic journals, criteria for inclusion and exclusion, search methodologies, and the databases utilized. The review process complies with the standards established in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Two independent reviewers carried out the article screening and data extraction process. The extracted information was systematically compiled into a summary table detailing the publication year, author(s), research methods, and key findings. The literature review spanned studies published between January 2014 and December 2024, using three major electronic databases: ScienceDirect, Google Scholar, and PubMed.

The search terms were determined according to Medical Subject Headings (MeSH) to identify related articles regardless of the authors' varying terminology or spellings. The search strategy utilized Boolean operators and Medical Subject Headings (MeSH) as follows: ("Graptophyllum pictum" OR "Justicia picta") AND ("anti-inflammatory" OR "inflammation inhibition") AND ("antiplatelet aggregation" OR "platelet aggregation inhibition"). Search filters were set to: article type = original research, language = English or Indonesian, publication date = 2014–2024. The criteria for inclusion encompassed: (1) documents categorized as original research articles, case reports, case studies, correspondence to the editor, concise communications, commentaries, editorials, and news items; (2) articles for which the complete text is accessible; and (3) articles that furnish information concerning the Graptophyllum pictum (L.) Griff.The criteria for exclusion within this systematic review consisted of: publications classified as systematic reviews, meta-analyses, or bibliometric assessments.

3 RESULTS

A total of 67 articles were initially retrieved through database searches. After removing 12 duplicate records, 55 articles remained for screening. No studies were excluded at this stage due to thematic irrelevance. Following full-text screening and eligibility assessment, 42 studies were excluded for not meeting the predefined inclusion criteria, such as lacking original experimental data or not focusing on *Graptophyllum pictum*. Additionally, no articles were excluded due to restricted access or irrelevance upon full-text review.

As a result, six studies satisfied all predetermined inclusion criteria and were incorporated into the ultimate synthesis. The procedure for selecting studies was executed in compliance with the PRISMA guidelines and is depicted in the PRISMA flow diagram (Figure 1). The comprehensive characteristics and outcomes of the studies that were included are delineated in Table 1.

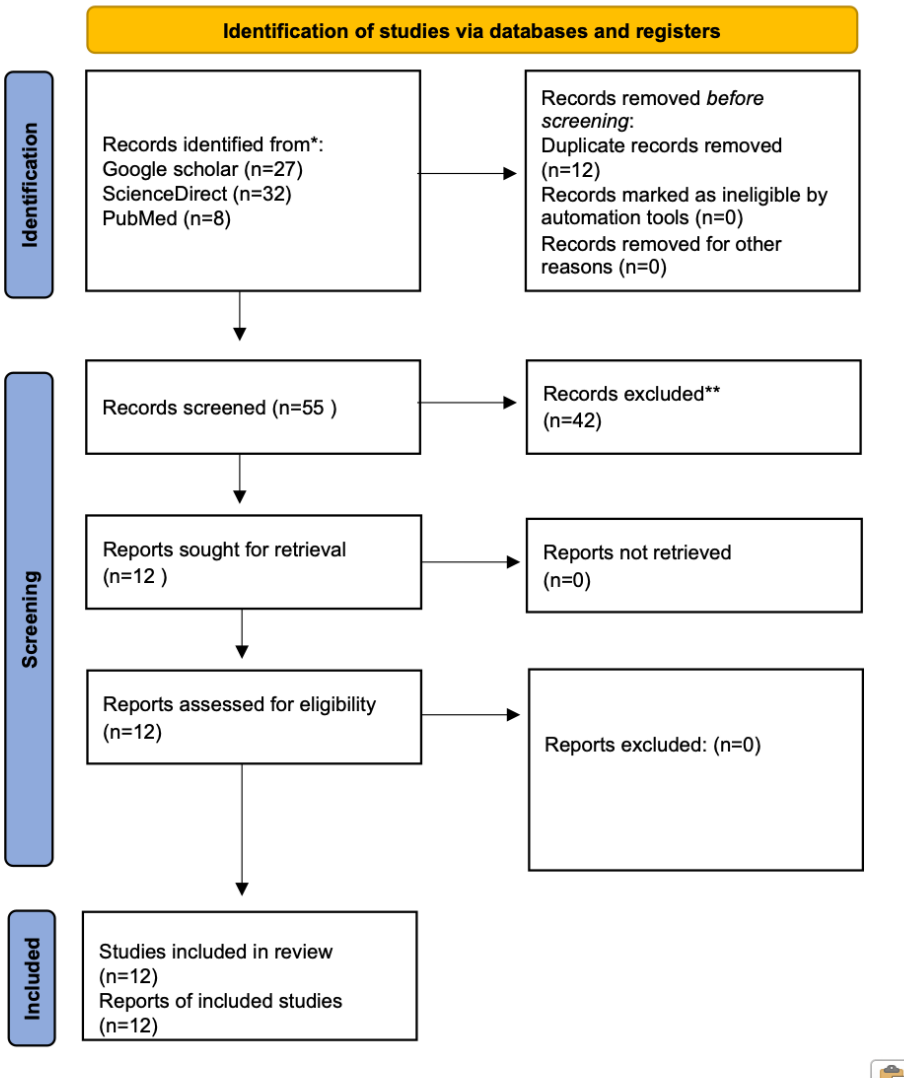

Figure 1. PRISMA flowchart for the screening and identification processes

From the screening results in this study, 6 eligible papers were found. These papers were tabulated (as in Table 1).

Table 1. Comprehensive descriptive overview of the incorporated studies**.**

No	Author's Name	Journal/ conference name	Year	Research Objectives	Method	Result
1	Makkiyah et al.	Pharmacogn	2021	The article compiles and presents the most recent findings on the phytochemical and pharmacological profiles of Graptophyllum pictum and outlines directions for prospective research.	quasi-experiment	The phytochemical assessment substantiated the existence of significant bioactive compounds, including flavonoids, steroids, glycosides, tannins, chlorophyll, anthocyanins, and non-toxic alkaloids. Additionally, the pharmacological investigation revealed a spectrum of therapeutic effects, encompassing antimicrobial, immunomodulatory, antioxidant, anti-inflammatory, analgesic, wound-healing, anti-hemorrhoidal, anti-diabetic, and estrogenic properties.
2	Rikomah SE et al	Der Pharmacia Lettre	2019	To evaluate the anti-inflammatory effectiveness of a topical preparation derived from the ethanolic extract of Graptophyllum pictum foliage in male specimens of Mus musculus.	Randomized controlled test	The formulated cream, prepared from ethanolic extracts of *G. pictum* leaves, showed statistically significant anti-inflammatory effects.

No	Author's Name	Journal/ conference name	Year	Research Objectives	Method	Result
3	Ratnasari Y et al.	Pharmaciana	2020	This investigation sought to examine the properties associated with anti-inflammatory effects and antiplatelet aggregation of the ethanolic extract obtained from Graptophyllum pictum (EEGP)	Randomized controlled test	The administration of the extract at dosages of 600 and 3000 mg/kg of body mass exhibited notable anti-inflammatory properties and significantly curtailed platelet aggregation, thereby underscoring its dual pharmacological efficacy.
4	Riwanto et al	Medica Hospitalia	2020	The objective of the present research was to examine the anti-inflammatory and antioxidant characteristics of Graptophyllum pictum extract within a model of hemorrhoid-induced male Wistar rats.	Randomized controlled test	A dosage of 100 mg/kg body mass of the extract exhibited noteworthy anti-inflammatory and antioxidant properties, as indicated by diminished serum levels of COX-2 and elevated levels of SOD. Additionally, a robust inverse correlation between COX-2 and SOD was discerned.
5	Triyandi R. et al.	Jurnal Farmasi Lampung	2020	To investigate the anti-inflammatory properties of the aqueous extract derived from Graptophyllum pictum (wungu leaf extract) in Wistar rat models.	Randomized controlled test	Statistical analysis demonstrated that all variations in dosage of the aqueous extract exhibited a significant reduction in edema when contrasted with the negative control cohort.

No	Author's Name	Journal/ conference name	Year	Research Objectives	Method	Result
6	Ocvinta S et al	Pharmaciana	2024	In order to evaluate the antioxidant, analgesic, and anti-inflammatory properties of ethanolic extracts derived from purple leaves, a Wistar rat model will be employed for comprehensive analysis.	Randomized controlled test	The extract exhibited significant antioxidant activity, evidenced by an IC50 value of 72.312 ± 24.406 µg/mL. Upon administration at a dosage of 100 mg/kg of body weight, it manifested the most pronounced analgesic effect, quantified at 129.64%, alongside an anti-inflammatory response characterized by a reduction in edema volume of 28.73% following a duration of six hours.

4 DISCUSSION

A total of Purple leaves have been used in Indonesia as a remedy for tonsillitis, abscess, rheumatism, breast swelling, breast abscess, hemorrhoids, and diabetes [7]. The non-toxic alkaloid compounds of this plant, such as flavonoids, tannins, alkaloids, sitosterols, glycosides, anthraquinone, carbohydrates, coumarins, and saponins, are very beneficial to the human body [2]. Phenolic or polyphenolic compounds such as flavonoids, tannins, and saponins in purple leaves are a source of natural antioxidants for the body [5]. Purple leaf exhibited diverse antioxidant activity, displaying levels of strength ranging from strong, moderate, to weak antioxidants [8].

The purple leaf is characterized by the presence of phenolic and flavonoid compounds, which possess the ability to donate hydrogen atoms to free radicals, thereby facilitating the formation of more stable molecular entities [9]. The inclusion of tannin and flavonoid compounds in the extract of purple leaves is instrumental in the mitigation of free radical markers.Historically, purple leaves have been employed in traditional medicinal practices for the treatment of inflammatory ailments, including hemorrhoids. A study conducted by Ozaki et al. (1989) demonstrated that the ethanol extract derived from G. pictum leaves exhibits considerable anti-inflammatory properties. This particular extract has been shown to effectively inhibit carrageenan-induced edema in rodent models, while concurrently alleviating vascular permeability and associated pain symptoms. The fraction identified as containing flavonoids has been recognized as the bioactive component accountable for these observed effects [10].

The anti-inflammatory properties of Graptophyllum pictum are predominantly ascribed to its flavonoid constituents, which function as antagonists to inflammatory

mediators, including prostaglandins and cytokines. Furthermore, a research investigation conducted by Riwanto et al. (2021) assessed the anti-inflammatory and antioxidant properties of G. pictum extract in Wistar rats subjected to experimental hemorrhoidal conditions. The findings revealed that the administration of the extract at a dosage of 100 mg/kg body weight markedly diminished serum COX-2 concentrations and elevated serum SOD levels, thereby suggesting its prospective anti-inflammatory and antioxidant efficacy [11].

A comprehensive investigation conducted by Elmitra Dan (2015) validated the existence of flavonoid constituents within the ethanolic extract of Graptophyllum pictum L. Griff. Drawing upon numerous empirical findings, it is broadly recognized that flavonoids serve as the principal agents responsible for the plant's anti-inflammatory properties. These bioactive compounds operate by disrupting initial inflammatory processes, particularly through the inhibition of the release of serotonin and histamine, which function as chemical mediators at the inflammatory site [12]. In support of this assertion, Prasetyo et al. (2023) revealed that the administration of 100 mg/kg body weight of G. pictum ethanol extract to Wistar rats with experimentally induced hemorrhoids resulted in marked anti-inflammatory effects, encompassing reductions in serum levels of IL-6, COX-2, TNF-α, and total leukocyte count in the anal tissue [13]. Additionally, the extract demonstrated no adverse effects on renal or hepatic functions. The investigation further underscored that flavonoids present within the extract modulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway, which constitutes a pivotal regulatory mechanism in the context of inflammation [14].

In addition to its notable anti-inflammatory properties, G. pictum also exhibits significant activity in inhibiting platelet aggregation. Research conducted by Ratnasari et al. (2020) systematically assessed the anti-inflammatory effects and platelet aggregation inhibition associated with ethanol extracts derived from the leaves of G. pictum in Wistar rats. The extracts administered at dosages of 600 and 3000 mg/kg body weight demonstrated a percentage of edema inhibition that is comparable to that of Na-diclofenac, while also effectively inhibiting platelet aggregation, akin to the action of aspirin. This finding suggests that the ethanol extract of G. pictum possesses the capability to act as an anti-inflammatory agent that concurrently inhibits platelet aggregation. Investigations indicate that Graptophyllum pictum exerts its antiplatelet effects by disrupting the synthesis of thromboxane A2 and obstructing the pathways of platelet activation. Alkaloids present in the plant may serve as antagonists to adenosine diphosphate (ADP) receptors, thereby attenuating platelet aggregation [15]. Comparative analyses with aspirin reveal that Graptophyllum pictum exhibits comparable efficacy in the inhibition of platelet function, although additional in vivo studies are requisite to substantiate its clinical applicability.

In summary, the accumulated evidence from in vivo studies strongly supports the anti-inflammatory and antiplatelet potential of *Graptophyllum pictum*, particularly through its flavonoid and alkaloid constituents. However, the current body of research remains largely preclinical, with diverse methodologies and limited standardization across studies. These findings highlight not only the therapeutic promise of G. pictum as a natural alternative to conventional drugs but also emphasize the urgent need for rigorous clinical trials to validate its efficacy and safety in human populations. As such, G. pictum represents a valuable candidate

for further pharmacological exploration in the context of inflammatory and cardiovascular diseases.

5 CONCLUSION

A comprehensive systematic literature review indicates that Graptophyllum pictum (L.) Griff. manifests substantial anti-inflammatory and anti-platelet aggregation properties, particularly attributed to the presence of flavonoids and alkaloids.Flavonoids play a pivotal role in the plant's capacity to inhibit inflammatory mediators including prostaglandins, cytokines, COX-2, IL-6, and TNF-α, while also modulating critical signaling pathways such as NF-κB. Moreover, the ethanolic extract of G. pictum effectively obstructs platelet aggregation through the disruption of thromboxane A2 synthesis and functions as an antagonist to ADP receptors, exhibiting comparable efficacy to aspirin in certain studies.The antioxidant attributes of this plant further augment its therapeutic potential by mitigating the effects of free radicals.These findings corroborate the traditional utilization of G. pictum in the management of inflammatory conditions such as hemorrhoids and illustrate its prospective application as an alternative therapeutic agent for inflammatory disorders and platelet aggregation.

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