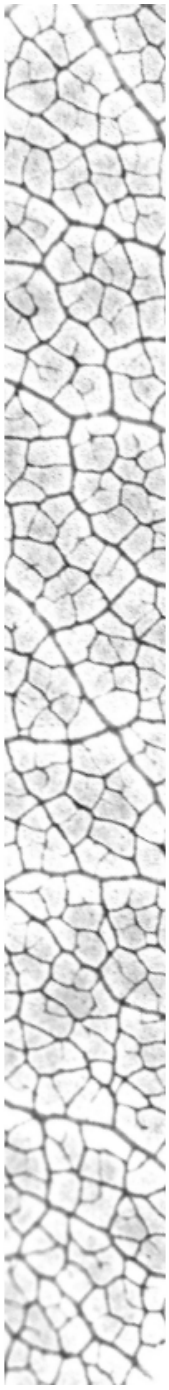

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Anti-inflammatory activities of *Curcuma aeruginosa* with membrane stabilization and carrageenan-induced paw oedema test

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Abstract
Although inflammation is a normal bodily response to injury, a prolonged inflammatory response can be detrimental for patients. To avoid the deleterious effects associated with prolonged inflammation, anti-inflammatory agents are often utilized, which can have many side effects. *Curcuma aeruginosa* Roxb., known locally as *temu ireng*, belongs to the family *Zingiberaceae* and is a potential natural alternative to existing anti-inflammatory agents, as this plant is used in traditional medicines to treat health problems caused by inflammation. This research aimed to identify natural alternatives to existing anti-inflammatory agents, and potential compounds were examined for *in vitro* anti-inflammatory activity using an erythrocyte membrane stabilization test. In addition, *in vivo* anti-inflammatory activity was measured in mice using a carrageenan-induced paw oedema method, followed by the measurement with a plethysmometer. The evaluation of erythrocyte membrane stabilization activity showed that the EC_{50} value for the positive control, indomethacin (26.4 ± 2.9 mg/mL) was lower than that for *C. aeruginosa* (47.8 ± 1.6 mg/mL). The results of the carrageenan-induced paw oedema method returned significant area under the curve AUC values for 100 mg/kg *C. aeruginosa* treatment (8.26 ± 0.50) compared with both the normal (10.01 ± 0.33) and drug control (6.50 ± 0.10) groups. Therefore, *C. aeruginosa* rhizome extracts have the potential for development as natural anti-inflammatory agents.

Keywords: *Curcuma aeruginosa*, anti-inflammatory, *in vitro*, *in vivo*

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INTRODUCTION

Inflammation is a normal bodily response to injury with four cardinal signs: calor, dolor, rubor, and tumor. Calor, or heat, and rubor, or redness, result from increased blood flow to the affected area, tumor, or bruise, is the result of vascular permeability, and dolor, or pain, is triggered by nerve fiber stimulation (Bellik et al. 2013). Inflammation affects enzyme activities, mediator release, fluid discharge, cell movements, tissue disintegration, and repair processes (Padmanabhan and Jangle 2012). Acute inflammation can be induced by various causes and is identified by the fast response at the injury site. Chronic inflammation can develop after acute inflammation and lasts several times as long as acute inflammatory processes (Souza et al. 2012). Although inflammation is a normal process, prolonged inflammatory responses can be detrimental to patients (Goodman et al. 2010). Anti-inflammatory agents are often used to counter prolonged inflammation, but many anti-inflammatory agents have been correlated with side effects and few are side-effect-free (Pountos et al. 2011). Gastrointestinal disorders are frequently associated with anti-inflammatory drug use, and many anti-inflammatory agents have been associated with increased risks of blood vessel occlusions due to blood clots (Siew and Francis 2010).

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Therefore, the search for ethnomedicinal plants with anti-inflammatory activities has become important. One significant species that has been associated with anti-inflammatory agents is *Curcuma longa* (turmeric), from the *Zingiberaceae* family. Studies have shown that *C. longa* has been used as a traditional medication for the treatment of inflammatory diseases. The rhizome of *C. longa* contains active compounds, including curcumin (Anilkumar 2010).

The genus *Curcuma* includes approximately 80 species, which are distributed throughout China, South Asia, and Southeast Asia. Indonesia contains a large diversity of *Curcuma* species. *C. longa* is the most common species used in traditional medicines in Indonesia. Relatively few studies have examined this particular species of *Curcuma*, although anti-inflammatory research has been performed using other *Curcuma* species (Kumar et al. 2009). Several *Curcuma* species have been used as herbal medicines in Indonesia, including *Curcuma aeruginosa* Roxb. (Subositi and Wahyono 2019). C*. aeruginosa* Roxb. is known by the local name *temu ireng* (Nurcholis et al. 2012). The rhizome of *C. aeruginosa* has been used in traditional medicines to treat asthma due to its anti-inflammatory effects (Paramita et al. 2018). Curcumin is an active ingredient found in *C. aeruginosa.* Many pharmacological effects of curcumin have been shown, including anti-inflammatory activity (Nurcholis et al. 2016). This study aimed to examine the anti-inflammatory activity of *C. aeruginosa* extracts to confirm its potential anti-inflammatory use in the clinic.

MATERIALS AND METHODS

Plant Preparation

C. aeruginosa rhizomes were harvested from the Kutai Kartanegara District, East Kalimantan. The Department of Biology, Faculty of Mathematics and Natural Sciences, Mulawarman University has identified the rhizomes. This study was performed in the Pharmacology Laboratory of the Faculty of Medicine, Mulawarman University. The Medical and Health Research Ethics Commission, Faculty of Medicine, Mulawarman University (no. 72/KEPK-FK/V/2019) has approved all protocols in this study. All possible attempts have been made to reduce or eliminate the discomfort experienced by animals used in this study.

In the laboratory, the *C. aeruginosa* rhizomes were shredded and preserved, at 25°C, for 3 days. Then, they were crushed and placed in a glass bottle. The crushed rhizomes were immersed in absolute ethanol for 5 days. The mixture was shaken periodically, using an orbital shaker, and evaporated, using a rotary evaporator. Dried extracts were obtained and stored at 4°C.

In vitro Anti-inflammatory Test

Anti-inflammatory activity *in vitro* was studied using the method of stabilizing the erythrocyte membrane. At room temperature, blood samples were collected and centrifuged. After removed the supernatant and washed packed erythrocytes in normal saline. The membrane stabilization test was performed using indomethacin as the control. The assay mixtures consisted of sodium phosphate buffer, hyposaline sodium chloride, the erythrocyte suspension, standard drugs, and *C. aeruginosa* extracts. Final mixtures were brought to equal volumes with normal saline. The final mixtures were incubated at 56°C for 30 min in a water bath. The tube was centrifuged at 5000 rpm for ten minutes. Then, the absorbance was then measured at 560 nm with spectrophotometer (Omale and Okafor 2008, Oyedapo et al. 2010).

In vivo Anti-inflammatory Test

Anti-inflammatory activity *in vivo* was studied using the method of paw oedema induced by carrageenan, followed by a plethysmometer measurement. The method of paw oedema, as defined by Winter et al, was induced in rats. (Winter et al. 1962). Experimental animals were divided into the following 5 groups: (i) Group 1 was negative control; (ii) Group 2 was a positive control, treated with 10 mg/kg indomethacin; (iii) Groups 3, 4, and 5 received different doses of medicinal plant extracts (100, 200, and 400 mg/kg BW, respectively). Each group contained 5 rats. Carrageenan (0.1 ml) was subcutaneously injected into the left paw of each rat. After the injection, the volume of paw oedema was evaluated using a plethysmometer. The measurement was repeated 1, 2, 3, 4, 5, and 6 hours after the carrageenan injection (Angel et al. 2013, Eddouks et al. 2012).

Data Analysis

Erythrocyte membrane stabilization activity is reported as the mean and SE (standard error), and the EC50 values were calculated. Differences between groups were evaluated using Student's t-test and were considered to be significant if $p < 0.05$. The mean and SE of the carrageenan-induced paw oedema measurements were calculated for each group, and then the area under the curve (AUC) values were calculated. Group comparisons were performed using an analysis of variance (ANOVA), followed by the Tukey post hoc test, and differences were considered to be significant if $p<0.05$. Statistical analyses were carried out using the SPSS software (version 16.0).

RESULTS AND DISCUSSION

In vitro Anti-inflammatory Activities

The erythrocyte membrane stabilization activity test showed that the EC_{50} value for indomethacin (26.4 ± 2.9 mg/mL), which was the positive control, was lower than that for *C. aeruginosa* (47.8 ± 1.6 mg/mL), as shown in **Tables 1** and **2**. A smaller EC_{50} value represents better anti-inflammatory activity. These results showed that

Table 1. Percentage membrane stabilization activity of indomethacin (drug control)

Dosage	% Membrane Stability			Mean
	1	2	3	
2.5	2.5	6.4	5.2	4.7 ± 2.0
5	17.4	19.5	29.5	22.1 ± 6.5
12.5	53.9	46.7	55.0	51.9 ± 4.5
25	76.7	79.1	80.4	78.7 ± 1.9
50	82.3	81.0	81.6	81.7 ± 0.6
100	87.7	85.3	84.5	85.9 ± 1.6
EC50	**27.9**	**28.2**	**23.0**	**26.4 ± 2.9**

Table 2. Percentage membrane stabilization activity of *C. aeruginosa* ethanol extract

Dosage	% Membrane Stability			Mean
	1	2	3	
2.5	2.5	4.5	3.6	3.5 ± 1.0
5	4.3	8.6	6.8	6.6 ± 2.1
12.5	15.6	20.4	16.9	17.6 ± 2.5
25	33.1	36.1	37.0	35.4 ± 2.1
50	66.1	70.7	70.0	68.9 ± 2.4
100	86.8	87.1	86.7	86.9 ± 0.2
EC50	**49.5**	**46.4**	**47.39**	**47.8 ± 1.6**

indomethacin had better anti-inflammatory activity than *C. aeruginosa*.

In vivo Anti-inflammatory Activities

The results of the carrageenan-induced paw oedema test are shown in **Table 3**. Comparisons between the effects of *C. aeruginosa* extracts and the negative and positive (indomethacin) controls are also shown in **Table 3**. *C. aeruginosa* extract treatments showed significant oedema reduction, with significant differences in the treatment groups ($p < 0.05$). Indomethacin, the positive control drug, also resulted in the significant inhibition of carrageenan-induced paw oedema.

Anti-inflammatory activity was observed for all three tested doses of the plant extract, based on the AUC. **Table 4** shows the paw oedema AUC values for *C. aeruginosa*. The lowest AUC value was observed for the 400 mg/kg BW dose of *C. aeruginosa* extract. Lower AUC values indicated reduced paw oedema. The Tukey post hoc test showed a significant effect of the 100 mg/kg *C. aeruginosa* treatment (8.26 ± 0.50) dosage compared with the negative control (10.01 ± 0.33) and indomethacin (6.50 ± 0.10). Oedema is an indication of inflammatory processes, and a reduced oedema volume following treatment with the plant extract indicates effective anti-inflammatory activity.

DISCUSSION

Among the *Zingiberaceae* family, which has been used in traditional medications for the treatment of disease, one effective anti-inflammatory agent that has been identified is *C. longa*. Many studies have described the use of *C. longa* or turmeric traditionally for the treatment of inflammatory problems. *C. longa* contains multiple chemical compounds, including curcumin, curcuminoid, dimethoxycurcumin, and bisdemethoxycurcumin (Lee et al. 2009). The anti-inflammatory effects of *C. longa* may be due to the inflammatory mediators inhibition (Dongre et al. 2015). *Curcuma* species used for herbal medicine in Indonesia include *C. longa*. *C. xanthorrhiza*, *C. zedoaria*, *C. aeruginosa*, *C. mangga*, *C. heyneana*, *C. rubescens*, and *C. caesia*. Turmeric was found in most species used in traditional medicinal in Indonesia (Subositi and Wahyono 2019). Few anti-inflammatory research studies have been performed in other *Curcuma* species (Kumar et al. 2009). *C. aeruginosa* is another *Curcuma* species that has been used as a traditional medicine to treat asthma, due to anti-inflammatory effects, with reports of tracheospasmolytic activity in an animal model (Paramita et al. 2018). This is the first study to explore the *in vitro* and *in vivo* anti-inflammatory activities of *C. aeruginosa*.

C. aeruginosa is known as *temu ireng* in Indonesia, and pink and blue ginger in English (Nurcholis et al. 2012, Simoh and Zainal 2015). The colour of fresh *C. aeruginosa* rhizome can be greenish-blue, with ginger-like aroma (Srivilai et al. 2011). *C. aeruginosa* has been used as an herbal medicine in Asia for the treatment of gastrointestinal and uterine disorders and parasitic and fungal infections. The pharmacological activities of *C. aeruginosa* include anti-androgenic, anti-microbial, antioxidant, anti-nociceptive, anti-pyretic, and anti-inflammatory activities (Theanphong et al. 2015). Sesquiterpenes have been identified as the primary chemical compounds in *C. aeruginosa*. The sesquiterpenes isolated from *C. aeruginosa* are germacrone, dehydrocurdione, zedoarone,

Table 4. The average AUC of carrageenan-induced paw edema inhibition after the administration of *C. aeruginosa* extracts

Group	AUC ± SE
Control	10.01 ± 0.33
Indomethacin	6.50 ± 0.10[a]
CA-I	8.26 ± 0.50[a,b]
CA-II	7.93 ± 0.44[a]
CA-III	7.76 ± 0.31[a]

Note: ANOVA significant $p<0.05$; CA-I = *C. aeruginosa* 100 mg/kg; CA-II = *C. aeruginosa* 200 mg/kg; CA-III = *C. aeruginosa* 400 mg/kg
Tukey post hoc test significant $p<0.05$ compared to control[a], and indomethacin[b]

Table 3. Average of carrageenan-induced paw edema inhibition after the administration of *C. aeruginosa* extracts

Group	Average inhibition (mm3) ± SE per-hour						
	H0	H1	H2	H3	H4	H5	H6
Control	1.44 ± 0.09	1.54 ± 0.09	1.30 ± 0.10	1.68 ± 0.13	2.09 ± 0.27[c]	1.80 ± 0.10	1.78 ± 0.21
IND	0.98 ± 0.05	0.92 ± 0.01	0.87 ± 0.15	1.09 ± 0.05	1.24 ± 0.03[a,b]	1.26 ± 0.09[a,b]	1.26 ± 0.01[a,b]
CA-I	0.99 ± 0.08	1.29 ± 0.12	1.34 ± 0.15	1.33 ± 0.12	1.38 ± 0.07	1.72 ± 0.19[a]	1.43 ± 0.06
CA-II	0.98 ± 0.09	1.09 ± 0.18	1.30 ± 0.07	1.36 ± 0.07	1.55 ± 0.09[a]	1.45 ± 0.13	1.39 ± 0.10
CA-III	0.98 ± 0.09	1.10 ± 0.05[a]	1.48 ± 0.04[b]	1.24 ± 0.08	1.50 ± 0.11[b]	1.30 ± 0.04	1.30 ± 0.05

Note: ANOVA significant $p<0.05$; IND = indomethacin; CA-I = *C. aeruginosa* 100 mg/kg; CA-II = *C. aeruginosa* 200 mg/kg; CA-III = *C. aeruginosa* 400 mg/kg
Tukey post hoc test significant $p<0.05$ compared to H0[a], H1[b], and H2[c]

zedoarondiol, curcumenol, and isocurcumenol (Suphrom et al. 2012). Many isolated chemical compounds from *C. aeruginosa* include zedoarol, zedoalactone, isofuranodiene, furanodienone, furangermenone, cycloisolongifolene, dihydrocostunolide, beta-pinene, beta-elemene, cineol, and camphor (Kamazeri et al. 2012).

The membrane stabilization test, using the red blood cell method, was selected to examine the *in vitro* anti-inflammatory activity of *C. aeruginosa*. The erythrocyte membrane is similar to the lysosomal membrane and the stabilization of the lysosomal membrane inhibits the release of lysosomal contents, which can trigger inflammation processes (Umapathy et al. 2010). The cell volume of erythrocytes is associated with the intracellular calcium level. Compounds from plant extracts could increase the ratio of surface area to volume cells, which could be caused by interactions with a membrane protein. The protective effects conveyed by *C. aeruginosa* to the erythrocyte membrane may be mediated by alterations in the influx of calcium. The membrane-stabilizing activity of the medicinal plant extract may be due to the combined effects of components, such as flavonoids, alkaloids, steroids, or terpenoids (Padmanabhan and Jangle 2012).

The carrageenan-induced oedema method was selected to examine *in vivo* anti-inflammatory activity. Carrageenan-induced oedema is a type of non-specific inflammation caused by a reaction to chemical mediators (Iranshahi et al. 2009), which is highly sensitive to non-steroidal anti-inflammatory drugs (NSAIDs) and has been approved as a useful method for the study of new anti-inflammatory agents. Carrageenan is a polysaccharide derived from seaweed, and carrageenan-induced oedema a standard test in anti-inflammatory research (Archera et al. 2015). Swelling caused by carrageenan injections is characterized by oedema with fluid and leukocytes, and injections in paws result in paw oedema in the animal model (Tasleem et al. 2014). The inhibition of carrageenan-induced oedema by *C. aeruginosa* extract may be the result of secondary metabolites in the plant (Padmanabhan and Jangle 2012).

The inflammation process involves three phases. The first, acute, transient, phase is characterized by local oedema caused by enhanced vascular permeability, which is triggered by mediator release (histamine, serotonin, and kinins). During the second, or delayed, sub-acute, phase, the migration of leucocytes and phagocytes occurs, with mediator release (prostaglandin and lysozymes enzymes). During the third, or chronic proliferation, phase, tissue degradation, and fibrosis occurs. Prostaglandins are the primary components during the inflammation process. Many anti-inflammatory drugs are inhibitors of the cyclooxygenase (COX) pathway, which includes prostaglandins (Anilkumar 2010). The mechanisms through which medicinal plants exert anti-inflammatory effects include antioxidant activation, the modulation of inflammatory cell activation, the modulation of pro-inflammatory enzyme activation, and the regulation of gene expression (Bellik et al. 2013).

Our study suggested that the anti-inflammatory activities of *C. aeruginosa* are the result of reduced capillary permeability and fluid exudation. *C. aeruginosa* extracts likely inhibit the discharge of inflammatory chemical mediators that increase vascular permeability. The anti-inflammatory activities of *C. aeruginosa* might be associated with the plant's secondary metabolites (Sunita et al. 2011). In one study, *C. aeruginosa* extracts decreased nitric oxide (NO) generation and enhanced NO maturation, which could also exert anti-inflammatory effects (Choudhury et al. 2013). The mechanism through which *C. aeruginosa* acts as an anti-inflammatory agent likely involves curcumin or other chemical compounds (Jurenka 2009), such as germacrone. In one study, germacrone isolated from *C. aeruginosa* extracts demonstrated impressive anti-nociceptive activity and potential anti-inflammatory activity (Hossain et al. 2015). Curcumin is a prominent chemical compound that has been isolated from *C. aeruginosa* and plays a role in anti-inflammatory activities (Nurcholis et al. 2016). Curcumin acts as an anti-inflammatory agent by reducing NO levels and COX expression (Ramadan et al. 2011). Curcumin also showed anti-inflammatory activities in the carrageenan-induced paw oedema assay (Al-Tahan 2012). Therefore, *C. aeruginosa* chemical compounds, such as curcumin and germacrone, are likely to play roles in the anti-inflammatory activities associated with these plants.

CONCLUSION

This is the first study to explore the anti-inflammatory effect of the *C. aeruginosa* extract using membrane stabilization and carrageenan-induced paw oedema method. Further research should be performed to validate this new natural product-derived anti-inflammatory agent and to determine the active compounds responsible for the anti-inflammatory effects. Further research should also focus on identifying the mechanisms of action through which *C. aeruginosa* extract exerts its anti-inflammatory activities.

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