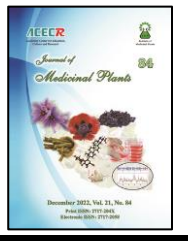
J. Med. Plants 2022; 21(84): 39-49

Institute of Medicinal Plants

Journal of Medicinal Plants

Journal homepage: www.jmp.ir



Research Article

Anti-inflammatory activity of Indonesian polyherbal product containing *Curcuma zanthorrhiza* and *Vitex trifolia* as the main ingredients in carrageenan- and histamine-induced inflammation in Wistar rats

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ARTICLE INFO

Keywords:
Polyherbal formula
Anti-inflammatory
Carrageenan
Histamine
Paw edema

ABSTRACT

Background: The pathophysiology of the upper respiratory diseases involves inflammatory reactions, both immunological and non-immunological inflammation. **Objective:** This study aimed to evaluate the activity of an Indonesian polyherbal product that combines the extracts of *Curcuma zanthorrhiza* Roxb. rhizome and *Vitex trifolia* L. leaves, as the main ingredients, and other medicinal plants for the anti-inflammatory effects in respiratory disorders. **Methods:** The effects of the polyherbal product at different doses (167.5, 335 and 670 mg/kg, p.o) on the right hind paw edema were measured by plethysmometer after induction by subplantar injection of either histamine (100 µl, 2 %) or carrageenan (100 µl, 0.1 %), to represent two types of inflammation. Rat paw edema volume as baseline (Vo) was measured at 30 min before oral administration of the polyherbal and every 30 min for 0-6 h after injection of histamine or carrageenan (Vt). Anti-inflammatory activity was calculated as the percent inhibition of paw edema relative to the negative control, CMC-Na. **Results:** The polyherbal formula significantly decreased paw edema compared with the negative control ($P < 0.05$). Inflammatory inhibition rates of 167.5, 335 and 670 mg/kg doses were 25.19, 32.77 and 47.03 %, respectively, in histamine-induced edema, and 20.12, 56.62 and 68.87 %, respectively, in carrageenan-induced edema. **Conclusion:** The anti-inflammatory properties of a polyherbal containing *C. zanthorriza* and *V. trifolia* as the main ingredients showed a dose-dependent manner. The other herbal components i.e. *Zingiber officinale* rhizome, *Citrus* bioflavonoid complex, and *Echinacea purpurea* herb may contribute to overall anti-inflammatory activity.

Abbreviations: AUC, Area Under Curve; BW, Body Weight; CMC, Carboxymethyl Cellulose; COX, Cyclooxygenase; GM-CSF, Granulocyte Macrophage Colony-Stimulating Factor; H1, Histamine-1; IgE, Imunoglobulin E; IL, Interleukin; iNOS, Induced Nitric Oxide Synthase; NFκB, Kappa-B Nuclear Factor; PLA_2, Phospholipase A2; PMF, Polymethoxy Flavonoid; SD, Standard Deviation; TNF, Tumor Necrosis Factor; Ve, Volume of right hind paw edema; Vo, Volume of right hind paw before inflammatory induction; Vt, Volume of right hind paw after inflammatory induction

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doi: 10.52547/jmp.21.84.39

Received 22 August 2022; Received in revised form 17 October 2022; Accepted 19 October 2022

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[DOR: 20.1001.1.2717204.2022.21.84.4.6]
[DOI: 10.52547/jmp.21.84.39]

1. Introduction

Natural products have long been used as alternatives for curative and promotive health care practices in many countries, including Indonesia. Combining several types of herbs can strengthen their efficacy due to the synergistic action of each component [1]. Our previous study confirmed that the combination of *Curcuma zanthorrhiza* Roxb. rhizomes and *Vitex trifolia* L. leaves at dose 4500 mg/day has significantly decreased IgE titer in rhinitis allergy patients after 2 weeks administration. This mechanism indicated the anti-allergy potential activity of the combination [2]. In addition, the tolerable and safe effect of the herbal product in the dose of 1500 and 4500 mg/day has been proven in healthy volunteer [3]. Continuing our previous study, we developed the herbal combination for wider indication to treat the symptoms of upper respiratory diseases like the common cold, influenza, and even mild COVID-19. For this purpose, we added the herbal combination with other herbal extracts, namely, *Citrus* bioflavonoid complex, *Zingiber officinale* Roscoe, and *Echinacea purpurea* (L.) Moench. They were expected to produce a synergistic beneficial effect in relieving the symptoms of upper respiratory diseases. Upper respiratory diseases like the common cold or influenza are characterized by several symptoms like pain, headache, nasal congestion, and cough. The pathophysiology of the diseases involved inflammatory reactions that contribute to the overall symptoms. It is of our interest to develop a herbal product that have anti-inflammatory activities, both immunological and non-immunological inflammation, represented by induction by histamine or carrageenan. Histamine, a biogenic vasoactive amine, causes symptoms such as allergies and trigger immunological response. While, carrageenan-induced inflammation has long been used as an *in vivo* model of local inflammation, which is considered as non-immunological inflammation.

Citrus species consist of major bioflavonoids, including hesperidin, hesperetin, naringin, naringenin, diosmin, quercetin, rutin, tangeretin, nobiletin, and others [4]. Oral administration of hesperidin inhibits histamine release from mast cells [5], decrease TNF-α (TNF-α: Tumor Necrosis Factor-alpha), and IL (Interleukin)-1β expression that acts as potent pro-inflammatory cytokine [6], reduce COX (Cyclooxygenase)-2 levels [7], and NFκB (Kappa-B nuclear factor) activation pathway [8]. Nobiletin and tangeretin suppress the scratching response in histamine-induced rats and thus diminish the levels of cytokine factors, such as IL-4, TNF-α, and NFκB [8]. *Citrus* flavonoids dominate free radical scavenging, antioxidant, and anti-inflammatory activity [4].

Z. officinale showed anti-inflammatory properties in carrageenan-induced local edema in Sprague Dawley rats [9]. The active substances of ginger, such as gingerol and shogaol, suppress prostaglandin and leukotriene biosynthesis and pro-inflammatory cytokines including IL-1, TNF-α, and IL-8, and downregulates nitric oxide production [10]. A clinical trial confirmed that ginger has an antihistamine property, which is as good as loratadine in improving nasal symptoms and allergic rhinitis patients' quality of life [11]. *E. purpurea*, well-known as an immune system booster agent, has an alkyl amide compound that exhibits anti-inflammatory activity by inhibiting COX-1, COX-2, TNF-α, IL-1, IL-6, iNOS (inducible nitric oxide synthase), and scavenging free radicals to reduce hind paw edema [12,13,14].

We previously reported the immunomodulatory activity of this polyherbal [15]. In this study, we would like to explore the

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anti-inflammatory activities of the polyherbal product to provide more scientific data to support the usage for therapy for common cold or upper respiratory illnesses.

2. Materials and Methods

2.1. Polyherbal formula

The polyherbal product formula was prepared by PT. Soho Industry Pharmasi, Jakarta, Indonesia, according to Good Manufacturing Practice standard, with the component as described in Table 1. For the assay, the herbal formula was prepared in stocks as a suspension in 0.5 % CMC-Na at 20, 40, and 50 mg/ml concentrations. Diclofenac sodium, cetirizine, histamine, and λ-carrageenan were purchased from Sigma-Aldrich.

Three different doses of tested polyherbal formula were determined from human dose (three tablets/day or 3714.09 mg/day) that equivalent to the rat (200 g) dose at conversion factor 0.018 [16]. The result (335 mg/kg body weight [BW]) was set as the middle dose, and dose 1 at 167.5 mg/kg BW and dose 3 at 670 mg/kg BB. The dose of the reference drug i.e. cetirizine and diclofenac sodium were also converted for the rat's daily dose.

2.2. Animals

Fifty 6–8 weeks old male Wistar (weight 150–250 g) were obtained from Laboratory Animal Breeding, Faculty of Pharmacy, Universitas Gadjah Mada, Indonesia. The animals housed in standard cages at a constant temperature of 22 ± 4 °C, relative humidity 30 % –70 %, and a light period of 12 h of dark–light cycle according to the standard animal handling guideline [17]. Five rats were placed in each cage and acclimatized for 3–5 d prior to the experiment. The animals were fed with food (commercial pellet diet) and water ad libitum and fasted before treatment for optimal absorption. The experiment had been approved by ethic committee of Universitas Gadjah Mada (No.: 00122/04/LPPT/XI/2018).

Table 1. Polyherbal product formula

Active Component	**Total (mg)**	**Total in tablet (%)**
Echinacea purpurea extract	150.00	12.11
Vitex trifolia extract	250.00	20.19
Zingiber officinale extract	100.00	8.08
Citrus bioflavonoid complex	100.00	8.08
Curcuma zanthorrhiza extract	250.00	20.19
Excipient	**Total (mg)**	**Total in tablet (%)**
Copovidone	18.00	1.45
Crospovidone	18.00	1.45
Microcrystalline cellulose	307.25	24.82
Colloidal Silicon Dioxide	2.25	0.18
Magnesium Stearate	4.50	0.36
Opadry II 85G58977 White	35.76	2.89
FD&C Blue No.1 Lake (CI 42090)	0.01	0.0008
FD&C Red No.3 Lake (CI 45430)	2.23	0.18
Purified water	0.03	0.002
TOTAL	**1238.03**	
Human dose (3 times in a day)	**3714.09**	

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2.3. Assay of Anti-inflammatory activities

2.3.1. Histamine-induced hind paw edema in rat

Immunological inflammation was induced by sub plantar injection of 0.1 ml of a 1 % histamine [18]. Male Wistar rats were fasted for 18–24 h before the experiment and given free access to water. The paw was marked with ink on the stage of lateral malleolus as a line indicator. The animals were weighed and randomly classified into five groups, with five animals each. Rats were pre-treated with herbal (167.5, 335, and 670 mg/kg, p.o), CMC-Na (0.5 % 10 ml/kg, p.o) as negative control, or cetirizine (0.9 mg/kg, p.o) as positive control, 30 min before histamine injection. Paw volume was measured before the administration of histamine (Vo) and every 30 min for 3 h after (Vt).

2.3.2. Carrageenan-induced hind paw edema in rat

A similar method was used to evaluate the anti-inflammatory activity on carrageenan-induced edema. The local edema was induced by injection of 0.1 ml of a 2 % suspension of carrageenan in saline into the sub plantar region of the right hind paw. Rats were pre-treated with herbal (167.5, 335, and 670 mg/kg, p.o), CMC-Na (0.5 % 10 ml/kg, p.o) as negative control, or diclofenac sodium (13.5 mg/kg, p.o) as positive control, 1 h before carrageenan injection. Paw volume was measured by immersing the paw into the mercury reservoir of the plethysmometer up to the line indicator before the sub plantar injection of carrageenan (Vo) and every 30 min for 6 h after (Vt).

2.4. Calculation of anti-inflammatory activities

The baseline value is the volume of the right paw before (Vo), and volume in a specific time (Vt) is the volume of the right paw of rats after carrageenan or histamine injection. Edema volume (Ve) was calculated using formula:

$$V_e = V_t - V_o$$

Quantitative data were calculated as the area under the curve (AUC) from Ve versus the time which represents the amount of inflammation that occurs. AUC was calculated as follow:

$$AUC_{t_{n-1}}^{t_n} = \frac{Vt_{n-1} + Vt_n}{2} (t_n - t_{n-1})$$

Vt_{n-1}: average of edema volume in t_{n-1}

Vt_n : average of edema volume in t_n

$t_n - t_{n-1}$: time interval of paw measurement (30 min)

Anti-inflammatory potency is represented as percent inhibition, where AUC_c and AUC_t are the mean AUC of placebo (negative control) and treatment (herbal formula and positive control) groups, respectively. Anti-inflammatory potency was calculated using formula:

$$\% \text{ Inhibition} = \frac{AUC_c - AUC_t}{AUC_c} \times 100\%$$

2.5. Statistical analysis

Data were expressed as mean ± SD. Shaphiro–Wilk, and Levene tests assessed data normality and homogeneity, respectively. Statistical analysis of the inflammatory inhibition rate was carried out by one-way ANOVA followed by an LSD test. Statistical significance was expressed as $P < 0.05$. The statistical analysis was conducted using SPSS 14 software.

3. Results

3.1. Effects of Polyherbal Formulation on Carrageenan-induced Rat Paw Edema

Rat paw edema volume of all groups was calculated in millimeters, as shown in Fig. 1. Subplantar injection of 2 % carrageenan in rats evoked maximum local edema within 2.5 h after injection and after that declined until the end of the test.

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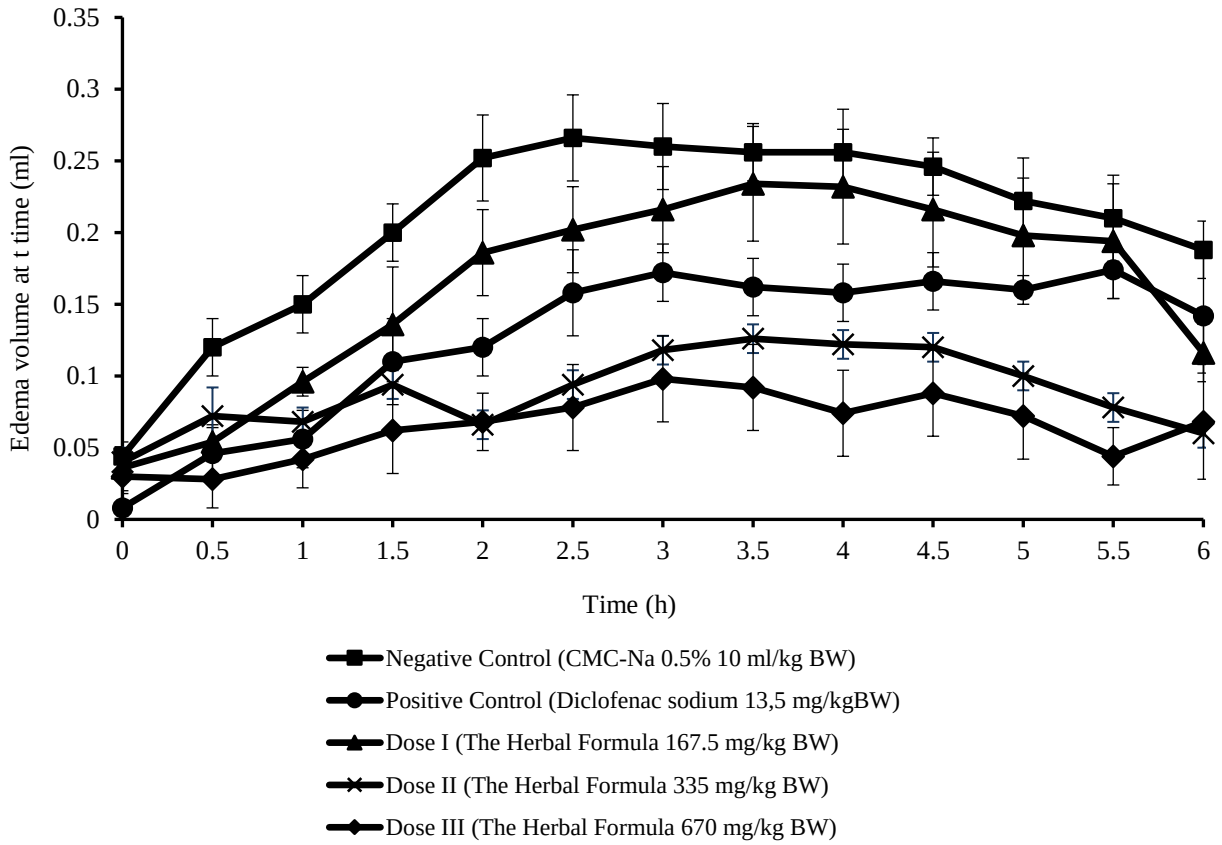

Fig. 1. Volume profile of hind paw edema $(Ve)_{0-6}$ in negative control as baseline (CMC-Na 0.5 % 10 ml/kg BW, n = 5), positive control (diclofenac sodium 13,5 mg/kg BW, n = 5), dose 1 (167.5 mg/kg BW, n = 5), dose 2 (335 mg/kg BW), n = 5) and dose 3 (670 mg/kg BW, n = 5) that induced by carrageenan 2 % (data in the form of Mean ± SD)

The AUC value was significantly decreased by oral treatment of polyherbal formula ($P < 0.05$), as shown in Table 2. The lower AUC value observed in polyherbal treatment compared to negative control indicates the inflammatory inhibition activity. The polyherbal formula at doses of 335 and 670 mg/kg exhibited a greater edema inhibition rate (% inhibition of inflammation ± SD) than the classical anti-inflammatory drug, diclofenac sodium (13.5 mg/kg, p.o). Meanwhile, the 167.5 mg/kg herbal formula exhibited lower potency than diclofenac sodium. LSD results revealed a significant difference between herbal treatments at the dose of 167.5 mg/kg with the other herbal doses ($P < 0.05$) and therefore was inadequate to inhibit inflammation compared to the other higher doses.

3.2. Effects of Herbal Formulation on Histamine-induced Rat Paw Edema

Paw edema induced by 1 % histamine was significantly attenuated by polyherbal formulation in a dose-dependent manner. Maximum local edema was observed at 30 minutes after the sub plantar injection of histamine. Afterward, inflammation exhibited a slowly decreasing trend. As summarized in Fig. 2, the herbal formula reduced the hind paw volume at different potency levels compared to the negative control.

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AUC value of antihistamine drug, cetirizine 0.9 mg/kg, and the polyherbal with various doses showed a decrease, which was significant to the negative control ($P < 0.05$). However, inflammatory inhibition of various doses of the herbal formulation was lower than that of cetirizine, as shown in Table 3. LSD results revealed a significant difference between herbal treatments at the dose of 167.5 mg/kg with cetirizine treatment ($P < 0.05$). This indicates that herbal formulation at 167.5 mg/kg was less potent than cetirizine to inhibit inflammation via histamine receptor blockade.

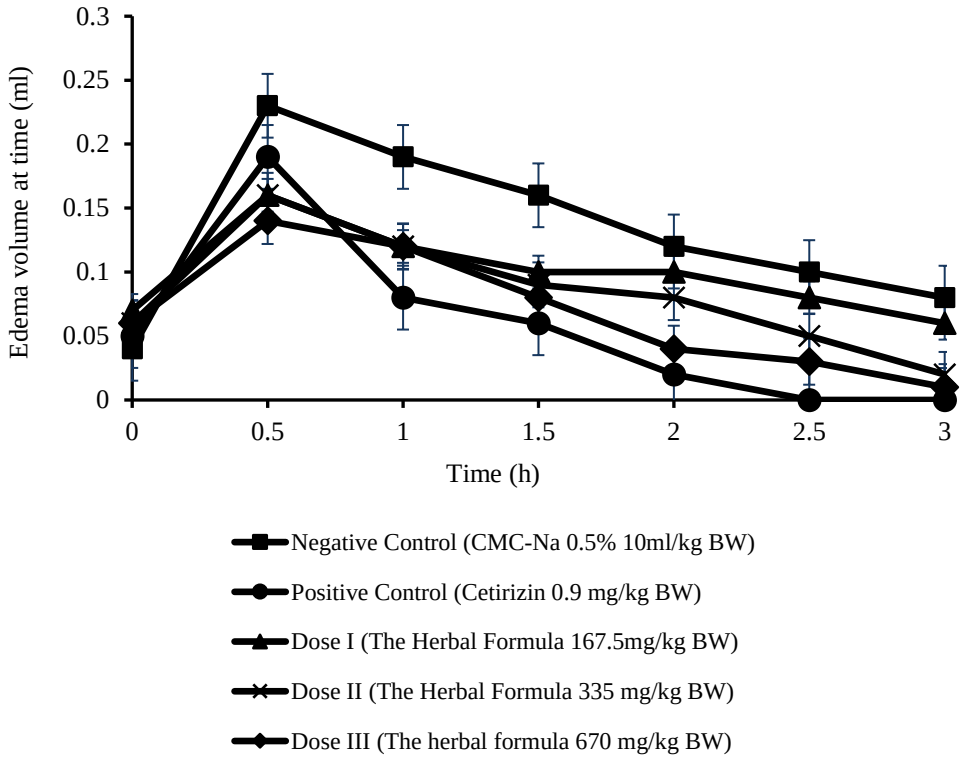

Fig. 2. Volume profile of histamine-induced hind paw edema in negative control as baseline (CMC-Na 0.5% 10 ml/kg BW, n = 5), positive control (cetirizine 0.9 mg/kg BW, n = 5), dose 1 (167.5 mg/kg BW, n = 5), dose 2 (335 mg/kg BW), n = 5), and dose 3 (670 mg/kg BW, n = 5) (data in the form of mean ± SD)

Table 2. % Inhibition of each group carrageenan-induced

Treatment (p.o)	AUC value ± SD (mg.h/L)	Mean of % inhibition of inflammation ± SD
Negative control (CMC 0.5% 10 ml/kg BW)	1.277 ± 0.14	-
Reference (Diclofenac sodium 13,5 mg/kg BW)	0.779[a] ± 0.11	39.04 ± 8.37
Dose 1 (167.5 mg/kg BW)	1.020 ± 0.17	20.12 ± 12.89
Dose 2 (335 mg/kg BW)	0.554[a] ± 0.04	56.62 ± 2.74[b]
Dose 3 (670 mg/kg BW)	0.398[a] ± 0.13	68.87 ± 10.50[b]

Statistical analysis ($P < 0.05$) by parametric ANOVA followed by LSD test. [a]$P < 0.05$: significantly different compared with negative control, [b]$P < 0.05$: significantly different compared with dose 1. % Inhibition: Anti-inflammatory inhibition percentage, SD: Standard Deviation

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Table 3. % Inhibition of each group histamine-induced

Treatment (p.o)	AUC value ± SD (mg.h/L)	Mean of % inhibition of inflammation ± SD
Negative control (CMC 0.5% 10 ml/kg BW)	0.43 ± 0.04	-
Positive control (Cetirizine 0.9 mg/kg BW)	0.20 ± 0.04[a]	54.79 ± 4.59
Dose 1 (167.5 mg/kg BW)	0.31 ± 0.03[a]	25.19 ± 4.39[c]
Dose 2 (335 mg/kg BW)	0.27 ± 0.03[a]	32.77 ± 13.84
Dose 3 (670 mg/kg BW)	0.22 ± 0.03[a]	47.03 ± 6.79

Statistical analysis ($P < 0.05$) by parametric ANOVA, followed by LSD test. [a]$P < 0.05$: significantly different compared with negative control, [c]$P < 0.05$: significantly different compared with the reference.
% Inhibition: Anti-inflammatory inhibition percentage, SD: Standard Deviation

4. Discussion

The immune system comprises innate and adaptive immune responses involving secreted proteins, receptor-mediated signaling, and intricate cell-to-cell communication [19]. When pathogens enter the body, the innate immune system responds with inflammation, pathogen engulfment, and secretion of immune factors and proteins. Meanwhile, the inflammatory response involves mast cells, macrophages, natural killer cells, monocytes, neutrophils, basophils, and cytokines [20]. Pro-inflammatory substances such as interleukin, TNF-α, NFkB, GM-CSF, and iNOS are the first cytokines to be produced [21], causing vasodilatation and increased vascular permeability. This process is characterized by localized redness, swelling, heat, and pain [20, 22].

In this study, the inflammatory activity of the herbal formula was investigated by inducing edema with carrageenan and histamine. Histamine is widely known as a mediator of allergy that binds to the H1 receptor and activates two pathways for NFκB release [23]. Carrageenan induces inflammation by stimulating the release of pro-inflammatory agents such as bradykinin, histamine, iNOS, and cytokines to activate inflammatory reactions that are acute, non-immune, and have a high reproducibility level. The carrageenan-induced paw edema model is a well-known acute inflammatory model frequently used to develop novel anti-inflammatory compounds [24]. Carrageenan injection into sub plantar surface region of rat paw generated biphasic edema. The early phase observed around 90-180 min is related to the release of histamine, bradykinin, serotonin, and other associated chemicals, whereas the latter phase (270-360 min) is attributed to neutrophil infiltration, followed by prostaglandin generation [25]. AUC and inflammation inhibition rate are the main parameters used to evaluate the anti-inflammatory activity, induced either by carrageenan or histamine. Before testing the herbal formula, analysis was conducted on the negative (CMC-Na 0.5%) and diclofenac sodium or cetirizine as positive controls. The test for positive control aims to ensure that the method is appropriate and can produce reliable data.

The solvent of the herbal formula and negative control, CMC-Na 0.5 %, did not affect the anti-inflammatory activity. Hence, both 2 % carrageenan and 1 % histamine were able to trigger inflammation optimally. The positive controls, cetirizine and diclofenac sodium exhibited an anti-inflammatory activity to prevent edema formation. Diclofenac sodium is an anti-inflammatory and analgesic drug of the NSAID group that inhibits the activity of COX-1 and COX-2 enzymes and is effective as an acute

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and chronic inflammatory therapy [26]. Cetirizine, a second-generation H1 antihistamine, acts as selective competitive antagonism of histamine binding to cellular receptors [27].

Diclofenac sodium at a dose of 13.5 mg/kg BW (equivalent to the daily dose of sodium diclofenac, 150 mg) showed a 39.04 % ± 8.37 % inhibition rate for inflammation Abbas et al. [28] reported a similar value of 39 % inhibitory inflammation using the same method and inductor of inflammation. According to its pharmacokinetic profile, the systemic absorption of diclofenac sodium tends to be fast (half-time elimination 1.2–1.8 h) and proportional to the provided dose. Cetirizine is a potent and non-sedative antihistamine for rhinitis treatment and is rapidly absorbed in a maximum concentration within 1 h of oral administration [29]. Cetirizine at 0.25 mg/kg BW dose showed a 73.58 % inhibition rate in CD-1 male mice whose paw was induced by 30 µg of histamine [30]. Using a similar method in rats, the present study obtained a 54.79% anti-inflammatory activity.

Each component of the herbal formula has been scientifically studied as a potential anti-inflammatory compound with diverse mechanisms. *V. trifolia* extract in aqueous solvents suppresses interleukin-1, interleukin-6, NF-kB, and iNOS mRNA synthesis [31]. Interleukin-1 is a cytokine that induces the expression of adhesion molecules in endothelial cells, thereby increasing phagocytosis and enzyme release into tissue cavities. NF-kB and iNOS mRNA are transcription factors that play an essential role in expressing pro-inflammatory mediators [32, 33]. Curcuminoid in *C. zanthorrhiza* and gingerol in *Z. officinale* inhibit LOX transcription factors, cytokines IL-1, IL-2, IL-6, and IL-12, and NF-kB, which is crucial in COX-2 expression; as a result, COX-2 enzyme activity is reduced [34, 35]. The flavonoids in oranges (*Citrus* sp.) such as PMFs, naringin, naringenin, and hesperidin inhibit the activity of neutrophils, macrophages, and cytokines and the components of the inflammatory reaction chain, such as PLA_2, COX-2, iNOS, TNF-α, and IL-6 [36]. The active ingredient of *E. purpurea*, alkyl amide, suppresses the activity of cytokines, iNOS, and COX-2 [13].

The anti-inflammatory activity of the five extracts has a significant influence on reducing rat paw edema. While the polyherbal formulation demonstrated anti-inflammatory activity in the early hours of the carrageenan-induced paw edema test, the histamine-induced paw edema was used to confirm histamine's role in the anti-inflammatory effect of herbal [37]. Each dose exhibits a significant difference to the negative control and thus was declared as anti-inflammatory activity. The largest dose showed the lowest AUC edema value and greatest inhibition percentage. However, the possible side effect must be considered for further development. Dose 1 (167.5 mg/kg) was inadequate as an anti-inflammatory compound. This phenomenon might be caused by the imbalance between the slow absorption rate and the rapid elimination rate that causes low availability in pharmacokinetics and failure to achieve the desired drug therapeutic. From our study, the polyherbal product showed anti-inflammatory activities, that might be useful to reduce the symptoms of upper respiratory diseases.

5. Conclusion

The polyherbal formula containing *C. zanthorrhiza* rhizomes and *V. trifolia* leaves, *Z. officinale* rhizomes, Citrus fruits, and *E. purpurea* herb extracts showed effects as an anti-inflammatory agent, both for immunological and non-immunological inflammation.

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Author contributions

Concept, design, supervision, and final approval: ZI; Data interpretation and critical revision of manuscript: TH; Data acquisition and statistical analysis: NLS, YKH; Drafting manuscript: YKH, ZI. The article was read and approved by all writers.

Conflict of interests

The authors have no conflicts of interest regarding this investigation.

Acknowledgements

The authors would like to thank the Directorate General of Research and Technology and Higher Education, the Republic of Indonesia, for the financial support through research grant No. 2526/UN1.P.III/DIT-LIT/LT/2017 and Ingrid Toha from PT. Soho Industry Pharmasi for preparing the herbal formula.

References

1. Zhang A, Sun H and Wang X. Potentiating therapeutic effects by enhancing synergism based on active constituents from traditional medicine. *Phytother. Res*. 2013; 28(4): 526-33. doi: 10.1002/ptr.5032.

2. Herdwiani W and Ikawati Z. Effect of combination of legundi leaf (*Vitex trifolia* L.) and temulawak rhizome (*Curcuma zantrohoeiza* Roxb) on total serum IgE and eosinophil levels of nasal mucosal swabs in patients with allergic rhinitis. *Thesis*. 2011. Faculty of Pharmacy, Gadjah Mada University (the article is originally published in Indonesian language).

3. Baroroh HN, Ikawati Z and Sudarman K. A Safety study of extract combination of legundi (*Vitex trifolia* L.) leaves and temulawak (*Curcuma zanthorrhiza* R.) rhizome as anti-allergy in healthy volunteers. *IJPTP*. 2011; 2(4): 165-170.

4. Mahmoud AM, Bautista RJH, Sandhu MA and Hussein OE. Beneficial effects of citrus flavonoids on cardiovascular and metabolic health. *Oxid. Med. Cell Longev*. 2019; 1-19. doi: 10.1155/2019/5484138.

5. Matsuda M, Yano M, Kubo M, Iinuma M, Oyama M and Mizuno M. Pharmacological study on citrus fruits: II. anti-allergic effect of fruit of *Citrus unshiu* MARKOVICH (2). on flavonoid components. *Yakugaku Zasshi*. 1991; 111(3): 193-198. doi: 10.1248/yakushi1947.111.3_193.

6. Bentli R, Ciftci O, Cetin A, Unlu M, Basak N and Cay M. Oral administration of hesperidin, a citrus flavonone, in rats counteracts the oxidative stress, the inflammatory cytokine production, and the hepatotoxicity induced by the ingestion of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). *Eur. Cytokine. Netw*. 2013; 24(2): 91-96. doi: 10.1684/ecn.2013.0337.

7. Hirata A, Murakami Y, Shoji M, Kadoma Y and Fujisawa S. Kinetics of radical-scavenging activity of hesperetin and hesperidin and their inhibitory activity on COX-2 expression. *Anticancer Res*. 2005; 25(5): 3367-3374.

8. Ghorbani A, Nazari M, Jeddi-Tehrani M and Zand H. The citrus flavonoid hesperidin induces p53 and inhibits NF-κB activation in order to trigger apoptosis in NALM-6 cells: involvement of PPARγ-dependent mechanism. *Eur. J. Nutr*. 2012; 51: 39-46. doi: 10.1007/s00394-011-0187-2.

9. Hassan NA, Karunakaran R, Sankar U and Aye KM. Anti-inflammatory effect of *Zingiber officinale* on sprague dawley rats. *Asian J. Pharm. Clin. Res*. 2017; 10(3): 353-355. doi: 10.22159/ajpcr.2017.v10i3.16251.

10. Mashhadi NS, Ghiasvand R, Askari GR, Hariri M, Darvishi L and Mofid MR. Anti-oxidative and anti-inflammatory effects of ginger in health and physical activity: review of current evidence. *Int. J. Prev. Med*. 2013; 4(Suppl 1): S36-42.

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[DOR: 20.1001.1.2717204.2022.21.84.4.6]
[DOI: 10.52547/jmp.21.84.39]

11. Yamprasert R, Chanvimalueng W, Mukkasombut N and Itharat A. Ginger extract versus loratadine in the treatment of allergic rhinitis: a randomized controlled trial. *BMC Complement. Med. Ther*. 2020; 20: 119. doi: 10.1186/s12906-020-2875-z.

12. Sloley BD, Urichuk LJ, Tywin, C, Coutts RT, Pang PKT and Shan JJ. Comparison of chemical components and antioxidant capacity of different *Echinacea* species. *JPP*. 2001; 53(6): 849-857. doi: 10.1211/0022357011776009.

13. Hinz B, Woelkartm K and Bauer R. Alkamide from echinacea inhibits cyclooxygenase-2 activity in human neuroglioma cells. *Biochemical and Biophysical Research Communications* 2007; 360(2): 441-446. doi: 10.1016/j.bbrc.2007.06.073.

14. Hou CC, Chen CH, Yang NS, Chen YP, Lo CP, Wang SY, Tien YJ, Tsai PW and Shyur LF. Comparative metabolomics approach coupled with cell- and gene-based assay for species classification and anti-inflammatory bioactivity validation of *Echinacea* plants. *JNB.* 2010; 21:1045-10. doi: 10.1016/j.jnutbio.2009.08.010.

15. Ikawati Z, Hertiani T and Izzati F. Immunomodulatory activity of an Indonesian herbal formulation for respiratory disorder. *Phcog. Mag*. 2019; 15(60): 130-134. doi: 10.4103/pm.pm_314_18.

16. Rockville, MD: US Food and Drug Administration; USFDA. Guidance for Industry: Estimating the Maximum Safe Starting Dose in Adult Healthy Volunteer. 2005.

17. Gad SC. Animal models toxicology. 2nd edition. United State: CRC Press; 2007. 150-180. doi: 10.1201/9781420014204

18. Tamaddonfard E, Farshid AA, Eghdami K, Samadi F and Erfanparast A. Comparison of the effects of crocin, safranal, and diclofenac on local inflammation and inflammatory pain responses induced by carrageenan in rats. *Pharmacol. Reports* 2013; 65(5): 1272-1280. doi: 10.1016/s1734-1140(13)71485-3.

19. Monar C and Gair J. Concept of biology. 1st Canadian Edition. Canada: B.C Campus Open Textbooks Project; 2019.

20. Hussein SZ, Yusoff KM, Makpol S and Yusof YAM. Gelam honey attenuates carrageenan-induced rat paw inflammation via NF-kB pathway. *PLoS ONE*. 2013; 8(8): e72365. doi: 10.1371/ journal.pone.0072365. eCollection 2013.

21. Abbas AK, Lichtman AH and Pillai SH. Cellular and molecule immunology, 7th edition. Philadelphia: WB Saunders Company; 2012.

22. Bakker RA, Schoonus SBJ, Smit MJ, Timmerman H and Leurs R. Histamine H(1)-receptor activation of nuclear factor-kB: roles for Gβγ - and $G\alpha_{q/11}$-subunits in constitutive and agonist-mediated signaling. *Molecular Pharmacol*. 2001; 60(5): 1133-1142. doi: 10.1124/mol.60.5.1133.

23. Winyard PG and Willoughby DA. Methods in molecular biology vol 225: inflammation protocols. Totowa: Humana Press Inc; 2013. (https://www.amazon.com/Inflammation-Protocols-Methods-Molecular-Biology/dp/0896039706).

24. Mansouri MT, Hemmati AA, Naghizadeh B, Mard SA, Rezaie A and Ghorbanzadeh B. A study of the mechanisms underlying the anti-inflammatory effect of ellagic acid in carrageenan-induced paw edema in rats. *Indian J. Pharmacol*. 2015; 47(3): 292-298. doi: 10.4103/0253-7613.157127.

25. Khan I, Nisar M, Ebad F, Nadeem S, Saeed M, Khan H, Samiullah, Khuda F, Karim N, and Ahmad Z. Anti-inflammatory activities of sieboldogenin from *Smilax china* Linn.: experimental and computational studies. *J. Ethnopharmacol*. 2009; 121(1): 175-177. doi: 10.1016/j.jep.2008.10.009.

[Downloaded from mail.jmp.ir on 2026-10-01]
[DOR: 20.1001.1.2717204.2022.21.84.4.6]
[DOI: 10.52547/jmp.21.84.39]

26. Alfaro RA and Davis DD. Diclofenac [Updated 2022 May 23]. StatPearls. Retrieved from https:// www.ncbi.nlm.nih.gov/ books/ NBK557879.
27. Baroody FM and Naclerio RM. Antiallergic effects of H1-receptor antagonists. *Allergy* 2000; 55 Suppl 64: 17-27. doi: 10.1034/j.1398-9995.2000.00803.x.
28. Abbas SS, Schaalan MF, Bahgat AK and El-Denshary ES. Possible potentiation by certain antioxidant of the anti-inflammatory effect of diclofenac in rats. *Scientific World J*. 2014; 1-9. doi: 10.1155/2014/731462.
29. Banerji A, Long AA and Camargo CA. Diphenhydramine versus nonsedating antihistamines for acute allergic reactions: a literature review. *Allergy Asthma Proc*, 2007; 28(4): 418-426. doi: 10.2500/aap.2007.28.3015.
30. Zalawadia R, Gandhi C, Patel V and Balaraman R. The protective effect of *Tinospora cordifolia* on various mast cell-mediated allergic reactions. *Pharm. Biol*. 2009; 47(11): 1096-1106. doi: 10.3109/13880200903008690.
31. Rosa SIG, Rios-Santos F, Balogun SO and Martins DT de O. Vitexin reduces neutrophil migration to inflammatory focus by down-regulating pro-inflammatory mediators via inhibition of p38, ERK1/2 and JNK pathway. *Phytomedicine* 2016; 23(1): 9-17. doi: 10.1016/j.phymed.2015.11.003.
32. Matsui M, Kumar-Roine S, Darius HT, Chinain M, Laurent D and Pauillac S. Characterization anti-inflammatory potential of *Vitex trifolia* L. (Labiatae), a multipurpose plant of the pacific traditional medicine. *J. Ethnopharmacol*. 2009; 126(3): 427-433. doi: 10.1016/j.jep.2009.09.020.
33. Matsui M, Adib-Conquy M, Coste A, Kumar-Roine S, Pipy B, Laurent D and Pauillac S. Aqueous extract of *Vitex trifolia* L. (Labiate) inhibits LPS-dependent regulation of inflammatory mediators in RAW 264.7 macrophages through inhibition of nuclear factor kappa B translocation and expression. *J. Ethnopharmacol*. 2012; 143(1): 24-32. doi: 10.1016/j.jep.2012.05.043.
34. Srinivasan K. Ginger rhizomes (*Zingiber officinale*) A spice with multiple health beneficial potentials. *Pharma Nutrition* 2017; 5(1): 18-28. doi: 10.1016/j.phanu.2017.01.001.
35. Oh JG, Hwang DJ and Heo TH. Direct regulation of IL-2 by curcumin. *Biochemical and Biophysical Research Communications* 2018; 495(1): 300-305. doi: 10.1016/ j.bbrc.2017.11. 039.
36. Gosslau A, Chen KY, Ho CT and Li S. Anti-inflammatory effects of characterized orange peel extracts enriched with bioactive polymethoxyflavones. *Food Science and Human Wellness* 2014; 3(1): 26-35. doi: 10.1016/j.fshw.2014.02.002.
37. Silva JC, Araújo C de S, de Lima-Saraiva SRG, de Oliveira-Junior RG, Diniz TC, Wanderley CW de S, Palheta-Júnior RC, Mendes RL, Guimarães AG, Quintans-Júnior LJ and Almeida JRG da S. Antinociceptive and anti-inflammatory activities of the ethanolic extract of *Annona vepretorum* Mart. (*Annonaceae*) in rodents. *BMC Complement. Alternat Med*. 2015; 15: 197. doi: 10.1186/s12906-015-0716-2.

How to cite this article: Ikawati Z, Hertiani T, Hartanti YK, Sigalih NL. Anti-inflammatory activity of Indonesian polyherbal product containing *Curcuma zanthorrhiza* and *Vitex trifolia* as the main ingredients in carrageenan- and histamine-induced inflammation in Wistar rats. ***Journal of Medicinal Plants*** 2022; 21(84): 39-49.
doi: 10.52547/jmp.21.84.39

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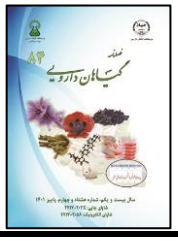

مقاله تحقیقاتی

فعالیت ضدالتهابی محصول چند گیاهی اندونزیایی حاوی گونه‌ای زردچوبه و پنج انگشت هندی به عنوان مواد اصلی در التهاب ناشی از کاراژینان و هیستامین در موش‌های صحرایی ویستار

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اطلاعات مقاله

گل‌واژگان:
محصول چند گیاهی
ضدالتهابی
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هسیتامین
ادم کف پا

چکیده

مقدمه: پاتوفیزیولوژی بیماری‌های دستگاه تنفسی فوقانی با واکنش های التهابی، هم التهاب ایمونولوژیک و هم التهاب غیر ایمونولوژیک همراه می‌باشد. **هدف:** هدف از این مطالعه، ارزیابی فعالیت یک محصول چند گیاهی اندونزیایی که ترکیبی از عصاره ریزوم گونه‌ای زردچوبه (*Curcuma zanthorrhiza* Roxb.) و برگ‌های پنج انگشت هندی (*Vitex trifolia*) به عنوان مواد اصلی و سایر گیاهان دارویی برای اثرات ضد التهابی در اختلالات تنفسی بود. **روش بررسی:** اثرات محصول چند گیاهی در دوزهای مختلف (۱۶۷/۵، ۳۳۵ و ۶۷۰ میلی‌گرم بر کیلوگرم، خوراکی) بر روی ادم کف پای راست عقب پس از القاء با تزریق موضعی هیستامین (۱۰۰ میکرولیتر، ۲ درصد) یا کاراژینان (۱۰۰ میکرولیتر، ۰/۱ درصد) در کف پا، با استفاده از پلتیسموتر برای نشان دادن دو نوع التهاب اندازه‌گیری شد. حجم ادم کف پای موش صحرایی به عنوان پایه (Vo) در ۳۰ دقیقه قبل از تجویز خوراکی محصول چند گیاهی و هر ۳۰ دقیقه برای صفر تا شش ساعت پس از تزریق هیستامین یا کاراژینان (Vt) اندازه‌گیری شد. فعالیت ضد التهابی به صورت درصد مهار ادم کف پا نسبت به کنترل منفی CMC-Na محاسبه شد. **نتایج:** فرمول چند گیاهی به طور معنی‌داری ($P < ۰/۰۵$) ادم کف پا را در مقایسه با شاهد منفی کاهش داد. نرخ مهار التهابی با دوزهای ۱۶۷/۵، ۳۳۵ و ۶۷۰ میلی‌گرم در کیلوگرم به ترتیب ۲۵/۱۹، ۳۲/۷۷ و ۴۷/۰۳ درصد، در ادم ناشی از هیستامین و برابر با ۲۰/۱۲، ۵۶/۶۲ و ۶۸/۸۷ درصد در ادم ناشی از کارراژینان بود. **نتیجه‌گیری:** خواص ضدالتهابی این فرآورده چند گیاهی حاوی گونه‌ای زردچوبه و پنج انگشت هندی به‌عنوان ترکیبات اصلی، وابسته به دوز بود. سایر اجزای گیاهی مانند ریزوم زنجبیل، کمپلکس بیوفلاونوئید مرکبات و گیاه سرخارگل ممکن است به فعالیت کلی ضدالتهابی کمک کنند.

مخففها: AUC، سطح زیر منحنی؛ BW، وزن بدن؛ CMC، کربوکسی متیل سلولز؛ COX، سیکلواکسیژناز؛ GM-CSF، فاکتور محرک کلنی گرانولوسیت- ماکروفاژ؛ H1، هیستامین ۱؛ IgE، ایمنوگلوبین ای؛ IL، اینترلوکین؛ iNOS، نیتریک اکسید سنتاز القایی؛ NFκB، فاکتور هسته‌ای کاپا بی؛ PLA_2، فسفولیپاز آ۲؛ PMF، پلی متوکسی فلاونوئید؛ SD، انحراف معیار؛ TNF، فاکتور نکروز تومور؛ Ve، حجم ادم کف پای راست عقب؛ Vo، حجم ادم کف پای راست عقب قبل از القای التهاب؛ Vt، حجم ادم کف پای راست عقب بعد از القای التهاب

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تاریخ دریافت: ۳۱ مرداد ۱۴۰۱؛ **تاریخ دریافت اصلاحات:** ۲۵ مهر ۱۴۰۱؛ **تاریخ پذیرش:** ۲۷ مهر ۱۴۰۱

doi: 10.52547/jmp.21.84.39

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