Borneo Journal of Pharmacy
Vol 8 Issue 4 November 2025
Pages 326 – 334

https://journal.umpr.ac.id/index.php/bjop/article/view/10168
DOI: https://doi.org/10.33084/bjop.v8i4.10168
e-ISSN: 2621-4814

Research Article

Pogostemon cablin from North Konawe Targets MCF-7 Cells and Inflammatory Responses Through Protein Denaturation and Membrane Stabilization

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Keywords:
Anti-inflammatory
Cytotoxicity
HRBC membrane stabilization
Pogostemon cablin
Protein denaturation

Abstract

Pogostemon cablin (Patchouli), a medicinal plant traditionally used in Indonesia, is gaining scientific attention for its potential pharmacological activities. This study aimed to investigate the anti-inflammatory and anticancer effects of *P. cablin* ethanolic leaf extract specifically sourced from North Konawe, Southeast Sulawesi. To evaluate its anti-inflammatory activity, two *in vitro* models were used: the protein denaturation inhibition assay, simulating inflammatory protein response, and the human red blood cell (HRBC) membrane stabilization assay, which mimics lysosomal membrane stability in inflamed tissues. The extract showed significant, dose-dependent inhibition of protein denaturation, with an IC_{50} value of 62.98 µg/mL. In the HRBC assay, the extract demonstrated membrane stabilization activity with a maximum inhibition of 64.24% at the highest tested concentration (100 µg/mL). The cytotoxic potential was assessed using the MTT assay on MCF-7 hormone-responsive breast cancer cells. The extract exhibited potent anti-proliferative activity, with an IC_{50} value of 91.56 ± 1.31 µg/mL, indicating its effectiveness in inhibiting breast cancer cell growth. These findings highlight *P. cablin* from North Konawe as a promising natural source of anti-inflammatory and anticancer agents, with the potential to contribute to the development of plant-based therapeutics. However, this study is limited to *in vitro* analyses; further investigations are needed to isolate active compounds and confirm efficacy through *in vivo* and mechanistic studies.

Received: June 28th, 2025
1st Revised: August 5th, 2025
Accepted: October 16th, 2025
Published: November 30th, 2025

INTRODUCTION

Breast cancer stands as the most prevalent malignancy among women and a primary cause of global mortality[1-3]. A substantial proportion of these cases are classified as hormone receptor-positive, specifically the estrogen receptor (ER)-

How to cite: Fristiohady A, Jafriati, Anwar I, Asasutjarit R, Purnama LOMJ, Haruna LA, et al. Pogostemon cablin from North Konawe Targets MCF-7 Cells and Inflammatory Responses Through Protein Denaturation and Membrane Stabilization. Borneo J Pharm. 2025;8(4):326-34. doi:10.33084/bjop.v8i4.10168

positive subtypes[4,5]. While the MCF-7 cell line serves as the standard ER-positive model for evaluating therapeutic efficacy[6,7], the clinical application of conventional chemotherapy and endocrine treatments is often hindered by drug resistance, high recurrence rates, and systemic toxicity. These challenges underscore the critical need for novel therapeutic agents, particularly those derived from natural sources that offer multi-target efficacy with improved safety profiles[8,9]. Historically, natural products have been pivotal in oncological pharmacology, accounting for over 60% of available anticancer agents. Medicinal plants provide a vast, largely unexplored reservoir of bioactive compounds with complex mechanisms of action[10,11].

Pogostemon cablin (Blanco) Benth., widely known as patchouli, has attracted considerable scientific interest due to its rich phytochemical profile and extensive history in Southeast Asian ethnomedicine[12,13]. Traditionally utilized for its antibacterial, antifungal, anti-inflammatory, and wound-healing capabilities, *P. cablin* is now being scrutinized for broader therapeutic applications. Key bioactive constituents, including patchouli alcohol, pogostone, flavonoids, and terpenoids, have been identified as primary contributors to its emerging anticancer potential[12-14]. Specifically, *P. cablin* alcohol and pogostone exhibit potent anti-inflammatory effects by modulating pro-inflammatory cytokines and inhibiting critical signaling pathways such as NF-κB, MAPK, and JNK[1,3,11,12,15,16]. The progression of cancer is intrinsically linked to inflammation[15,17,18]; chronic inflammatory microenvironments facilitate tumor development by promoting angiogenesis, inducing genetic instability, and suppressing adaptive immune responses[19,20]. Consequently, identifying agents that possess dual anti-inflammatory and anticancer properties represents a promising strategy for managing hormone-responsive breast tumors[21,22].

The North Konawe region in Southeast Sulawesi, Indonesia, has emerged as a promising cultivation site for *P. cablin*. The distinct agroclimatic conditions of this area are hypothesized to influence secondary metabolite production, potentially enhancing the plant's pharmacological profile. However, despite the plant's abundance and traditional utility, scientific data regarding the specific chemotype of *P. cablin* from North Konawe and its impact on cancer-related pathways remain scarce[23,24]. Given the limited research simultaneously evaluating the dual bioactivity of this specific variety, this study aims to investigate the therapeutic potential of *P. cablin* extract cultivated in North Konawe. We hypothesize that this extract exhibits dual bioactivity by inhibiting inflammation-induced protein denaturation and suppressing the proliferation of MCF-7 hormone-responsive breast cancer cells, thereby supporting the sustainable utilization of local medicinal resources for modern therapeutic applications.

MATERIALS AND METHODS

Materials

The plant material, *P. cablin* leaves, was sourced from North Konawe, Southeast Sulawesi, Indonesia. The material was formally identified by a local botanist from the laboratory at the Faculty of Pharmacy, Universitas Halu Oleo. All chemical reagents utilized in this study were of analytical grade. These included phosphate-buffered saline (PBS; pH 7.4) and bovine serum albumin (BSA) (both from Sigma-Aldrich, USA), Tris-base and sodium chloride (NaCl; both from Merck, Germany), and sodium carboxymethylcellulose (Na-CMC; Sigma-Aldrich, USA). For cell-based assays, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma-Aldrich, USA) and dimethyl sulfoxide (DMSO; Merck, Germany) were used. Cell culture was maintained using Dulbecco's Modified Eagle Medium (DMEM), fetal bovine serum (FBS), and penicillin-streptomycin (all from Gibco, USA).

The human breast cancer cell line used in this study, MCF-7, was sourced from the Indonesian Institute of Sciences (LIPI) in Cibinong, Indonesia. These cells were maintained in DMEM that was supplemented with 10% FBS and 1% penicillin-streptomycin solution. Cultures were kept in a humidified incubator at a temperature of 37°C under a controlled atmosphere of 5% CO_2 to ensure optimal growth and viability throughout the experimental period.

Methods

Sample collection and preparation

Fresh *P. cablin* leaves were collected manually using clean pruning tools to minimize contamination. The gathered samples were immediately sorted to exclude any damaged or diseased plant material, then meticulously washed under running

water to remove surface debris. Following washing, the leaves were air-dried in a shaded area until a constant weight was achieved. Finally, the dried leaves were cut into small, uniform pieces to increase the surface area and facilitate efficient subsequent extraction.

Extraction

The extraction of the dried *P. cablin* samples was performed using the maceration method, with ethyl acetate as the solvent. Ethyl acetate was strategically chosen for its intermediate polarity, a characteristic that facilitates the enrichment of semi-polar bioactive compounds, specifically flavonoids and terpenoids, which are recognized for their anti-inflammatory and anticancer properties. The dried plant material was submerged in the solvent and allowed to soak at room temperature for a total duration of 72 hours (in three consecutive 24-hour cycles). Following maceration, the resultant mixture was filtered through filter paper, and the solvent was subsequently removed under reduced pressure using a rotary evaporator maintained at 50°C to yield a semi-solid crude extract. While formal chemical standardization of this specific batch was not performed, prior characterizations of *P. cablin* extracts consistently report the presence of major phytochemical constituents, including patchouli alcohol and pogostone[23].

Protein denaturation

The *in vitro* anti-inflammatory activity was assessed using the protein denaturation method, which measures the stabilizing effect of the test compounds on BSA. To initiate the assay, 50 µL of the prepared sample solution was combined with 5 mL of 0.2% (v/v) BSA dissolved in Tris-buffered saline (TBS; pH 7.4). This mixture was first incubated at 25°C for 30 minutes to facilitate interaction between the sample and the protein. Protein denaturation was then deliberately induced by heating the mixture at 72°C for 1 minute. Following heating, the samples were allowed to cool to room temperature (25°C) for an additional 25 minutes. The resulting turbidity, indicative of protein denaturation, was measured spectrophotometrically at 660 nm using a UV-Vis spectrophotometer (Shimadzu UV-1800, Japan). The percentage inhibition of protein denaturation was calculated using the following **Equation 1**[25]:

$$\%\text{inhibition} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100\% \qquad [1]$$

HRBC membrane stabilization assay

The anti-inflammatory potential of the extract was evaluated using the HRBC membrane stabilization method, a procedure formally approved by the LPPM UHO Ethics Committee under approval number 938/UN29.20.1.2/PG/2025. Fresh blood was obtained from healthy volunteers after obtaining informed consent and was collected into heparinized tubes. The blood was then centrifuged at 3,000 rpm for 10 minutes at 25°C. The resulting cell pellet was washed three times with isosmotic saline before being resuspended in isosmotic saline to create a 10% (v/v) erythrocyte suspension. The assay mixture consisted of 0.5 mL of the erythrocyte suspension, 1 mL of PBS (pH 7.4), 2 mL of hyposaline solution, and 1 mL of the extract at varying concentrations (6.25, 12.5, 25, 50, and 100 µg/mL). This mixture was incubated in a water bath at 56°C for 30 minutes. Post-incubation, the mixtures were centrifuged at 5,000 rpm for 10 minutes, and the absorbance of the supernatant (representing released hemoglobin) was measured at 560 nm using a UV-Vis spectrophotometer. The percentage of hemolysis and membrane stability were calculated using the following **Equations 2** and **3**[25,26]:

$$\%\text{hemolysis} = \frac{\text{Sample absorbance}}{\text{Control absorbance}} \times 100\% \qquad [2]$$

$$\%\text{stability} = 100 - \frac{\text{Sample absorbance}}{\text{Control absorbance}} \times 100\% \qquad [3]$$

Data analysis

MTT antiproliferation assay

The cytotoxic activity of the extract against the MCF-7 human breast cancer cell line was determined using the MTT assay. Briefly, MCF-7 cells were seeded into 96-well plates at an approximate density of 1×10^4 cells/well and incubated for 24 hours at 37°C in a humidified atmosphere containing 5% CO_2 to ensure optimal cell attachment. Following this incubation

period, the attached cells were exposed to various concentrations of the extract (12.5, 25, 50, 100, 200, 400, and 800 µg/mL) for a subsequent 24 hours. After the treatment phase, 100 µL of MTT solution (5 mg/mL in PBS) was introduced to each well and incubated for an additional 4 hours. The resulting formazan crystals, indicative of metabolically active cells, were then solubilized by adding 100 µL of DMSO. The absorbance of each well was measured at 570 nm using a microplate reader. Cell viability, expressed as a percentage relative to the untreated control cells, was calculated using the following **Equation 4**. The half-maximal inhibitory concentration (IC_{50}) value was subsequently determined by non-linear regression analysis using GraphPad Prism™ 5[27,28].

$$\%\text{cell viability} = \frac{\text{Mean OD}}{\text{Control OD}} \times 100\% \qquad [4]$$

RESULTS AND DISCUSSION

This study investigated the anti-inflammatory and anticancer potential of *P. cablin* sourced from North Konawe, Southeast Sulawesi, Indonesia, through a series of *in vitro* assays. The biological activities assessed included the inhibition of protein denaturation, stabilization of the HRBC membrane, and cytotoxicity against the MCF-7 hormone-responsive breast cancer cell line, as determined using the MTT assay. The results collectively provide compelling evidence for the therapeutic utility of *P. cablin*, reinforcing its status as a promising candidate in natural product-based drug discovery.

Protein denaturation serves as a widely recognized *in vitro* model for evaluating anti-inflammatory activity[25,29]. In this assay, the ethanol extract of *P. cablin* exhibited a concentration-dependent inhibition of protein denaturation, yielding a potent IC_{50} value of 62.98 µg/mL (**Figure 1**). This mechanism suggests that the extract may modulate inflammatory processes either by directly protecting proteins from thermal stress or by interfering with pro-inflammatory mediators that cause protein unfolding[16,30]. Given that protein denaturation is a process strongly implicated in the pathogenesis of various inflammatory diseases, such as arthritis[31,32], these findings scientifically substantiate the traditional use of *P. cablin* in managing inflammation-related conditions.

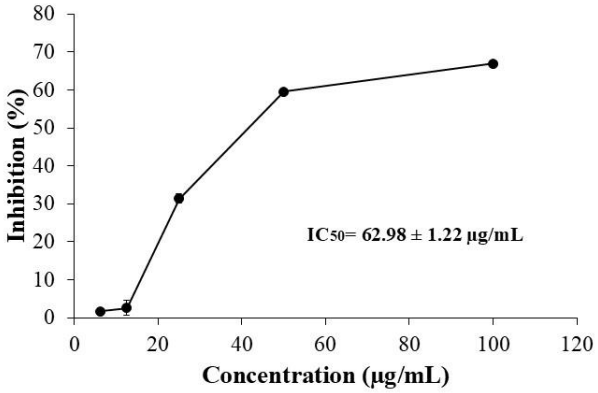

Figure 1. Dose-dependent inhibition of protein denaturation by *P. cablin* ethanol extract. Data represent the mean ± SD (n = 3).

Further investigation into the anti-inflammatory potential was conducted via HRBC membrane stabilization assay. The results demonstrated effective membrane-stabilizing activity (**Figure 2**), achieving a maximum protection of 64.24% at the highest tested concentration (100 µg/mL). This protective effect is significant because the HRBC membrane serves as a structural model for the lysosomal membrane. Preventing the lysis of the erythrocyte membrane suggests the extract's ability to stabilize lysosomal membranes, which is a crucial mechanism for limiting inflammation by preventing the release of pro-inflammatory lysosomal enzymes into surrounding tissues. Furthermore, the extract displayed favorable biocompatibility, exhibiting only low hemolytic activity (35.76% hemolysis) even at the maximum concentration tested, underscoring its potential for systemic safety and therapeutic use.

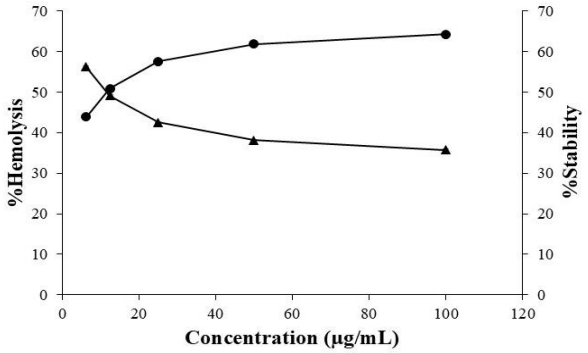

Figure 2. Concentration-dependent membrane stabilization and anti-hemolytic effects of *P. cablin* ethanol extract using HRBC method. Data represent the mean ± SD (n = 3). ▲: %hemolysis; •: %stability.

The combined results derived from both the protein denaturation and HRBC membrane stabilization assays strongly suggest that *P. cablin* cultivated in North Konawe mediates its anti-inflammatory effects through a multifaceted mechanism. Specifically, the extract demonstrates efficacy by preventing protein unfolding and stabilizing the cellular membrane, two critical processes in the inflammatory cascade. These observed anti-inflammatory activities are likely attributable to the plant's rich profile of phytoconstituents, which includes high concentrations of flavonoids, phenolics, terpenoids, and essential oil components such as patchouli alcohol and pogostone, all of which are widely recognized for their documented anti-inflammatory and potent antioxidant properties[12-14,33].

The cytotoxic potential of *P. cablin* extract was rigorously assessed against the hormone-responsive breast cancer cell line MCF-7 using the MTT assay. This method measures mitochondrial metabolic activity as a reliable indicator of cell viability. The results clearly demonstrated a concentration-dependent inhibition of MCF-7 cell proliferation, yielding an IC_{50} value of 91.56 µg/mL, as detailed in **Figure 3**. According to the National Cancer Institute (NCI) classification, this IC_{50} value signifies a moderate to strong cytotoxicity, positioning the *P. cablin* extract as an up-and-coming bioactive candidate for anticancer drug development. The potent and significant cytotoxic effect observed specifically against these ER-positive MCF-7 cells underscores the plant's potential as a valuable natural source of selective therapeutic agents for breast cancer[34,35].

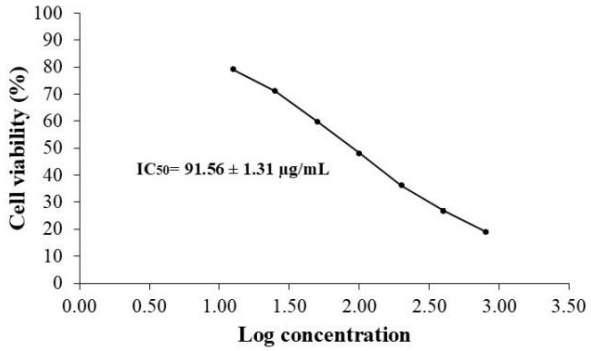

Figure 3. Dose-dependent cytotoxic effect of *P. cablin* ethanol extract on MCF-7 cells. Cell viability was assessed using the MTT assay. Data represent the mean ± SD (n = 3).

The relatively low IC_{50} value observed for the *P. cablin* extract, when compared to similar plant-based extracts, strongly suggests that its active constituents interfere with critical signaling pathways governing cancer cell survival, proliferation, and apoptosis[35-37]. Plausible mechanisms involve the downregulation of ER signaling, the induction of oxidative stress, and the activation of mitochondrial-mediated apoptotic pathways, all of which require detailed future mechanistic investigation. These findings align well with previous reports highlighting the significant antiproliferative and pro-apoptotic properties associated with *P. cablin* essential oils and polyphenols in diverse cancer models[13,38]. Moreover, preliminary toxicity screening indicated a lower cytotoxicity toward non-cancerous cells, suggesting a desirable level of selectivity against malignant cells, a key trait for promising chemotherapeutic agents. This selectivity may arise from the preferential uptake of phytochemicals by cancer cells or the inherent increased susceptibility of tumor cell mitochondria to phytochemical-induced oxidative stress[39].

The observed dual activity, which is both anti-inflammatory and cytotoxic, confers a significant therapeutic advantage. Chronic inflammation is intrinsically linked to tumor initiation and progression, mediated through oxidative DNA damage, enhanced angiogenesis, and the suppression of anti-tumor immune responses[18,40]. Consequently, an agent capable of concurrently attenuating inflammation and inhibiting proliferation may offer synergistic therapeutic benefits, particularly in hormone-responsive cancers, such as breast cancer, where inflammatory processes frequently coincide with hormonal dysregulation[17,34].

Collectively, these results suggest that the phytochemical constituents of *P. cablin* likely exert integrated biological effects by simultaneously modulating inflammatory mediators and interfering with oncogenic signaling pathways. Specifically, the cytotoxicity against MCF-7 cells may be attributed to compounds such as flavonoids, terpenoids, and other secondary metabolites within the extract. These compounds are known to induce apoptosis, disrupt the cell cycle, and elevate reactive oxygen species (ROS) levels, leading to the mitochondrial damage mechanisms commonly reported for phytochemicals with similar profiles[7,9,13,26,39]. The potential for anti-estrogenic or hormone-modulating effects in certain *P. cablin* compounds could further enhance this cytotoxicity, a hypothesis that warrants validation through molecular pathway and receptor-binding studies.

CONCLUSION

This study validates the traditional use of *P. cablin* (North Konawe chemotype) as a highly promising source of bioactive compounds with significant therapeutic relevance. The crude extract demonstrated notable dual biological activities, exhibiting both significant anti-inflammatory effects through protein stabilization and HRBC membrane protection, as well as potent cytotoxicity against hormone-responsive MCF-7 breast cancer cells. However, these findings are currently limited to *in vitro* assays, necessitating further research. Future work must prioritize the isolation and structural elucidation of the specific active phytochemicals responsible for these effects, alongside comprehensive molecular studies to fully clarify their mechanisms, including the modulation of apoptotic pathways, inflammatory cytokine profiles, ER signaling, and oxidative stress responses. Crucially, subsequent *in vivo* efficacy and safety assessments, followed by rigorous clinical validation, are essential steps required to advance *P. cablin*-derived compounds toward clinical therapeutic application.

ACKNOWLEDGMENT

The authors wish to express their profound gratitude to the Directorate of Research and Community Service under the Directorate General of Higher Education, Research and Technology, Ministry of Higher Education, Research and Technology, Republic of Indonesia. This research was made possible by the generous financial support received through the 2025 Regular Fundamental Research scheme, specifically under the main contract number: 068/C3/DT.05.00/PL/2025 and the derivative contract number: 06/UN29.20/PG/2025.

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DATA AVAILABILITY

None.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to this research.

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