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A review of calophyllolide from *Calophyllum inophyllum* L.: isolation, quantification, analytical method, and burn wound healing potential

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Abstract

Background: Calophyllolide is a dipyranocoumarin compound found in *Calophyllum inophyllum* L., known for its antimicrobial and anti-inflammatory properties, which are beneficial for burn wound healing. However, variability in its content and lack of standardized methods remain challenges.

Objective: This review aims to present a literature study on calophyllolide, including its sources, isolation techniques, bioactive content optimization, analytical methods, and pharmacological potential in burn wound healing.

Method: Data were retrieved from Scopus and PubMed using predefined keywords. Articles published in English between 2001 and 2021 and classified as original research were selected. Relevant studies were assessed for quality using the SYRCLE tool (animal studies) and the Young & Solomon checklist (non-clinical research).

Results: Seeds harvested in September had the highest calophyllolide content (0.23%). Enhancement through tissue culture using 2 mg/L IBA yielded up to 45.23 mg/100 g callus. Among analytical techniques, a validated GC-MS method showed high precision and recovery. Pharmacological studies confirmed its activity against *Staphylococcus aureus* and its ability to modulate inflammatory responses.

Conclusion: Calophyllolide shows strong potential as a natural agent for burn wound therapy. Standardized extraction, quantification, and production approaches are essential for further development.

Keywords: Calophyllolide, *Calophyllum inophyllum*, isolation, quantification, burn wound healing

1. Introduction

Calophyllum inophyllum L., commonly known as nyamplung in Indonesia or tamanu in various Pacific regions, is a tropical tree species widely distributed along coastal areas, including in Indonesia (Yuniastuti *et al*., 2021). Traditionally, the oil extracted from its seeds has been utilized as a renewable source for biodiesel production (Adenuga *et al*., 2021). This application continues to be explored and supported by institutions such as the Forestry Research and Development Agency (FORDA), Indonesia (Ong *et al*., 2011). Beyond its industrial relevance, *C. inophyllum* seed oil has long been employed in traditional medicine, especially in Vietnam, for the treatment of burns, skin disorders, rheumatism, and insomnia (Nguyen *et al*., 2017).

Phytochemical investigations of *C. inophyllum* have revealed the presence of a wide spectrum of bioactive secondary metabolites, including coumarins, xanthones, flavonoids, steroids, and triterpenoids (Praveena, 2013; Tsai *et al*., 2012). Among the major constituents identified, calophyllolide has garnered significant attention due to its pharmacological activities, including antimicrobial, cytotoxic, osteogenic, and anti-inflammatory effects

(Itoigawa *et al*., 2001; Yimdjo *et al*., 2004). Other notable compounds isolated from *C. inophyllum* oil include Inophyllum P, Inophyllum B, Calanolide A and B, 12-Oxocalanolide (Kostova & Mojzis, 2007), Inophyllum A, C, D, and E (Itoigawa et al., 2001; Yimdjo *et al*., 2004), Calanolide Gut 70 (Jin *et al*., 2011), and Pseudocalanolide D (Ishikawa, 2000). More recently, two novel neoflavonoids, Tamanolide E1 and E2, were also identified in this oil (Ginigini *et al*., 2019), reflecting the ongoing chemical diversity discovery from this species.

Among these bioactive compounds, calophyllolide stands out due to its dual antimicrobial and anti-inflammatory properties (Gunawan *et al*., 2020), which are particularly relevant in wound healing, especially for burn injuries. Effective burn treatment often requires both infection control and inflammation modulation (Radzikowska-Büchner *et al*., 2023). Thus, calophyllolide presents a promising candidate for therapeutic development in this area.

Despite its promising pharmacological properties, the broader application of calophyllolide remains constrained by several scientific challenges. Its concentration in *C. inophyllum* is influenced by factors such as the specific plant part used, harvesting period, and extraction method (Gupta & Gupta, 2020; Hapsari *et al*., 2023), leading to variability in yield and difficulties in standardization. Additionally, efforts to increase calophyllolide content, through approaches like plant tissue culture, phytohormone induction, and medium modification, are still scattered and lack a unified optimization strategy. While HPLC and GC-MS have been employed for quantification (Jaikumar *et al*., 2017; Liu *et al*., 2015), few studies have provided fully validated analytical methods that ensure accuracy, sensitivity, and reproducibility across different contexts.

This review aims to synthesize and evaluate scientific evidence of calophyllolide, including its sources, isolation techniques, content optimization strategies, analytical methods, and pharmacological potential in burn wound healing. By consolidating existing findings into a coherent narrative, this review seeks to support future research directions and encourage the development of calophyllolide as a therapeutically relevant natural compound.

2. Method

2.1. Literature search strategy

The literature search was conducted in December 2021 using two electronic databases: Scopus and PubMed. The selection of search terms was guided by the main research questions addressed in this review. The following keywords and keyword combinations were used:

"Calophyllolide content", "Calophyllolide AND Calophyllum", "4-substituted coumarin AND Calophyllum", "Calophyllolide expression", "Calophyllolide production", "dipyranocoumarin expression AND Calophyllum", "dipyranocoumarin production AND Calophyllum", "Calophyllolide analysis", "Calophyllolide determination", "antimicrobial AND Calophyllolide", and "anti-inflammatory AND Calophyllolide". Boolean operators (AND, OR) were applied to refine and broaden the search results where necessary.

2.2. Inclusion and exclusion criteria

Articles were included based on the following eligibility criteria: a) indexed in Scopus and/or PubMed, b) written in English, c) categorized as original research articles, and d) published between 2001-2021. Two reviewers independently performed screening and assessed titles and abstracts for relevance to the review objectives. Articles that met the initial criteria were then evaluated in full-text format.

2.2. Quality assessment

Quality assessment of the included studies was conducted with consideration of the study design to ensure methodological rigor and minimize potential bias. *In vitro* studies involving animal models were evaluated using the SYRCLE's Risk of Bias (RoB) tool, which was specifically developed by the Systematic Review Centre for Laboratory Animal Experimentation to assess the internal validity of preclinical animal research (Hooijmans *et al*., 2014). The Young and Solomon critical appraisal checklist was used for non-clinical or basic laboratory research studies. This tool provides structured criteria to assess scientific soundness, including clarity of objectives, appropriateness of methodology, quality of data presentation, and interpretation of findings (Young & Solomon, 2009).

3. Results and discussion

3.1. Article selection process

The initial search using predetermined keywords retrieved a total of 35 scientific articles. After applying the inclusion criteria, 21 articles remained. These articles were further screened based on their title and abstract relevance to the research questions, yielding 14 eligible studies. A full-text screening resulted in 10 final articles being included in this review. One article Nguyen *et al*. (2017) was categorized as an *in vitro* animal study and assessed using

SYRCLE's Risk of Bias tool. The remaining nine articles, classified as basic research, were appraised using the Young and Solomon checklist. The selection process is summarized in **Figure 1**.

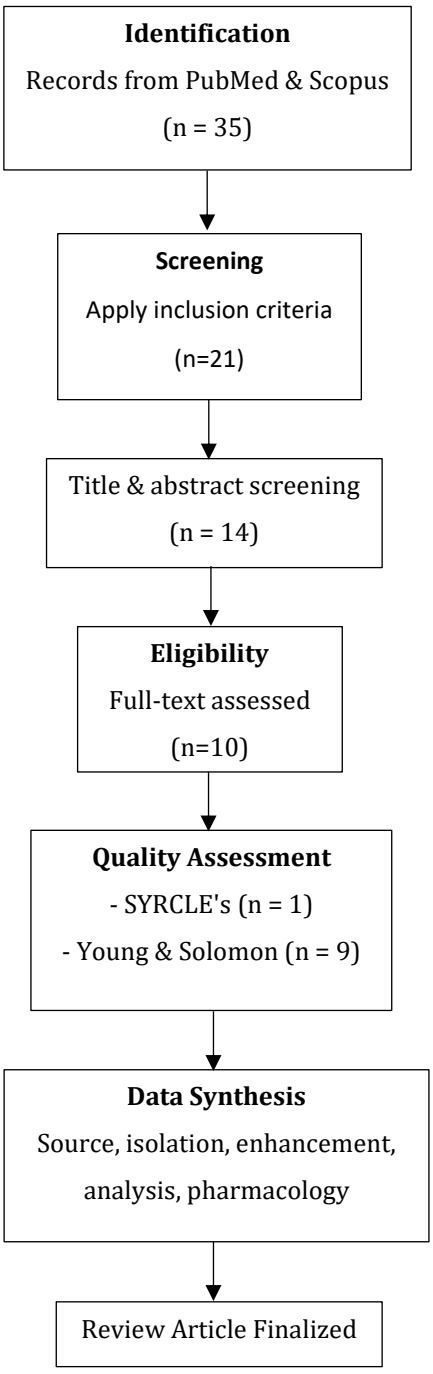

Figure 1. Article selection flowchart

3.2. Natural sources and isolation methods of calophyllolide

Calophyllolide is a naturally occurring coumarin derivative classified under the 4-phenyl pyranocoumarins, with the chemical name 5-methoxy-2,2-dimethyl-6-(2-methylbut-2-enoyl)-10-phenylpyrano [2,3-f] chromen-8(2H)-one (Kalyanaraman *et al*., 2014). Its structure is shown in **Figure 2**.

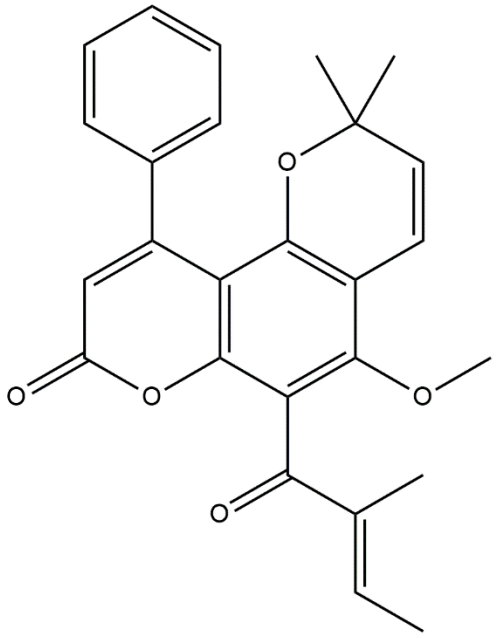

Figure 2. *Calophyllolide* chemical structure

As a member of the phenolic secondary metabolites, coumarins typically possess a C6-C3 core structure (Vermerris & Nicholson, 2008). Phytochemical screening of *C. inophyllum* leaf methanolic extract using cold percolation (2 x 72 hours) revealed the presence of various bioactive compounds such as alkaloids (11.51%), tannins (7.68%), polyphenols (2.53%), triterpenoids (2.48%), flavonoids (2.37%), and saponins (2.16%) (Susanto *et al*., 2017). Calophyllolide has been identified in various parts of the *Calophyllum* genus, with markedly variable content depending on plant part, extraction solvent, and processing method, as detailed in **Table 1**.

Among various plant organs, seeds consistently yielded the highest concentrations of calophyllolide, suggesting they are the primary storage site for this metabolite. For example, Yimdjo *et al*. (2004) obtained 0.118% calophyllolide from *C. inophyllum* seed powder using dichloromethane: methanol (1:1) maceration followed by extensive silica gel chromatography and methanol recrystallization, while Ito *et al*. (2003) reported a much lower yield of only

0.001% from the bark of *C. brasiliense* using acetone extraction at room temperature, followed by silica gel column chromatography and preparative thin-layer chromatography.

Table 1. Comparative calophyllolide contents from different *Calophyllum* plant parts and extraction methods

Plant source	Extraction and isolation method	Calophyllolide content	Reference
Bark of *C. brasiliense*	Room temperature extraction with acetone, silica gel column, and preparative TLC	0.001%	Ito *et al*., 2003
Dried seeds of *C. inophyllum*	CH2Cl2: MeOH (1:1) extraction; silica gel column chromatography with n-hexane: EtOAc	0.118%	Yimdjo *et al.*, 2004
Leaves from the French Polynesian islands	Ethyl acetate extraction (1 week); analyzed with HPLC-UV-DAD	0.0000116% (average)	Laure *et al.*, 2008
Resin of *C. inophyllum* seed oil	Methanol: water (9:1) extraction; vacuum liquid chromatography on silica gel using n-hexane: EtOAc	0.02803% of resin mass	Hien *et al*., 2011
Dried seeds (harvested in September)	Ethanol extraction, silica gel column, and Sephadex LH-20 chromatography	0.23%	Liu *et al.*, 2015
Dried seeds (harvested in December)	Ethanol extraction, silica gel column, and Sephadex LH-20 chromatography	0.16%	Liu *et al.*, 2015
Bark of *C. inophyllum*	Ethanol extraction, silica gel column, and Sephadex LH-20 chromatography	Not detected by HPLC	Liu *et al.*, 2015
Seed shell of *C. inophyllum*	Ethanol extraction, silica gel column, and Sephadex LH-20 chromatography	Not detected by HPLC	Liu *et al.*, 2015
Dried seeds of *C. inophyllum*	Cold press extraction; analyzed with GC-MS	0.0196% of dry seed weight	Charinrat *et al*., 2021

Extraction technique and solvent system also significantly impact calophyllolide yield. Ethanol-based extractions followed by multi-step purification tend to be more efficient. The highest yield (0.23%) was reported by Liu *et al*. (2015) using ethanol extraction, liquid-liquid partitioning with water and ethyl acetate, and subsequent purification with silica gel and Sephadex LH-20 chromatography. Notably, this yield was obtained from seeds harvested in September, whereas a reduced concentration (0.16%) was found in those harvested in December, indicating that seasonal and maturity factors may influence biosynthetic activity and metabolite accumulation.

In contrast, simpler extraction methods or non-seed plant parts tend to yield substantially lower concentrations. For instance, Laure *et al*. (2008) detected only trace amounts of calophyllolide (mean: 0.0000116%) from dried leaf extracts using ethyl acetate maceration over one week. Similarly, no detectable calophyllolide was found in the bark or seed coat using Liu *et al*. (2015) optimized method, reinforcing the idea that calophyllolide is either absent or present in negligible quantities outside the seeds.

Further analysis of processed products like oils also reflects this trend. Using GC-MS, Saechan *et al.* (2021) quantified calophyllolide in cold-pressed oil from oven-dried seeds at 0.0196%. In comparison, (Hien *et al*. 2011) obtained a slightly higher yield of 0.02803% from resinous seed oil extracted with methanol:water (9:1) and purified via vacuum liquid chromatography. These data emphasize that even within seed-derived products, extraction solvents and post-harvest treatments significantly affect compound recovery.

3.3. Optimization of calophyllolide content

Despite its pharmacological potential, the natural abundance of calophyllolide remains extremely low, making its large-scale extraction inefficient and unsustainable. This limitation has driven interest in biotechnological approaches, particularly plant tissue culture, as a means to enhance calophyllolide production. Tissue culture provides a controlled environment for inducing and optimizing secondary metabolite synthesis (Chandran *et al.*, 2020), thereby offering a promising platform for consistent and scalable production.

Pawar *et al*. (2007) investigated the effect of different types and concentrations of phytohormones on calophyllolide accumulation in *C. inophyllum* callus cultures derived from various explants (seeds, nodal/internodal segments, and leaves). The highest calophyllolide content (45.23 mg/100 g callus) was observed in seed-derived callus treated with 2 mg/L indole-3-butyric acid (IBA). Lower yields were recorded in nodal/internodal and leaf callus cultures under different hormone combinations. In contrast, lower yields were observed in calli from nodal/internodal, and leaf callus cultures, suggesting that callus cultures origin and hormonal balance critically influence biosynthetic capacity.

Further research by Pawar & Thengane (2009) investigated suspension cultures and found that the application of IBA (4.90 μM), alone or in combination with BAP or Picloram, significantly boosted calophyllolide synthesis. This was further optimized by modifying nitrate,

sulfate, and vitamin concentrations in the culture medium, resulting in an impressive 85-fold increase in dipyranocoumarin content compared to baseline levels.

To further augment metabolite levels, Pawar & Thengane (2011) introduced abiotic elicitors into the culture system. Among the tested compounds, cadmium, copper, chromium, and calcium chloride, cadmium produced the most pronounced enhancement in calophyllolide content. This suggests that stress-response pathways activated by metal ions may play a key role in stimulating coumarin biosynthesis. However, caution is warranted due to potential toxicity and regulatory limitations associated with heavy metal use in bioproduction systems.

While tissue culture has demonstrated considerable success in enhancing calophyllolide yield, its scalability and cost-effectiveness remain points of concern for industrial application. Therefore, future research should aim to integrate genetic engineering, elicitor screening, and environmental manipulation in field-grown plants (Malu *et al*., 2025) to establish a more holistic and sustainable strategy for calophyllolide production.

3.4. Analytical methods for calophyllolide quantification

As interest in the pharmacological application of calophyllolide continues to grow, it is essential to develop accurate, sensitive, and reproducible analytical methods for its quantification. Several studies have investigated various instrumental techniques, particularly high-performance liquid chromatography (HPLC) and gas chromatography-mass spectrometry (GC-MS), to determine the content of calophyllolide in *C. inophyllum*.

Liu *et al*. (2015) employed an HPLC method using a Cosmosil 5C18-AR-II analytical column coupled with a μBondpack C18 pre-column. The separation was achieved through gradient elution with a water: acetonitrile mixture. The elution profile consisted of water: acetonitrile (30:70, v/v) from 0 to 20 minutes, followed by a shift to 100% acetonitrile from 20 to 40 minutes. Detection was carried out at 254 nm using a UV detector. While the method demonstrated effective separation of calophyllolide, it lacked critical validation data such as linearity, precision, and recovery, thereby limiting its applicability for quality control or regulatory purposes.

A similar limitation was observed in the study by Laure *et al*. (2008), who utilized HPLC with UV-DAD detection to analyze calophyllolide in *C. inophyllum* leaf extracts. The method involved a gradient of isopropanol: isooctane (1–20%, v/v) over 25 minutes, followed by a 15-minute stabilization period. Detection was performed at 360 nm. However, like the method by

Liu *et al*. (2015), this protocol remained largely descriptive and did not report analytical validation parameters, leaving uncertainty regarding its reproducibility, specificity, or robustness.

In contrast, Hien *et al*. (2011) developed and validated a GC-MS method for calophyllolide quantification. Various column temperature programs were evaluated, with optimal conditions identified as an initial column temperature of 80 °C, followed by a temperature ramp of 40 °C/min to 300 °C, maintained for 9 minutes. Under these parameters, calophyllolide exhibited a sharp retention time of 12.83 ± 0.006 minutes with preserved ion characteristics. The method demonstrated a linear response within the 3.125–50 µg/mL range, intra- and inter-day precision with relative standard deviation (RSD) below 3%, and an average recovery rate of 101.22 ± 1.98% (RSD = 1.95%). This comprehensive validation sets the GC-MS method apart as the most reliable analytical protocol currently available for calophyllolide quantification. Its high precision and recovery rates support its use not only in research settings but also in routine quality control workflows for *C. inophyllum*-based preparations.

Overall, while HPLC-based methods provide a foundation for calophyllolide analysis, future work should prioritize full method validation to meet international standards. The established GC-MS method may serve as a benchmark for future protocol development, or even as a standardized analytical method for regulatory and industrial applications.

3.5. Burn wound healing potential of calophyllolide

Calophyllolide, a bioactive coumarin isolated from *C. inophyllum*, has garnered increasing attention due to its antimicrobial and anti-inflammatory properties (Gunawan *et al*., 2020). These two pharmacological actions are particularly crucial in addressing key challenges associated with burn wound healing, which involves complex inflammatory responses, a high risk of infection, and delayed tissue regeneration (Su *et al*., 2024).

Burn injuries disrupt the skin's protective barrier, creating a nutrient-rich environment that fosters microbial colonization. Under these compromised conditions, opportunistic pathogens, notably *Staphylococcus aureus* and *Pseudomonas aeruginosa*, can proliferate rapidly. This colonization often leads to delayed re-epithelialization, prolonged inflammation, and increased risk of systemic infection or sepsis (Hall et al., 2018). Consequently, effective burn wound management requires agents capable of both combating infection and modulating inflammation.

Over the years, several antimicrobial agents have been clinically employed, including silver nitrate, silver sulfadiazine, bacitracin, and neomycin (Glasser *et al*., 2010), as well as more advanced materials such as silver-chitosan acetate nanocomposites (Huang *et al.*, 2011). Likewise, anti-inflammatory treatments such as ibuprofen (Ambler *et al*., 2005) and the topical anti-IL-6R antibody MR16-1 (Sakimoto *et al*., 2012) have been shown to support tissue regeneration and reduce inflammatory damage. In this context, calophyllolide presents a unique advantage as a single compound that exhibits both antimicrobial and anti-inflammatory activity, suggesting its potential as a dual-function agent for burn wound treatment.

Yimdjo *et al*. (2004) demonstrated that calophyllolide exhibited the strongest antibacterial activity among various compounds isolated from *C. inophyllum*, including caloxanthone A, calophynic acid, brasiliensic acid, and several inophyllum derivatives. When tested against *S. aureus* at a concentration of 20 μg per disk, calophyllolide produced an inhibition zone diameter of 16.0 mm, greater than that observed for other individual compounds and crude extracts of the root bark and seeds.

In addition to its antimicrobial effect, calophyllolide has garnered attention for its anti-inflammatory properties, which could offer significant therapeutic value in managing complex wound healing scenarios. A study by Nguyen *et al*. (2017) explored this aspect using a murine full-thickness incision model, comparing the efficacy of calophyllolide (12 mg/mL), Povidone Iodine (PI, 200 mg/mL), and Phosphate Buffered Saline (PBS) over a 14-day treatment period. While the data are derived from a single preclinical source, the depth of investigation into inflammatory modulation warrants closer examination.

One of Nguyen *et al*. (2017) most notable findings was the phenotypic polarization of macrophages following calophyllolide treatment. There was a significant downregulation of pro-inflammatory M1 markers CD14 and CD127, alongside upregulation of reparative M2 markers CD163 and CD206. This polarization suggests a shift in the local immune environment toward resolution and regeneration, aligning with the physiological transition from the inflammatory to the proliferative phase of wound healing (Krzyszczyk *et al*., 2018).

Moreover, calophyllolide administration markedly suppressed pro-inflammatory cytokines, IL-1β, IL-6, and TNF-α, by up to 90% at days 5 and 7 post-injury (Nguyen *et al*., 2017). This was accompanied by a transient elevation of IL-10, a cytokine closely associated with anti-inflammatory macrophage activity and tissue repair (Kessler *et al*., 2017). Although the IL-10

surge diminished by day 7, its early presence may be critical for dampening excessive inflammation and initiating resolution pathways.

Another key outcome from the same study was the suppression of myeloperoxidase (MPO) activity, a surrogate marker for neutrophil infiltration and oxidative stress (Khan *et al*., 2018). Calophyllolide's ability to reduce MPO by approximately fourfold relative to PI suggests a protective mechanism against neutrophil-mediated tissue injury (Nguyen *et al*., 2017). While the study was limited to an animal model, and the findings require validation in human tissues, the comprehensive dataset provides a compelling case for further translational research.

The studies in this review span a wide range of research exploring calophyllolide, from its natural sources, extraction methods, and bioactive content optimization strategies to its pharmacological potential, particularly in wound healing. The strength of this review lies in its integrated discussion of both phytochemical and biomedical aspects, providing a comprehensive foundation for further development of calophyllolide as a therapeutic candidate. Nonetheless, the review is confined to studies published in English and sourced from selected databases, which may exclude relevant findings published in other languages or outside major indexing platforms. Such restrictions may limit the breadth of perspectives captured and underscore the need for broader, multi-source evidence synthesis in future reviews

4. Conclusion

This review highlights that *Calophyllum inophyllum* seeds, particularly those harvested in September, are the richest natural source of calophyllolide. Optimization through plant tissue culture, especially with 2 mg/L IBA, has shown promising results in increasing its content. Among analytical methods, the validated GC-MS approach provides reliable quantification. With its dual antimicrobial and anti-inflammatory properties, calophyllolide is a strong candidate for burn wound therapy. These findings support further development of calophyllolide-based products and reinforce its potential contribution to natural compound-based pharmaceuticals.

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