Volume 7, No. 11 November, 2026
p ISSN 2723-6927-e ISSN 2723-4339

Gyrinops Versteegii Leaves in Acne-Like Inflammation: A Literature Review

Veronika S. Ayu Hakim* , I Gusti Ayu Widianti
Universitas Udayana, Indonesia
Email: hakim.2580711050@student.unud.ac.id*

Keywords:
Gyrinops Versteegii; Cutibacterium Acnes; Interleukin-6; Histopathology; Acne Vulgaris.

ABSTRACT

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit characterized by dysregulated sebum production, follicular hyperkeratinization, Cutibacterium acnes-associated microbial dysbiosis, oxidative stress, and immune activation. Interleukin-6 (IL-6) expression and skin histopathological findings serve as important outcome measures in experimental models of acne-like inflammation, reflecting cytokine-mediated inflammatory responses and tissue damage. Gyrinops versteegii, an Indonesian agarwood-producing plant species, contains bioactive secondary metabolites with reported antioxidant and antibacterial activities. However, direct evidence linking G. versteegii leaves to the modulation of C. acnes-induced inflammatory pathways remains limited. This literature review, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, synthesized studies published between 2013 and 2026. Relevant literature was identified through searches of major biomedical databases, Indonesian scholarly databases, publishers' websites, and reference lists. Sixteen articles met the inclusion criteria and were included in the qualitative synthesis. The available evidence suggests that G. versteegii leaves exhibit antioxidant activity, potential suitability for topical applications, and antibacterial activity against selected microorganisms. Comparative evidence from the more extensively studied agarwood-producing genus Aquilaria supports the biological plausibility that agarwood-derived compounds may modulate nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways and their downstream inflammatory mediators, including IL-6. Nevertheless, these findings should be interpreted cautiously because they do not directly establish the anti-inflammatory efficacy of G. versteegii against C. acnes-induced inflammation. Experimental models involving C. acnes have demonstrated increased proinflammatory cytokine expression, inflammatory cell infiltration, erythema, edema, and histopathological alterations. Overall, G. versteegii leaves represent a biologically plausible candidate for the development of topical anti-inflammatory agents targeting acne-like inflammation, although direct species-specific evidence remains insufficient. Future in vivo studies should standardize extraction procedures and formulations, assess antibacterial activity against C. acnes, quantify IL-6 and other relevant inflammatory mediators, and employ blinded histopathological scoring in reproducible preclinical models.

INTRODUCTION

Acne vulgaris is one of the most common chronic inflammatory skin disorders, particularly among adolescents and young adults. It is characterized by noninflammatory lesions, including open and closed comedones, and inflammatory lesions, such as papules,

pustules, nodules, and, in severe cases, cyst-like lesions. Current clinical guidelines emphasize that acne is not merely a cosmetic concern, as it can lead to permanent scarring, impaired quality of life, anxiety, and substantial psychosocial distress (National Institute for Health and Care Excellence, 2026; Reynolds et al., 2024).

The pathogenesis of acne is multifactorial and involves four interconnected processes: increased sebum production, follicular hyperkeratinization, Cutibacterium acnes-associated microbial dysbiosis, and activation of cutaneous inflammatory responses (Burkhart, 2024; Huang et al., 2024). C. acnes interacts with keratinocytes, sebocytes, macrophages, and other immune cells through pattern recognition receptors, particularly Toll-like receptors (TLRs) (Bernales Salinas, 2021). These interactions activate intracellular signaling pathways, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), and inflammasome-associated pathways, resulting in increased production of proinflammatory mediators (Chuang et al., 2021; Kim et al., 2024; Noh et al., 2022; Shin et al., 2023).

Interleukin-6 (IL-6) is an important inflammatory cytokine involved in acne-like inflammation, reflecting innate immune activation and the amplification of local inflammatory responses. In vitro studies have demonstrated that exposure to C. acnes can increase the expression of interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), IL-6, interleukin-8 (IL-8), tumor necrosis factor alpha (TNF-α), and cyclooxygenase-2 (COX-2) in human epidermal keratinocytes (Noh et al., 2022). These findings are further supported by experimental animal studies demonstrating that C. acnes exposure can induce tissue swelling, erythema, inflammatory cell infiltration, and histopathological alterations (Chuang et al., 2021; Rimon et al., 2023; Shin et al., 2023; Sun et al., 2024). Therefore, combining IL-6 measurements with histopathological evaluation may provide a more comprehensive assessment of inflammatory responses and potential anti-inflammatory effects in preclinical acne research.

Conventional acne treatments include benzoyl peroxide, topical retinoids, topical and systemic antibiotics, azelaic acid, hormonal therapies, and oral isotretinoin for selected patients with severe or treatment-resistant acne (National Institute for Health and Care Excellence, 2026; Reynolds et al., 2024). Although these treatments have established clinical efficacy, several limitations remain, including skin irritation, dryness, treatment adherence difficulties, and concerns regarding antimicrobial resistance, particularly with antibiotic use. These challenges have encouraged investigations into complementary therapeutic candidates with anti-inflammatory, antioxidant, and antibacterial properties, including bioactive compounds derived from locally available medicinal plants.

Agarwood-producing plants, locally known as gaharu, belong primarily to the genera Aquilaria and Gyrinops within the family Thymelaeaceae. Among these species, Gyrinops versteegii is particularly relevant to Indonesia because of its reported distribution across several regions, particularly eastern Indonesia, and its potential as a locally available biological resource (Fiqa et al., 2020; Yulistyarini et al., 2020). Previous studies have identified several classes of secondary metabolites in G. versteegii leaves, including flavonoids, phenolic compounds, tannins, saponins, steroids, triterpenoids, and glycosides, which may contribute to their antioxidant and antibacterial activities (Batubara et al., 2022; Parwata et al., 2018; Parwata et al., 2026; Ramadhana et al., 2026). Although direct evidence supporting the effects of G. versteegii on C. acnes-induced inflammation remains limited, existing phytochemical, antioxidant, antibacterial, and dermatological findings provide a scientific basis for examining

its potential relevance to acne-like inflammatory mechanisms (Nurafni et al., 2022; Parwata et al., 2026; Ramadhana et al., 2026; Widianti et al., 2026).

This review aimed to systematically synthesize the available literature on the potential anti-inflammatory properties of Gyrinops versteegii leaf extracts, particularly in relation to IL-6 expression and histopathological alterations in experimental models of acne-like inflammation. Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework (Page et al., 2021), the review focused on three principal aspects: the phytochemical composition and biological activities of G. versteegii leaves; comparative pharmacological evidence from the agarwood-producing genera Gyrinops and Aquilaria; and the mechanistic relevance of C. acnes-induced IL-6 expression and histopathological changes in murine models. By integrating available phytochemical and pharmacological evidence while distinguishing mechanistic plausibility from experimentally demonstrated efficacy, this review sought to identify existing research gaps and establish a scientific rationale for future preclinical investigations of G. versteegii leaf extracts as potential topical anti-inflammatory agents.

METHOD

This study employed a PRISMA-guided systematic narrative review to synthesize evidence on the biological activities and potential mechanisms of Gyrinops versteegii leaves in Cutibacterium acnes-induced acne-like inflammation, focusing on interleukin-6 (IL-6) signaling and histopathological outcomes. Given the limited direct evidence involving G. versteegii and C. acnes-induced inflammation, studies involving Aquilaria species and experimental C. acnes models were included to provide comparative and mechanistic insights.

The literature search covered articles published between January 2013 and May 2026. Relevant studies were identified through PubMed, ScienceDirect, Google Scholar, GARUDA, SINTA-indexed Indonesian journals, publishers' websites, and manual reference screening. The primary search strategy combined terms related to Gyrinops versteegii, agarwood leaves, anti-inflammatory activity, antioxidant activity, antibacterial activity, Cutibacterium acnes, IL-6, histopathology, and acne-like inflammation using Boolean operators. Additional searches incorporated Aquilaria malaccensis, Aquilaria sinensis, agarwood flavonoids, nuclear factor kappa B (NF-κB), and mitogen-activated protein kinase (MAPK) signaling. Search strategies were adapted to the requirements of each database, and records were screened based on the relevance of their titles, abstracts, and indexed information to biological activity, inflammation, antimicrobial properties, skin biology, and experimental acne-like inflammation models.

Table 1. Search strategy and records identified across literature sources.

Source	Search strategy/keywords	Limits or notes	Records retained
PubMed	Gyrinops versteegii; agarwood leaves; anti-inflammatory; Cutibacterium acnes; IL-6; histopathology; NF-κB; MAPK	January 2013-May 2026; English-language biomedical records prioritized	12
ScienceDirect	agarwood leaves; Gyrinops; Aquilaria; flavonoid; antioxidant; antibacterial; inflammation	January 2013-May 2026; article title/abstract relevance screening	14
Google Scholar	Gyrinops versteegii leaves; gaharu leaves; acne-like inflammation; C. acnes; IL-6; histopathology	First relevance-ranked results screened; clearly unrelated records excluded	25
Garuda	daun gaharu; Gyrinops versteegii; antioxidant; antibakteri; inflamasi; gel	Indonesian-language records screened for biomedical relevance	6
SINTA-indexed Indonesian journals	Gyrinops versteegii; gaharu; ekstrak daun; fitokimia; aktivitas biologis	Local journal sources screened for full-text availability and relevance	5
Publisher websites	Specific author, species, compound, and pathway searches from cited literature	Used to confirm publisher metadata and retrieve relevant full texts	6
Manual reference tracking	Reference lists of eligible articles and relevant reviews	Other sources identified through backward citation checking	13
Total	-	-	81

The inclusion criteria encompassed original research and review articles published in English or Indonesian that investigated the antioxidant, antibacterial, anti-inflammatory, or dermatological properties of Gyrinops versteegii, Aquilaria species, or agarwood leaves. Studies examining Cutibacterium acnes-induced cytokine production, interleukin-6 (IL-6) expression, acne-like histopathological alterations, topical formulations, or preclinical models of skin inflammation were also included. Studies focusing exclusively on conservation, resin production, or fragrances without relevant biomedical outcomes were excluded, along with duplicate publications, abstracts without accessible full texts, and articles unrelated to inflammation, antibacterial activity, or skin biology.

Data were extracted and organized according to plant species or intervention, study design, experimental model, primary outcomes, and relevance to acne-like inflammatory mechanisms. Given the methodological heterogeneity of the included studies, which encompassed in vitro experiments, animal studies, review articles, and phytochemical investigations, a meta-analysis was not conducted. Instead, the findings were synthesized qualitatively to identify consistent mechanistic evidence, research gaps, and implications for future experimental investigations. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

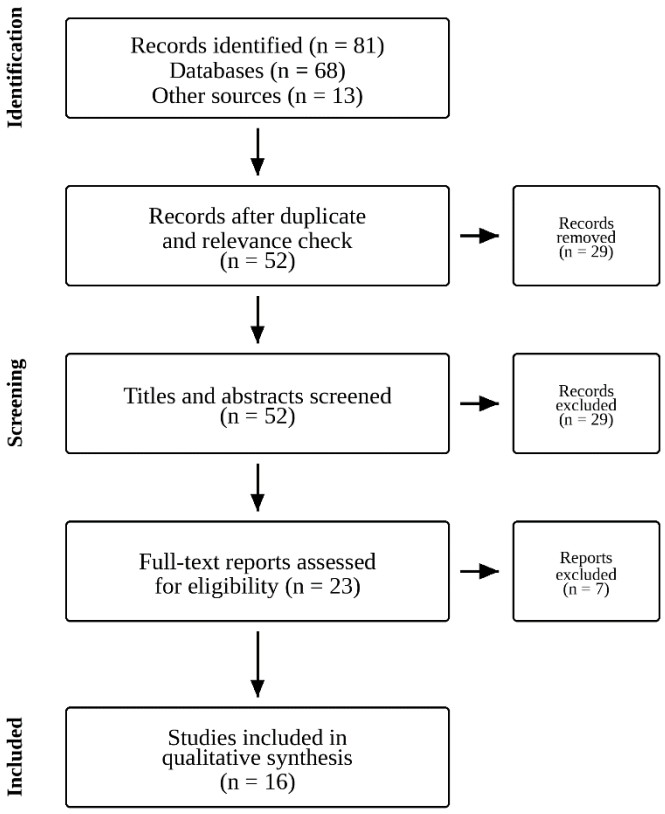


Figure 1. PRISMA 2020 flow diagram

RESULTS AND DISCUSSION

Biological basis of acne-like inflammation

The reviewed literature confirms that acne-like inflammation is not merely a follicular blockage process. C. acnes can activate keratinocytes and immune cells, resulting in cytokine production and amplification of inflammatory cascades. Noh et al. reported that C. acnes and particulate matter increased IL-1α, IL-1β, IL-6, IL-8, TNF-α, COX-2, TLR4, and phosphorylated NF-κB in human epidermal keratinocytes (Noh et al., 2022). This finding supports the relevance of IL-6 as a biochemical endpoint in acne-like inflammation models.

Animal models add tissue-level relevance. C. acnes-induced acne-like lesions in mice can be evaluated using clinical scores, histological scores, neutrophil infiltration, cytokine expression, erythema, and tissue swelling (Rimon et al., 2023; Shin et al., 2023). In this context, histopathology is not only confirmatory but also essential for demonstrating whether an intervention reduces inflammatory infiltration, edema, and tissue damage. The use of IL-6 and histopathology together is therefore appropriate for evaluating anti-inflammatory activity in preclinical acne-like inflammation models.

The combined assessment of IL-6 and histopathology is consistent with current mechanistic evidence because IL-6 reflects inflammatory signaling, whereas histopathology demonstrates structural tissue responses after C. acnes induction (Noh et al., 2022; Rimon et al., 2023; Shin et al., 2023). This combined approach strengthens the interpretation of whether a topical intervention affects cytokine activity and tissue morphology.

Gyrinops versteegii leaves as an antioxidant and antibacterial candidate

G. versteegii leaves contain multiple secondary metabolites relevant to inflammation control. Parwata et al. reported that water extract of G. versteegii leaves contained phenolics, flavonoids, tannins, alkaloids, and steroids, with very strong antioxidant activity (Parwata et al., 2018). Batubara et al. compared leaves of Aquilaria crassna, Aquilaria microcarpa, and G. versteegii and found antioxidant activity and chemical compounds that support the potential of agarwood leaves as bioactive materials (Batubara et al., 2022)

The most relevant point for acne-like inflammation is the presence of flavonoids and phenolic compounds. These compounds may reduce oxidative stress, inhibit lipid oxidation, and modulate inflammatory pathways. Although antioxidant activity is not identical to anti-inflammatory efficacy, oxidative stress and inflammation are interconnected in acne. Reactive oxygen species can amplify NF-κB activation and cytokine production, while antioxidant compounds may indirectly reduce the inflammatory microenvironment (Batubara et al., 2022; Noh et al., 2022; Parwata et al., 2018).

Antibacterial evidence for G. versteegii is emerging. Parwata et al. isolated and identified flavonoid groups from G. versteegii leaves with antibacterial activity against Staphylococcus aureus and Escherichia coli (Parwata et al., 2026). The study found that ethyl acetate extract had high flavonoid levels and active fractions with strong inhibition zones. This supports the antibacterial potential of G. versteegii, although the tested bacteria were not C. acnes. Therefore, the current evidence should be interpreted as indirect support. Direct testing against C. acnes remains an important research gap and should be prioritized in future experimental studies.

Other studies support the use of G. versteegii leaves in skin-related contexts. Parintak et al. showed photoprotective activity and spatial distribution of phenolic and flavonoid compounds in leaf tissues (Parintak et al., 2023). Nurafni et al. reported that gel of G. versteegii leaf extract had wound-healing activity in rats (Nurafni et al., 2022). These findings do not directly prove anti-acne efficacy, but they show that G. versteegii leaves can be formulated for topical use and may interact with skin repair processes.

Comparison between Gyrinops and Aquilaria

The comparison between Gyrinops and Aquilaria is important because Aquilaria has been studied more extensively as an agarwood genus, while G. versteegii is a locally relevant Indonesian species with fewer biomedical studies. Both genera belong to the Thymelaeaceae family and produce agarwood-related materials (Abd Rashed et al., 2024; Wangiyana, 2020; Widianti et al., 2026) Both also contain phenolics, flavonoids, terpenoids, tannins, and other secondary metabolites (Abd Rashed et al., 2024; Batubara et al., 2022; Parwata et al., 2018; Wangiyana, 2020; Widianti et al., 2026) However, the depth of evidence differs.

Aquilaria studies provide clearer anti-inflammatory evidence. A. malaccensis leaf extracts have demonstrated inhibition of protein denaturation in vitro, and A. sinensis-derived pilloin suppressed NF-kB/MAPK signaling and decreased TNF-α and IL-6 in macrophage and animal models (Tsai et al., 2018; Xie et al., 2024) A. malaccensis leaf ethanol extract has also shown antimicrobial activity against skin-associated bacteria and fungi, including Propionibacterium acnes, now named C. acnes (Batubara et al., 2021). These studies make Aquilaria useful as a comparative genus for building the rationale of G. versteegii research.

The key difference is that Aquilaria already has more direct anti-inflammatory and skin-microbe evidence, whereas Gyrinops evidence is stronger in antioxidant, photoprotective, and general antibacterial domains (Batubara et al., 2021; Batubara et al., 2022; Nurafni et al., 2022; Parintak et al., 2023; Parwata et al., 2018; Parwata et al., 2026; Tsai et al., 2018; Xie et al., 2024) This difference does not weaken the rationale of the review. Instead, it highlights a research gap: G. versteegii requires direct evaluation in C. acnes-induced inflammation using cytokine and histopathological endpoints.

Recent evidence strengthens this comparison. An integrated review published in 2026 describes agarwood from Aquilaria and Gyrinops as a promising anti-inflammatory resource and summarizes pathways such as NF-kB, MAPK, NLRP3, and cytokine regulation (Zhang et al., 2026). In Gyrinops, a 2025 transcriptomic study confirmed that fungal induction in G. versteegii seedlings can induce sesquiterpenes and chromone compounds, providing molecular support that Gyrinops shares important agarwood-related compound classes with Aquilaria (Hermawaty et al., 2025). Another 2025 study on G. versteegii agarwood tea from Lombok showed regional variation in tannin concentration and a significant tannin-preference correlation, while explicitly relating this pattern to agarwood tea from A. malaccensis (Wangiyana et al., 2025). Therefore, the comparison suggests biological overlap at the phytochemical level, but the anti-inflammatory evidence base remains more mature for Aquilaria than for G. versteegii.

Table 2. Summary of key studies included in the qualitative synthesis.

Author, year	Species/model	Design/outcome	Main relevance	Main limitation
Parwata et al., 2018	Gyrinops versteegii leaves	In vitro antioxidant and phytochemical identification	Shows very strong antioxidant activity and supports the oxidative-stress rationale for G. versteegii leaves.	Antioxidant assay only; no C. acnes, IL-6, histopathology, or topical acne-like model.
Batubara et al., 2022	Aquilaria crassna, Aquilaria microcarpa, and Gyrinops versteegii leaves	Comparative phytochemical and antioxidant study	Shows that G. versteegii belongs to a bioactive agarwood-leaf group with antioxidant potential.	Comparative chemical study; anti-inflammatory and C. acnes-specific outcomes were not evaluated.
Parintak et al., 2023	Gyrinops versteegii leaves	Photoprotective and spatial phytochemical evaluation	Supports phenolic and flavonoid distribution in leaf tissues and skin-protective potential.	Focused on photoprotection; no acne-like inflammation, IL-6, or histopathological endpoint.
Nurafni et al., 2022	Gyrinops versteegii leaf extract gel	Topical wound model in rats	Supports the feasibility of G. versteegii leaf extract in gel	Wound-healing model differs from acne; cytokine signaling and C.

			formulation for skin application.	acnes induction were not assessed.
Parwata et al., 2026	Gyrinops versteegii leaves	Antibacterial fractionation against Staphylococcus aureus and Escherichia coli	Shows antibacterial flavonoid potential, although C. acnes was not directly tested.	Antibacterial targets were not C. acnes; no inflammatory or histological analysis.
Ramadhana et al., 2026	Gyrinops versteegii leaves	Phytochemical evaluation of 70% ethanol extract	Supports the presence of bioactive compounds in ethanol extract of gaharu leaves.	Phytochemical screening only; biological activity and dose-response effects were not tested.
Widianti et al., 2026	Gyrinops versteegii leaf ethanol extract	In vivo experimental study	Supports systemic biological activity and protective effects of G. versteegii leaf extract in an animal model.	Model was not skin- or acne-specific; relevance to IL-6 and histopathology is indirect.
Wangiyana, 2020	Aquilaria and Gyrinops leaves	Medicinal-effect review	Highlights shared antioxidant, antibacterial, and medicinal potential of agarwood leaves from both genera.	Narrative review; evidence is heterogeneous and dependent on primary-study quality.
Manar et al., 2018	Aquilaria malaccensis leaves	Protein-denaturation anti-inflammatory assay	Provides comparator evidence that agarwood leaves may have direct anti-inflammatory activity.	In vitro assay using Aquilaria; no Gyrinops, C. acnes, IL-6, or animal histology.
Batubara et al., 2021	Aquilaria malaccensis leaves	Antimicrobial assay against skin-associated microbes	Shows antimicrobial activity against skin-related microbes, including Propionibacterium acnes or C. acnes.	Different genus; antimicrobial activity was not linked to cytokine or histological improvement.
Tsai et al., 2018	Aquilaria sinensis flavonoid pilloin	Macrophage and mouse inflammatory model	Demonstrates suppression of NF-κB/MAPK signaling and reduction of TNF-α and IL-6.	Isolated compound from Aquilaria; not a Gyrinops leaf extract and not an acne-specific model.

Noh et al., 2022	Human epidermal keratinocytes and C. acnes	In vitro acne-like inflammation model	Shows that C. acnes increases IL-6, IL-8, TNF-α, COX-2, TLR4, and phosphorylated NF-κB.	Cell-culture model only; does not evaluate Gyrinops or tissue histopathology.
Shin et al., 2023	Mouse C. acnes-induced skin inflammation	In vivo mouse model	Supports C. acnes-induced swelling, erythema, inflammatory cytokines, and dermal infiltration.	Tested a pharmacological inhibitor rather than Gyrinops or agarwood-derived compounds.
Rimon et al., 2023	Mouse C. acnes-induced acne-like lesions	In vivo mouse model with clinical and histological scoring	Supports histological scores, neutrophil infiltration, and inflammatory endpoints in acne-like lesions.	Intervention was phage therapy; findings are methodological comparators, not plant-extract evidence.
Sun et al., 2024	C. acnes-induced inflammatory model	Antibacterial and anti-inflammatory evaluation of berberine	Provides comparator evidence for natural-product suppression of C. acnes-related inflammation.	Different natural compound; cannot be extrapolated directly to G. versteegii.
Piazza et al., 2024	C. acnes-stimulated skin-related inflammatory model	Evaluation of Castanea sativa leaf extract on cytokines	Shows that plant leaf extracts may reduce C. acnes-related IL-6 and IL-8 responses.	Different botanical source and model context; evidence supports plausibility only.

Mechanistic plausibility of G. versteegii for C. acnes-induced IL-6

The biological plausibility of G. versteegii against acne-like inflammation can be constructed through three layers of evidence. First, G. versteegii leaves are rich in antioxidant phytochemicals, especially flavonoids and phenolics (Parintak et al., 2023; Parwata et al., 2018). Second, G. versteegii has antibacterial activity against representative Gram-positive and Gram-negative bacteria, indicating that its flavonoid-rich fractions can suppress bacterial growth (Parwata et al., 2026). Third, C. acnes-induced inflammation depends on cytokine pathways that can be modulated by plant phenolics and flavonoids, as demonstrated by mechanistic studies on C. acnes-induced inflammation, other natural products, and Aquilaria-derived flavonoid pilloin (Cros et al., 2023; Jiang et al., 2022; Mias et al., 2023; Noh et al., 2022; Teethaisong et al., 2025; Tsai et al., 2018).

This evidence does not establish G. versteegii as a proven anti-C. acnes agent. The more accurate interpretation is that G. versteegii is a biologically plausible candidate requiring direct testing in disease-relevant models. Future studies should move from indirect antioxidant and antibacterial evidence toward C. acnes-induced acne-like inflammation models that measure both IL-6 expression and histopathological outcomes.

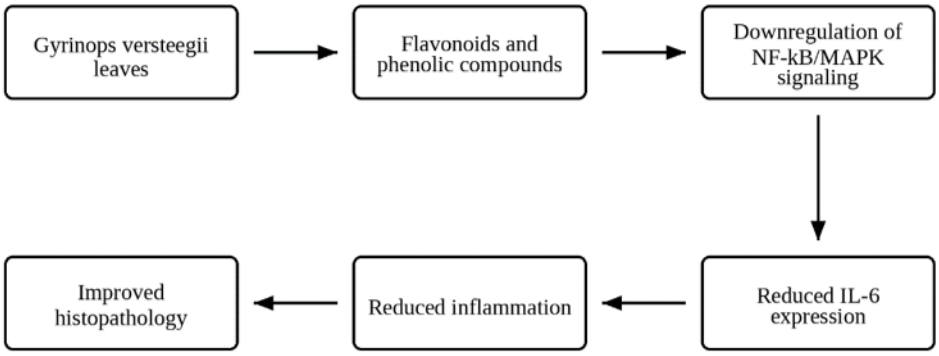


Figure 2. Proposed mechanism linking Gyrinops versteegii leaves with reduced IL-6-mediated acne-like inflammation.

The argument should therefore be framed carefully: G. versteegii leaves have antioxidant and antibacterial properties that may support anti-inflammatory effects in bacterial skin inflammation; however, their direct effect on C. acnes-induced IL-6 expression and histopathological changes remains limited and requires experimental verification. This wording is scientifically safer than stating that G. versteegii has already been proven to treat acne.

Table 3. Practical comparison between Gyrinops and Aquilaria as agarwood genera for this review.

Aspect	Gyrinops	Aquilaria	Implication for future research
Taxonomic context	Agarwood-producing genus in Thymelaeaceae; G. versteegii is relevant to Indonesia.	Agarwood-producing genus with wider pharmacological literature.	Aquilaria can be used as a comparator, not a substitute for Gyrinops data.
Evidence volume	Fewer biomedical studies; stronger evidence in antioxidant, photoprotective, wound, and general antibacterial assays.	More studies on anti-inflammatory, antimicrobial, immunomodulatory, and isolated compounds.	The review should explain why Gyrinops needs direct acne-like testing.
Key compounds	Flavonoids, phenolics, tannins, saponins, steroids/triterpenoids, glycosides.	Flavonoids, chromones, sesquiterpenes, fatty acids, phenolics.	Both genera contain compounds related to oxidative and inflammatory pathways.
Anti-inflammatory evidence	Indirect; expected through antioxidant and antibacterial mechanisms; direct C. acnes/IL-6 data limited.	More direct; some extracts/isolates suppress NO, NF-kB/MAPK, TNF-α, and IL-6.	Future Gyrinops studies may fill this gap by evaluating IL-6 and histopathological endpoints.
Skin/bacteria relevance	General antibacterial evidence exists, but C. acnes-specific data is still limited.	A. malaccensis has antimicrobial data against skin microbes including P. acnes in one study.	C. acnes induction is a logical next model for G. versteegii.

Histopathology as an endpoint in acne-like inflammation

Histopathology is a critical endpoint because it verifies whether biochemical suppression is accompanied by tissue repair. In C. acnes-induced models, expected microscopic findings include epidermal or dermal thickening, edema, inflammatory cell infiltration, and disruption of local skin architecture (Rimon et al., 2023; Shin et al., 2023). A topical anti-inflammatory candidate should reduce these changes compared with the induced untreated group.

In future preclinical studies, hematoxylin-eosin staining can be used to describe inflammatory cell infiltration, tissue edema, epidermal changes, and dermal structure. A semi-quantitative score can improve objectivity, for example: 0 = normal/no inflammation, 1 = mild infiltration, 2 = moderate infiltration with edema, 3 = severe infiltration with marked edema and structural disruption. This scoring should be performed by a blinded assessor when possible to reduce observer bias (Rimon et al., 2023; Shin et al., 2023).

The connection between IL-6 and histopathology should be framed as complementary. A decrease in IL-6 alone suggests reduced cytokine signaling. Improvement of histopathology suggests reduced tissue inflammation. When both endpoints improve, the interpretation of anti-inflammatory effect becomes more convincing (Noh et al., 2022; Rimon et al., 2023; Shin et al., 2023).

Implications for formulation as topical gel

Topical gel is suitable for acne-like lesions because it is generally less oily than ointment, spreads easily, and allows direct contact between active compounds and inflamed skin. A gel formulation is relevant for topical delivery and aligns with previous G. versteegii skin-related work in wound models (Nurafni et al., 2022).

However, formulation quality should be controlled. Important parameters include extract standardization, pH compatibility with skin, viscosity, homogeneity, spreadability, stability, microbial contamination, and dose consistency. For preclinical validity, the concentration of extract and the amount applied to each mouse should be standardized. If the manuscript is submitted as a review article, these formulation issues can be discussed as future requirements rather than reported as results (Nurafni et al., 2022).

Research gaps

No included study was found that directly tested G. versteegii leaf extract against C. acnes-induced IL-6 production in a mouse acne-like inflammation model (Noh et al., 2022; Nurafni et al., 2022; Parintak et al., 2023; Parwata et al., 2018; Parwata et al., 2026; Rimon et al., 2023; Shin et al., 2023).

Existing G. versteegii evidence is still concentrated on antioxidant activity, photoprotection, wound-related outcomes, and antibacterial activity against non-C. acnes bacteria (Nurafni et al., 2022; Parintak et al., 2023; Parwata et al., 2018; Parwata et al., 2026).

Aquilaria evidence is stronger for direct anti-inflammatory pathways, but genus-level extrapolation should be used cautiously because species, plant part, extraction method, and active constituents can differ (Batubara et al., 2021; Batubara et al., 2022; Tsai et al., 2018; Xie et al., 2024).

Future research should standardize extract composition, determine minimum inhibitory concentration against C. acnes, test cytotoxicity, evaluate IL-6 and other cytokines, and use

blinded histopathological scoring (Noh et al., 2022; Nurafni et al., 2022; Parwata et al., 2026; Rimon et al., 2023; Shin et al., 2023).

CONCLUSION

This systematic narrative review suggests that Gyrinops versteegii leaves represent a promising natural product candidate for managing acne-like inflammation due to their reported antioxidant and antibacterial properties, particularly those associated with flavonoids and phenolic compounds. Comparative evidence from Aquilaria, a more extensively studied agarwood-producing genus, further supports the biological plausibility that agarwood-derived bioactive compounds may modulate inflammatory signaling pathways, including nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), as well as downstream inflammatory mediators such as interleukin-6 (IL-6). However, direct experimental evidence demonstrating the effects of G. versteegii leaf extracts on Cutibacterium acnes-induced IL-6 expression and skin histopathological alterations remains insufficient. These findings highlight the need for further preclinical investigations using C. acnes-induced models of acne-like inflammation. Although G. versteegii leaves exhibit potential as a locally available source of bioactive compounds, their anti-acne efficacy has not yet been established. Future studies should therefore evaluate their anti-inflammatory activity through quantitative IL-6 measurements, standardized histopathological assessments, and appropriate experimental controls.

REFERENCES

Abd Rashed, A., et al. (2024). The therapeutic potential of agarwood as an antimicrobial and anti-inflammatory agent: A review. *Molecules, 29*(21), Article 5053. https://doi.org/10.3390/molecules29215053

Batubara, R., Hanum, T. I., Affandi, O., Julianti, E., & Ulfa, M. (2022). The antioxidant activities and chemical compounds of Aquilaria crassna, Aquilaria microcarpa, and Gyrinops versteegii leaves growing in Langkat, North Sumatra, Indonesia. *Biodiversitas Journal of Biological Diversity, 23*(12), 6619–6628. https://doi.org/10.13057/biodiv/d231260

Batubara, R., Wirjosentono, B., Siregar, A. H., Harahap, U., & Tamrin. (2021). Bioactive compounds of ethanol extract from agarwood leaves (Aquilaria malaccensis) and antimicrobial activity against bacteria and fungi growing on the skin. *Biodiversitas Journal of Biological Diversity, 22*, 2884–2890. https://doi.org/10.13057/biodiv/d220553

Bernales Salinas, A. (2021). Acne vulgaris: role of the immune system. *International Journal of Dermatology*, *60*(9), 1076–1081.

Burkhart, C. G. (2024). Assessment of Cutibacterium acnes: Acne biofilm, comedones, and future treatments for acne. *The Open Dermatology Journal, 18*, Article e18743722279314. https://doi.org/10.2174/0118743722279314240219091938

Chuang, L. T., Huang, W. C., Hou, Y. C., Chyuan, J. H., Chang, H., Chang, C. I., et al. (2021). Suppressive effect of two cucurbitane-type triterpenoids from Momordica charantia on Cutibacterium acnes-induced inflammatory responses in human THP-1 monocytic cell and mouse models. *Molecules, 26*(3), Article 579. https://doi.org/10.3390/molecules26030579

Cros, M. P., et al. (2023). New insights into the role of Cutibacterium acnes-derived extracellular vesicles in acne pathogenesis. *Scientific Reports, 13*, Article 16848. https://doi.org/10.1038/s41598-023-43354-w

Fiqa, A. P., Budiharta, S., Siahaan, F. A., & Rindyastuti, R. (2020). Population structure of Gyrinops versteegii within floristic community in Nggalak Protection Forest, Flores Island, Indonesia. *Biodiversitas Journal of Biological Diversity, 21*, 1561–1568.

Hermawaty, D., Setyobudi, T., Nugrahapraja, H., Turjaman, M., & Faizal, A. (2025). De novo transcriptome assembly and analysis during agarwood induction in Gyrinops versteegii Gilg. seedling. *Scientific Reports, 15*, Article 2977. https://doi.org/10.1038/s41598-025-87486-7

Huang, L., Yang, S., Yu, X., Fang, F., Zhu, L., Wang, L., et al. (2024). Association of different cell types and inflammation in early acne vulgaris. *Frontiers in Immunology, 15*, Article 1275269. https://doi.org/10.3389/fimmu.2024.1275269

Jiang, Z., Jin, S., Li, S., et al. (2022). Cannabidiol inhibits inflammation induced by Cutibacterium acnes-derived extracellular vesicles in keratinocytes. *Journal of Inflammation Research, 15*, 4833–4846. https://doi.org/10.2147/JIR.S376405

Kim, E. O., Park, D., Ha, I. J., Bae, S. E., Lee, M. Y., Yun, M., & Kim, K. (2024). The secretion of inflammatory cytokines triggered by TLR2 through calcium-dependent and calcium-independent pathways in keratinocytes. *Mediators of Inflammation, 2024*, Article 8892514. https://doi.org/10.1155/mi/8892514

Mias, C., Mengeaud, V., Bessou-Touya, S., & Duplan, H. (2023). Recent advances in understanding inflammatory acne: Deciphering the relationship between Cutibacterium acnes and Th17 inflammatory pathway. *Journal of the European Academy of Dermatology and Venereology, 37*(Suppl. 2), 3–11. https://doi.org/10.1111/jdv.18794

National Institute for Health and Care Excellence. (2026). *Acne vulgaris: Management* (NICE Guideline NG198). https://www.nice.org.uk/guidance/ng198

Noh, H. H., Shin, S. H., Roh, Y. J., Moon, N. J., Seo, S. J., & Park, K. Y. (2022). Particulate matter increases Cutibacterium acnes-induced inflammation in human epidermal keratinocytes via the TLR4/NF-κB pathway. *PLOS ONE, 17*(8), Article e0268595. https://doi.org/10.1371/journal.pone.0268595

Nurafni, S., Ratu, A. P., Marliana, T., & Rahmawati, E. (2022). Uji aktivitas obat herbal gel ekstrak daun gaharu (Gyrinops versteegii (Gilg.) Domke) terhadap luka diabetes pada tikus putih jantan (Rattus norvegicus). *Jurnal Ilmiah Ibnu Sina, 7*(2), 360–369. https://doi.org/10.36387/jiis.v7i2.1002

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, Article n71. https://doi.org/10.1136/bmj.n71

Parintak, R., Maryani, M., Hidayati, L., Wijayanti, N., & Nuringtyas, T. R. (2023). Evaluation of photoprotective of Gyrinops versteegii (Gilg.) Domke leaves extract with different solvents and its spatial distribution. *Journal of Pharmaceutical Science and Clinical Research, 8*(2), 265–277. https://doi.org/10.20961/jpscr.v8i2.58611

Parwata, A., Manuaba, P., & Yasa, S. (2018). The potency of flavonoid compounds in water extract Gyrinops versteegii leaves as natural antioxidants sources. *Biomedical and Pharmacology Journal, 11*(3), 1501–1511. https://doi.org/10.13005/bpj/1517

Parwata, I. M. O. A., Pratama, I. M. B., & Suaniti, N. M. (2026). Isolasi dan identifikasi senyawa golongan flavonoid yang memiliki aktivitas antibakteri pada daun gaharu (Gyrinops versteegii). *Jurnal Kimia, 20*(1), 27–34. https://doi.org/10.24843/JCHEM.2026.v20.i01.p04

Ramadhana, F., Widianti, I. G. A., & Widhiartini, I. A. A. (2026). Phytochemical potential of 70% ethanol extract of gaharu leaves (Gyrinops versteegii) obtained by maceration.

International Journal of Scientific Advances, 7(1), 185–189. https://doi.org/10.51542/ijscia.v7i1.23

Reynolds, R. V., Yeung, H., Cheng, C. E., Cook-Bolden, F., Desai, S. R., Druby, K. M., et al. (2024). Guidelines of care for the management of acne vulgaris. *Journal of the American Academy of Dermatology, 90*(5), 1006.e1–1006.e30. https://doi.org/10.1016/j.jaad.2023.12.017

Rimon, A., Rakov, C., Lerer, V., Sheffer-Levi, S., Alkalay Oren, S., Shlomov, T., et al. (2023). Topical phage therapy in a mouse model of Cutibacterium acnes-induced acne-like lesions. *Nature Communications, 14*, Article 1005. https://doi.org/10.1038/s41467-023-36694-8

Shin, J. H., Lee, S. E., Kim, S. C., et al. (2023). Pyrrolidine dithiocarbamate suppresses Cutibacterium acnes-induced skin inflammation by inhibiting inflammasome activation. *International Journal of Molecular Sciences, 24*(5), Article 4444. https://doi.org/10.3390/ijms24054444

Sun, L., Yu, Q., Peng, F., Sun, C., Wang, D., Pu, L., et al. (2024). The antibacterial activity of berberine against Cutibacterium acnes: Its therapeutic potential in inflammatory acne. *Frontiers in Microbiology, 14*, Article 1276383. https://doi.org/10.3389/fmicb.2023.1276383

Teethaisong, Y., et al. (2025). Identification of protocatechuic acid as an anti-acne agent targeting Cutibacterium acnes-induced inflammation. *International Journal of Molecular Sciences, 26*(12), Article 5660. https://doi.org/10.3390/ijms26125660

Tsai, Y. C., Wang, S. L., Wu, M. Y., et al. (2018). Pilloin, a flavonoid isolated from Aquilaria sinensis, exhibits anti-inflammatory activity in vitro and in vivo. *Molecules, 23*(12), Article 3177. https://doi.org/10.3390/molecules23123177

Wangiyana, I. G. A. S. (2020). Medicinal effect review of agarwood leaves from Aquilaria and Gyrinops genera. *Jurnal Silva Samalas, 3*(1), 36–43.

Wangiyana, I. G. A. S., Kurnia, N., & Triandini, I. G. A. A. H. (2025). Correlation of tannin concentration and respondent preference of agarwood tea (Gyrinops versteegii) taken from different regions in Lombok Island, Indonesia. *Food Research, 9*(5), 94–99. https://doi.org/10.26656/fr.2017.9(5).036

Widianti, I. G. A., Wardana, N. G., Widhiartini, I. A. A., Pratiwi, M. S. A., & Antari, N. W. S. (2026). Protective effects of Gyrinops versteegii leaf ethanol extract on Leydig cells and testosterone under excessive physical activity: An in vivo study. *Medisains, 24*(1), 21–25. https://doi.org/10.30595/medisains.v24i1.28611

Xie, C., Dong, J. Z., Lu, B. S., Yan, P. Y., Zhao, Y. S., Ding, X. Y., et al. (2024). Pharmacology and therapeutic potential of agarwood and agarwood tree leaves in periodontitis. *Frontiers in Pharmacology, 15*, Article 1468393. https://doi.org/10.3389/fphar.2024.1468393

Yulistyarini, T., Fiqa, A. P., Budiharta, S., & Rindyastuti, R. (2020). Distribution of Gyrinops versteegii (Gilg.) Domke in varying vegetation structures, soil properties, and microclimates in Manggarai, Flores, East Nusa Tenggara. *Biodiversitas Journal of Biological Diversity, 21*(5), 1800–1808. https://doi.org/10.13057/biodiv/d210505

Zhang, M. M., Wen, T., Cui, M. W., & Guo, Z. L. (2026). Anti-inflammatory properties of agarwood (Aquilaria spp.): An integrated review of phytochemistry, molecular mechanisms, and therapeutic applications. *Drug Design, Development and Therapy, 20*, 1–15. https://doi.org/10.2147/DDDT.S559380