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Metabolite profiling and bioactivity of *Pogostemon cablin* L. from North Konawe: GC-MS analysis, anti-inflammatory, and antinociceptive mechanisms via COX-2/cytokine inhibition

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ABSTRACT

Pogostemon cablin (Blanco) Benth. is a medicinal plant traditionally used to treat inflammation and pain. However, the phytochemical profile and pharmacological mechanisms of plants cultivated in North Konawe, Indonesia, are not well characterized. This study aimed to analyze the chemical constituents of its ethanolic extract using gas chromatography–mass spectrometry (GC-MS) and to evaluate its anti-inflammatory and antinociceptive effects through *in vivo* models. GC-MS analysis revealed 18 volatile compounds, with patchouli alcohol as the major component, followed by α-guaiene, seychellene, intermedeol, and β-caryophyllene derivatives.

The extract was tested in xylene-induced ear edema and formalin-induced nociceptive models in mice. Oral administration of the extract at doses of 25, 50, and 100 mg/kg significantly reduced ear edema thickness and pain responses in a dose-dependent manner. In the nociceptive model, the extract also suppressed systemic inflammatory responses, as indicated by reduced plasma levels of tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, and cyclooxygenase-2 expression. These findings demonstrate that *P. cablin* exerts anti-inflammatory and antinociceptive effects, likely through inhibition of peripheral inflammatory mediators. The study highlights the therapeutic potential of *P. cablin* from North Konawe as a promising source of natural agents for inflammatory pain management.

1. INTRODUCTION

Pain and inflammation are fundamental biological responses triggered by injury, infection, or immune dysregulation [1,2]. While acute inflammation and nociception serve protective roles, their chronic manifestation contributes to the pathophysiology of various disorders, including rheumatoid arthritis, neuropathic pain, cancer, and autoimmune diseases [3,4]. At the molecular level, these processes are regulated by a complex network of pro-inflammatory mediators, notably cyclooxygenase (COX)-2 (COX-2) [5] and cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [6]. These mediators represent key targets in the development of anti-inflammatory and analgesic agents [7,8].

Due to their central role in inflammatory signaling, pharmacological intervention through modulation of these mediators remains the mainstay for managing pain and inflammation, primarily using non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. These drugs inhibit

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COX enzymes and subsequent prostaglandin synthesis, thereby alleviating inflammatory symptoms and pain [9,10]. Nonetheless, their prolonged use is often limited by serious adverse effects such as gastrointestinal ulceration, renal toxicity, and elevated cardiovascular risk [11,12]. Consequently, there is a growing interest in exploring natural products, especially plant-derived compounds, as alternative or complementary anti-inflammatory therapies with potentially safer toxicity profiles [13,14].

Among the various medicinal plants investigated for their anti-inflammatory potential, *Pogostemon cablin* (Blanco) Benth., commonly known as patchouli, is a perennial aromatic herb widely cultivated in tropical regions of Asia, including Indonesia [15]. The plant is primarily known for its essential oil, which has been widely studied for antimicrobial, antioxidant, and insecticidal properties [16,17]. Beyond its aromatic uses, *P. cablin* has a long history in Southeast Asian traditional medicine for managing inflammatory conditions, fever, and various skin ailments [18,19]. However, despite its ethnomedicinal applications, scientific studies investigating its anti-inflammatory effects, particularly the bioactive compounds responsible and their mechanisms of action, remain limited and underexplored.

Phytochemical investigations have revealed that the essential oil derived from its leaves is rich in sesquiterpenes and other volatile compounds, many of which have demonstrated bioactivity in preclinical studies [18,20]. However, the phytochemical profile and therapeutic efficacy of *P. cablin* can vary considerably depending on environmental conditions, cultivation practices, and geographic origin [20,21].

Recognizing this variability, it is essential to investigate the chemical and pharmacological profile of *P. cablin* from distinct ecological regions. North Konawe Regency, located in Southeast Sulawesi, Indonesia, presents a particularly promising area for the cultivation and study of *P. cablin* due to its unique agroclimatic characteristics. This region experiences a tropical rainforest climate with high humidity, abundant rainfall, and a stable temperature range, factors conducive to the optimal growth and secondary metabolite production in aromatic and medicinal plants. These conditions are believed to enhance the quality and diversity of essential oil components, which in turn may influence the pharmacological potential of the plant [22,23]. In addition, extensive mining activities in the region may affect soil composition, increase heavy metal exposure, and induce environmental stress in plants, potentially altering their phytochemical profiles. These socio-environmental pressures, especially from large-scale nickel extraction, may also pose indirect risks to human health and ecological balance [24–26]. In this context, the development of natural therapeutic resources from within the region gains added significance. *P. cablin* not only represents a sustainable agricultural commodity but also holds potential as a locally sourced medicinal plant capable of addressing inflammation-related health concerns, which may be exacerbated by industrialization-related environmental stressors.

These abiotic factors can significantly alter the biosynthesis of secondary metabolites in medicinal plants such as *P. cablin*. This aspect has not been previously explored, as most published studies on *P. cablin* have used samples from regions with different environmental conditions (e.g., China, India, or Sumatra) [27–29]. Our study provides the first metabolite profiling of *P. cablin* cultivated in North Konawe, highlighting its potential chemical divergence.

Several studies have highlighted the broad pharmacological potential of *P. cablin*, encompassing antimicrobial, antioxidant [18,19,30], hepatoprotective [31], antidiabetic [19], and notably anti-inflammatory activities [18,19,32]. The essential oil of *P. cablin* is particularly rich in sesquiterpenes [33,34], including patchouli alcohol [17,35,36], α-bulnesene [17,34], and pogostol, which are bioactive compounds known for their therapeutic effects [37]. Among these, patchouli alcohol has been extensively studied for its anti-inflammatory properties, notably through inhibition of nitric oxide (NO) production [38,39] and suppression of the NF-κB signaling pathway in lipopolysaccharide (LPS)-stimulated macrophages [40–42].

Moreover, *in vitro* studies have demonstrated that extracts of *P. cablin* can effectively inhibit pro-inflammatory cytokines [19,43] and reduce oxidative stress markers [19,44]. According to Xian *et al*. [45], patchouli alcohol markedly suppressed TNF-α and IL-6 levels in LPS-induced RAW264.7 macrophages. Consistently, aqueous and ethanolic extracts of *P. cablin* have demonstrated anti-inflammatory effects by reducing edema and leukocyte infiltration *in vivo*, aligning with its ethnomedicinal applications [46,47].

Despite these promising findings, most research to date has primarily focused on the essential oil components of *P. cablin* and their *in vitro* bioactivities [19,45]. There remains a significant knowledge gap regarding the *in vivo* anti-inflammatory potential of ethanolic extracts, especially those derived from geographically distinct populations such as North Konawe, Southeast Sulawesi, Indonesia. Given that phytochemical composition can vary substantially with environmental factors, including soil type, altitude, and climate, as well as extraction methods [14], it is crucial to investigate the unique metabolite profiles and pharmacological efficacy of locally sourced *P. cablin*.

To date, no comprehensive study has integrated GC-MS-based metabolite profiling with *in vivo* anti-inflammatory evaluation of the ethanolic extract of *P. cablin* collected from North Konawe. Moreover, previous research has not simultaneously examined the extract's effects on the expression of key inflammatory biomarkers such as COX-2, IL-1β, IL-6, and TNF-α in an *in vivo* setting.

Therefore, this study aims to evaluate the anti-inflammatory and antinociceptive activities of the ethanolic extract of *P. cablin* from Southeast Sulawesi using GC-MS-based metabolite profiling and *in vivo* biomarker analysis. By examining a broader range of bioactive compounds beyond essential oils and correlating them with pharmacological effects and inflammatory biomarkers, this study offers novel mechanistic and chemotaxonomic insights. The *P. cablin* used was collected from North Konawe, a region with unique agroecological characteristics that may influence its metabolite profile and therapeutic potential.

2. MATERIAL AND METHODS

2.1 Materials

The materials used in this study included dried leaves of *P. cablin* (North Konawe chemotype) and analytical-grade reagents. Ethanol 96% (Bratachem®, Indonesia) was used as the extraction solvent, sodium carboxymethyl cellulose (Na-CMC) 0.5% was obtained from Sigma-Aldrich (USA), diclofenac sodium, EDTA, sodium citrate, and heparin. All solvents and reagents used were of analytical grade and used without further purification.

2.2 Collection, determination, and preparation of *P. cablin* leaves

Fresh *P. cablin* leaves were collected manually using clean pruning tools. The samples were then sorted to remove any damaged or contaminated material, thoroughly washed with running water, and air-dried. After drying, the leaves were cut into small pieces to facilitate the extraction process.

2.3 Extraction

Extraction was conducted using the maceration method with ethanol as the solvent.

Ethanol was chosen due to its efficiency in extracting a broad range of phytochemicals, including both polar and moderately non-polar compounds such as flavonoids, alkaloids, and phenolics, which are known for their anti-inflammatory activity. Moreover, ethanol is widely used in phytochemical research for its low toxicity and ability to preserve bioactive constituents. *P. cablin* samples were soaked in the solvent for 3 × 24 hours at room temperature. Subsequently, the ethanolic extract was filtered through filter paper, and the solvent was evaporated under reduced pressure using a rotary evaporator at 50°C to obtain a crude extract.

2.4 Phytochemical profiling by GC-MS

The ethanolic extract of *P. cablin* was analyzed using gas chromatography–mass spectrometry (GC-MS) to characterize its volatile constituents. A total of 1 g of the dried extract was dissolved in 2 ml of distilled water and homogenized using a shaker for 10 minutes. Then, 10 ml of ethyl acetate and 10 g of anhydrous sodium sulfate (Merck®, Germany) were added to eliminate water content. The mixture was sonicated for 10 minutes to enhance the extraction of bioactive compounds. After sonication, the sample was filtered through Whatman filter paper to remove solid residues. The filtrate was evaporated under ultrasonic conditions until all ethyl acetate solvent was removed. The resulting residue was reconstituted in 1 ml of *n*-hexane (Merck®, Germany) and transferred into a tightly sealed GC vial. GC-MS analysis was performed using an Agilent 8890 GC system coupled with a Xevo® TQ-GC mass spectrometer (UK). A DB-5MS column (30 m × 250 µm × 0.25 µm) was used with helium as the carrier gas at a constant flow rate of 1.0 ml/min. The oven temperature program was as follows: initially 110°C (held for 3.5 min), ramped at 10°C/min to 200°C (held for 1 min), followed by a second ramp of 5°C/min to 280°C (held for 12 minutes), with a total runtime of 41.5 minutes. The injector was set to splitless mode at 280°C, and 1 µl of the sample was injected. The mass spectrometer operated in electron ionization (EI+) mode, scanning a mass range of 50–500 m/z, with the ion source at 200°C and the transfer line at 250°C. Compound identification was carried out by comparing the mass spectra with those available in the NIST library (version 2011) [48]. No authentic standards were used, and retention indices were not determined.

2.5 Ethical approval

All experimental procedures involving animals were conducted in accordance with institutional guidelines and approved by the Institute of Research and Community Service, Universitas Halu Oleo, with ethical clearance number 3343/UN29.20.1.2/PG/2024.

2.6 *In vivo* anti-inflammatory assay

2.6.1. Experimental animals

18 male BALB-C mice (aged 8–10 weeks, body weight 20–30 g) were obtained from a certified laboratory animal supplier. Mice were housed under standard conditions (12 hours light/dark cycle, 22°C ± 2°C, relative humidity 60%–70%) with ad libitum access to standard food and water. All animals were acclimatized for at least 7 days before experimentation.

2.6.2. Inflammation induction and evaluation

Acute inflammation was induced by the topical application of 20 µl xylene to the anterior and posterior surfaces of the right ear of each mouse. Fifteen minutes after xylene application, mice were orally administered their respective treatments: 0.5% Na-CMC (negative control), diclofenac sodium 25 mg/kg BW (positive control), ethanolic extract of *Pogostemon cablin* (EEPC) at doses of 25, 50, and 100 mg/kg BW. A sham group received no xylene or treatment. The thickness of the right ear was measured using a digital ultrasonic thickness gauge at 15, 30, and 45 minutes after xylene application. The percentage of inflammation was calculated using the formula:

$$\% \text{ Inflammatory} = [(D_t - D_0)/ D_0] \times 100 \quad (1)$$

where D_t is the ear thickness at each time point and D_0 is the baseline thickness before induction. The percentage of inhibition was calculated as follows:

$$\% \text{ Inhibition} = [(a - b)/a] \times 100 \quad (2)$$

where a is the % inflammation in the naïve group and b is the % inflammation in the treatment group. The doses of 25, 50, and 100 mg/kg BW were selected based on preliminary studies and literature reporting the effective dose range of *P. cablin* extracts in similar pharmacological evaluations [49].

2.6.3. Determinations of cytokine levels

After the final ear thickness measurement at 45 minutes post-xylene induction, animals were sacrificed by cervical dislocation. Approximately 3 ml of blood was collected via

intracardiac puncture into EDTA-coated tubes. The collected blood was immediately centrifuged at 3000 rpm for 15 minutes to separate plasma. The plasma samples were then stored at −80°C until analysis. The concentration of TNF-α, IL-1β, and IL-6 was determined using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience®, Houston, TX, USA; Cat. No. E-EL-M0037, E-EL-M0039, and E-EL-M0046, respectively), according to the manufacturer's instructions [50]. In this experiment, the vehicle-treated group served as the negative control, and the diclofenac sodium-treated group was used as the positive control for cytokine inhibition.

2.7 *In vivo* antinociceptive assay

2.7.1. Experimental animals

18 male BALB-C mice (aged 8–10 weeks, body weight 20–30 g) were obtained from a certified laboratory animal supplier. Mice were housed under standard conditions (12 hours light/dark cycle, 22°C ± 2°C, relative humidity 60%–70%) with ad libitum access to standard food and water. All animals were acclimatized for at least 7 days before experimentation.

2.7.2. Induction and assessment of nociceptive response

Mice were fasted for 18 hours before the experiment but had free access to water. Animals were randomly divided into six groups (n = 3 per group): normal control, negative control (Na-CMC 0.5%), positive control (diclofenac sodium 50 mg/kg BW), and three test groups receiving *P. cablin* extract at doses of 25, 50, and 100 mg/kg BW orally. One hour after treatment, each mouse received a subplantar injection of 50 µl of 5% formalin into the left hind paw. Nociceptive behavior was observed for 60 minutes, and the time spent licking the injected paw was recorded in the early phase (0–5 minutes) and late phase (15–30 minutes). The percentage of inhibition was calculated compared to the negative control group [51].

$$\%\text{Protection} = \text{Rt (negative control} - \text{test substance)} / \text{Rt (negative control)} \times 100 \quad (3)$$

where Rt is the response time.

2.7.3. Measurement of cytokine and COX-2 levels

At the third hour after formalin injection, mice were euthanized, and blood samples were collected via cardiac puncture. The blood was placed in EDTA tubes and centrifuged at 2,500 rpm for 15 minutes to separate plasma. The plasma was stored at –80°C until further analysis. The concentrations of TNF-α, IL-1β, IL-6, and COX-2 in plasma were measured using a colorimetric commercial ELISA kit (Elabscience®, Houston, TX) according to the manufacturer's instructions [47]. The vehicle-treated group served as the negative control, and the diclofenac sodium-treated group was used as the positive control in the cytokine and COX-2 inhibition analysis.

2.8 Data analysis

The data obtained from all *in vivo* experiments, including xylene-induced ear edema, formalin-induced nociceptive response, and COX-2 levels, were analyzed using IBM SPSS Statistics version 22. Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A p-value < 0.05 was considered statistically significant. All results are presented as mean ± SD.

3. RESULTS AND DISCUSSION

3.1 GC-MS analysis of *P. cablin* essential oil from North Konawe

The GC–MS analysis provided detailed insights into the chemical composition of the ethanolic extract of *P. cablin* leaves collected from North Konawe, identifying 18 volatile constituents (Table 1), with the corresponding chromatogram presented in Figure 1. The major compound was patchouli alcohol, followed by **α**-guaiene, seychellene, intermedeol, neointermedeol, and β-caryophyllene derivatives. These sesquiterpenes are widely recognized for their anti-inflammatory, antioxidant, and antimicrobial activities (Table 2) [17,19,43]. Patchouli alcohol, in particular, is a well-established bioactive marker of ***P. cablin***, recognized for its anti-inflammatory and antiarthritic effects via inhibition of NO production and modulation of NF-κB signaling [35,39,40,42]. The presence of **α**-guaiene, seychellene, intermedeol, and β-caryophyllene further supports the anti-inflammatory potential of the extract, possibly through synergistic mechanisms among sesquiterpene constituents [34,37]. Additionally, eugenol, known for its analgesic, anti-inflammatory, and antioxidant properties [38], contributes to the extract's therapeutic relevance. Compounds with limited or no established pharmacological relevance were not emphasized in this discussion to maintain focus on the major bioactive constituents. Generally, the GC-MS profile reveals a phytochemical composition rich in pharmacologically active sesquiterpenes, supporting the potential of ***P. cablin*** from Southeast Sulawesi as a promising source of anti-inflammatory agents.

Based on the chromatographic profile, patchouli alcohol was identified as the predominant constituent, accompanied by **α**-guaiene, seychellene, intermedeol, neointermedeol, and β-caryophyllene, which is consistent with the patchoulol-type chemotype. Compared with other Indonesian regions, the North Konawe sample differs from ***P. cablin*** from Kolaka, Southeast Sulawesi, which contains lower patchouli alcohol but relatively higher δ- and **α**-guaiene, while Aceh oils typically show patchouli alcohol levels of 28.9%–42.8% with notable regional variation in guaiene and aciphyllene. International comparisons further reveal diversity: Chinese chemotypes include both patchoulol- and pogostone-types, Indian cultivars tend to yield high patchouli alcohol (~34%), whereas Vietnamese oils are more balanced, with patchouli alcohol (~32%) alongside **α**-guaiene and **α**-bulnesene [15,19–21]. These divergences are attributed to environmental, ecological, and agronomic factors [22–24], suggesting that the North Konawe sample represents a distinct patchoulol-type profile shaped by its local terroir.

3.2 *In vivo* anti-inflammatory activity of *P. cablin* ethanolic extract

To evaluate the anti-inflammatory potential of ***P. cablin***, the xylene-induced ear edema model in mice was

Table 1. Compounds identified in the ethanolic extract of *Pogostemon cablin* leaves from North Konawe by GC–MS analysis.

No	Retention time	Molecular weight (MW)	Match	Reverse match	Probability (%)	Compounds name	Biological activity
1.	4.417	106	678	681	12.9	o-Xylene (C_8H_{10})	Antibacterial
2.	10.864	338	614	623	10.1	Uvidin C, diacetate ($C_{19}H_{30}O_5$)	Antiinflammation, antioxidant
3.	10.864	164	636	636	13.3	Eugenol ($C_{10}H_{12}O_2$)	Antiinflammation, analgesic, anticancer, antioxidant
4.	13.092	204	703	706	5.74	α-Guaiene ($C_{15}H_{24}$)	Antiinflammation, antioxidant, antimicrobial
5.	13.648	204	686	687	11.2	Seychellene ($C_{15}H_{24}$)	Antimicrobial, antioxidant
6.	18.217	228	617	650	11.8	5-Bromoadamantan-2-one ($C_{10}H_{13}BrO$)	Anticancer
7.	21.042	222	662	675	7.91	Neointermedeol ($C_{15}H_{26}O$)	Antiinflammation, Antimicrobial
8.	21.042	222	657	672	6.85	Intermedeol ($C_{15}H_{26}O$)	Antiinflammation, antioxidant
9.	21.283	229	549	570	15.2	5-Methyl-1,2,4,5-tetrahydrospiro[benzo[c] azepine-3,1'-cyclohexane] ($C_{16}H_{23}N$)	Antidepressant, anticancer
10.	21.283	214	545	591	13.5	4H-1,2,4-Triazole, 4-(2,4,5-trimethylbenzylidenamino)- ($C_{12}H_{14}N_4$)	Antifungal, antimicrobial
11.	22.605	222	623	623	16.1	Patchouli alcohol ($C_{15}H_{26}O$)	Antiinflammation, antiarthritic, anticancer
12.	23.044	206	486	511	10.2	4-(2,4,4-Trimethyl-bicyclo[4.1.0]hept-2-en-3-yl)-butan-2-one ($C_{14}H_{22}O$)	Antioxidant
13.	24.235	368	505	611	19.8	Phenylphosphonic acid, dodecyl propyl ester ($C_{21}H_{37}O_3P$)	Antimicrobial
14.	24.619	372	646	657	4.43	i-Propyl 7,10,13,16,19-docosapentaenoate ($C_{25}H_{40}O_2$)	Antiinflammation, antihyperlipidemic
15.	26.131	338	614	623	10.1	Uvidin C, diacetate ($C_{19}H_{30}O_5$)	Antiinflammation, antioxidant
16.	26.453	204	447	632	20.9	Hydratropic acid, p-(2-methylpropenyl) ($C_{13}H_{16}O_2$)	Antiinflammation, antioxidant, antimicrobial
17.	23.63	224	653	655	69.7	4-Hydroxy-6-methyl-3-(4-methylpentanoyl)-2H-pyran-2-one ($C_{12}H_{16}O_4$)	Antiinflammation, anticancer
18.	25.18	218	636	655	19.1	2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-3-(1-methylethylidene)- ($C_{15}H_{22}O$)	Antimicrobial, antiinflammation

employed. After xylene induction, the mice were treated with EEPC at doses of 25, 50, and 100 mg/kg BW. Na-CMC (0.5%) was used as the negative control, while diclofenac sodium was the positive control. Ear edema was induced topically using xylene, and ear thickness was measured at 0 (pre-induction), 15, 30, and 45 minutes post-induction (Fig. 2).

As illustrated in Figure 2, the negative control group showed a time-dependent increase in ear thickness, peaking at 45 minutes. EEPC-treated groups significantly reduced ear edema compared to the negative control, with the 100 mg/kg dose exhibiting the strongest effect, comparable to diclofenac sodium ($p = 0.195$).

As illustrated in Figure 3, diclofenac sodium exhibited the highest edema inhibition (69.83% ± 1.83%). The EEPC 100 mg/kg group showed a comparable inhibition (69.28% ± 0.32%; $p = 1.000$), indicating no significant difference. The 50 and 25 mg/kg groups showed lower inhibition percentages of 60.82% ± 6.18% ($p = 0.062$) and 53.14% ± 4.42% ($p = 0.001$), respectively, suggesting a dose-dependent anti-inflammatory effect.

The development of ear edema is primarily triggered by the rapid release of inflammatory mediators, including histamine, serotonin, bradykinin, and prostaglandins, which contribute to enhanced vascular permeability and local plasma extravasation, leading to tissue swelling [52,53]. The anti-inflammatory effect observed in the ethanolic extract of *P. cablin* is likely attributed to its rich phytochemical composition, including patchouli alcohol, flavonoids, terpenoids, and phenolic compounds [20–21,29]. These bioactive constituents have been previously reported to exhibit anti-inflammatory properties by modulating the production of pro-inflammatory mediators and downregulating key pathways such as COX [54–56] and NF-κB signaling [40]. Specifically, patchouli alcohol has been shown to suppress the expression of TNF-**α** and IL-6 by inhibiting NF-κB activation and IκB-**α** phosphorylation in LPS-induced macrophages [42].

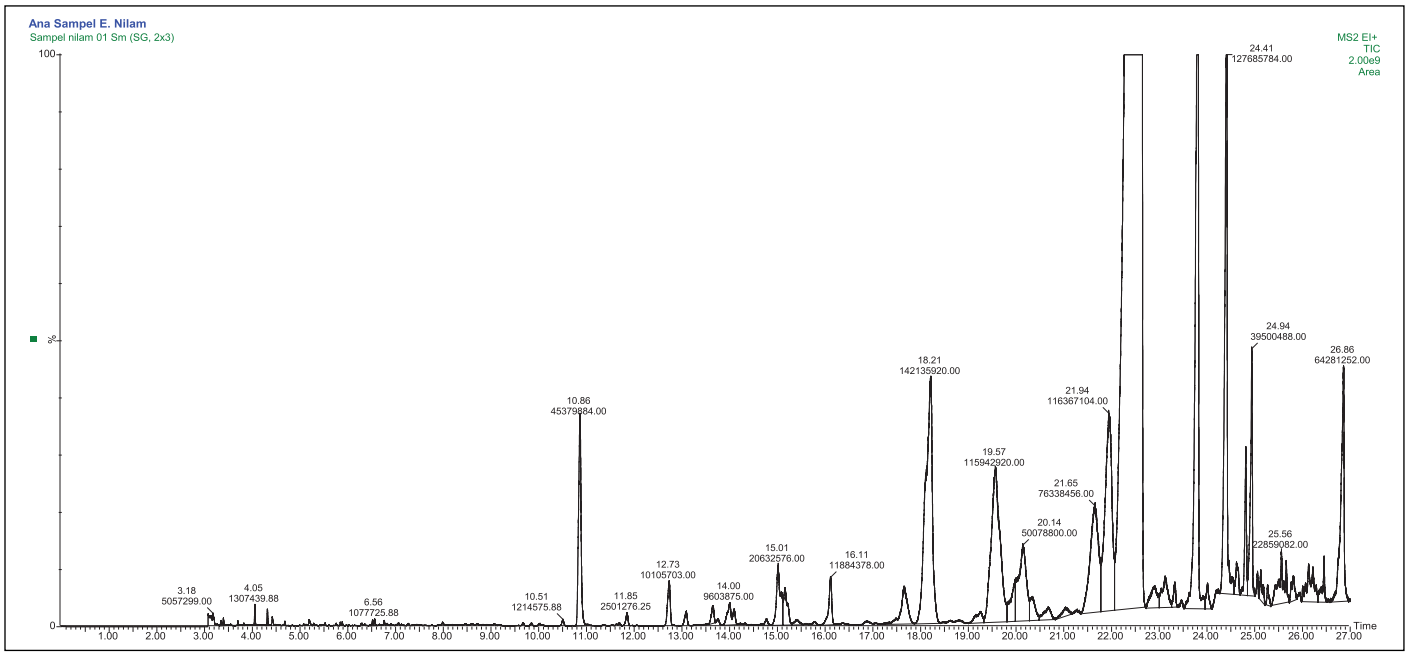

Figure 1. GC–MS chromatogram of ethanolic extract of ***Pogostemon cablin*** (Blanco) Benth leaves showing identified major constituents, including patchouli alcohol, **α**-guaiene, seychellene, and **α**-patchoulene. Compounds were identified based on retention time and mass spectral matching using the NIST library. Peak intensities are expressed in relative abundance (%).

Table 2. Summary of the major volatile metabolites identified from ***Pogostemon cablin*** ethanolic leaf extract, categorized by chemical class, based on GC-MS analysis.

Chemical class	Identified compounds
Sesquiterpenes	Patchouli alcohol, α-guaiene, seychellene, β-caryophyllene, intermedeol, neointermedeol
Phenolics	Eugenol
Fatty acid derivatives	Hydrastropic acid, uvidin C diacetate
Others	4-hydroxy-6-methyl-3-(4-methylpentanoyl)-2H-pyran-2-one

In general, anti-inflammatory agents may exert their effects through various mechanisms, including suppression of inflammatory cytokines (e.g., TNF-**α**, IL-1β, and IL-6) [19,43], inhibition of prostaglandin synthesis via COX-1/COX-2 inhibition [54,55], modulation of reactive oxygen species [57], or by downregulating transcription factors such as NF-κB [40]. The anti-inflammatory activity observed in EEPC-treated groups may involve one or more of these mechanisms.

These results confirm the dose-dependent anti-inflammatory effect of EEPC in an acute inflammation model. The comparable efficacy of the 100 mg/kg dose with diclofenac suggests that EEPC may serve as a promising alternative for managing early-stage inflammatory responses, likely through modulation of vascular permeability and mediator release.

3.3 Effect of *Pogostemon cablin* ethanolic extract on pro-inflammatory cytokine levels

To explore the molecular mechanism behind the anti-inflammatory effect observed, we analyzed the plasma levels of pro-inflammatory cytokines (TNF-**α**, IL-1β, and IL-6). EEPC treatment significantly attenuated these cytokines in a dose-dependent manner, with the 100 mg/kg dose showing comparable efficacy to diclofenac.

As shown in Figure 4, mice in the negative control group exhibited significantly elevated levels of TNF-**α**, IL-1β, and IL-6. Treatment with diclofenac sodium (25 mg/kg) markedly reduced the levels of these cytokines compared to the negative control group ($p = 0.000$). Similarly, all EEPC-treated groups (25, 50, and 100 mg/kg) significantly attenuated TNF-**α**, IL-1β, and IL-6 levels in a dose-dependent manner ($p = 0.000$). Notably, the 100 mg/kg EEPC group demonstrated cytokine inhibition that was statistically comparable to that of the diclofenac-treated group ($p = 0.053$).

The suppression of TNF-**α**, IL-1β, and IL-6 levels suggests that EEPC may exert its anti-inflammatory effects through the inhibition of early-phase inflammatory signaling. These cytokines play pivotal roles in recruiting immune cells, increasing vascular permeability, and promoting the synthesis of other inflammatory mediators such as prostaglandins and leukotrienes. Their inhibition could therefore explain the reduction in ear swelling observed in the edema model.

These findings are consistent with previous studies reporting the anti-inflammatory properties of ***P. cablin***, particularly due to its major bioactive constituents such as patchouli alcohol, flavonoids, terpenoids, tannins, and alkaloids. Patchouli alcohol, for instance, has been reported to inhibit NF-κB activation [40], reduce COX-2 expression [54,55], and modulate MAPK signaling pathways mechanisms [32] that collectively downregulate the production of pro-inflammatory cytokines and enzymes [19,43]. These compounds may work

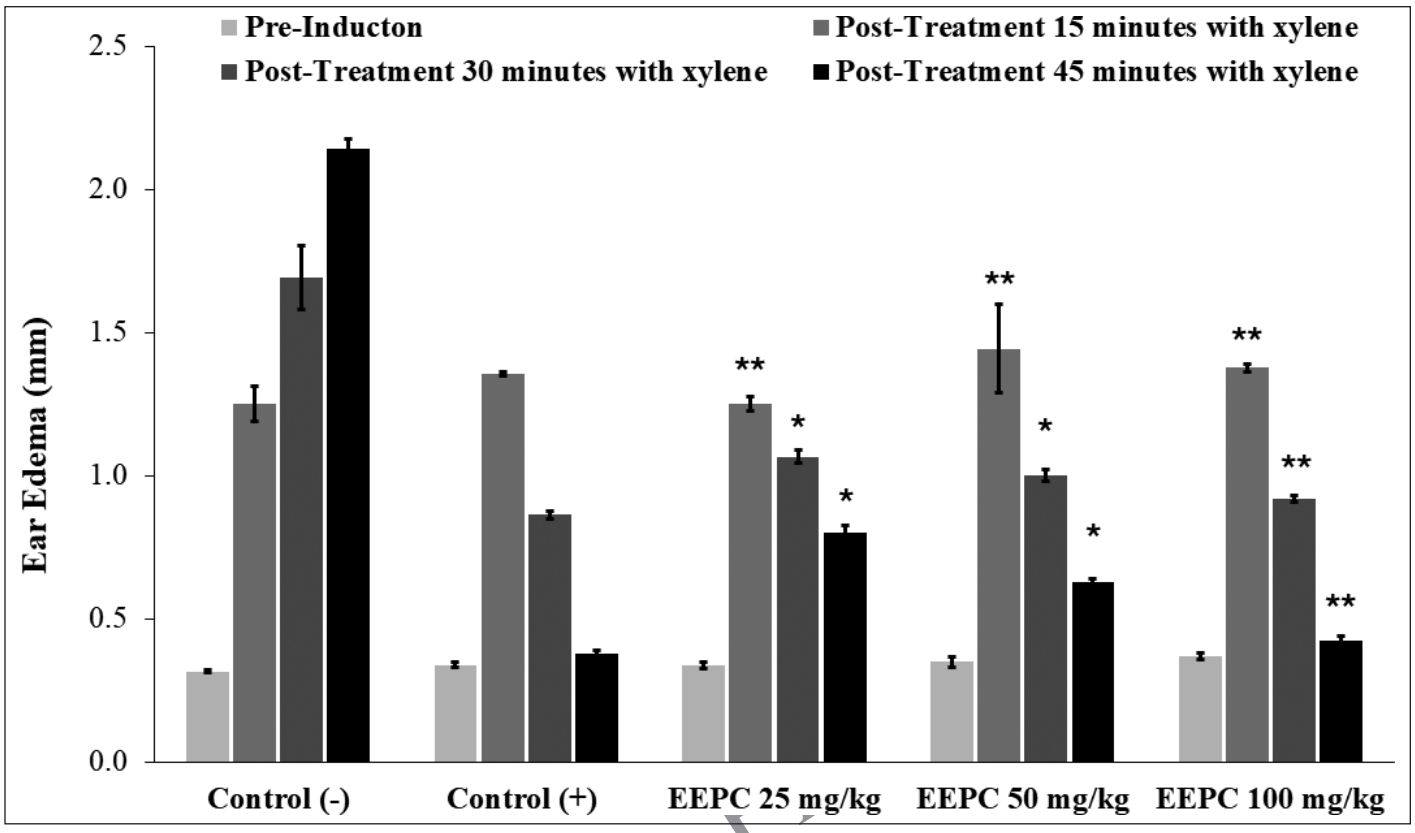

Figure 2. Effect of ethanolic extract of ***Pogostemon cablin*** (EEPC) on xylene-induced ear edema in mice. EEPC significantly reduced ear swelling compared to the control group. Data are represent mean ± SD (***n*** = 3). *Significantly different from diclofenac sodium (***p*** < 0.05); **Not significantly different (***p*** > 0.05).

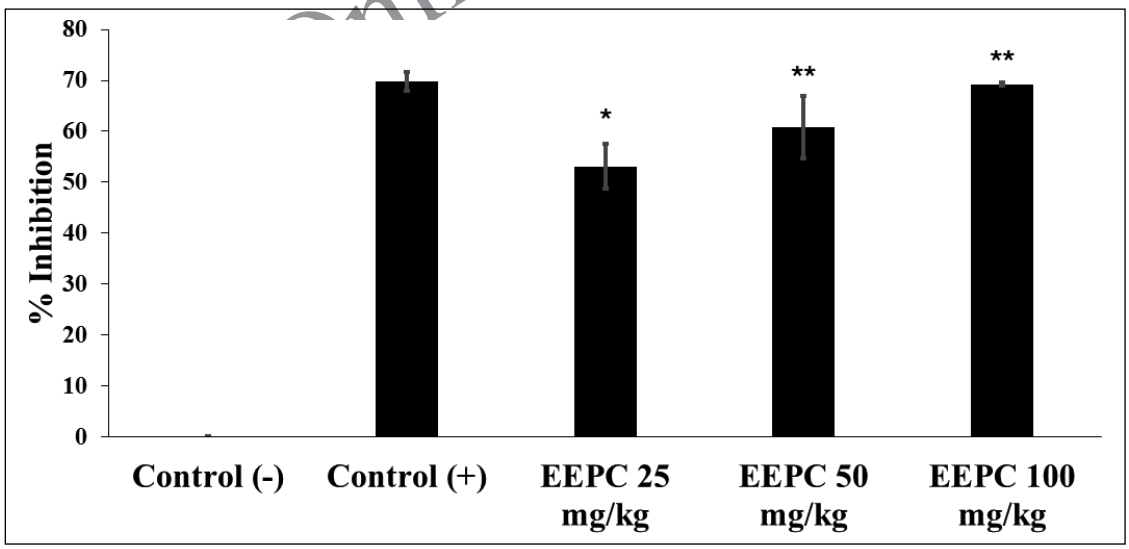

Figure 3. Percentage inhibition by ethanolic extract of ***Pogostemon cablin*** (EEPC) on xylene-induced ear inflammation in mice. EEPC demonstrated dose-dependent anti-inflammatory activity. Data is presented as mean ± SD (***n*** = 3). *Significantly different from diclofenac sodium (***p*** < 0.05); **Not significantly different (***p*** > 0.05).

synergistically to reduce cytokine production and alleviate tissue inflammation. The significant inhibition of TNF-**α**, IL-1β, and IL-6 levels reinforces the potential of ***P. cablin*** as a natural anti-inflammatory agent. Its ability to modulate key inflammatory mediators indicates a promising therapeutic value in managing inflammation-related conditions. However, further studies are warranted to isolate specific active compounds and elucidate their molecular targets within the inflammatory cascade.

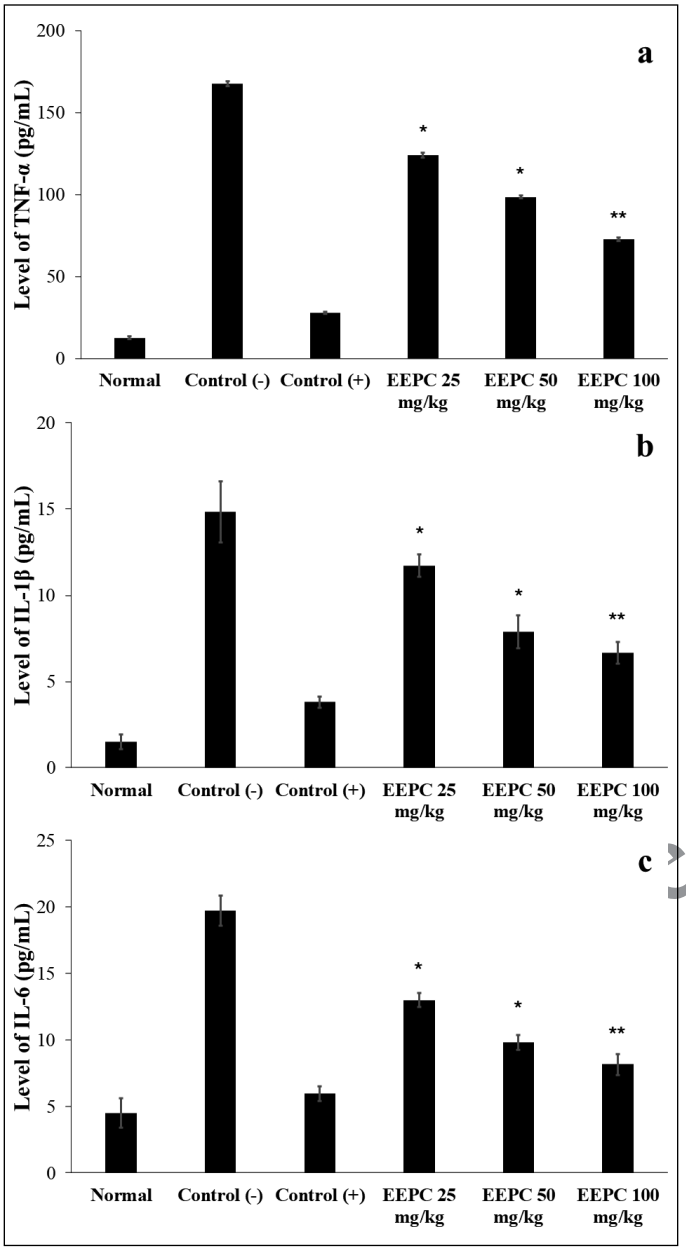

Figure 4. Plasma levels of pro-inflammatory cytokines in mice after treatment with ethanolic extract of ***Pogostemon cablin*** (EEPC): (a) TNF-**α**, (b) IL-1β, and (c) IL-6. Data are presented as mean ± SD (***n*** = 3). *Significantly different from diclofenac sodium (***p*** < 0.05); **Not significantly different (***p*** > 0.05).

3.4 Nociceptive activity of *P. cablin* ethanolic extract

The EEPC was evaluated for its antinociceptive effect using the formalin-induced pain model. As shown in Table 3, the negative control group exhibited the longest licking durations in both early (0–5 minutes) and late (15–30 minutes) phases, indicating high nociceptive activity due to the absence of analgesic treatment. In contrast, EEPC-treated groups showed a dose-dependent reduction in nociceptive response, with the 100 mg/kg group demonstrating the shortest licking duration. These findings align with Lu ***et al***. [58], who demonstrated that ***P. cablin*** extract exhibits significant antinociceptive activity in various pain models, particularly at higher doses. This activity is likely attributed to its major constituents, such as pachypodol, a methoxylated flavonoid known for its peripheral and central analgesic effects. Pachypodol may exert its antinociceptive properties by modulating opioid pathways, inhibiting COX activity, and suppressing pro-inflammatory mediators such as prostaglandins and cytokines. Additionally, it may interfere with key signaling pathways, including NF-κB and MAPK, which are involved in pain perception and inflammation [18,19,59].

The highest percentage of protection was observed in the 100 mg/kg group, reaching 66.32% ± 1.95% (early phase) and 67.49% ± 2.66% (late phase), which was close to the positive control with 73.69% ± 3.64% and 76.37% ± 2.57%, respectively (Fig. 5). The greater protection in the late phase reflects involvement of inflammatory mediators like prostaglandins and cytokines, where peripherally acting drugs such as NSAIDs are more effective.

The antinociceptive effect of EEPC is likely associated with its phytochemical constituents, including alkaloids, flavonoids, saponins, and tannins. Flavonoids in particular may act as COX-2 and PGE2 inhibitors, mimicking NSAIDs in reducing inflammatory pain. This inhibition suppresses the arachidonic acid pathway and limits prostaglandin synthesis, thereby alleviating pain and inflammation [56,60].

The 100 mg/kg dose of EEPC demonstrated an effect comparable to the positive control group, whereas the 25 and 50 mg/kg doses provided moderate protection, significantly reducing nociceptive response compared to the untreated control. Thus, EEPC at 100 mg/kg BW exhibited a comparable analgesic effect to diclofenac sodium, reinforcing its potential as a natural pain-relieving agent. These results support the potential of ***P. cablin*** ethanolic extract as an effective natural analgesic agent, particularly at a dose of 100 mg/kg BW, with effects comparable to diclofenac sodium in the formalin-induced pain model.

Table 3. Nociceptive activity of ***Pogostemon cablin*** ethanolic extract in the formalin-induced pain model in mice (mean ± SD, ***n*** = 3)

Sample	Early phase (0–5 min) response time (s)	Protection early (%)	Late phase (15–30 min) response time (s)	Protection late (%)
Control (−)	210.00 ± 10.00	0.00 ± 0.00	96.00 ± 3.61	0.00 ± 0.00
Control (+)	55.00 ± 5.00	73.69 ± 3.64	22.00 ± 2.00	76.37 ± 2.57
EEPC 100 mg/kg	70.67 ± 4.04	66.32 ± 1.95	29.67 ± 2.08	67.49 ± 2.66
EEPC 50 mg/kg	87.67 ± 2.52	58.17 ± 2.76	36.67 ± 3.06	59.15 ± 1.87
EEPC 25 mg/kg	101.00 ± 7.94	51.92 ± 2.51	43.33 ± 4.16	52.79 ± 3.84

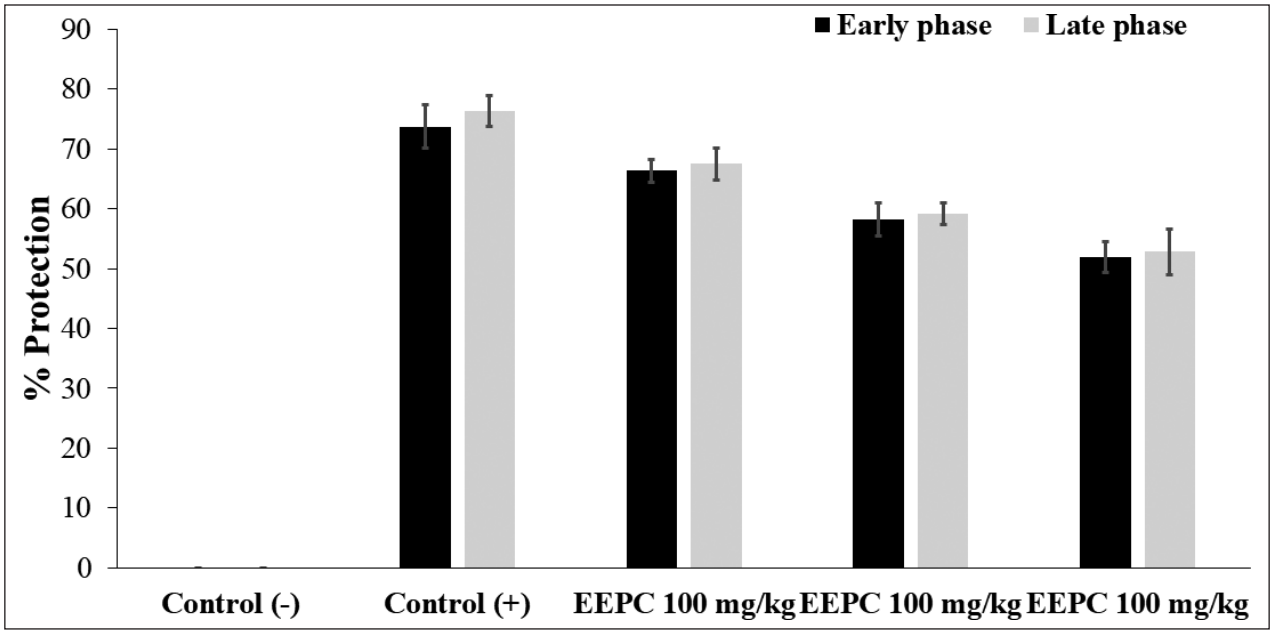

Figure 5. Percentage of nociceptive inhibition by ethanolic extract of *Pogostemon cablin* (EEPC) during the early (neurogenic) and late (inflammatory) phases of formalin-induced nociceptive response in mice. Data are presented as mean ± SD (n = 3).

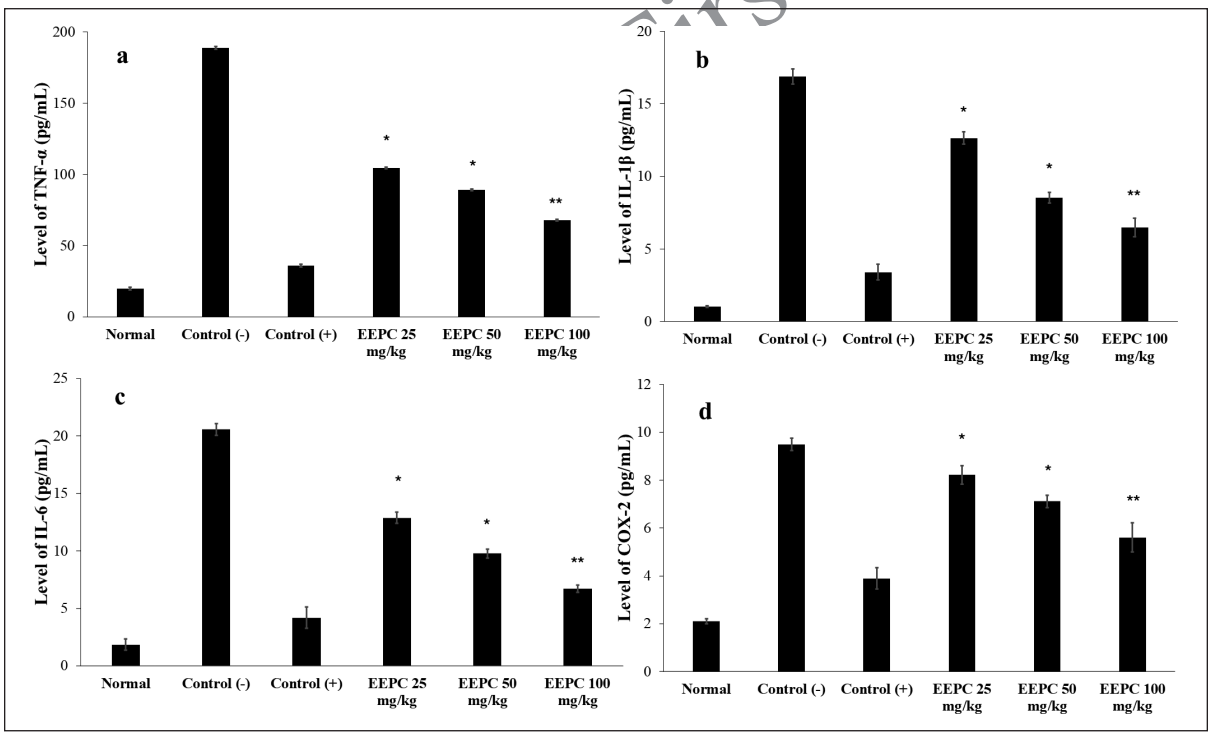

Figure 6. Levels of pro-inflammatory cytokines and COX-2 in mice plasma after treatment with ethanolic extract of *Pogostemon cablin* (EEPC): (a) TNF-α, (b) IL-1β, (c) IL-6, and (d) COX-2. Data are presented as mean ± SD (n = 3). *Significantly different from diclofenac sodium ($p < 0.05$); **Not significantly different ($p > 0.05$).

3.5 Cytokine levels and COX-2 expression in the nociceptive model

The plasma concentrations of TNF-α, IL-1β, IL-6, and COX-2 following nociceptive induction and treatment with EEPC are shown in Figure 6. The negative control exhibited elevated levels of TNF-α, IL-1β, IL-6, and COX-2 compared to the normal control group (p = 0.000), indicating strong systemic inflammation due to nociceptive stimulation.

All doses of EEPC produced a dose-dependent and statistically significant reduction in the levels of pro-inflammatory cytokines and COX-2 compared to the negative control group ($p = 0.000$). At 100 mg/kg, TNF-α was reduced to 67.86 ± 0.56 pg/ml, IL-1β to 6.28 ± 0.61 pg/ml, IL-6 to 6.80 ± 0.34 pg/ml, and COX-2 to 5.66 ± 0.73 pg/ml; these results were comparable to the positive control group ($p = 0.060$).

The marked reduction of TNF-α, IL-1β, and IL-6 levels supports the role of EEPC in modulating the inflammatory pathways that underlie nociceptive pain. These cytokines are known to sensitize peripheral nociceptors and amplify pain signaling, while COX-2 is a key enzyme in prostaglandin synthesis that enhances hyperalgesia. By attenuating these mediators, EEPC likely interferes with both peripheral and central components of the nociceptive cascade [40,45].

The phytoconstituents in *P. cablin*, such as patchouli alcohol and β-caryophyllene, may contribute to these effects via inhibition of NF-κB and MAPK signaling pathways or activation of cannabinoid type 2 receptors, both of which are implicated in cytokine suppression and COX-2 regulation [40,61]. These findings highlight the potential of *EEPC* as a natural antinociceptive agent through modulation of pro-inflammatory cytokines and COX-2 expression.

However, this study has some limitations. Although the extract showed significant anti-inflammatory activity at the tested doses, formal acute or chronic toxicity studies were not conducted. The absence of such data limits the ability to fully evaluate the safety profile of the extract, especially under prolonged or repeated use. Future studies should focus on detailed toxicological evaluations to establish the long-term safety and therapeutic window of *P. cablin* extract.

4. CONCLUSION

This study confirms that *P. cablin* essential oil from North Konawe possesses significant anti-inflammatory and antinociceptive activities, as demonstrated by the suppression of COX-2, TNF-α, IL-1β, and IL-6 levels in a nociceptive mouse model. These pharmacological effects are supported by the presence of bioactive compounds identified through GC-MS analysis. The findings suggest that *P. cablin* essential oil has strong potential as a natural therapeutic agent for managing inflammation-related conditions. Furthermore, the unique agroclimatic characteristics of North Konawe may contribute to the plant's phytochemical richness, reinforcing the value of promoting locally derived medicinal resources. Future studies are warranted to explore its mechanisms in more detail and to develop standardized formulations for clinical use.

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6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

7. CONFLICT OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

8. ETHICAL APPROVALS

Ethical approvals details are given in the 'Materials and Methods' section.

9. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

10. PUBLISHER'S NOTE

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11. USE OF AI TOOLS

Tools from artificial intelligence was used to assist in the preparation of this manuscript. Grammarly (Grammarly Inc.) was used for grammar correction, language editing, and clarity improvement. The authors extensively examined, validated, and revised every output produced by these instruments to guarantee precision, uniqueness, and conformity to scholarly standards. Data analysis and scientific interpretation were done without the assistance of AI techniques.

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